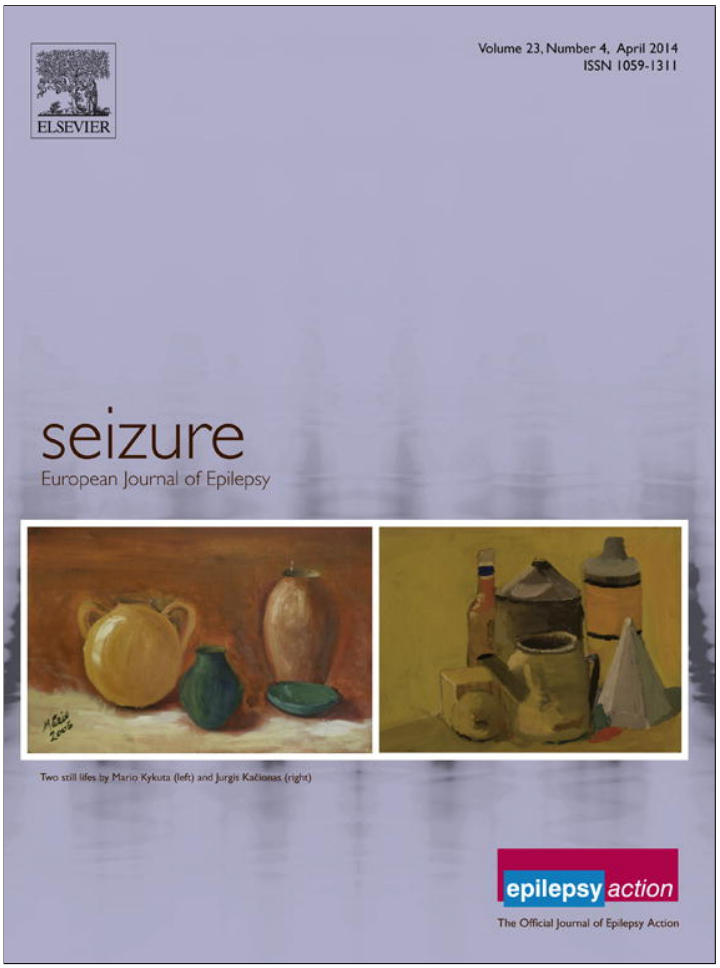

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Review

Praxis induction. Definition, relation to epilepsy syndromes, nosological and prognostic significance. A focused review

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ABSTRACT

Purpose: There is increasing awareness that reflex epileptic mechanisms provide unique insight into ictogenesis in human epilepsies. Several of the described triggers have in common that they imply complex visuomotor coordination and decision-making; they are today regarded as variations of one principle, i.e. praxis induction (PI). This focused review considers PI from the aspects of history and delineation, clinical and electroencephalographic presentation, syndromatic relations, prevalence, mechanisms of ictogenesis and nosological implications, treatment and prognosis.
Methods: We reviewed a series of published articles and case reports on PI in order to clarify clinical and electroencephalographic findings, treatment and outcome.
Results: Findings of both induction and inhibition by the same stimuli suggest widening the reflex epilepsy concept into a broader one of epilepsies with exogenous modification of ictogenesis. PI is closely related to juvenile myoclonic epilepsy (JME) where hyperexcitability and hyperconnectivity of the entire network of visuomotor coordination seem to provide the precondition for eliciting reflex myocloni in the musculature active in the precipitating task.
Conclusion: The conclusions on ictogenesis derived from PI support the concept of JME as a system disorder of the brain.

1. Background and definition

Over the last years, increasing awareness has developed that reflex epileptic mechanisms provide unique possibilities to study seizure generation (ictogenesis) in natural human epilepsies. Praxis induction (PI) is one of the reflex epileptic traits which have been in focus. It is defined as the precipitation of epileptic seizures or epileptiform EEG discharges (ED) by complex, cognition-guided tasks often involving visuomotor coordination and decision-making.

2. History and delineation

The term was first used by Daniele et al.[1] but there is an earlier literature presenting specific aspects of PI such as playing chess, card or other games,[2–5] calculations,[6,7] writing,[8,9] drawing[10] and decision making.[11] Inoue et al.[12] reviewed the literature and proposed to consider PI as a common denominator. They observed that the vast majority of patients suffered from idiopathic generalized epilepsy (IGE), particularly juvenile myoclonic epilepsy (JME).[12]

In 1980, Okuma et al.[13] devised an EEG activation method which they termed neuropsychological EEG activation (NPA) protocol involving speaking, reading, writing, calculation, constructive acts as drawing figures and block design tests (Table 1). This NPA protocol was carried out when paroxysmal discharges had been induced in a simpler form of a 5 min NPA comprising reading silently and aloud, speaking, mental and written calculation, writing and spatial construction during routine EEG examinations.[13] NPA was used by Matsuoka et al.[14] and also in a group of patients with "graphogenic epilepsy"[15] as well as in a large unselected patient group.[16]

Thinking-induced seizures[17] according to some authors are another variant of PI whereas others consider them a separate entity.[18] Since spatial thinking is central in thinking-induced seizures, any difference is probably gradual. However, Zifkin[18] in this discussion pointed out that seizures induced by thinking without any motor component often provoke absences and generalized tonic–clonic seizures (GTCS) but no myoclonic seizures. These cases typically involve the solution of complex arithmetic tasks which could be explained by a network including bilateral parietal cortical areas[19] but not more, unlike in PI. Guaranha et al.[20] confirmed that mere planning of precipitating actions was a trigger by itself, the difference being only quantitative. Induction by writing

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Table 1
Detailed neuropsychological EEG activation protocol.[13]

(1) Writing
1. Spontaneous writing
2. Dictation
3. Copying
4. Spontaneous writing blindfolded
5. Dictation blindfolded
6. Dictation by food
Each was examined for Japanese letters (Hiragana, Katakana, Kanji), Roman letters and English letters
(2) Speaking
1. Spontaneous speaking
2. Reading aloud
3. Repeating
Each was examined in Japanese and English
(3) Other verbal activation
1. Reading silently
2. Visualizing letters
3. Making sentences in the mind
(4) Calculation
1. Calculation with hands
2. Mental calculation
3. Calculation using an abacus
4. Calculation using an electric calculator
Each was examined for subtraction, addition, multiplication and division
5. Uchida-Kraepelins psychodiagnostic test
(5) Constructional praxis
1. Spontaneous drawing
2. Sketching maps
3. Copying figures
4. Matchstick pattern reproduction
5. Block design test (WAIS)
6. Making plastic models
(6) Other tests
1. Finger tapping
2. Fine movement of the finger (tremolo)
3. Using a screw-driver
4. Bourdon cancelation test
5. Undoing puzzle rings
6. Hand, eye and ear tests (H Head)
7. Finger gnosia tests
8. Dressing
9. Color classification
10. Humming
11. Singing

has been reported both with PI[12], with primary reading epilepsy (PRE)[21] and separately.[9] Because of the linguistic involvement its place can be debated. Likewise, seizures induced by video games are most often related to photosensitivity[22] but may also involve visuomotor coordination. The significance of these overlaps will become apparent below.

3. Description

Onset usually is in the second decade of life. Praxis-induced seizures typically start with a delay of some minutes of activity, occasionally more, as single or repetitive arrhythmic myocloni in muscles involved in the precipitating activity. A typical example is presented in Video 1. If the patient continues his activity they usually evolve into a GTCS, sometimes rather rapidly.

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2014.01.011.

Spontaneous seizures occur rarely in 76% of patients.[5] Occasionally, PI can commence later in life.[23,24] Some familial cases have been described, e.g. two sisters with seizures exclusively induced by writing,[9] and the genetic aspects seem not to differ from other patients with IGE.[25]

4. Prevalence and syndromatic relations

Matsuoka et al.[14] performed NPA in 25 JME patients. Mental activities involving the hands (writing, calculation and drawing) precipitated seizures in 19 patients (76%). NPA was more effective in inducing ED (21 patients = 84%) than established activation methods such as drowsiness (17 patients = 68%), hyperventilation (10 patients = 40%) and photic stimulation (9 patients = 36%).[14]

All 25 cases reported by Goossens et al.[5] had IGE with clinical patterns suggestive of either juvenile absence epilepsy or JME. These authors associated the occurrence of seizures to activation of the parietal lobe.

Senanayake[26] reported increase of ED and seizures with NPA in 148 JME patients. In twelve, >50% and in seven, all myoclonic seizures were precipitated by tasks involving problem solving, calculation and spatial processing. He agreed with Goossens et al.[5] that these patients presented regional hyperexcitability of the dominant parietal cortex.[26]

Because of their clinical and EEG similarities, Inoue et al.[12] compared the clinical features of 32 PI patients with 132 unselected JME patients. They concluded that all PI patients with a specific diagnosis had IGE (JME 21, juvenile absence epilepsy 3, unspecified IGE 4); 4/32 had undetermined epilepsy. Of their 132 unselected JME patients, 19 (14%) had predominantly, and another 24 (18%) incidental reflex seizures. However, patients with predominant PI differed from the others by a male predominance of 3.7/1 (in agreement with Goossens et al.[5]; ratio 3:1) and a lower incidence of the photoconvulsive response, suggesting a dispositional difference within JME.[12] In a Brazilian series younger male patients were more prone to PI induction than older ones (25% up to age 30 versus 6% above) which was attributed to more frequent activities demanding fine finger movements such as game playing and computer manipulation by the younger generation.[27]

According to Janz and Durner,[28] mental tasks involving hand movements, leading to psychic tension and demanding decision-making could provoke both myoclonic jerks and major seizures in JME.

Inoue and Kubota[29] reported PI in 27 of 213 JME patients (12.2%). They confirmed the following differences: slight male predominance (2.3:1); more absence seizures; no photosensitivity; higher amplitude of sensory evoked potentials (suggesting increased cortical excitability) and slightly less favorable treatment prognosis.[29]

Matsuoka et al.[16] in a multicenter study tested 480 unselected epilepsy patients with an enhanced NPA protocol for praxis-induced epileptiform activity and seizures. They found PI in 38 patients (7.9%), 36 of whom had IGE including JME. The most significant findings were with writing ($n = 26$, 68%), spatial construction ($n = 24$, 63.2%) and written calculation ($n = 21$, 58.3%). Of 45 JME patients ED were triggered in 22 (48.9%), by far the highest rate of all syndromes.[16]

Wolf and Mayer[30] reported on 62 JME patients who had answered a questionnaire addressing specific precipitation factors. PI was described by 19 (31%) comprising writing (7), decision-making (4), computer tasks and video games (6), calculations (6), thinking (8) and playing the piano (1). These authors, for the first time, emphasized another type of reflex myocloni in JME patients: the perioral reflex myoclonia (PORM) which were reported in 22 of the responses (35%).[29] In a follow-up study investigating 25 JME patients with video-EEG and using a modification of Matsuoka's NPA,[31] PORM were found in nine patients (36%), and PI in six (24%; 4 manipulating with Rubik cube, 2 writing and 1, calculating).

Karachristianou et al.[32] studied 30 JME patients with a NPA protocol and found EEG activation in 23 (76.6%) including manual tasks such as doodling figures in 18 (60%) or written calculations in 13 (43.3%), but also in non-manual activities like mental calculations in 15 (50%) and mental spatial manipulation in 15 patients (50%).

Among 75 Brazilian JME patients answering a questionnaire induction of seizures by hand activities and complex finger manipulations was known to 15 (20%)[27] whereas they considered stress (62 cases or 83%) and sleep deprivation (58 or 77%) by far the main seizure precipitants.

In a video-EEG NPA study, Guaranha et al.[20] described praxis induced discharges and/or myoclonic seizures in 22 of 76 patients (29%; puzzles in 19; written calculation in 9; writing in 6; drawing in 6).

It can therefore be concluded that PI is strongly associated with JME but also occurs in other types of IGE whereas it is very rare in other epilepsies. The prevalence figures in JME, however, vary

between 8% and 60%, probably due to differences in sampling and investigation protocols. But even in the studies using similar protocols there is variation from 24 and 29% in Germany and Brazil, and almost 50% in Japan. At present these different rates remain unexplained. Since cortical excitability varies during the day[33] and one of the strongest trigger in JME is stress[27] we may infer they must be related to differences in NPA protocols such as execution of tasks on awakening after sleep deprivation or a full night of sleep and specific characteristics of the tasks as the use of stressful material, their duration, complexity, etc.

5. Precipitation and inhibition

Matsuoka et al.[16] were puzzled by the finding that NPA in many cases seemed to inhibit rather than enhance ED when these were present in the unprovoked EEG; in a few patients even both, activation and inhibition were described. This was confirmed by Mayer at al.[31] and by Guaranha et al.[20] who paid special attention to this protean response. The question became the object of an international multicenter investigation of 60 JME patients with methods that took into consideration the spontaneous fluctuations of ED.[34] In this study inhibition by NPA was less frequent than in the earlier reports but was still seen in 29% of the patients whereas provocation occurred in 18%. However, provocation appeared to be task-specific whereas inhibition could be explained by a non-specific effect of cognitive activation or arousal as such.[34] The question remains open if the concept of reflex epilepsies needs to be replaced by a broader view of epilepsies with exogenous modification of ictogenesis.

6. Mechanisms of ictogenesis and nosological implications

The most interesting scientific aspect of reflex epilepsies is the possibility they provide to study natural ictogenesis in human epilepsy since in them, a specific, often even quantitatively defined stimulus evokes a specific epileptic response. Advanced study methods of brain function can provide insights of unprecedented precision into these relations. Thus, Moeller et al.[35] have demonstrated that the spike-wave discharges of the photoparoxysmal response result from a cascade of transcortical events not involving the thalamus.

PI is of particular interest because of its association with JME. Glenn et al.[23] hypothesized local excitation associated with proprioceptive input as a mechanism of seizure generation, analogous to photosensitivity and reading- or language-induced epilepsy. The hyperexcitation would then propagate to adjacent motor cortex through a transcortical pathway generating myoclonus.[36] This requires a stimulus strong enough to activate a critical mass of cortex to produce epileptic activity.[37]

Zylicz et al.[38] discussed the role of specific functional anatomical systems acting as a whole. Patients with reflex seizures would have sensitive areas within such systems. Specific areas involved in sensory or cognitive stimulation would overlap with hyperexcitable areas so a restricted stimulus could influence an entire system.

But reflex myocloni usually are quite restricted. Thus, whereas cognitive functional anatomical subsystems become overexcited as a whole the epileptic response is generated locally within the system, e.g. proprioception of hand movements involved in a complex ictogenic activity precipitates, in a true pathological reflex mechanism, myocloni in the active hand.

A highly important contribution to the understanding of the ictogenesis in JME highlighting the mechanisms of PI was made by Vollmar et al.[39] who exposed 30 patients with JME to a demanding frontal lobe test of visuo-motor coordination and working memory. They performed as well as 26 healthy controls but their fMRI showed, with increasing cognitive demand, increasing coactivation of the primary motor cortex and supplementary motor area, and increased functional connectivity between the motor system and frontoparietal cognitive networks. Furthermore, the concomitant physiological deactivation of the default mode network during the task was impaired. They concluded that, together, these findings provide an explanation how cognitive effort can cause myoclonic jerks in JME.[39]

These findings add a new dimension to earlier considerations about the role of functional anatomical systems in IGE which were based upon photosensitivity and pattern sensitivity as reviewed by Binnie[40]. They provided an important contribution to the theory of system epilepsies[41,42] because they demonstrated that the central mechanisms of seizure generation in these epilepsies "hijack", by hyperexcitation, pre-existing functional anatomic subsystems of the central nervous system (CNS). The system epilepsies concept therefore provides a better understanding of these conditions than the misleading term "generalized" epilepsies.[42]

7. EEG

Normal background and generalized spike and wave or polyspike and wave complexes were found in the resting EEG or during hyperventilation.[25] In five subjects with "graphogenic epilepsy" and a clinical diagnosis of IGE a NPA protocol proved remarkably provocative, inducing either brief bursts of generalized spike-and-wave complexes 3–5 Hz or bilateral spike-and-wave complexes predominating in the central regions, frequently asymmetrical and often accompanied by myoclonic seizures.[15]

In some patients the paroxysms verified during the execution of motor tasks are isolated, fast spikes, followed by slow waves or short volleys of low amplitude, poorly formed, very fast and brief spike and wave complexes morphologically similar to those recorded while reading and in reading epilepsy (Fig. 1). Sometimes they are so brief that it is difficult to distinguish them from the accompanying myogenic artifacts.[21,27,31]

8. Significance for treatment and prognosis

Goossens et al.[5] described PI as an easily controllable condition with satisfactory response to treatment, with three of the 25 patients seizure free only by avoiding precipitating factors. When antiepileptic drugs (AEDs) were required, valproic acid (VPA) and benzodiazepines such as clonazepam and clobazam were effective. Most case reports indicated good seizure control especially with VPA. It is difficult to assess the ultimate remission rate since most patients continued to take antiepileptic medication and the rate of spontaneous remission is fundamentally unknown.[7,9,23,24]

Matsuoka,[43] however, reported negative impact of sensibility to NPA on prognosis of JME. Among 32 JME patients, nine with seizures from 20 to 39 years despite treatment with VPA with or without other AEDs, besides more focal discharges on EEG, had much stronger response to NPA from the onset. The author suggested that NPA would be a predictor of prognosis in JME and that the severity of disease process itself rather than psychosocial factors might be crucial to determine its long term course.[43]

Inoue et al.[12] reported that seizure-freedom for more than three years dropped from 49/71 (69%) in patients with none or only non-specific triggers to 5/16 (31.2%) for predominantly praxis sensitive patients. Two patients were particularly medically refractory. Almost all patients in the PI group could recognize impending seizures and tried to avoid precipitating stimuli in their daily lives. VPA, clonazepam and zonisamide were the most effective drugs.[12]

Similarly, Inoue and Kubota[29] analyzing a series of 134 JME patients, reported that seizure-freedom for more than three years dropped from 53/77 (69%) in patients with none or only

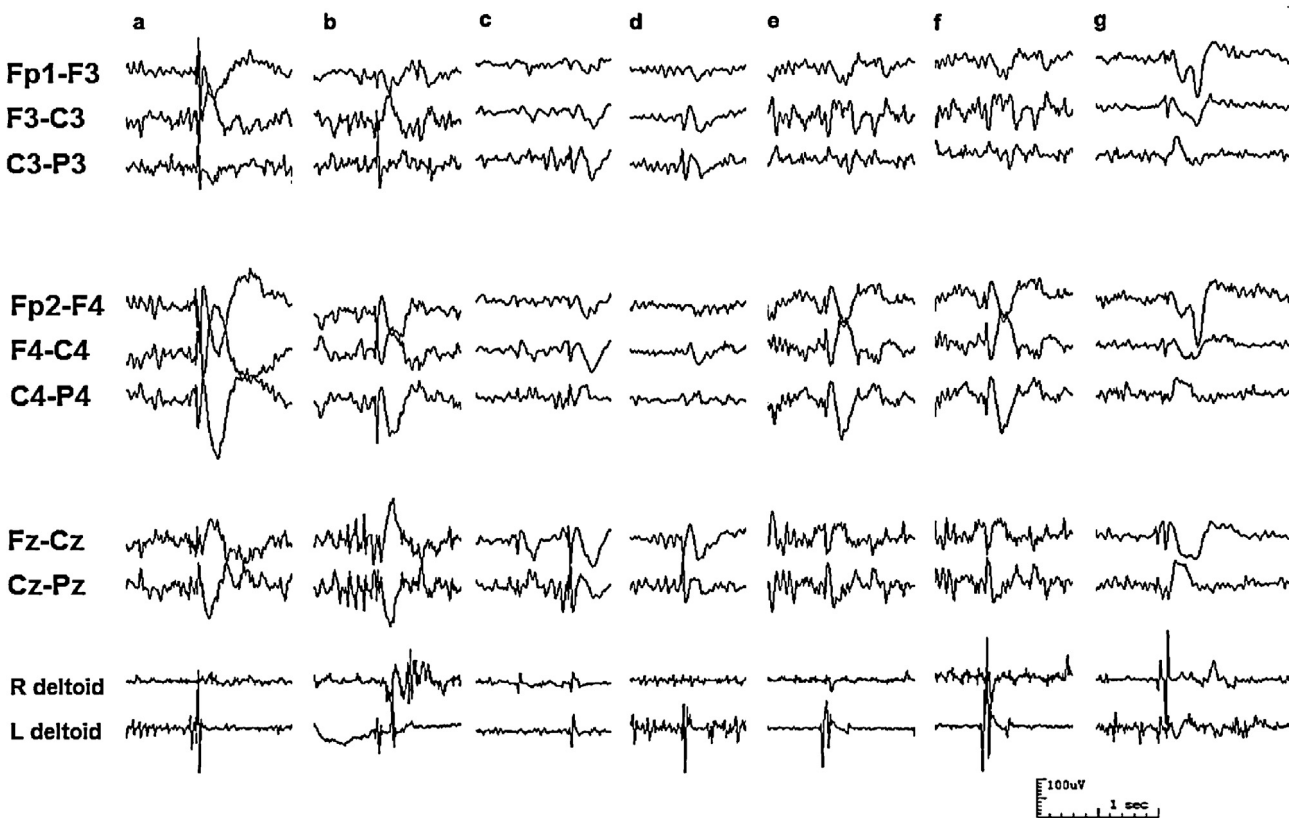

Fig. 1. Ictal EEG of a 35-year-old patient (MK) who presented the first generalized tonic–clonic seizure (GTCS) at the age of 14 years. By the age of 16 he started presenting myoclonia on awakening mainly in the morning, sometimes followed by GTCS. At 17, increase in seizure frequency precipitated by fasting, stress, flashing lights, speaking in public, hand activities, planning, decision-making and calculating. His seizures were refractory to multiple antiepileptic drugs in different combinations including carbamazepine, valproate, phenobarbital, phenytoin, piracetam. At the time of the video-EEG recordings he was being treated with valproic acid (2000 mg/day), clobazam (20 mg/day) and topiramate (200 mg/day) and had no further photosensitivity. Brief paroxysms of very fast spikes followed by a slow wave mainly in the frontocentroparietal areas accompanied by uni- or bilateral deltoid myoclonia were seen when planning an action (a); drawing (b–d); writing (e, f) and making Rubik cube (g).

non-specific triggers to 18/32 (56%) in photosensitive and 12/25 (48%) for praxis sensitive patients. This seemed to suggest that reflex epileptic traits could represent an aggravating feature in JME.

In two JME patients described by Matsuoka et al.[44] PI under a continuous identical drug regimen persisted up to the fifth decade of life despite decrease of spontaneous myoclonic seizures, suggesting that the seizure propensity of JME improves over time but persists long.

Likewise, in three of a group of four patients with reflex seizures induced by complex stimuli, language and praxis, triggered by combined specific activities such as visuo-spatial tasks, praxis, decision-making and emotional components, it was observed that PORM and PI persisted for one to two decades after epilepsy onset although treatment with VPA and other AEDs was considered reasonable effective in IGE and JME.[27]

Again, Guaranha et al.,[45] following JME patients treated for 5.72 ± 1.91 years with VPA, lamotrigine, topiramate, phenobarbital and benzodiazepines, found that the rate of seizure freedom dropped from 15/27 (55.6%) in patients with none or non-specific triggers to 5/22 (22.7%) for patients with PI as documented in video-EEG.

9. Conclusions

PI is a reflex epileptic trait closely related to IGE, in particular JME where in video-supported studies it was found in 24–49% of patients. Functional imaging studies indicate as an underlying ictogenic mechanism hyperexcitability of the functional anatomical CNS network physiologically subserving visuomotor coordination. On this background, local myocloni in the active musculature manifest as the reflex epileptic response. The findings with PI support the view of JME as a system epilepsy. PI may identify a subset of JME with less favorable treatment response and prognosis.

Conflict of interest

None of the authors has any conflict of interest to disclose.

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