Central nervous system abnormalities in vaginismus

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Abstract

Objective: To investigate possible altered CNS excitability in vaginismus.

Methods: In 10 patients with primary idiopathic lifelong vaginismus, 10 with vulvar vestibulitis syndrome accompanied by vaginismus and healthy controls we recorded EMG activity from the levator ani (LA) and external anal sphincter (EAS) muscles and tested bulbocavernosus reflex (BCR). Pudendal nerve somatosensory evoked potentials (SEPs) were tested after a single stimulus. Pudendal-nerve SEP recovery functions were assessed using a paired conditioning-test paradigm at interstimulus intervals (ISIs) of 5, 20 and 40 ms.

Results: EMG in patients showed muscular hyperactivity at rest and reduced inhibition during straining. The BCR polysynaptic R2 had larger amplitude ($p < 0.01$) and longer duration ($p < 0.01$) in patients from both groups than in controls. In controls, paired-pulse SEPs were suppressed at the 5 ms ISI for N35–P40 ($p < 0.05$) and P40–N50 ms ($p < 0.001$) and facilitated at the 20 ms ISI for N35–P40 ($p < 0.05$) and P40– N50 ($p < 0.05$). No significant differences were found in the paired-pulse N35–P40 in patients and controls but the cortical P40–N50 at 20 ISI was facilitated in patients ($p < 0.05$).

Conclusions: EMG activity is enhanced and the cortical SEP recovery cycle and BCR are hyperexcitable in vaginismus.

Significance: The neurophysiological abnormalities in patients with vaginismus indicate concomitant CNS changes in this disorder.

1. Introduction

Vaginismus, currently classified in the DSM-IV revised text (DSM-IV-RT) as a sexual pain disorder, is characterized by recurrent or persistent involuntary spasms that involve the outer third of the vaginal muscles and interfere with sexual intercourse (American Psychiatric Association, 2000). The correct diagnosis of vaginismus requires the presence of involuntary pelvic floor muscle contraction (Lamont, 1978).

Whether primary idiopathic lifelong vaginismus (LLV) is a mental or organic disorder is still debated. Several studies have hypothesized that vaginismus has a psychiatric origin (Drenth et al., 1996; Reissing et al., 1999, 2004; van Lankveld et al., 2006) or a general defense reaction (van der Velde et al., 2001).

Vulvar vestibulitis syndrome (VVS) is an idiopathic disease consisting of vulvar erythema and often inducing pain during intercourse (superficial vaginismus) and also vaginal spasms (Munday and Buchan, 2004). The local and generalized decrease in the tactile and pressure pain thresholds in patients with VVS or vulvodynia suggests a central sensitization component (Giesecke et al., 2004; Pukall et al., 2002).

Although electromyography (EMG) of the pelvic floor muscles is useful for documenting spasm in patients with vaginismus this neurophysiological procedure has been rarely used and techniques need standardizing (Shafik and El Sibai, 2002). The inhibitory and excitatory mechanisms of the pelvic floor functions can also be investigated by testing the oligosynaptic bulbocavernosus reflex R1 and polysynaptic reflex R2 (Rushworth, 1967; Vodusek and Janko, 1990; Vodusek and Fowler, 1999), or the pudendal-nerve somatosensory evoked potential (SEP) recovery cycle. Although no studies have investigated the excitatory and inhibitory phases of the pudendal-nerve SEP recovery cycle, investigation on lower limb SEPs – responses that yield spinal and cortical components with similar shape and stimulate pathways anatomically close to those of pudendal SEPs – showed a U-shaped recovery cycle with an early suppression period at the 5 ms interstimulus interval (ISI), followed by facilitation at 20 ms and inhibition at 40 ms ISIs (Lueders et al., 1984; Saito et al., 1992). The first inhibitory period reflects neuronal refractoriness, the second phase depends on excitatory and the third phase on inhibitory interneuronal mechanisms (Saito et al., 1992). To our knowledge, no previous study has described pudendal-nerve SEPs evoked by paired stimuli in healthy subjects, or in patients with vaginismus. Currently knowledge, including information from neurophysiological testing, therefore leaves open the question of central nervous system (CNS) dysfunction in vaginismus. Having this information is important in improving the difficult clinical management of vaginismus.

With the aim of investigating the CNS control mechanisms underlying pelvic floor functioning in patients with vaginismus, we recorded EMG activity from pelvic floor muscles, the bulbocavernosus reflex (BCR), the pudendal-nerve SEPs by single stimuli and the recovery cycle of pudendal-nerve SEPs in patients with primary idiopathic LLV and with VVS accompanied by vaginismus, and healthy controls.

2. Patients and methods

We enrolled 10 patients (mean age ± SE, 34.1 ± 2.2 years) with primary idiopathic LLV diagnosed according to the Lamont classifi- cation and 10 patients (age 34.6 ± 2.6 years) with VVS associated with vaginismus all of whom had EMG documented hyperactivity of the pelvic floor levator ani (LA) muscles. Ten healthy women matched for age (age 37.6 ± 5.5 years) served as controls. None of the patients had other gynecological diseases and all of them were participating in our ongoing experimental study on the use of botulinum toxin type A (BoNT-A) for vaginismus. None of the patients have ever been treated with BoNT-A before entering the study. All subjects gave their informed consent before participating in the study, and the protocol was approved by the Local Ethical Committee.

EMG activity was recorded from the LA and external anal sphincter (EAS) muscles with a concentric needle (diameter 0.46 mm) inserted perpendicularly into the LA muscle and into the subcutaneous layer of the EAS. The EMG activity was measured in the EAS muscle and in the LA muscle between the anal and vaginal orifices. Motor unit potentials were collected and analyzed by a standard EMG system (Keypoint, Dantec Medical, filter settings 5 Hz–10 kHz, gain 100–500 µV/division, sweep speed 20 ms/division). The EMG recording was evaluated for tonic activity at rest, voluntary activity and straining, and classified as 0, no activity; 1, physiologic tonic activity, when sustained firing of isolated motor unit potentials at a low

rate is present (Kimura, 2001); 2, EMG with a reduced interference pattern, some motor units can still be identified on the baseline EMG recording when the full muscle power is exerted or during involuntary contraction; and 3, EMG activity with a full interference pattern, the baseline is completely obscured by motor unit activity (Binnie et al., 1995; Kimura, 2001). This analysis generated separate trials for the three experimental conditions, baseline tonic activity, maximum voluntary activity and straining, and separate recordings for LA and EAS muscles. The patients and controls were instructed to fully void the bladder and bowel before EMG. During EMG, participants lay on the right side with hips and knees flexed and, after being trained to do the exercise, were asked to fully relax the sphincters when spontaneous activity was evaluated at rest and to attempt straining or contract the sphincters when recruitment patterns were tested.

The BCR was elicited by stimulating the dorsal nerve of clitoris (stimulus duration 0.5 ms, intensity range 30 mA) with surface electrodes and responses were recorded by a concentric needle electrode (diameter 0.46 mm) inserted into the bulbocavernosus muscle (Vodusek and Fowler, 1999).

Two resulting components were analyzed: the first early response (R1) and second late response (R2). Repeated trials (between four and six times) were obtained for each subject. The average value of the shortest latency and amplitude and the longest duration of these trial responses in subjects became the result used in the statistical analysis. Traces were rectified. During BCR testing subjects were asked to mildly contract the pelvic floor.

In the SEP recording session, subjects were instructed to lie supine on an examination couch in a relaxed and comfortable position. The dorsal clitoris nerve was stimulated with surface electrodes (cathode proximal; impedance below 5 kX). Electrical square stimuli of 0.1 ms duration were delivered at a rate of 3.3 Hz. The earth electrode was placed over the anterior iliac spine. The stimulus intensity was three times the sensory threshold (mA). The pudendal nerve was stimulated with single stimuli and with paired (conditioning and test) stimuli (S1 + S2) at the ISIs of 5, 20 and 40 ms. The sequence of these trials were randomized among the subjects. Samples with excess interference were automatically rejected from the average. Five hundred sweeps were averaged for each trial. Summating tracings of two repeatable averages were used for amplitude and latency measurements. Analysis time was 100 ms and filtering band-width was 5–1500 Hz (_6 dB oct roll-off). SEPs were recorded with an ESAOTE BIOMEDICA Reporter (ESAOTE BIOMEDICA Florence, Italy). Recording electrodes were placed over the vertex, Cz0 (2 cm behind Cz) referred to a median frontal (Fpz) electrode. Acoustic feedback helped the subjects to maintain full muscle relaxation at the registration sites. We identified the following SEP components: the cortical N35–P40 and P40–N50 (Cz'–Fpz) components that both originate from the primary somatosensory cortex (Opsomer et al., 1989; Vodusek, 1990). Similarly to the cortical lower limb SEPs, N35–P40 could reflect the arrival of the afferent volley in the somatosensory cortex and P40–N50 the intra-cortical response (Rossini et al., 1981). To ensure that baseline shift had no influence on the measured variables, all SEP amplitudes were measured from the preceding peak (peak-to-peak), whereas latencies were measured at the peak of each component. SEPs in response to the test (S2) stimulus were recognized by subtracting SEPs of the S1-only response to paired (S1 + S2) stimuli; the amplitudes of the SEPs in response to the test (S2) stimulus test were compared with SEP amplitudes in response to the conditioning (S1) stimulus at each ISI. The amplitude ratio (S2/S1) x 100 of the test response was expressed as a percentage of the amplitude of the component obtained in S1 condition for each ISI.

For statistical analysis, we used an analysis of variance (ANOVA) for non-parametric data (Kruskall–Wallis). We used Spearman's correlation test to compare amplitude of cortical N35–P40 and P40–N50 components at 20 and 40 ms ISIs in the

patients with LLV and VVS. We analyzed EMG data semiquantitatively without a statistical comparison. The level of significance was set at $p < 0.05$. Values in the text are mean ± SE.

3. Results

In all the patients, EMG recordings from the LA muscle showed prolonged increased tonic activity at rest and during a correct attempt at straining further motor units were recruited leading to paradoxical muscle activation. The EMG recording during a voluntary muscle contraction showed a full, physiological interference pattern. The same EMG activity was recorded in all the EAS quadrants. None of the EMG recordings from controls showed muscular hyperactivity at rest or during attempted straining (**Table 1** and **Fig. 1 a and b**).

Although no significant differences were found in R1 latency, amplitude and duration and R2 latency between patients and healthy subjects, the polysynaptic R2 was significantly higher in amplitude ($p < 0.01$) and duration ($p < 0.01$) in patients than in controls (**Table 2** and **Fig. 2**).

The sensory threshold to electrical stimuli on the dorsal nerve did not differ significantly among groups: controls, mean 6.4 ± 0.44 mA; patients with LLV, 8.07 ± 1.11 and patients with VVS, 6.1 ± 0.5. No significant differences were found in SEP amplitudes in response to single stimuli between patients and controls for cortical N35– P40 (LLV 0.68 ± 0.12 μV, VVS 0.77 ± 0.23 and controls 0.62 ± 0.18) and cortical P40–N50 (LLV 1.48 ± 0.15 μV, VVS 2.8 ± 0.8 and controls 1.46 ± 0.51). No differences were found in SEP latencies for any of the tested potentials between patients and controls.

In normal healthy subjects, the (S2/S1) 100 amplitude ratio for pudendal SEPs was significantly suppressed at the ISI of 5 ms, for N35–P40 ($p < 0.05$) and P40–N50 ms ($p < 0.001$), and significantly facilitated at the ISI of 20 ms, for N35–P40 ($p < 0.05$) and P40– N50 ($p < 0.05$). Paired stimulation at the ISI of 40 ms elicited not significant suppression of cortical components. The cortical P40– N50 amplitude of the test (S2) response at the 20 ms ISI was significantly larger in patients with LLV ($p < 0.03$) and VVS ($p < 0.05$) than in controls; no significant differences with controls were found for P40–N50 at the other tested ISIs, although it was larger in patients with LLV than in controls at 40 ms ISI; at none of the tested ISIs was the (S2/S1) x 100 ratio for the N35–P40 signifi- cantly higher in patients than in controls, although this ratio was higher at 20 and 40 ms ISIs in patients with LLV and at the 20 ms ISI in patients with VVS (**Figs. 3 and 4**). There was no significant correlation between N35–P40 and P40–N50 SEP abnormalities (Spearman's correlation at the 20 ms ISI: $R = 0.2$ for VVS, $R = 0.2$ for LLV; at the 40 ms ISI: $R = 0.7$ for VVS, $R = 0.6$ for LLV).

At all tested ISIs, in healthy subjects and patients, latencies of S2 responses were greater or similar to latencies of S1 responses for N35–P40 and for P40–N50 and did not differ significantly among groups.

4. Discussion

In this study we found several neurophysiological abnormalities in patients with vaginismus. EMG recordings from the pelvic floor muscles in patients typically showed prolonged spontaneous muscle activity at rest and a lack of appropriate inhibition. The late polysynaptic BCR response, R2, a response originating in the CNS, had prolonged amplitude and duration. Whenwedelivered paired-pulse stimulation in patients, the recovery cycle for pudendal-nerve SEPs disclosed significant hyperexcitability at the level of the cortical P40–N50 component. The abnormal excitability we detected within the CNS in

patients with primary idiopathic LLV and VVS might explain why both disorders manifest with abnormal and excessive functioning of pelvic floor muscles. Whatever the etiology of vaginismus, the new findings in our patients with vaginal spasm clearly indicate concomitant CNS changes in this disorder.

Unlike previous studies that failed to show increased LA muscle activity at rest and during a correct attempt at straining in vaginismus (Engman et al., 2004; van der Velde and Everaerd, 2001), in our study all patients EMG recordings showed prolonged spontaneous muscle hyperactivity in the LA and EA muscles and lack of appropriate voluntary inhibition. Only in recent decades have physicians begun to consider muscular spasms as an important diagnostic key in this disorder (Brin and Vapnek, 1997; Shafik and El Sibai, 2002). Other Authors using EMG and manometry have already reported pelvic muscle hyperactivity in chronic genital pain syndromes (Abbott et al., 2008; Hetrick et al., 2006; Jarvis et al., 2004; Romito et al., 2004). The EMG abnormalities in our patients with vaginismus also resemble those described in patients with painful spasms related to focal dystonias and characterized by involuntary EMG activity that lasts from a hundred milliseconds to several minutes. The presence in our patients of abnormal pelvic floor muscle activation, together with evidence of dyssynergic activation of the LA and EAS muscles with straining, although patients had practiced the exercise, recalls the co-activation of agonist and antagonist muscles typically characterizing focal dystonia. Similarly to focal dystonia, the involuntary muscular hyperactivity seen in our patients may provoke a sustained involuntary contraction, thus explaining the difficulty in having normal sexual intercourse and, eventually, their vaginal pain. Whether prolonged pain could provoke muscular hyperactivity in vaginismus as in other genital pain syndromes (Glazer et al., 1998; Pool-Goudzwaard et al., 2005) remains unclear.

The second noteworthy neurophysiological finding in our patients with VVS and LLV was the prolonged duration of the late BCR response, R2. The bulbocavernosus R1 is an oligosynaptic response, but the R2 is polysynaptic in origin (Vodusek and Janko, 1990; Vodusek and Fowler, 1999). The BCR R2 amplitude and duration increase we observed in our patients with vaginismus suggests an abnormal excitability of the CNS polysynaptic ways in this disorder.

Our new findings obtained by testing pudendal-nerve SEPs evoked by paired stimuli extend current knowledge on the CNS control underlying pelvic floor functioning in patients with vaginismus. To our knowledge, no previous study has described pudendal- nerve SEPs evoked by paired stimuli in healthy subjects, or in patients with vaginismus. In our healthy controls, the recovery cycle of pudendal-nerve SEPs showed a multiple recovery phase of the vertex N35–P40 and P40–N50 components consisting of synaptic inhibition at the 5 ms ISI and facilitation at 20 ms. Data from our controls resemble those for lower limb (from posterior tibial nerve) SEP recovery functions showing a U-shaped recovery of the far-field N35–P40 and cortical P40–N50 components consisting of synaptic inhibition at the 5 ms ISI, recovery and facilitation at the 20 ms ISI and an inhibitory post-synaptic potential effect at 40 ms (Saito et al., 1992). Conversely, we found no significant SEP inhibition at the 40 ms ISI, probably because the pudendal nerve has a prominent sensory component similar to that of the lower limb sural nerve (Saito et al., 1992). In patients with vaginismus, pudendal-nerve SEPs evoked by paired stimuli are signifi- cantly facilitated at the level of P40–N50, a response that originates from the primary somatosensory cortex (Vodusek, 1990). Although we found no significant difference in the P40–N50 recovery cycle at the 40 ms ISI and in the N35–P40 recovery cycle at 20 and 40 ms ISIs, the amplitude ratio was higher in patients than in controls (**Fig. 4**). The facilitation of the cortical P40–N50 at the 20 ms ISI suggests abnormal excitability within the somatosensory cortex in vaginismus. A similar facilitation has been reported in patients with pain syndromes and motor control disorders. For example, the upper limb SEP recovery cycle and SEP habituation are reduced in migraine (Valeriani et al., 2005; Ozkul and Uckardes, 2002) and in dystonia

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(Frasson et al., 2001): in pain syndromes and motor control disorders a similar abnormal dishinibition could take place at CNS level.

Although our findings leave the precise neurophysiological mechanism responsible for vaginismus unclear we conjecture an abnormality involving multiple levels in the CNS. CNS involvement receives strong support from the polysynaptic R2 hyperexcitability of the RBC in all the patients and also the hyperexcitability of the primary somatosensory cortical SEP component, P40–N50, at the 20 ms ISI in response to paired stimuli to the pudendal nerve.

The neurophysiological abnormalities we observed in patients with vaginismus does not per se indicate whether the CNS hyperexcitability is primary or secondary to several factors, such as pain or inflammation. Although the aetiopathology of VVS and primary idiopathic LLV remains poorly understood, inflammation or abnormal painful inputs could cause or maintain vaginal spasms (Bornstein et al., 2004; Halperin et al., 2005; Graziottin and Brotto, 2004). Recent evidence points to the presence of sensory abnormalities in VVS, particularly the heightened processing of tactile and pain sensation in the vulvar vestibule (Pukall et al., 2002). Pain perception is enhanced in women with vulvodynia not only at regional level but also at other body parts suggesting that there is an abnormality of sensory input processing probably at CNS level (Giesecke et al., 2004). Functional magnetic resonance imaging showed higher activation levels in the insular and frontal cortical regions in women with VVS and heightened sensitivity to touch (i.e. allodynia) than in controls (Pukall et al., 2005) in response to the application of pressure stimuli to the vulvar vestibule. In women with VVS, chronic pain could cause neural changes at CNS level determining the occurrence of allodynia followed by pelvic muscle spasms as a defence reaction. In women with LLV, no studies have yet addressed possible neural correlates of genital sensory inputs and changes at CNS level. We recently described neurophysiological abnormalities in a unique case of coexisting idiopathic cervical dystonia and LLV suggesting possible common impaired central sensorimotor processing (Bertolasi et al., 2008). In our patients with vaginismus, the enhanced EMG activity and BCR polysynaptic responses rather indicate motor hyperexcitability and the reduced cortical SEP inhibition to paired stimuli could connote concomitant somatosensory facilitation. We suggest that the pathophysiology of vaginismus might deserve further investigations.

In conclusion, EMG activity is enhanced and the cortical SEP recovery cycle and BCR are hyperexcitable in vaginismus. Our preliminary data suggest to extend future investigations on the neurophysiological changes in vaginismus and we encourage physicians to widen the diagnostic exams when they suspect vaginismus so that their patients can undergo to the best diagnostic and treatment options.

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Table 1

Clinical and electromyographic (EMG) data from the patients and controls.

Disease	Age in years	Disease duration in years	EMG LA			EAS			Associated symptoms
			Rest activity	Voluntary contraction	Straining	Rest activity	Voluntary contraction	Straining	
Patients									
LLV									
1	21	Lifelong	2	3	3	2	3	2	VV, anorgasm
2	37	Lifelong	2	3	3	2	3	3	VV, constipation
3	40	Lifelong	2	3	3	2	3	2	VV
4	34	Lifelong	2	3	3	2	3	2	VV
5	41	Lifelong	2	3	3	2	3	3	VV, constipation, micturition urgency
6	28	Lifelong	2	3	3	2	3	3	Phobia, constipation, anorgasm
7	37	Lifelong	2	3	3	1	3	3	VV
8	40	Lifelong	2	3	3	2	3	3	Phobia, constipation
9	28	Lifelong	2	3	3	2	3	3	VV, constipation
10	35	Lifelong	2	3	3	2	3	3	VV, constipation
VVS									
1	27	9	2	3	3	2	3	3	Constipation
2	27	1	2	3	2	2	3	2	Cystitis, mycosis
3	36	1	2	3	2	2	3	2	Mycosis
4	45	6	2	3	2	3	3	2	Cystitis, micturition difficulty
5	47	12	2	3	2	2	3	2	Cystitis, anorgasm
6	40	8	2	3	2	3	3	2	Cystitis
7	36	5	2	3	2	2	3	2	Cystitis
8	25	2	2	3	2	2	3	2	Cystitis, constipation
9	28	5	2	3	2	1	3	2	Cystitis
10	35	4	2	3	3	2	3	2	Constipation
Controls									
1–10			1	3	0	1	3	0	

The EMG recording was classified as 0, no activity; 1, physiologic tonic activity; 2, EMG with a reduced interference pattern, some motor units can still be identified on the baseline EMG recording; and 3, EMG activity with a full interference pattern, the baseline is completely obscured by motor unit activity (Binnie et al., 1995). VVS, vulvar vestibulitis syndrome; LLV, idiopathic lifelong vaginismus; VV, periodic vulvar vestibulitis during LLV; LA, levator ani; EAS: external anal sphincter; yrs, years.

Table 2

Bulbocavernosus reflex recorded from the patients and controls.

Bulbo-cavernosus reflex	Lifelong vaginismus		Vulvar vestibulitis syndrome		Controls	
	R1	R2	R1	R2	R1	R2
Latency (ms)	32 ±10	65 ± 18	28 ±15	64 ± 15	35.9 ± 9	60 ± 20
Amplitude (μV)	90.5 ± 65	378.75 ±41.0[*]	85.5 ± 72	342.4 ± 55.4[*]	100 ± 70	150 ± 80
Duration (ms)	13 ± 9.1	110.6 ± 12.8[*]	11 ± 8.8	89.7 ± 12.5[*]	10.3 ± 8.5	41.2 ± 25
		[*]p < 0.01		[*]p < 0.01		

R1, first oligosynaptic response; R2, second polysynaptic response of the bulbocavernosus reflex. Values are means ± SE. Amplitude is expressed in lV, or mV when specified; latency and duration are expressed in ms.

Fig. 1

Traces of electromyographic activity from the levator ani (LA) muscle.
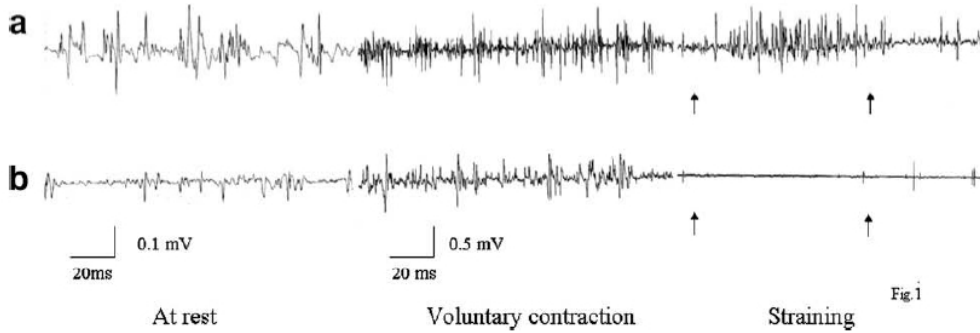
(a) a representative patient with lifelong vaginismus. From right to left, increased tonic activity at rest, full interference pattern during voluntary contraction and subinterference pattern during straining (between arrows);

(b) a representative healthy subject showing physiologic tonic activity at rest, full interference pattern during voluntary contraction and no activity during straining (between arrows).

Fig. 2

Electromyographic traces of the bulbocavernosus reflex.
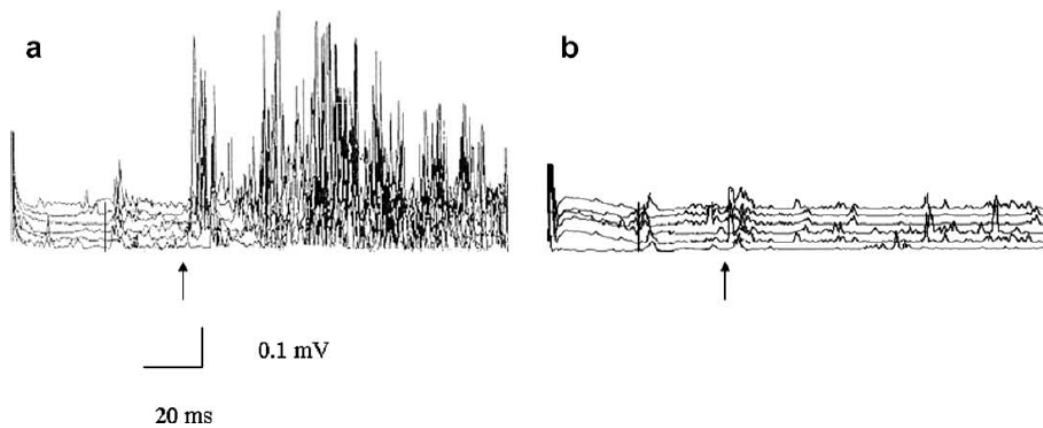
(a) representative patient with lifelong vaginismus (LLV)

(b) representative control. Line indicates R1, the early response, and the arrow indicates R2, the late polysynaptic response.

Note the increased duration and amplitude of R2 in the patient with LLV.

Fig. 3

Cortical pudendal somatosensory evoked potentials (SEPs) of the baseline control response S1 and test response S2 at interstimulus intervals (ISIs) of 5, 20 and 40 ms in two patients one (a) with lifelong vaginismus (LLV) and the other (b) with vulvar vestibulitis syndrome (VVS). Note the high facilitation of the cortical P40–N50 at the 20 ms ISI in the patients. (c) Cortical pudendal somatosensory evoked potentials (SEPs) of the baseline control response S1 and test response S2 at ISIs of 5, 20 and 40 ms in a healthy woman. Note the inhibition of test response amplitude at the 5 ms ISI, and the facilitation at 20 ms.
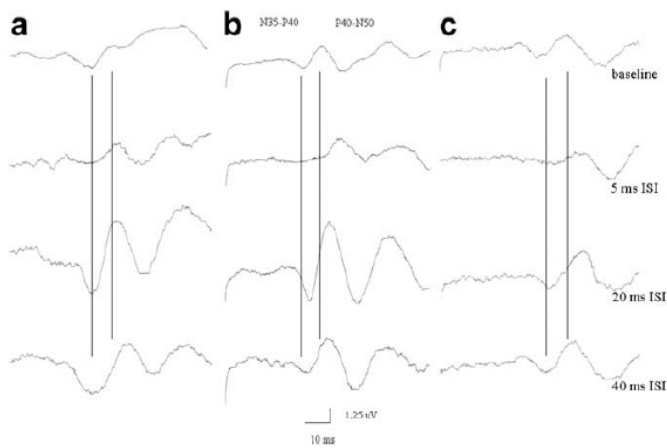
Fig. 4

Histograms of the mean amplitude ratio [expressed as (S2/S1) x 100] at the interstimulus intervals (ISIs) of 5, 20 and 40 ms for the vertex N35–P40 and P40–N50. Note that the mean ratio of the cortical P40–N50 potential at the ISI of 20 ms was significantly higher in patients than controls. LLV: primary idiopathic lifelong vaginismus; VVS: vulvar vestibulitis syndrome.