Prevalence of epilepsy in rural Bolivia

A door-to-door survey

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Article abstract—*Objective:* To carry out a door-to-door survey in rural areas of the Cordillera Province, Santa Cruz Department, Bolivia, to determine the prevalence of neurologic diseases (epilepsy, stroke, parkinsonism, and peripheral neuropathy) in a sample of approximately 10,000 inhabitants. *Methods:* A team of nondoctor health workers administered a standard screening instrument for neurologic diseases—a slightly modified version of the World Health Organization protocol. All subjects found positive during the screening underwent a neurologic examination. *Results:* On screening, the authors found 1,130 positive subjects, of whom 1,027 were then investigated by neurologists. On the basis of the definition proposed by the International League Against Epilepsy, we detected 124 epileptic patients (prevalence, 12.3/1,000), 112 of whom had active epilepsy (prevalence, 11.1/1,000) on the prevalence day (November 1, 1994). Peak age-specific prevalence occurred in the 15 to 24-year age group (20.4/1,000). Sex-specific prevalence was higher in women (13.1/1,000) than men (11.4/1,000). Eighty-nine patients (71.8%) underwent a standard EEG recording. Considering both EEG and clinical data, partial seizures were the most common type (53.2%) based on the classification of the International League Against Epilepsy. The mean age at onset was 20.7 years for partial seizures and 13.6 years for generalized seizures. Only 10.5% of patients had received specific treatment for more than 2 months of their life. *Conclusion:* This report on epilepsy prevalence in Bolivia confirms that epilepsy is a major health problem in rural areas of developing countries. **Key words:** Epilepsy—Neuroepidemiology—Developing countries—Bolivia.

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Studies on the magnitude of neurologic diseases in developing countries are limited. Major difficulties encountered are the relative absence of accurate case registers or medical records, the lack of sophisticated technology, and the concentration of specialist-trained medical staff in urban centers. Moreover, studies have used varying definitions of epilepsy. Sometimes disease activity is not taken into account, and the methodological approaches used in developed countries are often unsuitable for developing countries, especially for rural populations.[1] These factors may explain the differing prevalence found in studies from developing countries in which prevalence of epilepsy ranges from 2.47 to 57/1,000.[2-4]

Studies are frequently carried out by door-to-door community surveys of urban or rural populations. Such surveys are usually performed with a two-phase design, in which the first phase consists of a screening interview by field workers and the second phase comprises a complete neurologic evaluation by neurologists, often using the World Health Organization (WHO) research protocol for neurologic disorders.[5]

We studied the prevalence of major neurologic disorders, including epilepsy, using such a design in the rural population of the Cordillera Province, Bolivia. In our study we used the Sicilian Neuroepidemiological Study (SNES) screening instrument,[6] a slightly modified version of the WHO protocol,[5] and we followed the guidelines for epidemiologic studies on epilepsy proposed by the International League Against Epilepsy (ILAE) in 1993.[7]

Methods. The study was carried out in the Cordillera Province, Santa Cruz Department, in the southeastern part of Bolivia. Bolivia has a total land surface of 1,098,591 km^2 and a population of 6,400,000. Background and methods have been described elsewhere.[8] According to the Bolivian National Institute of Statistics, the life expectancy at birth is 60 years, and the infant mortality rate is 88/1,000 for urban areas and 145/1,000 for rural areas.[9] These indicators show that Bolivia (along with Paraguay) has the worst health indicators in Latin America.[10] The Cordillera Province covers 86,245 km^2 and has a population of 88,628 inhabitants, 32,953 of whom live in urban areas and 55,675 of whom in rural areas.[9] The province is divided administratively into 10 rural areas with 3,000 to 8,000 inhabitants in each. Racially, the population is a mixture of mestizos, descendants of intermarriage between Spanish colonists and the native tribes (the Guaraní–

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Table 1 Age and sex distribution of the study population

Age, y	Men, n (%)	Women, n (%)	Both sexes, n (%)
0–4	997 (19.9)	921 (18.4)	1,918 (19.2)
5–14	1,593 (31.6)	1,605 (33.0)	3,198 (32.3)
15–24	827 (16.2)	749 (15.2)	1,576 (15.7)
25–34	485 (9.8)	521 (10.5)	1,006 (10.2)
35–44	471 (9.3)	445 (9.0)	916 (9.2)
45–54	323 (6.6)	318 (6.4)	641 (6.5)
55–64	206 (4.0)	198 (4.1)	404 (4.0)
65+	133 (2.5)	163 (3.3)	296 (2.9)
Total	5,035 —	4,920 —	9,955 —

Chiriguanos), and approximately 30% pure Guaraní Indians. The majority of the population speaks both Spanish and Guaraní; a minority speak only Guaraní. The health care infrastructure consists of a district hospital, nine area hospitals, and rural health centers.

This study was conducted with the agreement of the National Department of Epidemiology of the Ministry of Social Welfare and Public Health and with the support of the Guaraní political organization (Asamblea del Pueblo Guaraní [APG]).

This prevalence survey served as the framework for a case–control study to estimate the association between cysticercosis, toxocariasis, and epilepsy, and the sample size was calculated to provide a sufficient number of patients for the latter study. A cluster survey method was used with the 10 areas acting as strata. Within each stratum, communities were selected at random and each constituted one cluster. Sampling was designed to select approximately 20% of the population in each area. Urban areas, defined as a community with more than 2,000 inhabitants, were excluded from the sampling frame. In total we selected 10,124 people in 55 communities, of whom 9,955 were screened effectively (table 1). Demographic data obtained from the Bolivian National Census combined with records available at area hospitals allowed us to estimate that the rural population in 1994 was 54,324.[9] The prevalence of epilepsy was determined as a point prevalence defined as the proportion of patients with epilepsy in a given population at a specified time (prevalence day, November 1, 1994). Inhabitants were only eligible if they had been resident in the communities for 6 months preceding prevalence day. Thus, the estimated point prevalence refers to this date.

This was a two-phase study. During phase 1, the sample of the rural communities selected from the 10 areas of the Cordillera Province was screened door-to-door to identify persons who may have had a disorder of neurologic interest. The screening included standardized questions and simple tasks. The interviewers who carried out the screening were 26 Guaranì nondoctor health workers, all selected from the 10 areas involved in the survey and who were able to speak both Spanish and Guaranì fluently. The 26 field workers received prior training and were always supervised by at least one of the two local physicians involved in the study and the health representative of the APG. During phase 2, all subjects who tested positive during screening underwent a complete neurologic examination that was performed by Spanish-speaking neurologists. Furthermore, a local physician and the health representative of the APG, who could speak Guaranì, assisted in the neurologic field work.[8]

We adopted the SNES screening instrument,[6] a slightly modified version of the WHO neuroscience research protocol.[5] During the SNES study, the sensitivity of the screening instrument was 100% for parkinsonism; 96% for peripheral neuropathies, stroke, and epilepsy; and the specificity was 86%.[11] The instrument was translated into Spanish and pretested in the field. We performed a pilot study to determine compliance with the screening instrument and to evaluate the comprehension of each item. All members of the field staff carried out the pilot investigation in October 1994 in two small communities of 291 inhabitants.[8]

We accepted the definition proposed by the ILAE: "Epileptic seizure is a clinical manifestation presumed to result from an abnormal and excessive discharge of a set of neurons in the brain."[7 (p. 593)] "Epilepsy is a condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause. Multiple seizures occurring in a 24-h period are considered a single event. Individuals who have had only febrile or neonatal seizures are excluded from this category."[7 (p. 593)] "Active case of epilepsy is defined as a person who has had at least one epileptic seizure in the previous five years, regardless of any anti-epileptic drug (AED) treatment".[7 (p. 593)]

On the basis of these ILAE definitions, we considered "prevalent cases" of epilepsy patients to be indicative of those who had at least two epileptic seizures at prevalence day. "Active prevalent cases" were considered to be patients with a prevalent case of epilepsy who had had at least one epileptic seizure during the 5 years preceding prevalence day.

All data collected were discussed by an international panel of neurologists to reach consensus diagnoses. In an attempt to determine the accuracy of classification, patients with a clinical diagnosis of epilepsy underwent a standard EEG recording. We performed all EEG recordings in the field using 20-channel (portable) equipment. Electrodes were placed according to the International 10-20 System of Jasper, using referential and bipolar montages. Hyperventilation and intermittent photic stimulation were used routinely during EEG recording. We classified the EEG records as normal or with abnormalities consistent with generalized, focal, or multifocal epileptiform discharges. EEG records were analyzed independently by two observers. Seizure types were identified on the basis of the classification proposed by the ILAE in 1981.[12]

Analyses were carried out using the Csample module of EPI-INFO 6 to allow for cluster sampling.[13] All results presented are adjusted for both area stratification and clustering. In addition, results were age adjusted to the world standard population, as used in cancer incidence in five continents, to facilitate international comparison.[14]

Results. The survey began the day after prevalence day and was completed in November 1996. Fifty-five communities were selected by cluster sampling from the 10 areas of the Cordillera Province. They contained 1,941 households. The eligible population consisted of 10,124 subjects. At the

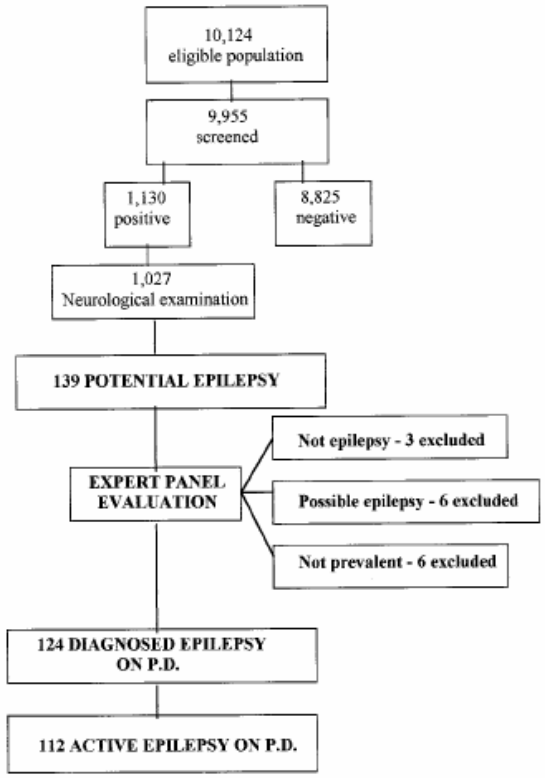

Figure 1. General design of the door-to-door prevalence survey. P.D. = prevalence day.

end of the screening, 9,955 questionnaires had been completed. Table 1 presents the age and sex distribution of the eligible population.

Of the 9,955 subjects screened, 1,130 (11.3%) were found positive by the screening instrument. Of these, 1,027 were examined directly by neurologists during phase 2. A total of 103 subjects (10%) were not examined (7 refused, 86 could not be found, and 10 died during the study period). After an extensive neurologic evaluation of the positive subjects detected during phase 1, we found 139 potential epileptic subjects—20 with febrile seizures and 26 with single seizures, of whom three experienced acute symptomatic seizures (one related to acute alcohol intoxication, one that occurred during a course of active CNS infection, and one who had a case of eclampsia).[7]

After the evaluation by the neurology panel of 139 potential epileptic subjects, 3 subjects were excluded because their history was not consistent with the diagnosis, and 6 subjects were considered to have possible epilepsy because their history was doubtful. The diagnostic criteria were fulfilled for 130 subjects, of whom six were not considered to be a prevalent case. Thus, we detected 124 prevalent patients with epilepsy, 112 of whom had active epilepsy on prevalence day (figure 1). The prevalence of epilepsy was 12.3/1,000 (13.5/1,000, age adjusted to the world standard population) and was 11.1/1,000 for active epilepsy (12.0/1,000, age adjusted to the world standard population).

Table 2 presents age- and sex-specific prevalence for epilepsy. Table 3 presents age- and sex-specific prevalence for active epilepsy. Age-specific prevalence increased in the first 10 years of life, with a peak in the 15 to 24-year group (20.4/1,000), and showed a slow decline with age. With the exception of the two youngest age groups (0 to 4 years and 5 to 14 years), prevalence was always higher in women, particularly in the 15 to 24-year group (women, 26.0/1,000; men, 5.3/1,000). Overall, the prevalence was slightly higher in women (13.1/1,000) than in men (11.4/1,000). Prevalence in the 10 areas ranged from 6.2 to 23.6/1,000. Cluster-specific prevalence ranged from 0.00 to 76.4/1,000.

The types of seizures, evaluated on clinical grounds only, were classified in 82 patients (66.1%) as generalized seizures (63 of whom had generalized tonic–clonic seizures, 10 who had absence seizures, and nine who had other types of generalized seizures [myoclonic, n = 3; tonic, n = 5; atonic, n = 1]) and in 42 patients (33.9%) as partial seizures (eight of whom had partial simple seizures without secondary generalization, 29 who had partial simple seizures with secondary generalization, one who had partial complex seizures without secondary generalization, and four who had partial complex seizures with secondary generalization; table 4).

Of the 124 defined patients, 89 (71.8%) had a standard

***Table 2** Age- and sex-specific prevalence of epilepsy (cases per 1,000)*

Age, y	Men, n (%); 95% CI	Women, n (%); 95% CI	Both sexes, n (%); 95% CI
0–4	8 (7.7); 2.8–12.5	3 (2.7); 0–5.8	11(5.3); 2.6–8.0
5–14	21 (13.3); 7.7–18.9	12 (7.4); 2.7–12.1	33 (10.3); 7.1–13.5
15–24	13 (15.3); 6.4–24.2	18 (26.0); 9.7–42.3	31 (20.4); 11.6–29.2
25–34	4 (8.0); 0–16.4	10 (16.1); 4.4–27.9	14 (12.2); 4.5–19.9
35–44	3 (5.9); 0–15.1	12 (24.9); 7.5–10.3	15 (15.2); 5.3–25.1
45–54	5 (17.0); 0–36.1	5 (17.4); 0–36.1	10 (17.2); 4.0–30.4
55–64	3 (10.7); 0–21.5	3 (17.3); 0–34.9	6 (14.0); 3.6–24.4
65+	2 (9.2); 0–30.5	2 (13.3); 0–31.6	4 (13.0); 9.6–14.9
Total	59 (11.4); 8.1–14.7	65 (13.1); 9.8–17.3	124 (12.3); 1.0–1.4 13.5*

* Age adjusted to the world population.

Table 3 Age- and sex-specific prevalence of active epilepsy (cases per 1,000)

Age, y	Men, n (%); 95% CI	Women, n (%); 95% CI	Both sexes, n (%); 95% CI
0–4	8 (7.7); 2.8–12.5	3 (2.7); 0–5.8	11 (5.3); 2.5–8.0
5–14	20 (12.6); 7.4–17.8	12 (7.4); 2.7–12.1	32 (10.0); 6.9–13.0
15–24	12 (14.1); 5.2–22.9	17 (24.5); 8.3–40.7	29 (19.1); 10.1–28.0
25–34	4 (8.1); 0–16.4	9 (15.1); 3.7–26.5	13 (11.6); 4.1–19.2
35–44	2 (3.7); 0–9.0	10 (20.0); 6.6–33.4	12 (11.7); 3.6–19.7
45–54	4 (14.8); 0–33.4	2 (9.6); 0–25.6	6 (12.2); 0.1–24.3
55–64	2 (7.2); 0–16.6	3 (17.3); 0–34.9	5 (12.2); 2.1–22.3
65+	2 (12.5); 0–30.5	2 (13.4); 0–31.6	4 (13.0); 0.7–25.2
Total	54 (10.5); 7.3–13.7	58 (11.8); 7.6–16.0	112 (11.1); 8.4–13.9
			12.0*

* Age adjusted to the world population.

interictal EEG recording performed. Twenty-seven patients (21.8%) had a normal EEG, 18 patients (14.5%) had multifocal discharges, 26 patients (21.0%) had a focal discharge, and 18 patients (14.5%) had a pattern consistent with generalized seizure.

Several patients diagnosed with generalized seizures were reclassified as partial seizures with secondary generalization when the EEG recording was combined with clinical data. No attempt was made to distinguish partial complex and partial simple with secondary generalization. Thirty-five patients did not undergo EEG recording, and in these patients seizure classification is based on clinical grounds only. On the basis of the electroclinical classification, 66 patients (53.2%) were classified as having partial seizures, 10 (8.1%) of whom had partial seizures without secondary generalization and 56 (45%) of whom had partial seizures with secondary generalization. Fifty-eight patients (46.8%) were classified as having generalized seizures (absence, n = 9; myoclonic, n = 3; tonic, n = 2; tonic–clonic, n = 43; atonic, n = 1). Of the 112 active epileptic patients, 80 (71.4%) underwent EEG recording. Sixty-two of these patients (55.4%) were classified as having partial seizures (with or without secondary generalization) and 50 had (44.6%) generalized seizures.

Using the electroclinical criteria, the mean age at onset for generalized seizures (13.6 years) was lower than that for partial seizures (20.7 years).

In terms of frequency of seizures, 23 patients (18.5%) had more than one per week, 20 patients (16.1%) had more than one per month but less than one per week, 39 patients (31.5%) had only one seizure per month, 23 patients (18.5%) had more than one per year but less than one per month, and 19 patients (15.3%) had sporadic seizures only (less than one per year). Only 13 patients (10.5%) had taken an AED for more than 2 months in their life (phenobarbitone, n = 4; phenytoin, n = 2; carbamazepine, n = 1; unspecified drugs, n = 10). Only 21 patients (16.9%) had been to a physician during their lifetime for seizures, and only two patients had previously had an EEG recording. Forty-one patients (33.1%) reported a family history of epilepsy in parents, brothers, or sisters.

On the basis of the clinical history and the neurologic examination, we detected a number of possible causes of epilepsy: 13 patients with pre- and perinatal risk factors, six patients with head injuries with loss of consciousness, two patients with cerebrovascular disease, one patient with tumor, and one patient who abused alcohol.

Table 4 Clinical and electroclinical seizure classification

Type of seizure	Clinical classification, n (%)	Electroclinical classification, n (%)
Partial simple	9 (7.3)	10 (8.1)
Partial simple with secondary generalization	33 (26.6)	56 (45.2)
Absence	10 (8.1)	9 (7.3)
Tonic–clonic	63 (50.8)	43 (34.7)
Other generalized	9 (7.3)	6 (4.8)
Total	124 (100)	124 (100)

Discussion. Epilepsy is considered an important health problem in developing countries, although studies on the magnitude of this problem are limited. The lack of use of standardized definitions, differences in case ascertainment, and other methodological aspects of several previous surveys carried out in developing countries make comparison difficult.[1]

One of the essential requirements for the implementation of neuroepidemiologic studies in rural areas of developing countries is community collaboration. In this study, the establishment of a working relationship with the APG was particularly important. The involvement of local health workers favored acceptance by this rural population, and thus the refusal rate was very low. We did not find language a major barrier. In fact, the vast majority of the population understands Spanish. In the few isolated communities where some women and children speak only Guaraní, the local physician and health workers utilized the local language.[8]

Most of the data on epilepsy available from developing countries are based on community surveys in urban or rural areas generally carried out with door-to-door case ascertainment with a two-phase design.

Low prevalence values, close to values from industrialized countries, that range from 3 to 9/1,000[2] were detected in several studies carried out in developing countries (rural Kashmir, India, 2.47/1,000[3]; Parsi community, Bombay, India, 4.7/1,000[16]; Nigeria, 5.7/1,000[16]). Conversely, very high prevalence values are reported in other studies such as in Gran Bassa Liberia (28/1,000)[4] and Boca del Toro, Panama (57/1,000).[17]

Our prevalence values of 12.3/1,000 (13.5/1,000, adjusted to world standard population) and 11.1/1,000 for active cases (12.0/1,000, adjusted to world standard population) are close to the values reported from rural areas of Tanzania (10.2/1,000),[18] Uruguay (11.5/1,000),[19] Ecuador (15.4/1,000),[20] Pakistan (14.8/1,000),[21] and Guatemala (8.5/1,000).[22]

Most of the studies report a higher prevalence in men, probably due to a higher frequency of head injury. In our survey, sex-specific prevalence is slightly higher in women (13.1/1,000) than in men (11.4/1,000). This is similar to the data from Tanzania (women, 13.0/1,000; men, 10.4/1,000)[18] and Colombia (women, 22.9/1,000; men, 15.5/1,000).[23] The age- and sex-specific prevalence, except for the first two age groups (0 to 4 years and 5 to 14 years), is always higher in women, particularly in the 15 to 24-year group. The reason for this is unclear, but is possible that in community surveys men do not admit the occurrence of seizures as frequently as women.[16] In several published studies, age-specific prevalence increases in the first 10 years of life, reaching a peak in the 15 to 24-year group.[16,18,21,22]

The mean age at onset (13.6 years for generalized seizures and 20.7 years for partial ones) is similar to data reported in other retrospective studies in developing countries (Parsi community, Bombay, India, 19 years[15]; Pakistan, 13.3 years[21]; Panama, 12 years[4]). These values are also consistent with the few incidence studies carried out in Latin America that show a peak of age-specific incidence in adolescents and young adults (Ecuador, 268.3/100,000 in the 10 to 19-year group[20]; Chile, 144.8/100,000 in the 15 to 29-year group[24]).

In several studies carried out in rural areas of developing countries, seizure classification is based only on clinical grounds due to the unavailability of EEG recordings. In the majority of these studies, a higher frequency of generalized seizure is reported.[3,4,18,20,21,25] Considering only the clinical data, generalized seizures are the most common type in our sample as well (66.1%). An overestimation of generalized seizures may be due to a misdiagnosis of partial seizures with rapid secondary generalization. In fact, partial seizures with secondary generalization are often indistinguishable from tonic–clonic seizures, especially when partial onset is ignored or progression to generalization is so rapid that no partial signs can be observed.

When the electroclinical classification was utilized in our patients, the percentage of partial seizures (with or without secondary generalization) increased from 33.9 to 53.2%. This emphasizes the importance of the EEG recording to identify correctly the types of seizures in these populations.

The percentage of epileptics who received medical attention for their seizures was very low. Only 17% went to a physician during their lifetime for seizures, and only 10% had taken an AED for more than 2 months. These data are consistent with those reported from several studies carried out in developing countries, especially in rural areas.[19] Several factors explain these findings: Seizure disorders in rural Bolivia are still believed to be inflicted by supernatural forces, and epileptic patients often only consult a traditional healer. Moreover, the poor development of the health care infrastructure and the cost of treatment play important roles in health-seeking behavior in rural developing countries. Our findings underline the necessity of educational and treatment programs.

Several articles report that neurocysticercosis is the most important cause of epilepsy in Latin America.[1,2] It is likely that neurocysticercosis plays a role in our study area, where lack of latrines, free-ranging pigs near the household, and pork consumption are common. Data from this prevalence study served as a basis for a case–control study to evaluate the relationship between some parasitic infections, cysticercosis and toxocariasis, and epilepsy. Results of this case–control study are being prepared for publication.

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Menstrual cycle effects on cortical excitability

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Article abstract—*Objective:* To determine whether there are menstrual cycle–related effects on cortical excitability in normal women. *Background:* Ovarian steroid hormones affect neurotransmission in the brain. Data from animal experiments have shown that progesterone metabolites enhance the action of gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the cortex, producing benzodiazepine-like (e.g., diazepam and lorazepam) physiologic and behavioral effects. Estradiol has excitatory effects on measures of neuronal excitability, possibly acting through the glutamate system. These effects have been difficult to detect in women using conventional techniques. However, recently, paired transcranial magnetic stimulation (TMS) has been used to detect the effects of GABAergic and glutamatergic drugs in humans. We used this method to measure the effects of the menstrual cycle in normal women. *Methods:* We tested 13 healthy women during the follicular (low-progesterone) and luteal (high-progesterone) phases of the menstrual cycle using paired TMS. The effect of a subthreshold conditioning pulse on the cortex was tested by measuring the response to a second suprathreshold test pulse and comparing it with the response elicited by the test pulse administered alone. *Results:* Conditioning TMS produced more inhibition in the luteal phase than in the follicular phase ($p = 0.01$), of similar magnitude to the reported effect of benzodiazepine drugs. *Conclusions:* This study provides the first direct evidence of changes in the excitability of a cortical network with the menstrual cycle. The results also show a potential confound for studies using transcranial magnetic stimulation in populations that include menstruating women. **Key words:** Motor cortex—Menstrual cycle—Magnetic stimulation—Paired stimulation—Neurosteroids—Gamma-aminobutyric acid receptors—Progesterone.

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Female sex hormones, e.g., progesterone and its neuroactive metabolites[1] as well as estrogen,[2,3] can modulate neuronal excitability via effects on ion channels. Progesterone tends to reduce neuronal excitability, raising the seizure threshold[4,5] and exerting effects on behavior like those of antianxiety drugs.[6,7] Progesterone's neurosteroid metabolites appear to produce these effects by binding to a site on the gamma-aminobutyric acid A ($GABA_A$) receptor. This increases the receptor's affinity for GABA,[8]

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