The Importance of Boron Nutrition for Brain and Psychological Function*

JAMES G. PENLAND

US Department of Agriculture, Agricultural Research Service, Grand Forks Human Nutrition Research Center, PO Box 9034, Grand Forks, ND 58202-9034

ABSTRACT

Boron (B) nutriture has been related to bone, mineral and lipid metabolism, energy utilization, and immune function. As evidence accumulates that B is essential for humans, it is important to consider possible relationships between B nutriture and brain and psychological function. Five studies conducted in our laboratory are reviewed. Assessments of brain electrical activity in both animals and humans found that B deprivation results in decreased brain electrical activity similar to that observed in nonspecific malnutrition. Assessments of cognitive and psychomotor function in humans found that B deprivation results in poorer performance on tasks of motor speed and dexterity, attention, and short-term memory. However, little support was found for anecdotal reports that supplementation with physiologic amounts of B helps alleviate the somatic and psychological symptoms of menopause. Parallels between nutritional and toxicological effects of B on brain and psychological function are presented, and possible biological mechanisms for dietary effects are reviewed. Findings support the hypothesis that B nutriture is important for brain and psychological function in humans.

Index Entries: Boron nutrition; brain function; electroencephalogram; psychological function; cognition; behavior; toxicology; human; animal.

INTRODUCTION

During recent years, boron (B) nutriture has been related to bone, mineral and lipid metabolism, energy utilization, and immune function (1,2). As evidence accumulates to establish that B is essential for humans, it is important to consider possible relationships between B nutriture and brain and psychological function. The results of five independent studies conducted in our laboratory over the past 8 years (3–7) that address this issue are reviewed. All were controlled experiments, and four were conducted with humans. Some interesting parallels between nutritional and toxicological effects of B on brain and psychological function will be presented, and possible biological mechanisms by which B intake and status might affect brain and psychological function are reviewed.

EXPERIMENT 1

Brain electrophysiology of mature rats was assessed to determine whether B nutriture affected brain function of animals (3). Eighty 100-d-old Long Evans rats (40 male and 40 female) were assigned on the basis of sex and weight to one of four dietary groups created by the factorial combination of B (0.12 and 2.7 µg/g diet, as boric acid) and Mg (80 and 325 µg/g diet, as acetate). Rats were fed a diet adequate in all nutrients for a 7-d equilibration period and then fed their assigned diets for 60 d, at which time cortical electrodes were implanted over the left and right hemispheres of the brain (8). Following a 2-wk recovery period during which all animals continued on the assigned diets, a 60-s electrocorticogram (ECoG) was recorded without anesthesia during the dark phase of the light–dark cycle. Rats were sacrificed within 24-h of the ECoG, and femur samples were analyzed to verify the efficacy of the dietary manipulation. Spectral analysis of cortical electrical activity yielded measures of power (amplitude) across the 2–12 Hz frequency spectrum and separately for each frequency in that spectrum for each hemisphere. In addition, a measure of the relative distribution of power among the different frequencies for each hemisphere was determined by calculating the percentage of total power across the frequency spectrum represented in each frequency and in several important frequency bands (3).

Contrasted with high B intake (2.7 µg/g diet), low dietary B (0.12 µg/g) was associated with the following significant ($p < 0.05$) effects:

1. Decreased left-hemisphere log power in the 3-, 6-, 7-, and 9- to 12-Hz frequencies.
2. Decreased right-hemisphere log power in the 8-, 9-, and 11-Hz frequencies.
3. Increased percentage of total power in the 4- and 5-Hz frequencies in both hemispheres (Fig. 1).
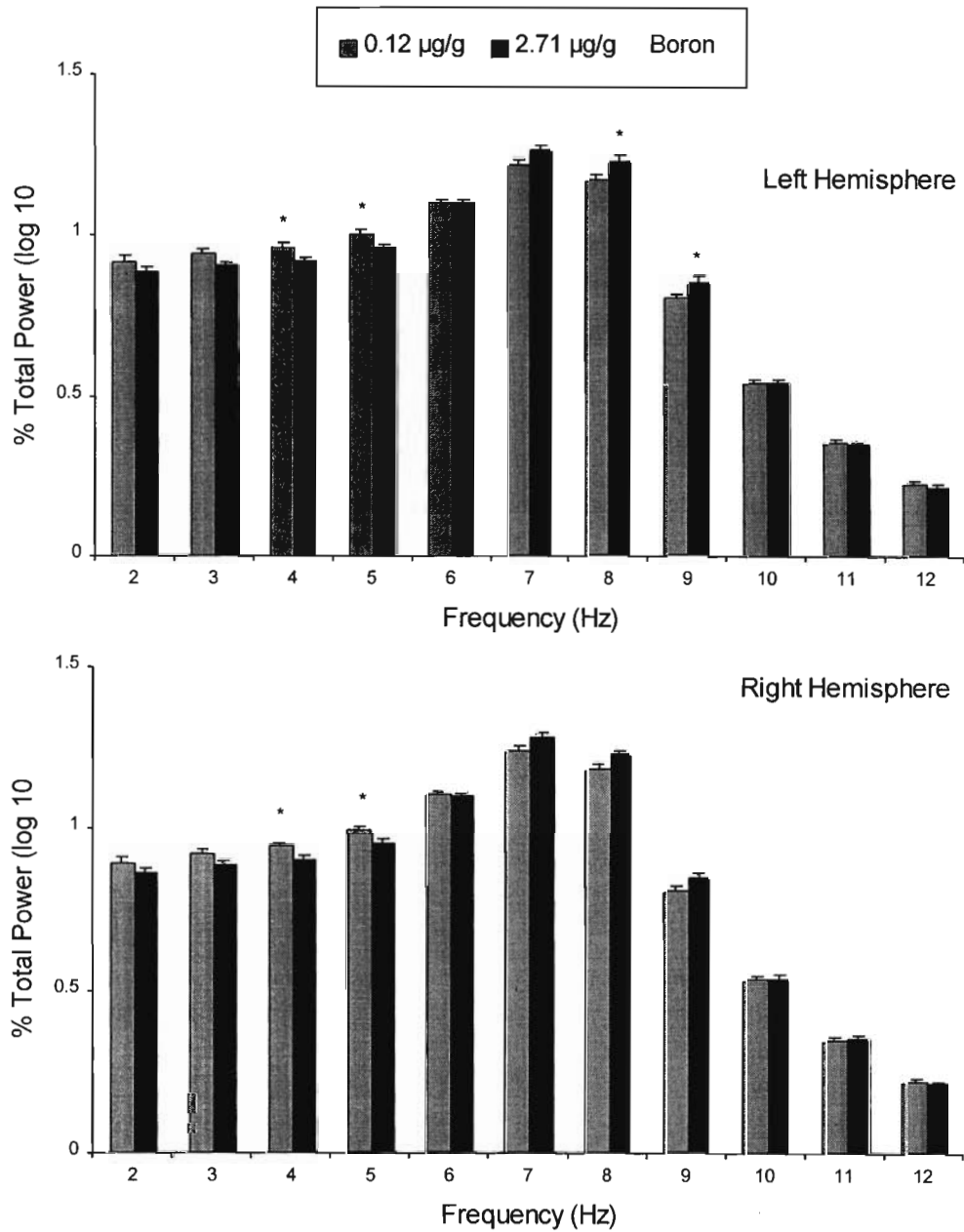
Fig. 1.   B effects on percentage of ECoG power at each frequency relative to the total power in the 2- to 12-Hz spectrum (Experiment 1). Data are presented separately for the left (upper) and right (lower) hemispheres. *$p < 0.05$.

4. Decreased percentage of total power at 8 and 9 Hz in the left hemisphere.
5. Decreased total power in the 5- to 9- and 8- to 12-Hz bands in both hemispheres.
6. Decreased total power across the spectrum in the left hemisphere.
7. Increased percentage of low-to-high frequency activity in the right hemisphere.

Dietary Mg was not significantly related to cortical electrical activity, nor were there any significant interactions between B and Mg with respect to cortical activity. There was significantly less B and less Mg in the femurs of rats fed low B and low Mg, respectively, which indicated the appropriate differences in dietary intakes and absorption.

The results of Experiment 1 indicate that dietary B intakes systematically influence brain electrical activity in mature rats under conditions that control for the effects of dietary Mg and time, and suggest that the principal effect of manipulating B intake is on the relative distribution of activity among frequencies. Specifically, B deprivation was associated with decreased high-frequency and increased low-frequency brain electrical activity, consistent with decreased arousal. Thus, in physiologic concentrations, B may play an important role in the maintenance of brain activation in animals.

EXPERIMENTS 2–4

Three human experiments were performed that assessed the effects of dietary B on brain function measured by the electroencephalogram (EEG), and on psychological function measured by performance on a computerized battery of cognitive (attention, perception, and memory), spatial, and psychomotor (simple motor speed, dexterity, and eye–hand coordination) tests. All studies contrasted low physiologic B intakes (<0.3 mg/d) with high physiologic B intakes (~3.25 mg/d). Typical dietary intakes of B in the US range from about 0.7 to 0.9 mg/d for adults *(9)*. Two of the three studies found that when compared to high B intakes, low B intakes resulted in EEG changes consistent with deceased brain activation, and similar to those observed in protein–calorie malnutrition and Pb toxicity. Low intakes were also associated with poorer performance on several tasks measuring cognitive and motor function, when compared to high intakes. These tasks included motor speed and dexterity, attention, and working memory; the latter two tasks showed better performance with high compared to low B intakes in all three experiments. Because these experiments shared many design features in common, they are reviewed together. Additional details are available elsewhere *(4–6)*.

Subjects

For Experiment 2, 13 healthy postmenopausal women aged 50–78 yr were recruited nationally to participate in a 6-mo, live-in study of Mg and B nutrition. Subjects were not on estrogen-replacement therapy. For Experiments 3 and 4, 15 healthy older adults, 5 men, 5 postmenopausal women on estrogen-replacement therapy, and 5 postmenopausal women not on estrogen-replacement therapy were recruited from the local community. Subjects ranged in age from 44 to 69 yr. In Experiment 3, one woman not receiving estrogen began to menstruate shortly after the

study began and her data were excluded. In Experiment 4, one man withdrew during the first month.

Diets

Subjects in all three experiments were fed a diet consisting of conventional foods with a 3-day menu rotation *(10)*. This basal diet supplied approx 115 mg Mg and 0.25 mg B/2000 kcal/d, and was supplemented as necessary to approximate typical intakes and ensure nutritional adequacy of all vitamins and minerals except Mg and B *(10)*. Despite supplementation, dietary Cu was marginal (1.6 mg/2000 kcal) in Experiments 2 and 3, but this potential source of confounding evidence was removed from Experiment 4 by supplementing the basal diet with an additional 0.8 mg Cu/d *(11)*. Energy in the diet was distributed as 11% protein, 54% carbohydrate, and 35% fat; caloric intakes necessary to maintain initial body weight ($\pm 2\%$) were determined separately for each subject. Water was consumed *ad libitum*, but added only about 0.022 mg to the daily intake of B.

Experiment 2

Following a 21-d equilibration period during which the diet was supplemented with 200 mg Mg and 3 mg B/2000 kcal/d, as Mg gluconate and Na-B capsules, respectively, each subject was given all four supplement combinations created by the factorial crossing of 0 (placebo) and 200 mg Mg with 0 (placebo) and 3 mg B for 42 d each. Mg and B placebo capsules both contained lactose powder. Supplements were administered in a double-blind, Latin-Squares order. Diets were consumed while subjects resided 24 h/d in the metabolic research unit at the Grand Forks Human Nutrition Research Center, which permitted strict control of dietary intakes, exercise, and data collection, and provided a common environment.

Experiments 3 and 4

These studies began with a 14-d equilibration period, followed by a 63-d B-depletion period, and concluded with a 49-d B repletion period. The basal diet was supplemented with 3 mg B/d, as Na-B, during the equilibration and B-repletion periods. During all dietary periods in Experiment 4, the diet also was supplemented with 200 mg Mg/d, as Mg gluconate. In Experiments 3 and 4, subjects lived at home and maintained their usual work and recreational activities. One meal per day (either breakfast or lunch) was consumed in the laboratory Monday through Friday. Foods for all other meals were packed in coolers for consumption at home.

Electrophysiology Recording and Processing

The EEG was recorded from electrodes located over the left and right frontal (F_3 and F_4 in the notation of the International Ten-Twenty System of Electrode Placement), temporal (T_3 and T_4), parietal (P_3 and P_4)

and occipital (O_1 and O_2) lobes, referenced to linked ear electrodes. EEG records were made while the subject was at rest (i.e., the subject was instructed to relax, and there were no explicit task demands) for 40 s with the eyes open and then for 40 s with the eyes closed.

Following editing to remove extracerebral artifact, EEG data recorded from each electrode location (i.e., lobe) were spectrally analyzed by the Cooley-Tukey Fast Fourier transform. This technique converts time series data to a representation in the frequency domain, and yields a standardized measure of amplitude or signal power. Power, determined for each electrode location, corresponds to the absolute amount of electrical activity in each frequency component of the complex EEG signal and reflects the degree of synchronous cortical activity among neurons in a localized region of the brain. Given 1-s epochs, the power spectrum had a resolution of 1 Hz. Further computation allowed the mean power of the signal to be determined for each of four frequency bands: 1–3 Hz (Δ), 4–7 Hz (θ), 8–12 Hz (α), and 13–18 Hz (β). Coherence, the correlation between a pair of signals for each frequency band, was computed for all possible pairs of electrode recording sites to assess the relationship between activity in different regions of the brain.

Additional measures were derived from the EEG. Percent-total power, a measure of the relative distribution of power among the different frequency bands for each electrode location, was determined by calculating the percentage of total power across the frequency spectrum represented in each frequency band. As a measure of the frequency distribution of cortical activity, percent-total power defines the dominant frequency in the signal and is highly sensitive to frequency shifts. To assess the degree of asymmetry between the two hemispheres, reflecting the spatial distribution of cortical activity, the difference between left and right hemisphere power measures was determined for each frequency band recorded from the frontal, temporal, parietal, and occipital lobes. To assess cortical responsiveness to external stimulation, α reactivity was computed by subtracting α power determined during eyes-open periods from α power determined during eyes-closed periods.

Cognitive and Psychomotor Assessment

Table 1 lists the cognitive and psychomotor tasks performed by subjects in each experiment and the area of function emphasized by each task. The tasks in this battery are computerized versions of standardized tasks commonly used in neuropsychological assessment and experimental cognitive psychology. Finger-tapping and visuo-motor tracking tasks were used to assess manual dexterity, eye–hand coordination, concentration, and simple motor fatigue. Trail-making was used to assess eye–hand coordination and visual perception. Search-count was used to assess attention. Continuous vigilance was used to assess sustained attention and dyscontrol (impulsivity). Color-name identification and time estimation

Table 1
Test Battery Used to Assess Cognitive
and Psychomotor Performance

Experiment	Function / Task	Experiment	Function / Task
	Psychomotor /		Memory /
2 3[a] 4[a]	Tapping	2[a] 3[a] 4[a]	Symbol-Digit
2 3[a] 4	Tracking	2	Shape Recognition
2	Trail Making	2	Cube Recognition
	Attention /	2	Letter Recognition
2[a] 3[a] 4[a]	Search-Count	2[a]	Word Recognition
2	Continuous Vigilance		
	Perception /		Spatial /
2 3 4[a]	Color-Name	2	Maze
2 3 4	Time Estimation		

[a]Experiment showing significant ($p < 0.05$) effect of dietary B on performance.

were used to assess visual perception and depth of processing. Symbol-digit was used to assess encoding and short-term or working memory. Cube and shape recognition were used to assess memory for figural and meaningful spatial information. Letter and word recognition were used to assess verbal memory. Finally, a maze task was used to assess spatial orientation and memory for spatial information. Additional details on tasks are available elsewhere (6).

Data Analysis

EEG data were transformed to achieve a more symmetrical distribution prior to statistical analysis. For Experiment 2, dietary effects on EEG and performance measures were tested for significance by a B × Mg × period repeated-measures analysis of variance; period was included as a factor in the model to remove effects associated with order of supplement administration (i.e., time effects). For Experiments 3 and 4, dietary effects on all measures were tested for significance by contrasting the B-depletion and B-repletion conditions with the Student's t-statistic for repeated-measures designs. To maximize statistical power by increasing sample size, data from the three subgroups of subjects in Experiments 3 and 4 (men, women on estrogen therapy, and women not on estrogen therapy) were combined for all analyses.

Results

Spectral analysis of electroencephalographic data showed effects of dietary B in two of the three studies. When the low B intake was compared to the high intake, there was a significant ($p < 0.05$) increase in the proportion of low frequency activity and a decrease in the proportion of high frequency activity, an effect often observed in response to general malnutrition and heavy metal toxicity. Performance (e.g., response time) on various cognitive and psychomotor tasks also showed an effect of dietary B. When contrasted with the high B intake, low dietary B resulted in significantly ($p < 0.05$) poorer performance on tasks emphasizing manual dexterity (Experiments 3 and 4), eye–hand coordination (Experiment 3), attention (all experiments), perception (Experiment 4), encoding and short-term memory (all experiments), and long-term memory (Experiment 2).

Electroencephalogram (EEG)

Although there were numerous effects of dietary Mg on the EEG in Experiment 2, the number of B × Mg interactions did not exceed chance nor did they involve the following main effects of dietary B. When contrasted with the high B intake, low dietary B significantly increased Δ (1–3 Hz) power in left parietal and left occipital regions under the eyes-open condition. These were the only significant effects of diet on absolute power. However, as shown in Fig. 2, low B increased percent-total Δ power in the frontal regions, while decreasing percent-total right frontal θ (4–7 Hz), percent-total right frontal α (8–12 Hz), and percent-total left frontal β (13–18 Hz) power. These effects were again limited to the eyes-open condition. Under both recording conditions, low B generally increased signal coherence, particularly in the Δ frequencies among posterior regions of the brain.

Experiment 3 showed the greatest number of effects of dietary B on the EEG parameters. Figure 3 presents significant findings from analysis of absolute power. When contrasted with the high B intake, low dietary B increased Δ power in the left temporal and parietal regions, decreased α power across the head, decreased right frontal β power, and decreased θ and β power in the right parietal and right occipital regions. With the exception of the first finding, all effects were significant under both eyes-closed and eyes-open recording conditions. Figure 4 presents significant findings from analysis of percent-total power. Low B increased percent-total Δ power in the posterior regions, decreased percent-total α power across the head, and decreased percent-total θ and β power in the parietal regions. Low B also resulted in increased bias toward greater activity in the left than right hemisphere in the parietal region under the eyes-closed condition, and in the frontal and parietal regions under the eyes-open condition. In addition, low B significantly decreased α reactivity in the right frontal and left occipital regions. Finally, as shown in Fig. 5, low B increased coherence among several regions across the
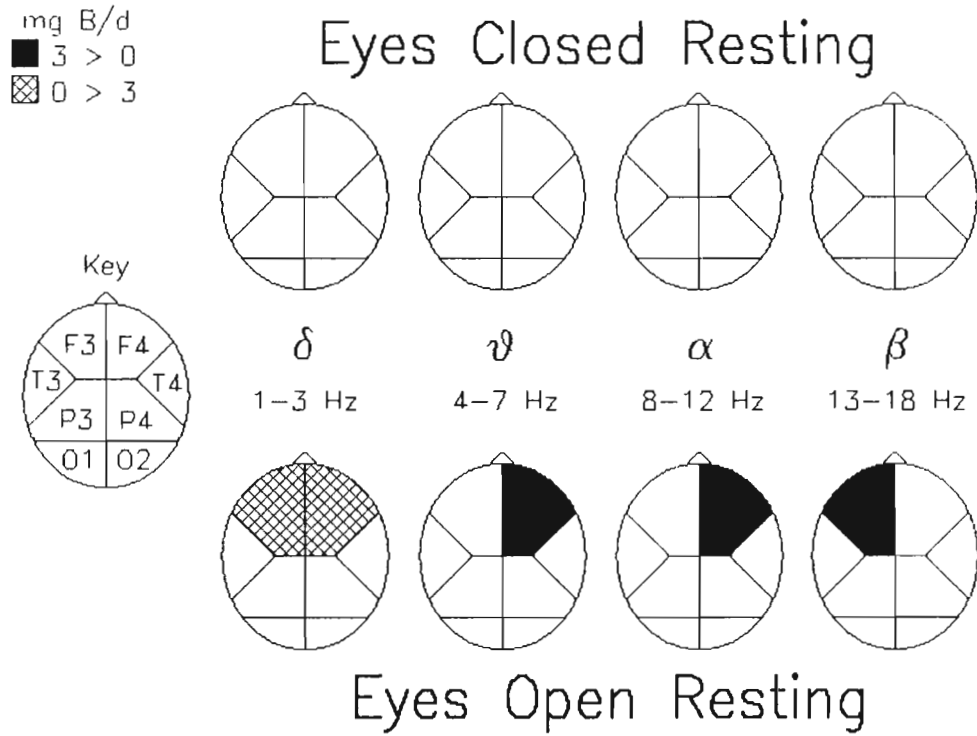
Fig. 2. B effects on percent-total EEG power (Experiment 2). Significant ($p < 0.05$) dietary B effects on mean percent-total EEG power during eyes-closed and eyes-open conditions, separately for each recording site and frequency band. Diet with greater proportion is keyed. Labeled head at far left identifies each recording site relative to the region of the brain sampled.
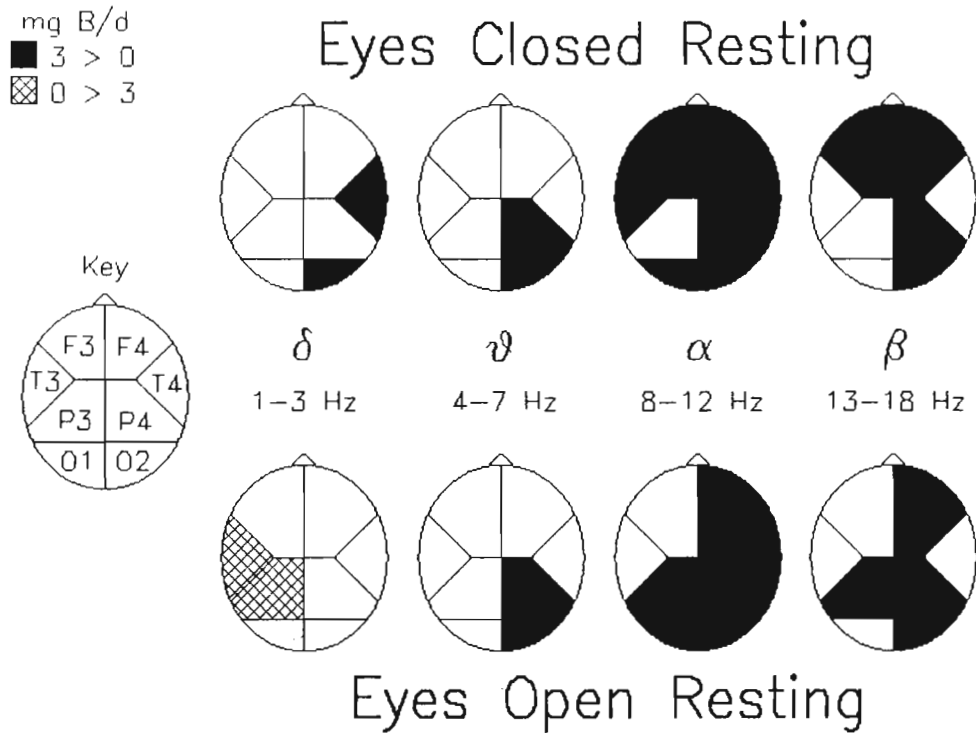

Fig. 3. B effects on EEG power (Experiment 3). Significant ($p < 0.05$) dietary B effects on mean EEG power during eyes-closed and eyes-open conditions, separately for each recording site and frequency band. Diet with greater power is keyed. Labeled head at far left identifies each recording site relative to the region of the brain sampled.
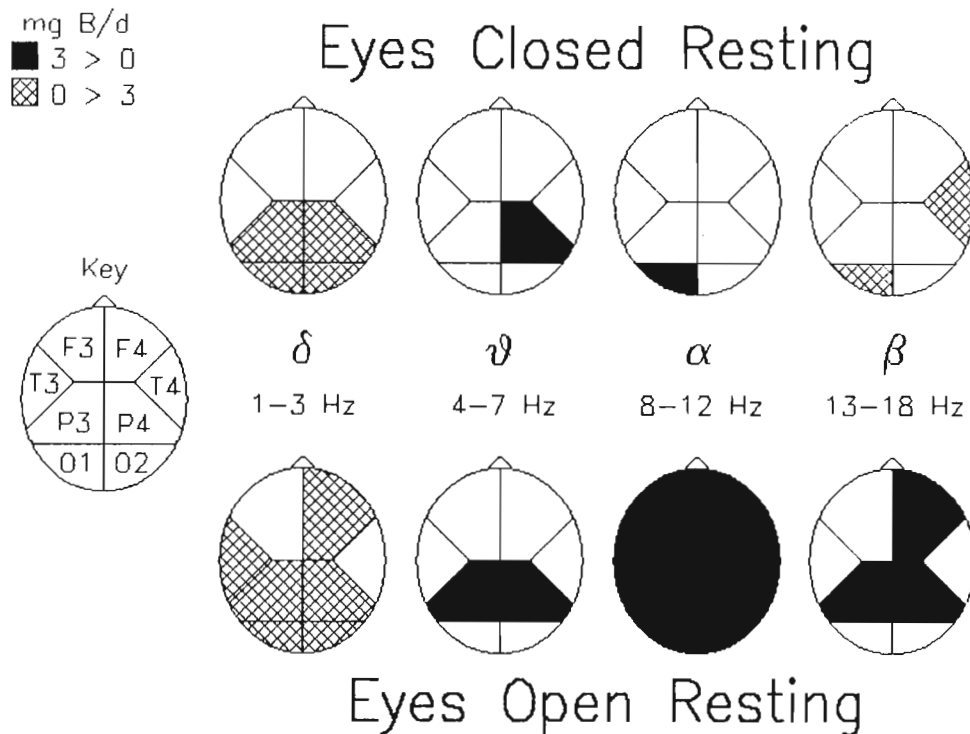
Fig. 4.   B effects on percent-total EEG power (Experiment 3). Significant ($p < 0.05$) dietary B effects on mean percent-total EEG power during eyes-closed and eyes-open conditions, separately for each recording site and frequency band. Diet with greater proportion is keyed. Labeled head at far left identifies each recording site relative to the region of the brain sampled.

head in the Δ frequencies and decreased coherence in the θ, α, and β frequencies among posterior regions, under both eyes-open and eyes-closed recording conditions.

Cognitive and Psychomotor Performance

Table 2 shows the effects of B intake on the Tapping and Tracking tasks performed in all three studies. When contrasted with the high B intake, low dietary B resulted in fewer complete sequences tapped overall, and fewer taps for both long and short sequences in Experiments 3 and 4. Experiment 3 also found that low B resulted in decreased percent time on target when all tracking trials were combined, but particularly when the target was following a nonrandom (i.e., predictable) path. There were no significant dietary B effects on psychomotor performance in Experiment 2.

Table 3 shows the effects of B intake on Search-Count response times. When contrasted with the high B intake, low dietary B resulted in increased response times during search and count in all three studies, and during search only in Experiments 3 and 4. Table 4 shows the effects of B intake on Color-Name Identification response times. When contrasted with the high B intake, low dietary B resulted in increased response times to identify color names regardless of presentation color in Experiment 4;
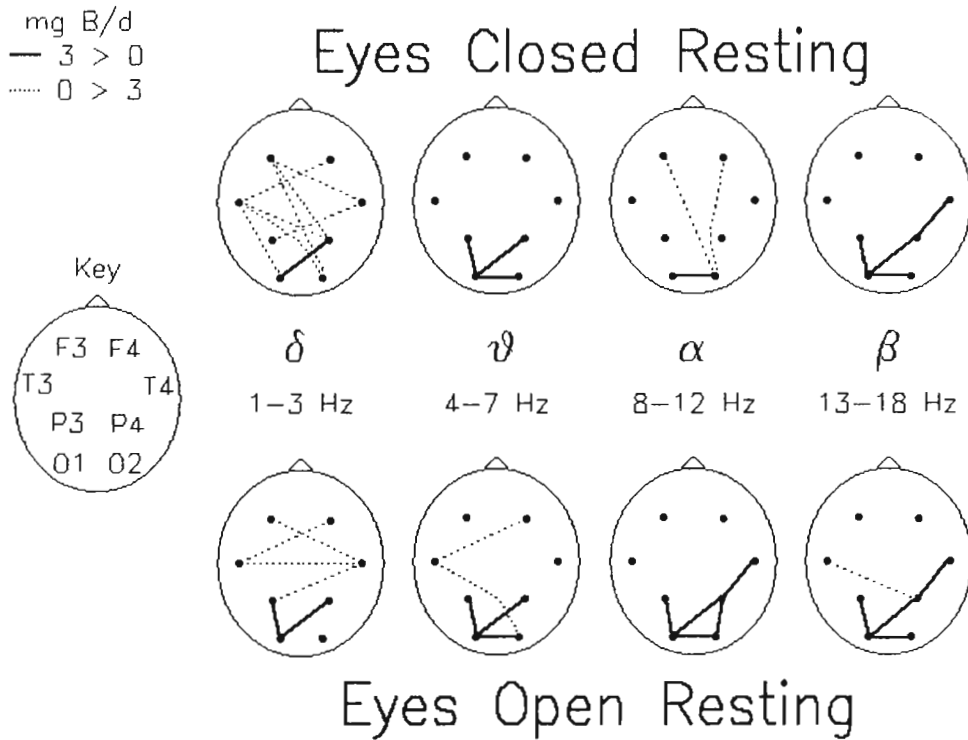
Fig. 5. B effects on EEG coherence (Experiment 3). Significant ($p < 0.05$) dietary B effects on mean EEG coherence during eyes-closed and eyes-open conditions, separately for each recording site and frequency band. Diet with greater coherence is keyed. Labeled head at far left identifies each recording site relative to the region of the brain sampled.

Table 2
Effects of B Intake on Tapping and Tracking Performance

	Experiment 2[a]		Experiment 3		Experiment 4	
Boron Supplement (mg/d)	0	3	0	3	0	3
Tapping (# tapped/30 sec)						
All Sequences	23.0±0.3[b]	23.0±0.3	22.1±1.0[d]	24.2±1.0	23.2±1.0[c]	24.6±0.8
2-Key Sequences	31.0±0.4	31.1±0.4	30.2±1.3[d]	32.5±1.2	32.3±1.2[c]	33.6±1.1
4-Key Sequences	15.0±0.2	14.8±0.2	14.0±0.7[d]	15.9±0.7	14.1±0.8[d]	15.5±0.6
Tracking (% time on target)						
All Paths	19.2±0.6	18.5±0.6	22.8±2.5[d]	26.4±2.3	16.0±1.7	17.5±1.6
Random Paths	16.3±0.6	15.7±0.6	23.4±1.7	25.2±1.5	15.7±1.4	15.1±1.0
Nonrandom Paths	20.0±0.7	19.2±0.7	22.6±2.9[d]	26.6±2.7	16.1±1.9	18.1±1.8

[a]B main effects from B × Mg × Period ANOVA.
[b]Mean ± SEM.
[c]$p < 0.05$.
[d]$p < 0.01$.

Table 3
Effects of B Intake on Search-Count Response Times(s)

Boron Supplement (mg/d)	Experiment 2[a]		Experiment 3		Experiment 4	
	0	3	0	3	0	3
Search Only	3.34±0.08[b]	3.15±0.07	3.43±0.32[d]	2.63±0.21	3.52±0.33[d]	3.02±0.29
Search and Count						
All Conditions	7.37±0.21	6.80±0.20	7.05±0.57[d]	6.27±0.52	7.73±0.83[d]	6.84±0.66
Targets Present	7.20±0.20[c]	6.62±0.20	6.95±0.57[d]	6.18±0.52	7.53±0.79[d]	6.72±0.64
Targets Absent	8.22±0.27[c]	7.32±0.27	8.11±0.83[c]	6.83±0.59	8.66±1.02	8.15±0.98

[a]B main effects from B × Mg × Period ANOVA.
[b]Mean ± SEM.
[c]$p < 0.05$.
[d]$p < 0.01$.

Table 4
Effects of B Intake on Color-Name Identification Response Times (ms)

Boron Supplement (mg/d)	Experiment 2[a]		Experiment 3		Experiment 4	
	0	3	0	3	0	3
Name + Color	844±11[b]	858±11	774±24	760±21	783±31[c]	746±32
Presentation Color (Name Identification Only)						
Consistent	772±18	806±18	729±27	713±24	731±26[d]	680±28
Neutral	815±15	833±15	752±32	738±24	765±32[d]	718±30
Inconsistent	907±18	921±18	813±35	787±27	822±39	783±42
Inhibition	92	88	61	49	57	65
Facilitation	43	27	23	25	34	38

[a]B main effects from B × Mg × Period ANOVA.
[b]Mean ± SEM.
[c]$p < 0.05$.
[d]$p < 0.01$.

this effect was not statistically significant when the color name was inconsistent with the presentation color. There were no significant effects of dietary B on Color-Name performance in Experiments 2 and 3, or on ability to estimate cued time intervals (Time Estimation) in any study.

Table 5 shows the effects of B intake on Symbol-Digit and Word Recognition performance. When contrasted with the high B intake, low dietary B resulted in increased response times to encode and recall symbol-digit pairings in all three studies, and increased response times

Table 5
Effects of B Intake on Symbol-Digit and Word Recognition Performance

	Experiment 2[a]		Experiment 3		Experiment 4	
Boron Supplement (mg/d)	0	3	0	3	0	3
Symbol-Digit						
Response Times (s)	2.30 ± 0.02^{bc}	2.23 ± 0.02	2.14 ± 0.06^{d}	1.88 ± 0.05	2.27 ± 0.11^{d}	1.98 ± 0.08
Error (%)	2.34 ± 0.43	2.65 ± 0.43	3.25 ± 0.36	2.85 ± 0.41	2.78 ± 0.55	2.26 ± 0.50
Word Recognition						
Response Times (s)	2.46 ± 0.04^{c}	2.33 ± 0.04	Not Administered		Not Administered	
Error (%)	7.85 ± 0.73	7.44 ± 0.72	Not Administered		Not Administered	

[a]B main effects from B × Mg × Period ANOVA.
[b]Mean ± SEM.
[c]$p < 0.05$.
[d]$p < 0.01$.

to recognize recently presented words in Experiment 2. There were no significant effects of dietary B on error rates for either task in any study. Tasks administered only in Experiment 2 to assess letter, shape, and cube recognition also showed no significant effects of dietary B (Table 1).

Discussion

Experiments 2–4 provide converging evidence that relatively short periods (42–73 d) of restricted B intake can affect brain function and cognitive performance in otherwise healthy older women and men. Two of the three experiments showed an effect of B intakes at physiologic concentrations on EEG parameters. The most consistent EEG finding, based on the derived measure of percent-total power, was that low B intake resulted in a shift toward more activity in the low frequencies and less activity in the high, dominant frequencies of the EEG spectrum. This is a particularly important finding, considering that the same effect is often observed in response to nonspecific malnutrition (12,13) and heavy metal toxicity (14–16). Increased low frequency activity is typical of states of reduced behavioral activation (i.e., drowsiness) and mental alertness (17), and has been associated with poorer performance on vigilance and psychomotor tasks (18,19). In addition, decreased higher frequency activity (e.g., α) has been related to impaired memory performance under some conditions (20).

Several other effects of B intake on EEG parameters were observed that merit further investigation. Coherence was apparently altered by dietary B in two experiments, but there were some inconsistencies between experiments in the location and direction of these effects. Nevertheless,

because coherence reflects the degree of physical and functional connectivity between two cortical regions *(21)*, diet-induced changes in coherence would be of great importance. Further, one study (Experiment 3) showed dietary B affected hemisphere asymmetries, α reactivity to stimulation (eye opening), and total activity across the frequency spectrum (1–18 Hz). Failure to replicate these effects in the other two studies suggests that these may be weak effects dependent on the presence of additional, unknown stressors. Dietary Cu may have been a confounding factor in the shift from higher to lower frequency activity, discussed above, which was observed in Experiments 2 and 3, but not 4. The basal diet contained a luxuriant amount of Cu in Experiment 4. Perhaps the effect of B on some EEG parameters is dependent on marginal Cu intake or status *(2)*.

Behaviorally, low B intake apparently results in poorer performance on tasks that emphasize psychomotor skills, and the cognitive processes of attention, perception, and memory. In Experiments 2–4, Search-Count, a measure of attention, and Symbol-Digit, a measure of encoding skills and short-term memory, consistently showed effects of dietary B on response times. However, not all tasks administered showed an effect of dietary B in all studies. Performance on Tapping, an extremely simple task measuring manual dexterity and fatigue, was impaired by low B intake in two of three studies (Experiments 3 and 4). Pursuit, a measure of eye–hand coordination and tracking skills, was impaired by low B intake only in Experiment 3, whereas low dietary B increased response times during some conditions of the Color-Name Identification task, only in Experiment 4. Low dietary B also increased response times during a word recognition task, administered only in Experiment 2. Performance on several tasks showed no reliable relationship to B intake (Table 1). Low dietary B was fed for only 42 d in Experiment 2, whereas low B was fed for 63 d in Experiments 3 and 4. Perhaps the shorter duration dietary periods were the reason that only 3 of 13 tasks were significantly related to B intake in Experiment 2. Similar to the EEG measures of brain function, the effect of B on cognitive and psychomotor performance in most instances may also depend on the presence of one or more additional stressors. However, performance on two tasks, Search-Count and Symbol-Digit, was affected by B intake in all three experiments, which suggests a robust effect of dietary B on the cognitive processes of attention and memory.

Collectively, the data from these three experiments indicate that B plays a role in human brain function and cognitive performance, and provides additional evidence that B is an essential nutrient for humans.

EXPERIMENT 5

The most recent experiment was designed to evaluate the possible impact of B nutrition on menopausal symptoms *(7)*. Approximately 60% of otherwise healthy women experience vasomotor symptoms (e.g., hot
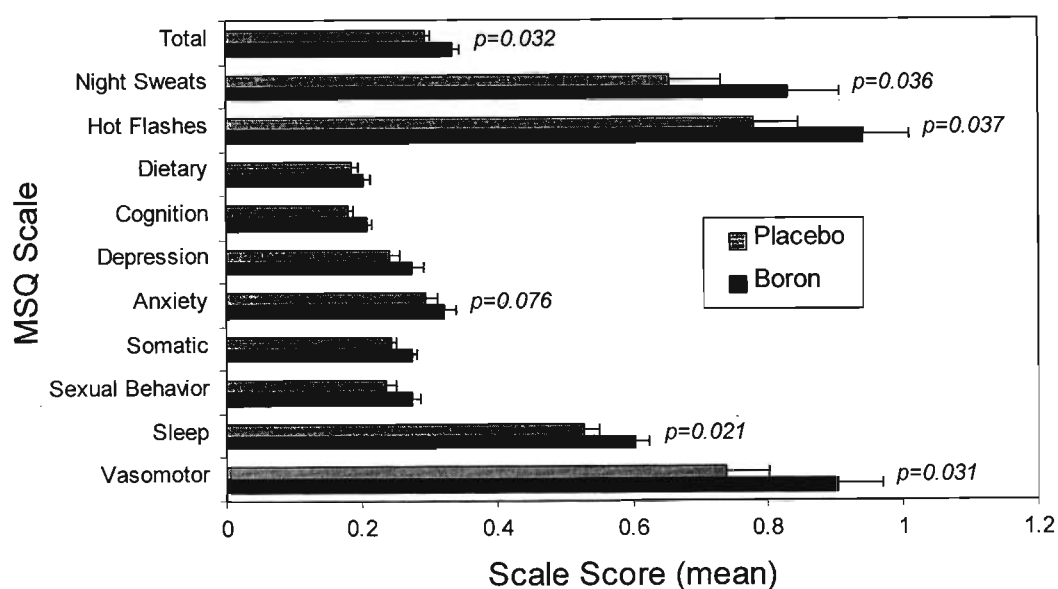
Fig. 6. B supplementation effects on menopausal symptoms and scales derived from propsective questionnaire (Experiment 5). Exact probabilities shown when $p < 0.05$.

flashes) and sleep problems (e.g., night sweats) during the climacteric phase of life. Anecdotal reports suggested that increasing B intakes might relieve these and other somatic and psychological symptoms, whereas clinical reports from a previous study (Experiment 2) suggested an opposite effect.

Forty-six healthy perimenopausal women were given 3 mg B/d as Na borate capsules for 60 d, followed by (22 women) or preceded by (24 women) 90 d when they received a placebo capsule containing lactose powder. The experiment thus controlled for time effects by crossover design, and treatment was double-blind. Each day, women completed a symptom checklist with a 5-point scale to indicate the presence or absence of 60 symptoms, and severity of symptoms when present. Responses to related symptoms were averaged to yield composite scores for vasomotor symptoms, sleep problems, somatic symptoms (e.g., dizziness), sexual problems (e.g., loss of interest, vaginal dryness), anxiety, depression, and cognitive problems (e.g., poor memory). Hot flashes and night sweats were also treated as separate scores, and a grand average yielded a total symptom score. Symptoms reported during the entire B-supplemented period were compared to those from the last 60 d of the placebo period by using a Supplement × Treatment Order analysis of variance.

Women reported more frequent and severe vasomotor problems ($p < 0.031$) and hot flushes ($p < 0.037$), more sleep problems ($p < 0.021$) and night sweats ($p < 0.036$), and more total symptoms ($p < 0.032$) when they were receiving the B supplement (Fig. 6). Parallel results were obtained when data were coded for simple presence or absence of symptoms, except that only sleep problems and total symptoms achieved statistical significance. Approximately 50% of the women in the study

showed exacerbating effects of supplemental B, 35% little or no effects, and 15% beneficial effects. These findings indicate that at least for the majority of women, supplementation with B is unlikely to relieve symptoms associated with the climacteric and menopause. The beneficial effects experienced by a minority of women may result from an increased need for B among these women.

PARALLELS WITH B TOXICITY?

A review of the literature on B toxicity effects on central nervous system function reveals some interesting parallels with the dietary B deprivation and supplementation effects on brain and psychological function reviewed here. Most toxicology studies address effects of compounds that are substantially different from the common dietary forms (e.g., boric acid, sodium borate). Clearly, toxicological effects depend on the form or speciation of B (e.g., boric oxide, decaborane, tetraborate, boric acid, sodium borate), route of exposure (i.e., ingestion [oral], inhalation, surface contact, injection), exposure duration (acute or chronic), and concentration (or dosage). Further, toxicological effects vary among species. Notwithstanding, there is remarkable consistency in the central nervous system effects of frank B toxicity across form, exposure route, and duration, and across species, including mice, rats, guinea pigs, rabbits, dogs, monkey, goats, cows, and humans. Early and mild toxicological effects include behavioral depression, hypotonicity, ataxia, poor motor control, and drowsiness, whereas later and more severe effects include restlessness, tremors, shivering, confusion, seizures, convulsions, and abnormal EEG activity characterized by high-amplitude, low-frequency EEG activity (22–31). These effects are consistent with observed increases in brain B and reductions in brain histamine, serotonin, and norepinepherine, as well as acetylcholine stores (24,32–34). B toxicity effects on more complex forms of behavior include impaired operant learning of continuous and discrete avoidance (35) and impaired performance on spatial, sustained attention, and short-term memory tasks (36). Consistent with the effects of B nutriture on brain electrophysiology and psychological function found in the experiments reviewed in this article, B toxicity primarily affects the relative activity among frequencies recorded by the EEG and motor function, attention, and short-term memory. Interestingly, Reynolds and Back (35) noted that performance decrements on avoidance tasks following decaborane administration preceded all other clinical symptoms in more than half the monkeys they tested.

BIOLOGICAL MECHANISMS

Possible biological mechanisms by which changes in B intake and status might cause the observed effects in brain and psychological function

are many. Accumulating evidence indicates that B nutriture is related to metabolism of other mineral elements, including Ca, Cu, Mg, Mo, and P; that B intakes affect energy metabolism, indicated by changes in glucose, triglycerides, and insulin production; that B selectively accumulates in certain areas of the brain and affects the concentration of other minerals in the brain; that B nutriture affects cell membrane function and hormone metabolism; and that B intakes may affect catecholamine and histamine metabolism *(1,2,10–11,37–39)*. It is probable that one or more of these biological activities of B play a determining role in the B–brain-behavior relationship.

CONCLUSION

Brain electrophysiologic and behavioral performance effects of reduced B intake are complementary. Determination of which EEG parameters are reliably sensitive to B intake and status awaits future study, but measures of the relative activity among frequencies seem to hold the most promise. Future studies must also determine precisely which cognitive processes and psychomotor skills are involved when performance is affected by dietary B. To understand better the relevance of B to both types of function, future studies must also address the potential importance of additional stressors, dietary and otherwise, that might interact with B. Examination of functional consequences of B toxicity also may be useful, although it must be emphasized that the studies reviewed here used physiologic intakes of B; low B diets contained about ⅓ the amount of typical intakes, whereas high B diets contained about four times the amount of typical intakes. With this knowledge, a meaningful connection can be made between B-related changes in brain electrophysiology and those in behavior and psychological function. Findings to date support the hypothesis that B in physiologic amounts is an important nutrient for brain and psychological function in higher animals and humans, although further research is needed to characterize their relationship more fully. Hopefully, these findings will also serve as additional impetus to study biological mechanisms that might underlie the relationship between B nutriture and brain and psychological function so that the essentiality of B for animals and human can be established.

ACKNOWLEDGMENTS

from subject recruitment through data analysis. Special recognition is due Tonya Murphy, Jay Dahlgren, and Barb Bentz for collection of animal and human electrophysiologic data, Gloria Krank, Steve Olson, and Shannon Carsen for collection of performance data, Becky Stadstad for collection of menopausal symptom data, and Lawrence Siu for computer support. Finally, the author gratefully acknowledges the commitment of all those individuals who participated as subjects.

REFERENCES

1. C. D. Hunt, Boron, in *Encyclopedia of Food Science, Food Technology and Nutrition,* vol. 1, R. Macrae, R. K. Robinson, and M. J. Sadler, eds., Academic, London, pp. 440–447 (1993).
2. F. H. Nielsen, The saga of boron in food: from a banished food preservative to a beneficial nutrient for humans, *Curr. Topics Plant Biochem. Physiol.* **10**, 274–286 (1991).
3. J. G. Penland and M. J. Eberhardt, Effects of dietary boron and magnesium on brain function in mature male and female Long-Evans rats, *J. Trace Elem. Exp. Med.* **6**, 53–64 (1993).
4. J. G. Penland, Qualitative analysis of EEG effects following experimental marginal magnesium and boron deprivation, *Magnesium Res.* **8**, 341–358 (1995).
5. J. G. Penland, Effects of low dietary boron (B) and magnesium (Mg) on the brain function of healthy adults, *FASEB J.* **3**, A1242 (1989).
6. J. G. Penland, Dietary boron, brain function and cognitive performance, *Environ. Health Perspectives* **102(Suppl. 7),** 65–72 (1994).
7. J. G. Penland and F. H. Nielsen, Supplemental boron affects somatic and psychological symptoms in healthy perimenopausal women, *FASEB J.* **9**, A585 (1995).
8. J. G. Penland, B. G. Salwer, and L. M. Klevay, Brain electrophysiology in adult rats fed copper deficient diets, *J. Trace Element Exp. Med.* **2**, 239–256 (1989).
9. S. L. Meecham and C. D. Hunt, Dietary boron intakes in selected populations of the United States, *Biol. Trace Element Res.* (this vol.).
10. F. H. Nielsen, L. M. Mullen, and S. K. Gallagher, Effect of boron depletion and repletion on blood indicators of calcium status in humans fed a low-magnesium diet, *J. Trace Element Exp. Med.* **3**, 45–54 (1990).
11. F. H. Nielsen, Boron enhances the effect of estrogen therapy in postmenopausal women, *FASEB J.* **5**, A1646 (1991).
12. R. D. Griesel, Psychophysiological sequelae of Kwashiorkor, in *Malnutrition and Behavior: Critical Assessment of Key Issues*, J. Brozek and B. Schurch, eds., Nestle Foundation, Lausanne, Switzerland, pp. 157–163 (1984).
13. K. N. Agarwal, D. Das, D. K. Agarwal, S. K. Upadhyay, and S. Mishra, Soft neurological signs and EEG pattern in rural malnourished children, *Acta Pediatr. Scand.* **78**, 873–878 (1989).
14. R. W. Thatcher and D. S. Cantor, Electrophysiological techniques in the assessment of malnutrition, in *Malnutrition and Behavior: Critical Assessment of Key Issues*, J. Brozek and B. Schurch, eds., Nestle Foundation, Lausanne, Switzerland, pp. 116–136 (1984).
15. T. L. Petit and D. P. Aflano, Neurobiological and behavioral effects of lead, in *Neurobiology of the Trace Elements*, vol. 2, I. E. Dreosti and R. M. Smith, eds., Humana, Clifton, NJ, pp. 97–139 (1983).
16. T. L. Petit, *Aluminum Neurobiological Toxicology*, vol. 2, I. E. Dreosti and R. M. Smith, eds., Humana, Clifton, NJ, pp. 237–274 (1983).
17. A. Rechtschaffen and A. A. Kales, *Manual of Standardized Terminology, Techniques and Scoring for Sleep Stages of Human Subjects*, Brain Information Service, University of California, Los Angeles (1968).
18. A. Gale, Some EEG correlates of sustained attention, in *Vigilance*, R. R. Mackie, ed., Plenum, New York, pp. 263–283 (1977).

19. N. Roth and G. Sack, Relations between slow (4 cps) EEG activity, sensorimotor speed, and psychopathology, *Int. J. Psychophysiol.* **9**, 121–127 (1990).
20. W. Klimesch, H. Schimke, G. Ladurner, and G. Pfurtscheller, Alpha frequency and memory performance, *J. Psychophysiol.* **4**, 381–390 (1990).
21. R. A. Zappulla, Fundamentals and applications of quantified electrophysiology, *Annals of the New York Academy of Sciences*, vol. 620, pp. 1–21 (1991).
22. J. M. R. Delgado, Cerebral effects of decaborane on the monkey, *Arch. Int. Pharmacodyn.* **148**, 459–470 (1964).
23. H. J. Low and G. Freeman, Boron hydride (borane) intoxication in man, *Arch. Ind. Health* **16**, 523–531 (1957).
24. C. C. Pfeiffer, L. F. Hallman, and I. Gersh, Boric acid ointment. A study of possible intoxication in the treatment of burns, *J. Am. Med. Assoc.* **128**, 266–274 (1945).
25. A. S. Gordon, J. S. Pritchard, and M. H. Freedman, Seizure disorders and anemia associated with chronic borax intoxication, *Can. Med. Assoc. J.* **108**, 719–724 (1973).
26. J. H. Merritt, E. J. Schultz, and A. A. Wykes, Effect of decaborane on the norepinephrine content of the rat brain, *Biochem. Pharmacol.* **13**, 1364–1366 (1964).
27. H. M. Rozendaal, Clinical observations on the toxicology of boron hydrates, *Arch. Ind. Hyg.* **4**, 257–260 (1951).
28. D. B. Sisk, Acute, fatal illness in cattle exposed to boron fertilizer, *J. Am. Vet. Med. Assoc.* **193**, 943–945 (1988).
29. Subcommittee on Mineral Toxicity in Animals, *Boron*, National Academy Sciences, Washington, DC, pp. 71–83 (1980).
30. J. L. Svirbely, Acute toxicity studies of decaborance and pentaborane by inhalation. *Arch. Ind. Hyg. Occup. Med.* **10**, 305–311 (1954).
31. R. von Berg, Toxicology update, *J. Appl. Toxicol.* **12**, 149–152 (1992).
32. R. W. Schayer and M. A. Reilly, Effect of decaborane on histamine formation in mice, *J. Pharmacol. Exp. Ther.* **177**, 177–180 (1971).
33. J. H. Merritt and T. S. Sulkowski, Inhibition of aromatic L-amono acid decarboxylation by decaborane, *Biochem. Pharmaol.* **16**, 369–373 (1967).
34. U. S. von Euler and F. Lishajko, Catecholamine depletion and uptake in adrenergic nerve vesicles and in rabbit organs after decaborane, *Acta Physiol. Scand.* **65**, 324–330 (1965).
35. H. H. Reynolds and K. C. Back, Effect of decaborane injection on operant behavior of monkeys, *Toxicol. Appl. Pharmacol.* **8**, 197–209 (1966).
36. R. P. Hart, J. J. Silverman, L. K. Garrettson, C. Schulz, and R. M. Hamer, Neuropsychological function following mild exposure to pentaborane, *Am. J. Ind. Med.* **6**, 37–44 (1984).
37. C. D. Seaborn and F. H. Nielsen, Boron and silicon: effects on growth, plasma lipids, urinary cyclic amp and bone and brain mineral composition of male rats, *Env. Toxicol. Chem.* **13**, 941–947 (1994).
38. C. D. Hunt, Dietary boron modified the effects of magnesium and molybdenum on mineral metabolism in the cholecalciferol-deficient chick, *Biol. Trace Element Res.* **22**, 201–220 (1989).
39. C. D. Hunt and B. J. Stoecker, Deliberations and evaluations of the approaches, endpoints and paradigms for boron, chromium and fluoride dietary recommendations, *J. Nutr.* **126**, 2441S–2451S (1996).