Drug Development Research 2:481–488 (1982)

Electrophysiological Profile of Neurotropics (Hydergine, Piracetam, Pyritinol) in Organic Brain Disease in the Aged

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ABSTRACT

Zimmermann, P., E.W. Fünfgeld, R. Seidel, and W. Nischwitz: Electrophysiological profile of neurotropics (hydergine, piracetam, pyritinol) in organic brain disease in the aged. Drug Dev. Res. **2**:481–488, 1982.

The effects of neurotropics on brainstem and cortical neuronal activity were compared between three groups of patients suffering from chronic organic brain disease (arteriosclerotic or senile dementia). Hydergine (6–9 mg/day), piracetam (1,200 mg/day), or pyritinol (600 mg/day) were administered orally for 8 wk. EEG power spectral analysis, visual evoked potentials (VEP) and blink reflexes were performed after an initial wash-out period of 2 wk, 2 and 8 wk of neurotropic medication, and a final wash-out period of 2 wk. EEG power spectra following hydergine show a significant decrease in slow alpha activity (7.5—10 Hz) and after pyritinol in the slow theta range (3–5 Hz) in the occipital region. In the piracetam group the power of the fast theta (5–7.5 Hz) and slow alpha activity decrease in the occipital region of the dominant hemisphere. Only during pyritinol medication do these signs of cerebral activation correlate with an increase in the amplitude of P_{350} of VEP and of the R_2 component of the blink reflex.

Key words: **organic brain disease in the aged-EEG, VEP, blink reflex (cortical and brainstem effects), hydergine, piracetam, pyritinol**

INTRODUCTION

The effectiveness of neurotropics in the dementias of old age remains uncertain; this may be partially related to inadequate methodology. Therefore, this pilot study was initiated to evaluate

Received April 22, 1982; accepted June 12, 1982.

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0272-4391/82/0205-0481$02.50

the effects of three typical neurotropics—hydergine, piracetam, and pyritinol—with electrophysiological methods. These methods were chosen because quantitative EEG analysis has resulted in a reproducible *decrease* in theta activity and an *increase* in the dominant alpha frequency during hydergine [Kugler et al., 1978], piracetam [Bente et al., 1978], and pyritinol [Künkel and Westphal, 1970; Heinze and Künkel, 1979] treatment. We have added to the quantitative EEG analysis the flash-induced visual evoked potentials (VEP) and the blink reflex to get more information on drug-induced changes in the pattern of cortical and subcortical activity.

METHODS

The controlled study followed an open design with parallel groups. Twenty-eight patients received oral doses of hydergine (6–9 mg/day), piracetam (1.2 g/day), and pyritinol (600 mg/day) for 8 wk. The treatment was started with a wash-out period of neurotropic drugs for 1 wk. Measurements were made before drug administration and at 2, 4, and 8 wk after drug intake which was followed by a last measurement after a final wash-out period of 2 wk. Indices measured included EEG, VEP, and blink reflex.

SUBJECTS

Twenty-eight patients suffering from mild to moderate symptoms of organic brain syndrome of the aged (International Classification of Diseases, Numbers 290.0 and 290.4; Table 1) were included in this study. The degree of severity was rated as "mild" to "moderate" according to the Sandoz Clinical Assessment Geriatric Rating Scale (SCAG) [Shader et al., 1974].

The nature of the study, risks, and anticipated effects were described to each patient verbally, and they gave their consent prior to participation. All patients had their lunch 2 hr before their sessions. All sessions began between 2:00 and 3:00 P.M.

PROCEDURES

EEG

Electroencephalograms (silver disc electrodes; 10–20 International System) were recorded on stripchard and fed in the EEG-Trend Monitoring System (ETM 2002, Schwarzer). Electrode derivations were F3-A1 and 01-A1 (left side as dominant hemisphere in all patients). Throughout the recording period of 10 min the patients' eyes were closed and they were alerted if the technician noticed signs of drowsiness in the stripchard records. With the ETM 2002, Fourier algorithm is applied on 64 frequency values in the 0.25–16 frequency range of an EEG signal of an 8-second period. Then an averager calculates the mean of 30 periodograms. The total power is calculated in units of μV^2 (based on a 50-μV calibration signal). The relative power values, expressed as a percentage of the average total power, is calculated for the following bands: 0–3, 3–5, 5–7.5, 7.5–10, and 10–16 Hz.

VEP

The light-flash stimulation was applied synchronously with a frequency of 1 Hz, an intensity of 2.1×10^6 lux, and a flash duration of 10 μsec (Knott Strobotest). A sound-proved stroboscope

TABLE 1. Comparability

Drug dosage	Hydergine 6–9 mg/day	Piracetam 1.2 g/day	Pyritinol 600 mg/day
Age	67–84	63–89	63–86
Sex (F/M)	9/1	8/0	4/6
Diagnosis:			
Alzheimer	6	4	6
Multiinfarct	4	4	4

was positioned about 1 m from the root of the nose. The recordings were made unipolary with Ag-AgCl disc electrodes against the ear on the same side of the dominant hemisphere at position 01. The biosignals were amplified by a Disa-EMG amplifier, Type 15 C 01 (sensitivity 10 μV, upper limit frequency 0.1 kHz, lower limit frequency 2 Hz). Sixty-four signals and the calibration signal were averaged (Type 15 G 07 Disa-averager), this process being repeated three times per measurement time. The components of VEP were defined in accordance with Allison et al. [1977] and the number of evaluable components of the VEP was determined per measurement time and per patient. Therefore comparison was only possible between the component P_{350} at all the measured times. The maximum distance P_{350} from the baseline was measured manually.

Blink Reflex

The blink reflex was evoked by stimulation of the right supra orbital nerve via silver disc electrodes with single square pulses (duration: 0.5 msec, frequency: 0.1 Hz, intensity; 10–20 mA). The channels were fed through a Disa-EMG-amplifier, Type 15 C 01 upper limit frequency 1 kHz, lower limit frequency 200 Hz). This procedure was repeated ten times. The latencies and peak-to-peak amplitudes of the first component (R_1) and second component (R_2) were measured manually.

RESULTS

Unspecific influences on cerebral reactivity caused by repeated measurements during the 8 wk of drug treatment should be reduced to a minimum. Therefore comparisons of the data of EEG, VEP, and blink reflex were performed between the treatment period and after the final 2 wk of wash-out.

The EEG power spectral analysis showed an increase of theta activity in most of the patients after 2 wk of wash-out of hydergine and pyritinol (Fig. 1). In the slow and fast alpha band the wash-out of piracetam caused an increase of activity. In this spectral region the wash-out of hydergine was also accompanied by an increase in the relative power. No changes were seen in the higher frequency range with the three types of drugs.

The analysis of VEP showed a deterioration of the structure of the potentials after the wash-out of pyritinol—i.e., the number of identifiable peaks was reduced in comparison to the data after 8 wk of treatment. With one exception, the amplitude of P_{350} decreased after 2 wk of wash-out of pyritinol contrary to a small increase in the piracetam group (Fig. 2). No change was measurable in the VEP of the hydergine-treated patients. Figure 3 indicates that the amplitude of the R_2 component of the blink reflex is consistently reduced *only* after 2 wk of wash-out of pyritinol. No changes in latencies of both components and the amplitude of the R_1 component were measurable (Fig. 3).

DISCUSSION

The therapeutic effects of neurotropics in gerontopsychiatry can be only fully recognized after long-term application [Kugler et al., 1978]. On the other hand, the evaluation of drug action in long-term studies needs repeated measurements of outcome which usually increase unspecific drug effects. This holds not only for the application of behavioral scales and psychological tests but also for quantitative electrophysiological methods. Unspecific changes of electrical brain activity are described as a decrease in the amplitude of electrical signals after repetitive stimulation [Harris, 1943; Thompson and Spencer, 1966]. Therefore, it seems necessary to compare the results of electrophysiological measurements during long-term treatment with those after a *final* wash-out period; an increase in response indicates a real drug effect, whereas a decrease allows no differentiation between unspecific habituation and the reduction of a stimulating drug effect during wash-out. Using this type of analysis we were not only able to differentiate hydergine, piracetam, and pyritinol according to their effects on the EEG frequency pattern but also according to their specific action on cortical and subcortical structures (Fig. 4). In Figure 4 it is shown that hydergine and

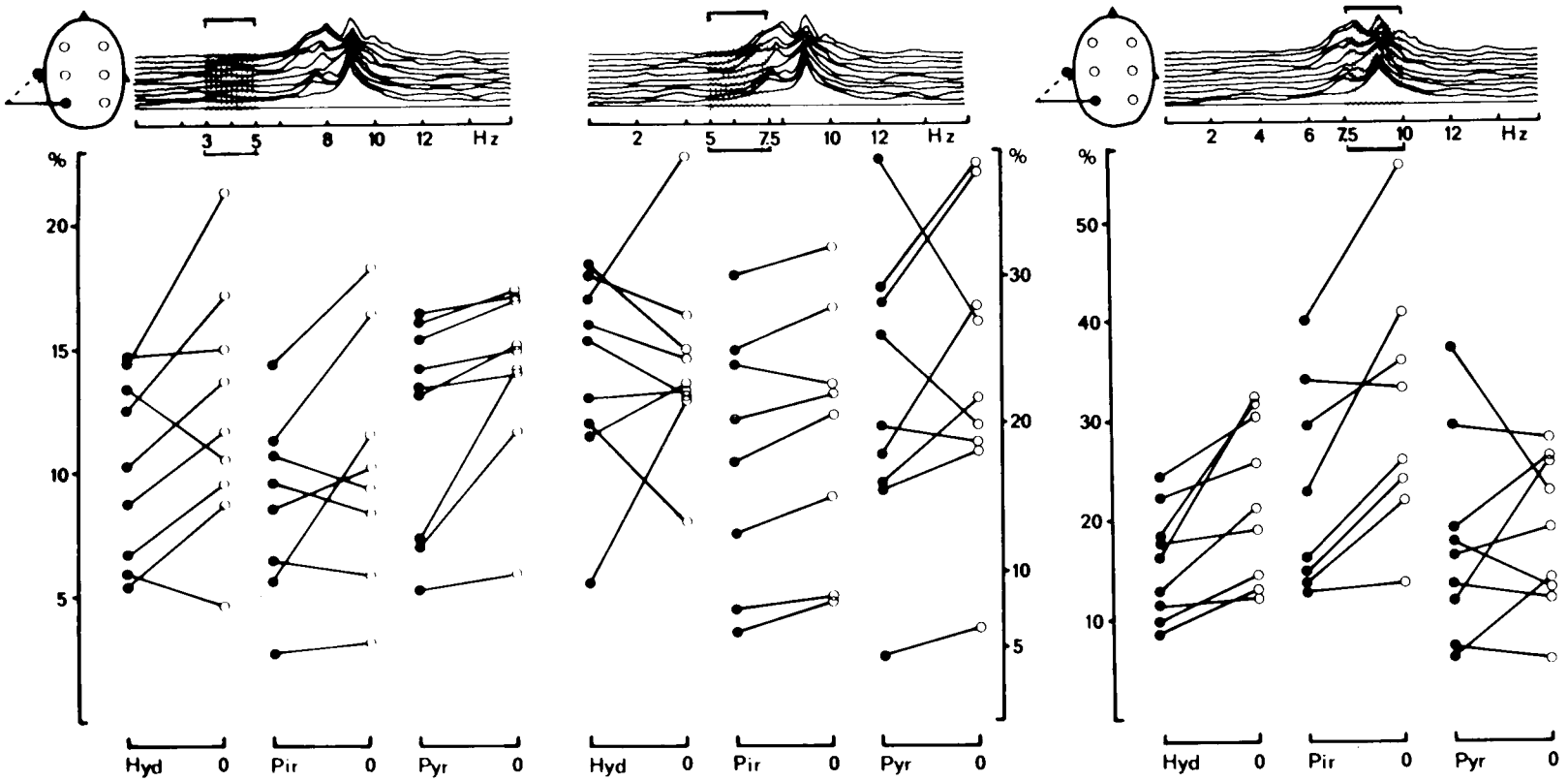

Fig. 1. Comparison of the power spectral analysis of EEG between 8 wk of treatment with hydergine (Hyd), piracetam, (Pir) and pyritinol (Pyr) with a final wash-out period (0) of 14 days.

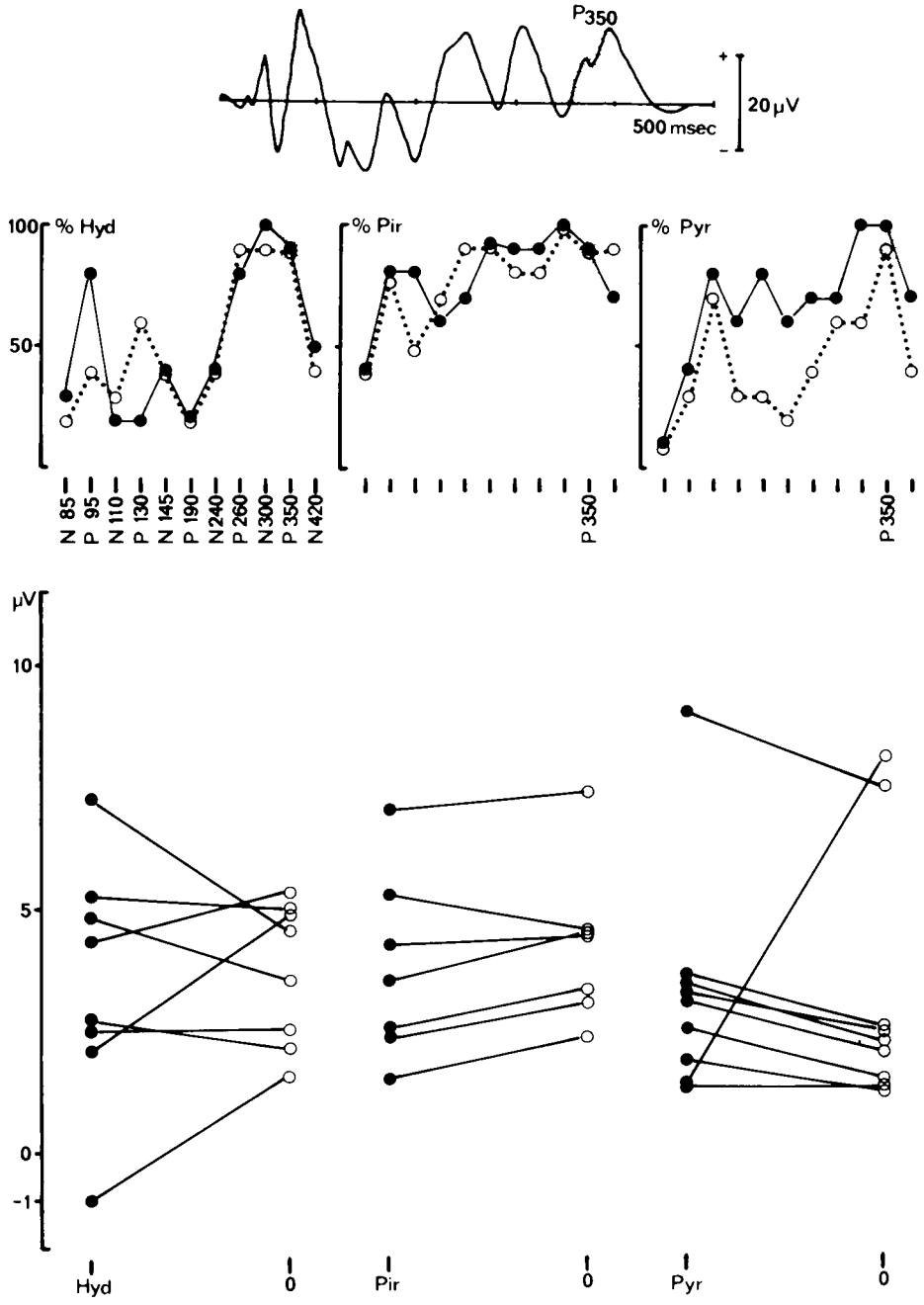

Fig. 2. Comparison of the change in VEP between 8 wk of treatment with hydergine (Hyd), piracetam (Pir), and pyritinol (Pyr) with a final wash-out period (0) of 14 days. Upper diagram: number of identified peaks (%). Filled circles, drug; open circles, wash out. Lower diagram: amplitude of P_{350} (μV).

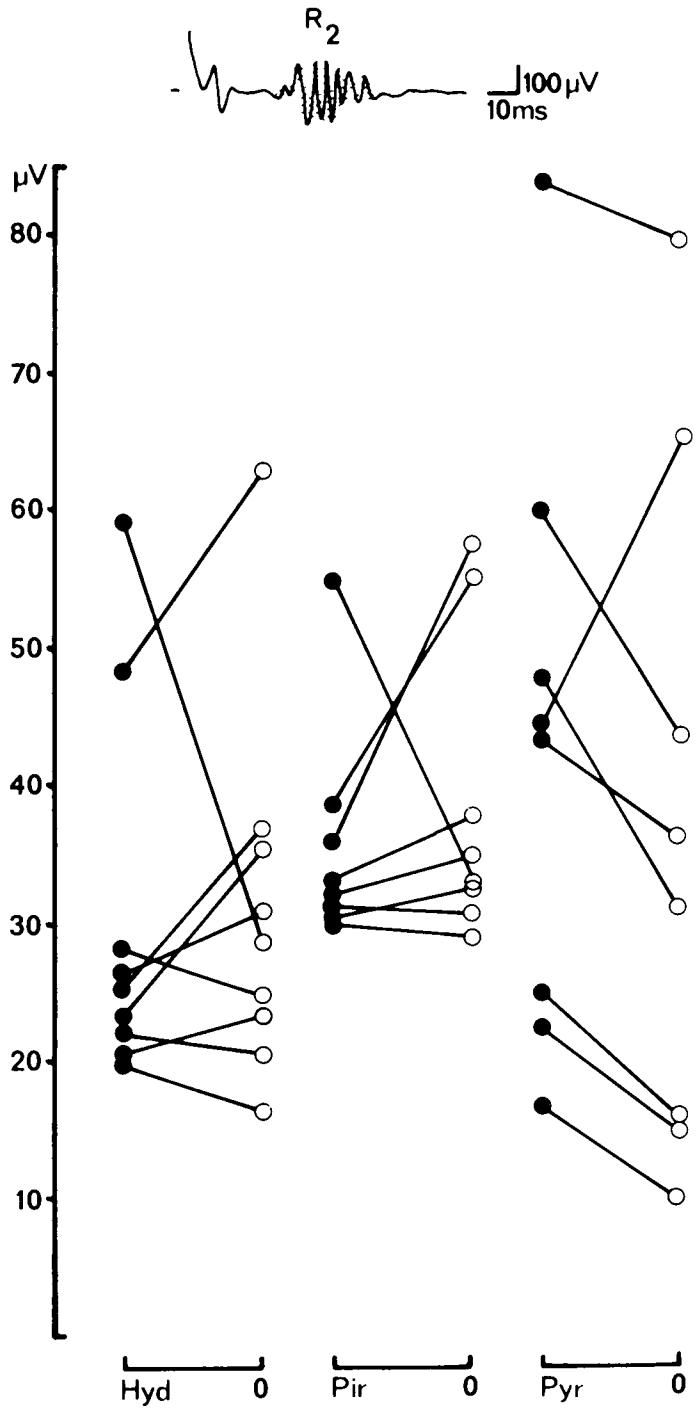

Fig. 3. Comparison of the change in the amplitude of R_2 component of the blink reflex (μV) between 8 wk of treatment with hydergine (Hyd), piracetam (Pir), and pyritinol (Pyr) with a final wash-out period (0) of 14 days.

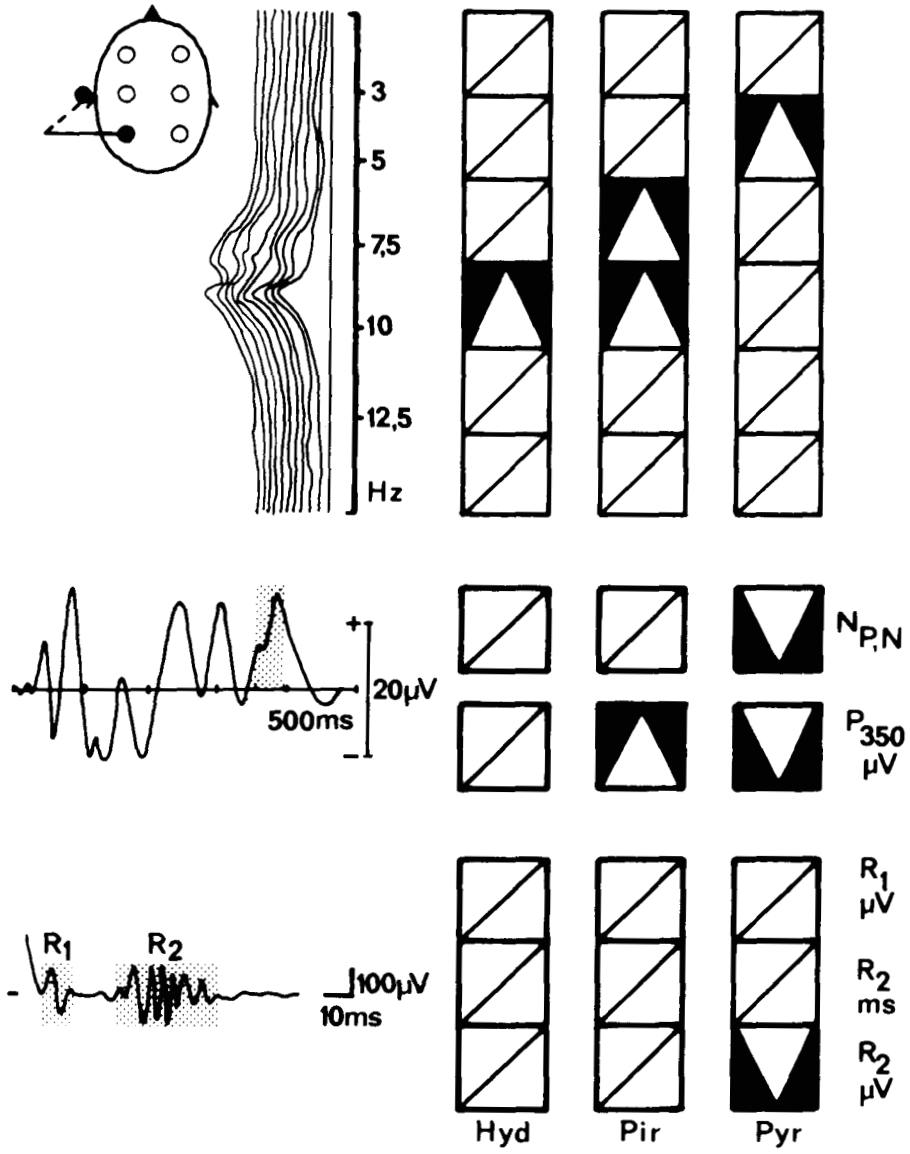

Fig. 4. Summary of the effects of hydergine (Hyd), piracetam (Pir), and pyritinol (Pyr) on EEG, VEP ($N^{P,N}$, number of identified peaks; P_{350} μV amplitude of P_{350} and blink reflex (R_1 μV, amplitude of R_1 component; R_2 ms, latency and R_2 μV, amplitude of R_2 component). Comparison between 8 wk of drug treatment with the final wash-out period of 14 days. △, increase; ▽, decrease in the parameter significantly changed.

piracetam possibly elicited their main effects on cortical structures, indicated by changes in the more unspecific EEG frequency pattern, whereas pyritinol has an effect on cortical electrical activity (changes of EEG frequency pattern and VEP) as well as on the brainstem (R_2 component of the blink reflex).

In conclusion, the results of this pilot study indicate that the simultaneous analysis of cortical and brainstem activity may help to differentiate the effects of neurotropics in gerontopsychiatry.

REFERENCES

Allison, T., Matsumiya, Y., Goff, G.D. and Goff, W.R.: The scalp topography of human visual evoked potentials. Electroenceph. Clin. Neurophysiol. **42:** 185–197, 1977.

Bente, D., Glatthaar, G., Ulrich, G. and Lewinsky, M.: Piracetam und Vigilanz. Elektroenzephalographische und klinische Ergebnisse einer Langzeitmedikation bei gerontopsychiatrischen Patienten. Arzneim. Forsch./ Drug. Res. **28:** 1529–1530, 1978.

Harris, J.D.: Habituatory response decrement in the intact organism. Psycholog. Bull. **40:** 385–422, 1943.

Heinze, H.-J. and Künkel, H.: The significance of personality traits in EEG evaluation of drug effects. Pharmakopsychiatr. Neuropsychopharmakol. **12:** 155–164, 1979.

Kugler, J., Oswald, W.D., Herzfeld, U., Seus, R., Pingel, J. and Welzel, D.: Langzeittherapie altersbedingter Insuffizienzerscheinungen des Gehirns. Dtsch. Med. Wochenschr. **103:** 456–462, 1978.

Künkel, H. and Westphal, M.: Quantitative EEG analysis of pyrithioxine action. Pharmakopsychiatr. Neuropsychopharmakol. **3:** 41–49, 1970.

Shader, R.I., Harmatz, J.S. and Salzman, C.: A new scale for clinical assessment in geriatric populations; Sandoz Clinical Assessment—Geriatric (SCAG). J. Am. Geriatr. Soc. **22:** 107–113, 1974.

Thompson, R.F. and Spencer, W.A.: Habituation: A model phenomenon for the study of neuronal substrates of behavior. Psycholog. Rev. **73:** 16–43, 1966.