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The acute and chronic administrations of Piracetam affect the movement-related brain macropotentials

Giuseppe Augusto Chiarenza, Cecilia Ragaini and Adriana Guareschi Cazzullo

Istituto di Neuropsichiatria Infantile, Milano (Italy)

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Neurophysiological and neurochemical studies have demonstrated that Piracetam improves learning and memory both in animals and humans. In recent years it has been shown that when a subject is engaged in a motor perceptual task, some psychomotor functions are correlated with a consistent pattern of brain electrical activity. Given the relationship between the movement-related brain macropotentials (MRBMs) and the cognitive processes associated with them, we considered the MRBMs particularly suitable for the neurophysiological assessment of the efficacy of Piracetam in man. The aim of this study was to test the acute and chronic effect of Piracetam administration on the MRBMs in normal children during the performance of a motor perceptual task. The design was a triple-blind study, during which the subjects took either placebo or Piracetam in random sequence, with a washout period of 3 weeks. The dose was 170 mg/kg for the acute treatment and 140 mg/kg/day for chronic treatment. No side-effects were reported by the children during or after acute or chronic treatment with Piracetam. There was no statistically significant difference between placebo or Piracetam treatment with regard to 'performance', which was already optimal at baseline, and to electromyographic activity. On the contrary, the MRBMs were significantly modified by treatment. In particular the Bereitschaftspotential was present as a positive shift during acute treatment with Piracetam and increased after chronic treatment. Skilled performance positivity (SPP) amplitudes were significantly increased and SPP latency reduced by chronic treatment with Piracetam. Piracetam appears to act on the catecholaminergic and cholinergic systems via an increase of the inhibitory hyperpolarizing processes.

INTRODUCTION

Piracetam (2-oxo-1-pyrrolidin-acetamide, P) is considered the first representative of a new class of compounds acting on the central nervous system, the nootropic drugs (Giurgea, 1973, 1978; Giurgea and Salama, 1977).

Neurophysiological and neurochemical studies have demonstrated that P improves learning and memory in both animals (Giurgea and Moura-vieff-Lesuisse, 1972; Buresowa and Bures, 1976; Bartus et al., 1981) and humans (Stegnick, 1972; Mindus et al., 1976; Bente et al., 1978) and has therapeutic effects in a wide variety of disorders: vertigo, disorders of perception, motor disturbances (Ekman, 1976; Giurgea, 1978). More recently, P has been reported to improve verbal memorizing and reading skills in disabled children (Wilsher et al., 1979, 1987).

In recent years it has been shown that when a subject is engaged in a motor perceptual task some psychomotor functions are correlated with a consistent pattern of brain electrical activity. The task consisted of self-paced button pressing, initiating with one hand an oscilloscope trace and terminating the sweep within a specific period of time with the other hand (Papakostopoulos, 1978a). Visual feedback was provided. For correct performance the task demands good two-handed coordination and memorization of the scores in

Correspondence: G.A. Chiarenza, Istituto di Neuropsichiatria Infantile, Via Besta n. 1, 20161 Milano, Italy.

order to improve performance. The brain electrical activity associated with this task consists of the movement-related brain macropotentials (MRBMs) (Papakostopoulos, 1978b).

The Bereitschaftspotential (BP, Kornhuber and Deecke, 1965) is a slow negative potential that precedes motor activity by about 800 ms with a greater amplitude in the fronto-central than the parietal regions. Its amplitude is also greater during skilled than unskilled conditions. It is absent in children under 6 and increases with age, reaching adult values in adolescence (Chiarenza et al., 1983). It has been shown that BP is absent in chronic schizophrenics (Chiarenza et al., 1985a), variously modified in those suffering from Parkinson's disease (Deecke et al., 1977; Papakostopoulos and Banerji, 1980; Papakostopoulos et al., 1985a), dyslexia and dysgraphia (Chiarenza et al., 1986), learning disorders (Chiarenza et al., 1982), Down's Syndrome (Chiarenza et al., 1985b) and by anticholinergic and neuroleptic drugs (Papakostopoulos et al., 1985b).

Motor cortex potential (MCP) is another negative potential that follows BP and peaks about 32 ms after the EMG peak. It is considered an index of reafferent activity (Papakostopoulos et al., 1975). The amplitude of MCP is greater during skilled than unskilled conditions. It is present in the precentral but absent from the parietal regions. It is present in both children and adults, its amplitude decreasing with senescence (Papakostopoulos and Banerji, 1980). It is reduced in chronic schizophrenics (Chiarenza et al., 1985a) and those with learning disorders (Chiarenza et al., 1982) and is not affected by the anticholinergic drugs (Papakostopoulos et al., 1985b).

N100 is a negative potential considered to be the response evoked by the oscilloscope trace that is partially suppressed in the central and precentral areas during movement. N100 has a latency of about 100 ms.

P200 is a positive potential following N100 with a latency of about 200 ms from the start of light stimulation.

Skilled performance positivity (SPP) has a latency of about 460 ms. It only appears in skilled conditions and in relation to the subject's knowledge and evaluation of the results of his performance (Papakostopoulos, 1980). It appears at about 9 years old in the frontocentral regions and increases in amplitude with age (Chiarenza et al., 1983). Its amplitude is greater in the parietal regions. It is absent in chronic schizophrenics (Chiarenza et al., 1985a) and reduced in amplitude in children with learning disorders (Chiarenza et al., 1982), with dyslexia-dysgraphia (Chiarenza et al., 1986) and with mental retardation (Chiarenza et al., 1985b).

Given the relationship between the MRBMs and the cognitive processes associated with them during the performance of this motor perceptual task, we considered the MRBMs particularly suitable for the neurophysiological assessment of the efficacy of P in man.

Before starting a study on a large group of learning-disabled children, we carried out a pilot-study on a group of normal subjects in order to evaluate the acute and chronic effect of P administration on the MRBMs during the performance of a motor perceptual task.

MATERIALS AND METHODS

Six volunteer normal right-handed boys aged 10–14 years (mean age 12.5 years) acted as subjects. Both parents and children were fully informed about the experimental procedure and written consent was obtained. In order to rule out possible psychological or psychiatric problems, the following tests were administered to the subjects: Weschler intelligence scale for children (WISC), Draw a man and a family test. Moreover, a family and a personal anamnesis were collected. All the subjects were not cigarette smokers and during the whole period of the research did not receive any additional medication or drink any caffeinated drinks.

All the subjects were of normal intelligence (mean I.Q. 122, S.D. $\pm$ 20) and free of neurological and psychiatric problems. A neurological examination was performed before and after the experiment that resulted in the normal range.

Experimental design

The study was triple-blind with crossover: neither parent/child, investigator, nor examining

staff knew the administration sequence, which was kept by the drug monitor until after the study was completed. All MRBM measurements were conducted without knowledge of the drugs assignment.

The experimental procedure was divided into 2 'phases' during which the 6 subjects were treated with a placebo (Pl) or in random sequence. The two 'phases' were separated by a 3-week wash-out period. Each 'phase' consisted of two sessions during which the MRBMs were recorded at 4 different 'times'. The first session involved recording before treatment (baseline = first time) and after acute treatment (acute = second time). The second session involved recording after 15 days' chronic treatment (chronic-third time) and after additional acute treatment (chronic-acute = fourth time).

All recordings were performed after 14.00 h, the subjects previously having been told to eat a light meal at least 2 h before recording time. We used oral doses of P (UCB Laboratories, Turin, Italy) amounting to 170 mg/kg for acute treatment and 140 mg/kg per day for chronic treatment. Due to the pharmacokinetics of P (Gobert and Baltès, 1976), the motor perceptual task was performed one hour after the administration of the compound, and 4 blocks of 25 artefact-free trials, each of them recorded every 15 min, were collected.

The entire experimental procedure lasted about $3\frac{1}{2}$ h: $\frac{1}{2}$ h for the electrode fitting, 1-h interval between the two recording session of 1 h each.

The motor perceptual task (MPT)

The subject sat in a comfortable chair facing the 10-cm screen of a cathode ray oscilloscope (CRO) at a distance of 70 cm. In each hand he held a button fitted with a special hand grip. Button travel was 5 mm.

The task consisted of initiating a single sweep of the oscilloscope trace by a thumb press of a button held in the left hand, and of stopping the sweep within a defined central area of the CRO by a thumb-press of a button held in the right hand. The subject's goal was to stop the sweep within this area (i.e. within 40–60 ms) after its initiation. The velocity of the trace was 10 ms/cm. The interval between the left and right thumb-presses was then computed and its value defined as 'performance time'. The distance from the ideal target interval (40–60 ms) was also calculated and referred to as 'performance shift'. The number of targets scored, that is, when the subject hit the central area (40–60 ms), was also calculated and referred to as 'target performance'.

Recording procedure and identification of the MRBMs

Ag/AgCl EEG electrodes were placed at Fpz, Fz, Cz, Pz, P3, P4. Also left and right precentral electrodes (left precentral = LPC, right precentral = RPC) were located on each hemisphere 2 cm anterior to a point 5 cm from the midline on a line extending from 2 cm behind the vertex to each auditory meatus. Each electrode was referred to linked mastoid electrodes. Bipolar electro-oculogram was recorded from over and below the right eye to monitor blinking and eye movements. Surface EMG was recorded from the left and right forearm flexor muscles. The impedance of the electrodes was less than 3 kΩ. The time constant and high frequency response (-6 dB) was 4.5 s and 70 Hz for the EEG, and 0.03 s and 700 Hz for the EMG respectively. The EEGs and EMGs were stored on FM magnetic tape for off-line analysis. Data acquisition started with sampling a ± 25 μV square wave for calibration on each channel. A trigger pulse generated by the press of the left-hand button, began the 3.2-s EEG epoch which was sampled at a rate of 250 Hz. Of this epoch, 2.2 s preceded the trigger pulse and 1 s immediately followed it. The average of the first second was used to establish the baseline.

The amplitude of the EMG prior to movement and the EMG rise time of the rectified surface left and right electromyograms were calculated after locating the EMG onset and the EMG peak. The following potentials were measured: area and BP amplitude, MCP amplitude, SPP latency and amplitude. The area of BP was measured from the BP onset to the point corresponding to that of the EMG onset. The mean amplitudes of BP and MCP were computed for 200-ms periods, immediately preceding the left-EMG onset, BP, and immediately following it, MCP. The MCP value

was measured as the difference between the BP and MCP values measured from the baseline. SPP amplitudes were taken as average values over 200 ms centred around the main positive (SPP) peak value in the latency band between 350 and 650 ms from the trigger. SPP was measured against the baseline and the preceding peak (peak-to-peak measurement). SPP latencies were measured from the trigger pulse. Since each of the 6 subjects performed 8 tasks making a total of 48 MPTs recorded and each SPT consists of 4 blocks of 25 trials each, a total of 192 blocks were measured.

Undoubtedly the small number of subjects precludes a complete design of variance analysis but nevertheless ANOVA was used to assess the effect of phases, times, treatment, subjects and relative interactions. Naturally, there were a large number of statistical comparisons and some of these could be significant by chance alone. Of the ANOVA we report, the treatment effect and the treatment × time interactions. Furthermore, Student's *t*-test for correlated data and confidence limits of 95% and 99% were employed in order to obtain a direct comparison between 'times' within the framework of each individual treatment and between treatments in the same 'times'.

RESULTS

No clinical side-effects were observed in the children during and after acute and chronic treatment with P.

Performance

The children treated with P improved their performance in terms of performance time even though the time differences were not statistically significant. A direct comparison between performance time, performance shift and target performance in relation to the different treatment showed no significant differences (Table I).

Electromyograms

Student's *t*-test indicated that the rise-time and amplitude of the left and right EMG was not significantly influenced by treatments.

TABLE I

Means and S.D. of the performance of the subjects during treatment with Piracetam (P) and placebo (Pl)

	Performance time (ms)	*Performance shift (ms)*	*% Target performance*
Base			
P	68.95 ±34.79	16.66 ±27.67	38.83 ±46.99
Pl	64.64 ±33.65	16.49 ±24.55	33.66 ±42.53
Acute			
P	65.70 ±32.89	16.83 ±25.04	33.33 ±47.17
Pl	63.48 ±36.69	18.45 ±27.02	32.60 ±46.91
Chronic			
P	69.43 ±41.47	20.72 ±34.18	28.52 ±45.19
Pl	66.73 ±34.68	16.94 ±23.15	28.66 ±45.25
Chronic + acute			
P	63.89 ±31.77	16.30 ±22.98	31.38 ±46.44
Pl	61.61 ±48.58	17.69 ±41.80	32.83 ±46.99

MRBMs

Consistent variations were observed on the MRBMs after P treatment. Fig. 1 shows the difference between all P and all Pl treatments. P significantly reduces BP and MCP amplitude and increases SPP amplitude. The effects on BP arose immediately after acute treatment, those on MCP and SPP were more consistent after chronic and chronic-acute treatment.

BP

Variance analysis revealed a significant decrease in BP amplitude on the frontal, central and left precentral areas after P treatment. The treatment × time interaction was significant on all recording sites (Table II). The acute administration of P significantly reduced the BP amplitude in comparison to the baseline in frontal, precentral and parietal regions. A significant positive BP in respect to baseline was recorded after chronic P treatment on all areas except Fpz. Chronic-acute treatment with P further increased the positive BP

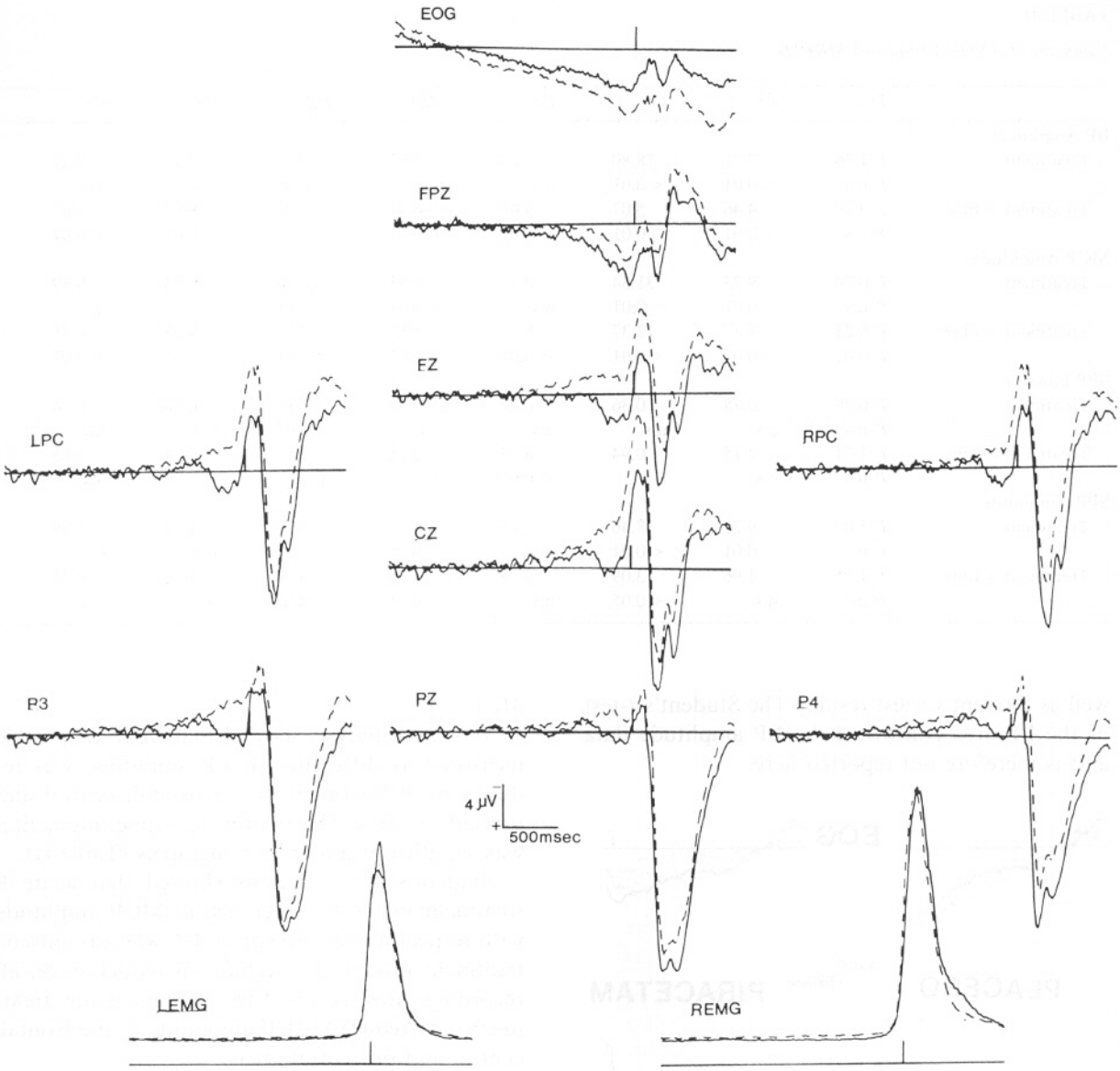

Fig. 1. Grand average of MRBMs and EMGs of all P (unbroken line)–Pl (broken line) treatments. The vertical bar indicates the instance of the computer trigger.

in all areas. In contrast, the comparison between the 3 administrations of placebo vis-à-vis the baseline showed no significant difference in BP amplitude except for LPC and Cz for acute treatment and P3 and P4 during chronic-acute administration. Fig. 2 shows the effect of P and Pl treatment at the different 'times' on the left precentral region. Comparison of the acute Pl–P treatments showed that P significantly decreased the BP amplitude only at Pz and P3. Chronic and chronic-acute treatment with P had a similar effect. BP had positive values in all recorded locations and values were significantly different from those produced by placebo treatment. Table III shows the mean values and S.D.s of BP amplitude during the various times of P and P1 treatments as

TABLE II

Summary of ANOVA results of MRBMs

		Fpz	*Fz*	*Cz*	*Pz*	*RPC*	*LPC*	*P4*	*P3*
BP Amplitude									
Treatment	*F* 1,36	7.71	18.80	0.29	1.91	5.32	0.17	0.27
	P n.s.	< 0.01	< 0.01	n.s.	n.s.	< 0.05	n.s.	n.s.
Treatment × time	*F* 3.29	4.46	5.07	9.05	6.81	8.46	8.03	8.62
	P n.s.	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
MCP Amplitude									
Treatment	*F* 0.74	9.23	31.84	0.38	11.58	16.50	0.84	0.89
	P n.s.	< 0.01	< 0.01	n.s.	< 0.01	< 0.01	n.s.	n.s.
Treatment × time	*F* 6.21	9.77	12.37	5.25	15.62	19.53	9.58	6.55
	P 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
SPP Latency									
Treatment	*F* 0.29	0.78	0.36	0.29	0.89	5.88	0.86	0.16
	P n.s.	n.s.	n.s.	n.s.	n.s.	0.05	n.s.	n.s.
Treatment × time	*F* 1.71	2.15	0.94	4.22	1.11	1.57	2.51	2.63
	P n.s.	n.s.	n.s.	< 0.01	n.s.	n.s.	n.s.	n.s.
SPP Amplitude									
Treatment	*F* 1.08	9.28	8.46	2.03	4.79	3.74	1.51	1.99
	P n.s.	< 0.01	< 0.01	n.s.	< 0.05	n.s.	n.s.	n.s.
Treatment × time	*F* 1.05	1.96	3.09	1.38	4.19	3.56	1.30	0.56
	P n.s.	n.s.	< 0.05	n.s.	< 0.01	< 0.05	n.s.	n.s.

well as Student's *t*-test results. The Student's *t*-test of the BP area confirmed the BP amplitude data and is therefore not reported here.

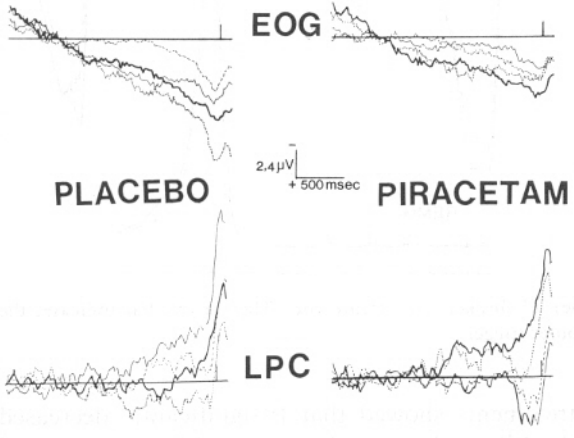

Fig. 2. Grand average of BP amplitude produced by P–Pl treatment at the various 'times' (unbroken line, baseline; dotted line, acute; thick unbroken line, chronic; broken line, chronic + acute). Note the progressive decrease in BP amplitude with the various treatments. It becomes positive after chronic treatment and the positivity increases further with chronic + acute treatment. The vertical bar indicates the instance of the computer trigger. The traces represent the first 2312 ms.

MCP

Variance analysis showed that MCP amplitude measured as difference in BP amplitude was reduced by P treatment in the frontal, central and precentral areas. The treatment × time interaction was significant in all recording areas (Table II).

Student's *t*-test analysis showed that acute P treatment made no difference to MCP amplitude with respect to base except on P3, whereas chronic treatment produced a significant reduction on all recording sites except FPz. Chronic-acute treatment only reduced MCP amplitude in the frontal, central and precentral areas.

Pl treatment produced no variations at the different 'times' except for a decrease in MCP amplitude under acute treatment in Fz and an increase in MCP amplitude under chronic-acute treatment on all recording areas.

Direct comparison between P and Pl at the various 'times' showed a significant decrease in MCP amplitude in Fz, Cz, RPC, LPC, P3 and P4 under chronic treatment and on all recording sites under chronic-acute treatment. Table IV shows mean and S.D. MCP amplitudes during the vari-

ous periods of P and Pl treatment as well as the Student *t*-test results.

SPP

Variance analysis showed that SPP latency was not significantly changed by treatment except on LPC. The treatment × time interaction was significant on Pz (Table II).

Student's *t*-test analysis showed that chronic administration of P reduces significantly SPP latency on P4 ($t = 3{,}14$, $P < 0.01$). Acute placebo treatment produced a significant increase in SPP latency on Pz and P4 in respect to baseline (Pz: $t = 2{,}64$, $P < 0.02$; P4: $t = 2{,}66$, $P < 0.02$).

Variance analysis showed that SPP amplitude was significantly increased by P treatment on Fz, Cz and RPC. The treatment × time interaction was significant on the central and precentral areas (Table II).

Acute Pl treatment increased significantly in respect to baseline the amplitude of SPP in all areas. This effect remained only on Pz and P3 after chronic-acute treatment. Acute treatment with P with respect to baseline produced an increase in SPP amplitude on all brain areas and a significant one on Cz, P4, P3. Unlike Pl, P maintained this effect during chronic and chronic-acute treatment with the difference becoming significant

TABLE III

Means and S.D. of BP amplitude during Placebo (Pl) and Piracetam (P) treatment

In this table and in the following ones, T1 represents the result of direct comparison between the various treatments, each one on its own base; the T2 value represents the comparison between treatments at the same 'time'.

		Fpz	*Fz*	*Cz*	*Pz*	*RPC*	*LPC*	*P4*	*P3*
Base									
P	$\bar{x}$	2.05	−2.29	−3.84	−4.11	−4.09	−4.49	−4.89	−5.84
	S.D.	±4.52	±5.16	±8.92	±4.73	±4.30	±4.23	±4.96	±5.24
Pl	$\bar{x}$	23.17	−1.24	−5.09	−0.14	−1.57	−2.55	−0.74	−1.33
	S.D.	±6.25	±6.23	±9.16	±5.91	±7.29	±7.10	±6.36	±6.06
Acute									
P	$\bar{x}$	2.69	0.83	−2.07	−0.70	−1.37	−1.15	−1.71	−0.96
	S.D.	±4.23	±5.17	±6.23	±4.09	±4.98	±6.59	±5.17	±4.87
	T1	0.48	2.31 *	0.91	2.98 ***	2.71 **	2.66 **	2.99 ***	4.40 ***
	T2	0.31	0.43	0.46	2.08 *	0.49	0.20	1.81	2.47 *
Pl	$\bar{x}$	3.18	0.85	−2.15	0.13	0.37	0.40	−0.66	−0.66
	S.D.	5.43	8.70	11.82	6.80	9.48	9.42	6.59	6.99
	T1	0.01	1.62	2.15 *	0.24	1.64	2.59 **	0.07	0.59
Chronic									
P	$\bar{x}$	3.97	2.62	0.94	1.52	2.30	2.00	1.26	0.78
	S.D.	±3.73	±4.51	±5.94	±4.35	±4.42	±4.42	±4.26	±4.29
	T1	1.60	3.70 ***	2.61 **	4.35 ***	5.87 ***	6.42 ***	5.24 ***	5.03 ***
	T2	1.00	2.47 *	1.57	2.97 ***	3.36 ***	6.42 ***	3.91 ***	3.93 ***
Pl	$\bar{x}$	3.51	−0.97	−3.64	0.12	−0.46	−1.06	−0.87	−0.63
	S.D.	±4.32	±7.65	±10.38	±4.80	±8.96	±8.24	±5.50	±6.04
	T1	0.29	0.30	1.19	0.20	0.95	1.39	0.12	0.60
Chronic + acute									
P	$\bar{x}$	5.11	3.17	1.65	1.43	2.15	3.23	−0.55	0.50
	S.D.	±4.32	±4.11	±5.34	±5.03	±3.24	±3.85	±5.49	±5.27
	T1	2.02	4.34 ***	3.61 ***	4.52 ***	6.33 ***	8.07 ***	3.57 ***	4.81 ***
	T2	2.48 *	2.85 ***	3.20 ***	3.74 ***	3.89 ***	5.46 ***	3.16 ***	4.52 ***
Pl	$\bar{x}$	0.85	−2.17	−6.64	−3.32	−3.40	−4.23	−4.68	−4.29
	S.D.	±86.07	±7.37	±8.03	±4.87	±7.39	±7.63	±6.14	±5.11
	T1	1.46	0.61	0.96	2.02	1.10	1.24	2.32 *	2.30 *

* $P < 0.05$; ** $P < 0.02$; *** $P < 0.01$.

TABLE IV

Means and S.D. of MCP amplitude during Placebo (Pl) and Piracetam (P) treatment

		Fpz	*Fz*	*Cz*	*Pz*	*RPC*	*LPC*	*P4*	*P3*
Base									
P	$\bar{x}$	0.59	−5.71	−8.98	−2.93	−7.44	−7.79	−4.13	−5.71
	S.D.	±4.72	±6.04	±12.48	±8.88	±6.82	±8.10	±7.27	±9.36
Pl	$\bar{x}$	2.91	−4.40	−10.07	0.13	−5.56	−6.11	−0.67	−1.92
	S.D.	±5.60	±6.90	±13.08	±8.24	±9.84	±9.11	±7.84	±7.66
Acute									
P	$\bar{x}$	1.97	−3.60	−8.95	−2.30	−6.49	−6.46	−3.41	−2.13
	S.D.	±4.53	±5.55	±10.50	±9.74	±7.74	±7.93	±7.85	±6.72
	T1	0.96	1.55	0.02	0.53	0.81	1.05	0.78	2.32 *
	T2	0.53	0.25	1.07	1.07	0.44	0.45	0.88	2.16 *
Pl	$\bar{x}$	3.26	−1.80	−7.88	−1.10	−3.86	−3.89	−1.51	−2.72
	S.D.	±6.13	±8.30	±13.47	±7.98	±9.37	±10.89	±7.84	±8.40
	T1	0.29	2.72 **	1.65	0.83	1.51	1.83	0.62	0.68
Chronic									
P	$\bar{x}$	2.38	−1.13	−3.74	1.09	−0.42	−1.52	1.04	−1.50
	S.D.	±3.87	±4.70	±9.08	±9.02	±6.64	±7.00	±8.89	±9.95
	T1	1.16	2.78 **	2.76 **	2.65 **	5.45 ***	4.62 ***	4.60 ***	2.93 ***
	T2	1.58	2.80 **	2.50 **	1.93	3.94 ***	3.42 ***	3.77 ***	2.32 *
Pl	$\bar{x}$	2.31	−5.28	−10.48	−0.37	−5.77	−6.46	−1.56	−2.40
	S.D.	±5.36	±9.20	±13.87	±6.40	±10.82	±10.54	±7.56	±8.35
	T1	0.46	0.89	0.36	0.30	0.20	0.30	0.67	0.40
Chronic + acute									
P	$\bar{x}$	4.52	0.58	−3.24	−0.90	0.03	−1.64	−2.91	0.50
	S.D.	±7.78	±6.45	±11.45	±11.21	±7.33	±7.55	±9.99	±11.30
	T1	1.78	7.49 ***	2.84 ***	1.86	4.87 ***	5.29 ***	2.00	1.89
	T2	3.57 ***	3.88 ***	3.83 ***	3.35 ***	4.14 ***	5.29 ***	3.73 ***	5.02 ***
Pl	$\bar{x}$	1.64	−7.66	−14.87	−4.69	−9.63	−10.80	−6.81	−7.81
	S.D.	±6.61	±8.53	±11.51	±6.10	±8.43	±10.14	±7.76	±7.89
	T1	2.56 **	2.07 *	2.52 **	2.84 ***	2.18 *	3.19 ***	3.56 ***	4.96 ***

* $P < 0.05$; ** $P < 0.02$; *** $P < 0.01$.

on the frontal and precentral regions as well. Fig. 3 shows the effect of P and Pl treatments on SPP at various 'times' on the left precentral area of a single subject.

Direct comparison between P and Pl at the various 'times' showed a significant increase in SPP amplitude after chronic administration of P in the frontal and right precentral areas. Table V shows the mean and S.D. SPP amplitude during the various periods of P and Pl treatment as well as the Student *t*-test results.

DISCUSSION

All the children were motivated in taking part in the experiment. Their interest was expressed by their efforts to get a good 'target performance' score and if possible to improve on their last score. In fact, right from the first session the children got very good scores, similar to those obtained by adults (Papakostopoulos, 1978a). The particular nature of the task required excellent bimanual coordination in order to estimate the correct time interval (40–60 ms) that had to be programmed in advance. As a result even adults after a period of training do not obtain a 'target performance' score of over 40%. This explains why the children's 'target performance' did not significantly improve after P intake since they were doing their best right from the start. This also explains why the direct comparison between P and Pl treatments was not statistically significant.

TABLE V

Means and S.D. of SPP amplitude during Placebo (Pl) and Piracetam (P) treatment

		Fz	*Cz*	*Pz*	*RPC*	*LPC*	*P4*	*P3*
Base								
P	$\bar{x}$	3.41	5.23	19.83	4.96	5.80	11.33	15.06
	S.D.	±6.49	±8.86	±12.82	±4.03	±5.14	±10.68	±8.92
Pl	$\bar{x}$	1.37	2.42	16.60	4.27	4.50	10.46	13.13
	S.D.	±8.14	±11.53	±12.90	±9.51	±6.82	±14.03	±9.52
Acute								
P	$\bar{x}$	5.30	8.54	22.36	7.02	6.71	16.52	21.51
	S.D.	±8.69	±11.65	±16.05	±10.34	±7.97	±16.35	+11.68
	T1	0.46	2.96 ***	1.06	1.88	1.25	2.35 *	3.30 **
	T2	0.75	2.00	1.42	1.19	0.05	1.13	0.06
Pl	$\bar{x}$	5.73	10.85	23.75	10.00	9.75	18.33	18.66
	S.D.	±9.32	±12.22	±12.07	±8.88	±9.58	±11.31	±9.85
	T1	2.72 **	3.72 ***	3.27 ***	4.06 ***	3.41 ***	3.87 ***	2.88 ***
Chronic								
P	$\bar{x}$	7.89	11.80	21.98	11.26	10.52	16.03	17.25
	S.D.	±9.01	±11.54	±13.73	±10.63	±9.36	±13.03	±10.48
	T1	2.19 *	3.32 ***	0.83	3.41 ***	2.75 **	2.09 *	1.47
	T2	2.74 **	0.91	0.76	3.00 ***	1.39	0.40	0.54
Pl	$\bar{x}$	2.30	6.41	21.72	6.24	6.36	13.99	17.44
	S.D.	±7.73	±11.16	±11.25	±11.30	±8.56	±10.18	±10.63
	T1	0.29	1.79	2.22 *	1.46	1.15	2.02	1.47 **
Chronic + acute								
P	$\bar{x}$	7.17	9.58	22.45	11.19	10.15	14.92	17.92
	S.D.	±10.43	±14.82	±15.48	±12.01	±9.81	±16.05	±10.36
	T1	2.91 **	2.63 **	1.21	3.01 ***	3.33 ***	2.26 *	2.93 ***
	T2	1.08	0.80	0.18	1.75	1.55	1.29	0.97
Pl	$\bar{x}$	1.42	4.51	18.33	4.69	5.31	11.03	17.01
	S.D.	±8.01	±9.12	±9.38	±7.74	±5.89	±8.04	±8.12
	T1	0.09	1.12	1.15	0.06	0.93	0.29	2.21 *

* $P < 0.05$; ** $P < 0.02$; *** $P < 0.01$.

Unlike other classical CNS stimulants, P appeared to have no effect on muscle activity either as EMG rise-time or as baseline EMG amplitude. As far as the MRBMs are concerned, P produces significant changes in BP, MCP and SPP.

The neurochemical mechanisms underlying the genesis of the slow potentials are still not perfectly clear and recently interpretative models have been put forward by Marczynski (1978) and Timsit-Berthier (1981). Nor has the action mechanism of P been thoroughly clarified. Hence any interpretation of the modifications to the MRBMs caused by P can only be provisional and based on currently available knowledge. Most of the subjects interviewed, reported feeling more awake, more relaxed and efficient after P intake when compared to placebo.

Experiments on animals have shown that acute administration of different nootropic drugs interferes with the higher telencephalic integrative activity by increasing acetylcholine (Ach) turnover (Wurtman et al., 1980; Pepeu and Espignoli, 1986). This interference is direct and selective, taking the form of control over the normal functioning of the sensory gating system and the mechanisms of selective attention (Giurgea and Salama, 1977). Cholinergic mechanisms have been held responsible for the genesis of slow negative and positive

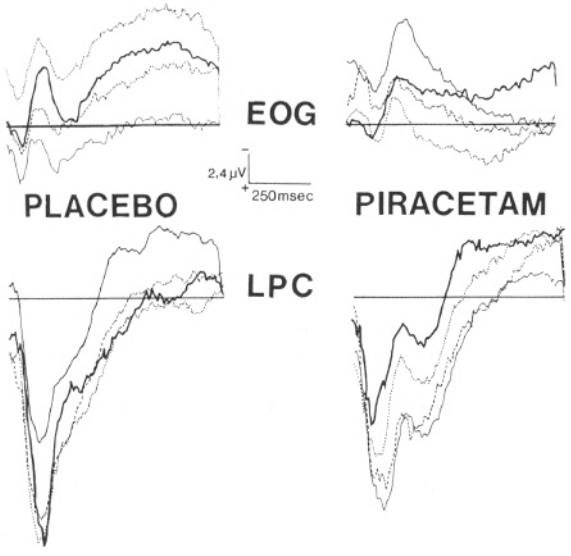

Fig. 3. SPP amplitude of P–Pl treatment at various 'times' (unbroken line, baseline; dotted line, acute; thick unbroken line, chronic; broken line, chronic + acute) in one subject. Note the appearance of SPP with acute P treatment and its increased amplitude with chronic and chronic + acute treatments compared to Pl treatment. The traces represent the last 912 ms.

potentials (Marczynski, 1978). The neurophysiological data show that BP amplitude is reduced by acute doses of P and becomes positive with chronic treatment. The reduction in BP amplitude could be interpreted as a possible expression of an inhibitory hyperpolarizing effect on the cortical motoneurons. Both excitatory and inhibitory effects of acetylcholine on the cortical neurons have been observed (Phillis, 1970).

MCP is considered an indicator of reafferent activity coming from the receptors of the skin and muscles and is a characteristic phenomenon in the central and precentral regions (Papakostopoulos et al., 1975). The reduction in MCP amplitude in the frontal and precentral regions after P treatment might be explained as an increase in the inhibitory action on the sensory gating systems. Unlike the effect on BP, this has only been observed after chronic treatment with P. It also confirms the view that the neuronal generators of MCP are different from those of BP (Chiarenza et al., 1983; Papakostopoulos, 1980).

The appearance of surface positive potentials, such as reward contingent positive variation in animals and skilled performance positivity in humans, immediately after a motor performance, is probably due to a suppression of the ascending reticular activating catecholaminergic system that allows recurrent inhibitory interneurons to function (Marczynski, 1978). On the basis of anatomical and electrophysiological evidence, it seems likely that an increase of Ach levels can reduce catecholaminergic activity leading to cholinergic hyperactivity (Marczynski, 1978).

The increase in SPP after chronic P treatment might be explained as a hyperactivity of the inhibitory interneurons. This activity is related to those neuronal systems which underlie a related pattern able to acquire and use experiences from the outcome of previous actions.

The SPP latency reduction is evident after chronic treatment. This may be considered a sign of increased ability in processing task information. The placebo effect on SPP after acute treatment disappears after subsequent administrations. The same effect on the latency of N100 has been described recently in dyslexic children (Conners et al., 1987).

Psychological studies have shown that effective reading comprehension (Tallal et al., 1984), verbal learning and verbal conceptualizing ability (Wilsher et al., 1979, 1987) are improved in dyslexic children after P treatment.

In conclusion, P acts mainly on the potentials linked to preparation processes (BP), the processing of sensory information (MCP), the learning and memorizing of results (SPP). The next step will be to test children with specific learning disorders who have been found in earlier studies to be deficient in the above-mentioned processes (Chiarenza et al., 1982, 1986).

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REFERENCES

Bartus, B.T., Dean, R., Sherman, K.A., Friedman, E. and Beer, B. (1981) Profound effect of combining choline and Piracetam on memory enhancement and cholinergic function on aged rats. *Neurobiology of Aging*, 2: 105–111.

Bente, D., Glatthaar, G. and Lewingsky, M. (1979) Piracetam and vigilance: electroencephalographic and clinical results of long-term therapy in gerontopsychiatric patients. *Arzneim. Forsch.*, 28: 1529–1531.

Buresova, O. and Bures, J. (1976) Piracetam-induced facilitation of interhemispheric transfer of visual information in rat. *Psychopharmacology*, 46: 93–102.

Chiarenza, G.A., Papakostopoulos, D., Guareschi Cazzullo, A., Giordana, F. and Giammari Aldè, G. (1982) Movement-related brain macropotentials during skilled performance task in children with learning disabilities. In G.A. Chiarenza and D. Papakostopoulos, (Eds.), *Clinical Application of Cerebral Evoked Potentials in Pediatric Medicine*, Excerpta Medica, Amsterdam, pp. 259–292.

Chiarenza, G.A., Papakostopoulos, D., Giordana, F. and Guareschi Cazzullo, A. (1983) Movement-related brain macropotentials during skilled performances. A developmental study. *Electroencephalogr. Clin. Neurophysiol.*, 56: 373–383.

Chiarenza, G.A., Papakostopoulos, D., Dini, M. and Cazzullo, C.L. (1985a) Neurophysiological correlates of psychomotor activity in chronic schizophrenics. *Electroencephalogr. Clin. Neurophysiol.*, 61: 218–228.

Chiarenza, G.A., Papakostopoulos, D., Grioni, A., Tengattini, M.B., Ganguzza, D., Mascellani, P., Cazzullo, A.G. and Cazzullo, C.L. (1985b) Neurophysiological evaluation of motor-perceptual function in Down's syndrome subjects by movement-related brain macropotentials. In C. Morocutti and P.A. Rizzo (Eds.), *Evoked Potentials. Neurophysiological and Clinical Aspects*. Elsevier, Amsterdam, pp. 409–412.

Chiarenza, G.A., Papakostopoulos, D., Grioni, A., Tengattini, M., Mascellani, P. and Guareschi Cazzullo, A. (1986) Movement-related brain macropotentials during a motor perceptual task in dyslexic-dysgraphic children. In W.C. McCallum, R. Zappoli and F. Denoth (Eds.), *Cerebral Psychophysiology: Studies in Event-related Potentials*, Elsevier, Amsterdam, pp. 489–491.

Conners, C.K., Reader, M., Reiss, A., Caldwell, J., Caldwell, L., Adesman, A., Mayer, L., Berg, M., Clymer, R. and Erwin, R. (1987) The effects of piracetam upon visual event-related potentials in dyslexic children. *Psychophysiology*, 24, 5: 513–521.

Deecke, L., Englitz, H.G., Kornhuber, H.H. and Schmitt, G. (1977) Cerebral potentials preceding voluntary movement in patients with bilateral or unilateral Parkinson akinesia. In J.E. Desmedt (Ed.), *Attention, Voluntary Contraction and Event-related Cerebral Potentials, Prog. Clin. Neurophysiol. Vol. 1,* Karger, Basel, pp. 151–163.

Eckman, F. (1976) Klinische Untersuchungen mit Piracetam, *Munch. Med. Wschr.*, 118: 957–958.

Giurgea, C. (1973) The nootropic approach to the pharmacology of the integrative activity of the brain, *Conditional Reflex*, 8: 108–115.

Giurgea, C. (1978) The pharmacology of nootropic drug gerophysiatric implications. In P. Deniker, C. Raduco-Thomas and A. Wilneuve (Eds.), *Neuropharmacology, Vol. 1*, Pergamon, New York, pp. 67–72.

Giurgea, C. and Mouravieff-Lesuisse, F. (1972) Effect facilitateur du Piracetam sur un apprentissage répétitif chez le rat. *J. Pharmacol. (Paris)*, 3: 17–30.

Giurgea, C. and Salama, M. (1977) Nootropic drugs. *Prog. Neuropsychopharmacol.*, 1: 235–247.

Gobert, J.G. (1972) Genès d'un médicament: le Piracetam métabolisation et recherche biochimique. *J. Pharm. Belg.*, 3: 281–304.

Gobert, J.G. and Baltès, E.L. (1976) Availability and plasma clearance of Piracetam in man. *Il Farmaco. Ed. Pr.*, 32, 2: 83–91.

Kornhuber, H.H. and Deecke, L. (1965) Hirnpotentialänderungen bei Willekurbewegungen und passiven Bewegungen des Menschen: Bereitschaftspotential und reafferente Potentiale. *Pflügers Arch. ges. Physiol.*, 284: 1–17.

Marczynski, T.J. (1978) Neurochemical mechanisms in the genesis of slow potentials: a review and some clinical implications: In D.A. Otto (Ed.), *Multidisciplinary Perspectives in Event-related Brain Potential Research*, U.S. Government Printing Office, Washington, pp. 25–35.

Mindus, P., Crowholm, B., Levander, S.E. and Shaling, D. (1976) Piracetam-induced improvement of mental performance. A controlled study in normally ageing individuals. *Acta Psychiat. Scand.*, 54: 150–160.

Papakostopoulos, D. (1978a) The serial order of self-paced movement in terms of brain macropotentials in man. *J. Physiol. (Lond.)*, 280: 70–71.

Papakostopoulos, D. (1978b) Electrical activity of the brain associated with skilled performance. In D.A. Otto (Ed.), *Multidisciplinary Perspectives in Event-related Brain Potential Research*, U.S. Government Printing Office, Washington, pp. 134–137.

Papakostopoulos, D. (1980) A no-stimulus, no-response event-related potential of the human cortex. *Electroencephalogr. Clin. Neurophysiol.*, 48: 622–638.

Papakostopoulos, D. and Banerji, N. (1980) Movement-related brain macropotentials during skilled performance in Parkinson's disease. *Electroencephalogr. Clin. Neurophysiol.*, 49: 93.

Papakostopoulos, D., Cooper, R. and Crow, H.J. (1975) Inhibition of cortical evoked potentials and sensation by self-initiated movement in man. *Nature (Lond.)*, 258: 321–324.

Papakostopoulos, D., Banerji, N.K. and Pocock, P.V. (1985a) Brain macropotentials related to self-paced skilled performance in Parkinson's disease. *Electroencephalogr. Clin. Neurophysiol.*, 61: S42.

Papakostopoulos, D., Banerji, N.K., Pocock, P.V., Newton, P. and Kelly, N.J. (1985b) Drug-induced Parkinsonism and brain electrical activity. In D. Papakostopoulos, S. Butler

and I. Martin (Eds.), *Clinical and Experimental Neuropsychophysiology,* Croom Helm, London, pp. 256–285.

Pepeu, G. and Espignoli, G. (1986) Effect of oxiracetam on cognitive and brain cholinergic mechanisms. In W. Bunney, E. Costa and S.G. Potkin (Eds.), *Clinical Neuropharmacology, Vol. 9 Suppl. 4*, Raven, New York, pp. 298–300.

Phillis, J.W. (1970) *The Pharmacology of Synapses*, Pergamon, London, pp. 174–180.

Stegnick, A.J. (1972) The clinical use of Piracetam, a new nootropic drug. *Arnzneim Forsch. Drug Res.*, 22: 975–981.

Tallal, P., Chase, C., Schmitt, L. and Russe, G. (1984) Piracetam effects with dyslexia: results from the San Diego study. Annual INS Meeting San Diego California. *INS bull.*, p. 73.

Timsit-Berthier, M. (1981) A propos de l'interprétation de la variation contingente négative en psychiatrie. *Electroencephalogr. Clin. Neurophysiol.*, 11: 236–244.

Wilsher, C.R., Atkins, G. and Manfield, P. (1979) Piracetam as an aid to learning in dyslexia: preliminary report. *Psychopharmacology*, 65: 107–109.

Wilsher, C.R., Bennet, D., Chase, H., Conners, C., Di Janni, M., Feagans, L., Hanvik, J., Helfott, E., Koplewicz, H., Overby, P., Reader, J., Rudel, R.G., Tallal, P. (1987) Piracetam and dyslexia: effects on reading tests. *J. Clin. Psychopharmacol., Vol. 7*, 4: 230–237.

Wurtman, R., Mangil, S.G. and Reinstein, D.K. (1980) Piracetam diminishes hippocampal acetylcholine levels in rats. *Life Sci.*, 28: 1091–1093.