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An Electrophysiological Correlate of Amphetamine Revealed Motor Imbalance in Albino Rats

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SHAVIT, Y. AND M. MYSLOBODSKY. *An electrophysiological correlate of amphetamine revealed motor imbalance in albino rats.* PHARMAC. BIOCHEM. BEHAV. **10**(2) 195–199, 1979.—Ten out of eleven Wistar rats displayed a reliable interhemispheric asymmetry of the secondary slow negative wave (SNW) of the visual evoked potential. A more synchronized EEG was observed on the side of facilitated SNW. The analysis of rotation directionality in the rotometer of these rats after IP (+)-amphetamine administration (1.25 mg/kg) showed that rats reliably rotated towards the side with a more facilitated SNW. It is believed that an imbalance of nigrostriatal DA content underlies the interhemispheric asymmetry of EEG and evoked potentials.

Rotation behavior Visual evoked potential Hemispheric asymmetry Dopamine asymmetry

RATS with unilateral lesions in the nigrostriatal dopamine system have been shown to display a consistent rotation behavior directed toward the side of the lesion [35–37]. This circling behavior can be remarkably sharpened with a drug such as (+)-amphetamine [34–36] which is believed to release presynaptic dopamine stores [15]. Dopamine precursors or agonists such as L-Dopa or apomorphine elicit turning in the opposite (i.e., contralateral) direction. The reversal of the direction of rotation by agents having a direct postsynaptic effect [12] has been attributed to the greater reactivity (i.e., supersensitivity) of denervated striatal cells ipsilateral to the lesion [8, 35, 36]. These findings suggest a principle according to which animals rotate away from the more activated striatum [36].

An injection of (+)-amphetamine to intact rats also produced consistent rotation either to the left or to the right side [21] and it was interpreted as an indication of an intrinsic hemispheric asymmetry in dopamine receptor activity accentuated by drugs. Indeed, the dopamine contents of the right and left striata were found to differ by 10–15%, and after administration of (+)-amphetamine, the dopamine asymmetry has been found to reach 25% [13]. In accordance with the above mentioned principle, naive rats also rotated away from the side with a higher dopamine concentration [14]. Since all neurotransmitters which are believed to be involved in the regulation of rotation behavior (dopamine, acetylcholine and γ-aminobutyric acid) are known to affect spontaneous and evoked electrocortical activity, it was anticipated that the motor imbalance should be reflected in the asymmetry of the electrical activity of the cerebral hemispheres.

This study was designed to compare arousal sensitive components of the bilaterally recorded visual evoked potentials and to correlate their parameters with the rotation behavior in rats.

METHOD

Animals and Surgery

Eleven albino Wistar female rats (190–260 g and 150–210 days old, at the beginning of the experiment) were kept under standard laboratory conditions with ad lib access to food and water. Epidural electrodes were implanted bilaterally over symmetrical points of the visual cortex (4mm bilaterally to midline and 7.2mm caudally from bregma). Indifferent electrodes were placed over the cerebellum. The area of the electrode tip making contact with dura was approximately 0.063 mm^2. Electrodes were secured to the calvarium with dental acrylic and the whole connector-pedestal was reinforced with two screws. After completion of the experiments the rats were sacrificed with an overdose of barbiturate and their brains were removed and examined for possible cortical damage, electrode penetration or excessive electrode pressure. All data reported here were from brains accepted on the basis of macroscopic analysis.

Apparatus and Procedure

After a 7–12 day period of postsurgical recovery, the ani-

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mals were taken to the experimental cage and connected to the cable of a swivel, mounted on its top to provide artifact-free EEG recordings in unrestrained rats. Following about 15 min of dark adaptation, photic stimuli were presented randomly with an interstimulus interval of not less than 5 sec. Photic stimulation was produced with a Grass PS 22 photostimulator. A flash of 10 μsec duration set at intensity "2" was delivered to a dark electrostatically isolated cage with mirror walls, through one wall with a built-in strobe. Brain potentials were amplified with a Beckman Type R Dynograph (bandwidth 0.53 Hz to 30 Hz). They were recorded on magnetic tape for further off-line processing on a PDP-8 computer, and displayed on the oscilloscope (Dual Beam, Textronix 5030). Samples of visual evoked potentials were averaged over a 0.5 sec epoch (500 addresses of 1 msec in each channel) and plotted on a paper by X-Y plotter (Hewlett-Packard 7035B).

Blocks of 20–25 artifact-free potentials were recorded on a tape for further summation. After that the animal was disconnected from the cable, mounted in a special harness and placed in a transparent glass bowl "rotometer" [37]. The number of turns in each direction was recorded automatically and cumulative scores were displayed on four electromechanical counters (for recording 45° and 360° turns in each direction, separately). Fifteen min were allowed for assessment of pre-drug rotation rate, followed by IP administration of 1.25 mg/kg of (+)-amphetamine after which the animal remained in the rotometer for 45 min and the number of turns in each direction was scored for the last 30 min.

Data Analysis

Only the secondary slow negative wave (SNW) or N_3 wave according to Creel *et al.* [9], which is most sensitive to arousal [3, 4, 25, 28] with a peak latency of about 170 msec, was analyzed in this study. The latter was measured as a peak-to-peak distance between the SNW and the neighbouring positive peaks of P_2 (latency of about 60 msec) and P_3 (latency of about 110 msec) (Fig. 1). ANOVA was performed on SNW measures (P_2–N_3 and P_3–N_3 amplitudes, and SNW area) to analyze the effects of electrode sites (hemispheres), directionality of rotation, and conditions (pre-drug and post-drug) as repeated factors. To assess the relative increase in the VEP in one hemisphere versus the other, a one-tailed *t*-test for matched groups was employed for comparing the amplitudes and area of the SNW. To compensate for individual VEP differences and their remarkable changes after amphetamine administration, an asymmetry index was computed, representing the difference in SNW parameters between hemispheres over the maximal SNW values. The same index was computed to characterize the degree of motor imbalance (the net rotation score over the dominant side score).

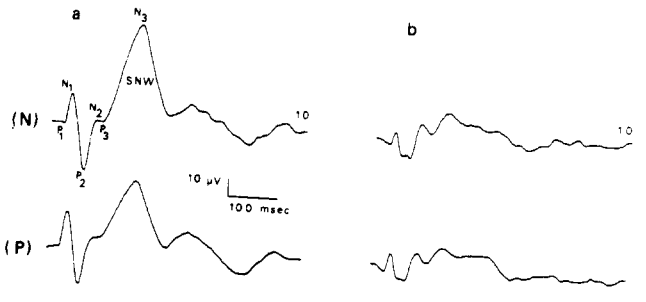

FIG. 1. Mean VEPs from all subjects in pre-drug condition (a) and after 1.25 mg/kg d-amphetamine administration (b). All potentials derived from the hemisphere contralateral to the preferred (P) and non-preferred (N) sides are pooled together. The individual VEPs are averages of 20 stimuli; bin width 1 msec. The mean potentials are calculated from 10 individual VEPs (as indicated on the right of each curve). The letters on the upper left curve denote standard positive and negative peaks according to the nomenclature of Creel *et al.* [9]. Negativity of the active electrode is upwards. The presentation of the stimulus coincides with the beginning of the curve.

RESULTS

The averaged VEP was composed of a primary negative-positive (N_1–P_2) or positive-negative-positive "primary" complex, followed by two negative waves N_2 (latency about 90 msec) and N_3 (latency about 170 msec). It was similar to that described formerly in our laboratory as well as in others [3, 9, 25]. Ten out of eleven naive non-drugged rats had a stable asymmetry of evoked potentials predominantly in the region of N_3, i.e., the slow secondary negative wave (SNW). This asymmetry proved to be reliable in the binomial test ($p<0.006$). Fig. 1a demonstrates this asymmetry in an averaged evoked potential for the whole group of rats prior to amphetamine administration. In one rat the asymmetry of the N_3 (SNW) component was of a dynamic nature, with a higher potential recorded at times over the right or over the left hemisphere. The averaging procedure in this case resulted in a rather symmetrical visual evoked potential. The same rat displayed a dynamic asymmetry of sensory afterdischarges (SAD).

The higher amplitude of the SNW correlated positively with a more synchronized EEG on the same side ($p<0.03$). In 10 out of 11 rats there was an increase in the amplitude and in the duration (by 40%) of the activity in the 6–8 Hz frequency band, in the occipital and somatosensory cortex, on the side of the facilitated SNW. When a rat was motionless and sleep developed, a higher amplitude of sleep spindles and slow waves was observed on this side (Fig. 2).

The parameters of the SNW generated in both hemispheres contralateral to preferred and neglected direction are summarized for the same condition in Table 1. It shows that the amplitude and area of the SNW in the two hemispheres are reliably different, although the lateral motor bias was infinitesimal.

In accord with previous reports [21] d-Amphetamine (1.25 mg/kg, IP) administration induced vigorous rotation in all rats. A mean score in preferred direction (full turns) reached 128 ± 62.26 and the score of the rotation to the neglected side was 17.6 ± 23.83, $t(9)=4.62$; $p<0.001$. Unexpectedly, SNW asymmetry decreased after amphetamine (Table 2). ANOVA indicated significant main effects of conditions, $F(1,9)=23.14$; $p<0.01$, and directionality, $F(1,9)=8.64$; $p<0.05$, for all the SNW parameters. The site effect, however, failed to reach significance, $F(1,9)=0.242$; NS.

Amphetamine is known to decrease the SNW amplitude [25] and, as apparent from Fig. 1b and Table 2, these effects seem to be associated with SNW suppression. Of importance is the fact that when the absolute magnitudes of bilateral evoked potential were converted to the asymmetry indices and the values of SNW asymmetry in pre- and post-drug states were subjected to *t*-test for matched groups, neither SNW measures proved to be significantly different.

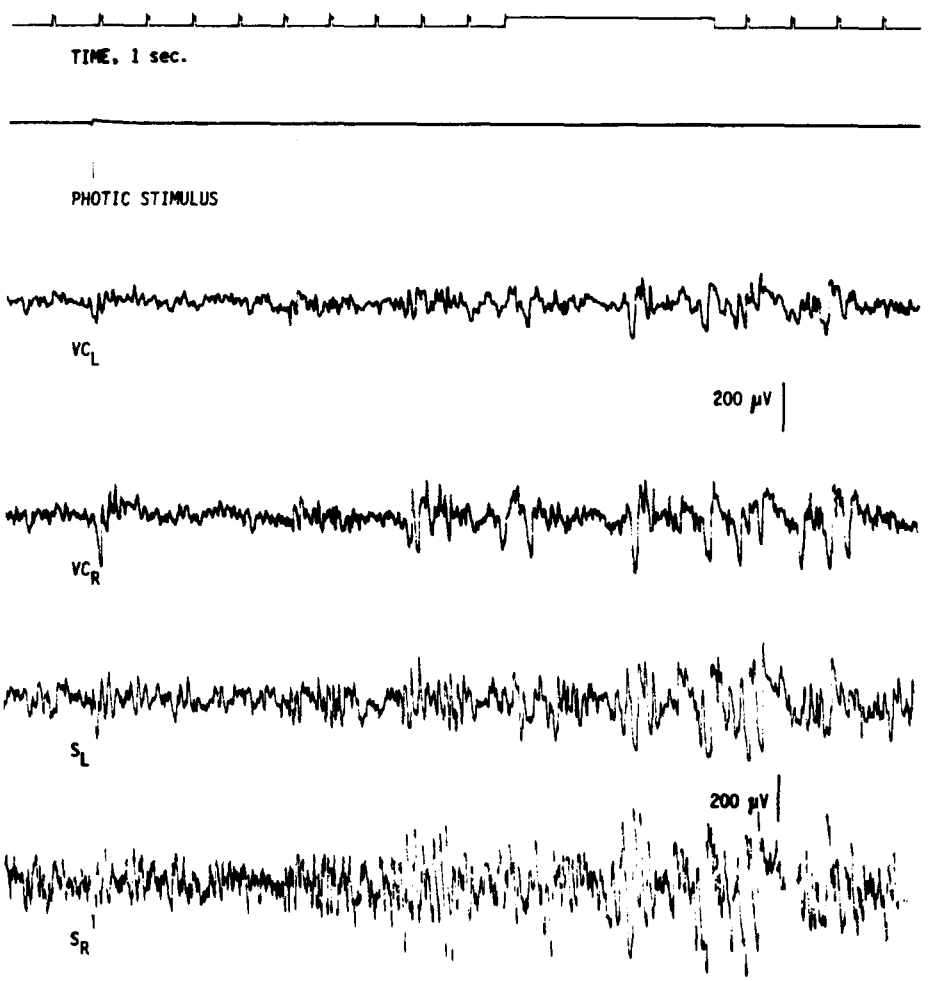

FIG. 2. A fragment of sleep EEG with higher amplitude in the right hemisphere in a naive rat consistently rotating towards the right side in the rotometer. VCL and VCR are correspondingly the left and right visual cortex. SL and SR—the left and right sensorimotor cortex.

TABLE 1

COMPARISON OF SNW PARAMETERS (MEAN ± SD) BETWEEN THE TWO HEMISPHERES, CONTRALATERAL TO THE PREFERRED AND NON-PREFERRED SIDE, IN PRE-DRUG CONDITION

Hemisphere	Mean no. of turns pre-drug	SNW parameters P_2–N_3*	P_3–N_3*	Area in cm^2
Non-preferred	6.9 ± 3.76	171 ± 92.75	130 ± 75.20	13.60 ± 6.74
Preferred	6.6 ± 4.12	142 ± 92.62	103 ± 72.80	10.80 ± 7.20
Student's *t*	0.17	2.54	2.46	2.22
df	9	9	9	9
$p <$	NS	0.025	0.025	0.05

*P_2–N_3 and P_3–N_3 amplitude measures are represented in arbitrary units (10 μV correspond to 16 average units).

This proves that although amphetamine sharpens side preference it decreases rather than increases the SNW asymmetry.

DISCUSSION

Several writers used later VEP components, i.e., SNW and SAD as "compressed" indices of electrocortical arousal

TABLE 2

COMPARISON OF SNW PARAMETERS (MEAN ± SD) BETWEEN THE TWO HEMISPHERES, CONTRALATERAL TO THE PREFERRED AND NON-PREFERRED SIDE, IN POST-AMPHETAMINE CONDITION

Hemisphere	Mean no. of turns pre-drug	SNW parameters P_2–N_3*	P_3–N_3*	Area in cm^2
Non-preferred	128.1 ± 62.26	79 ± 50.65	55 ± 35.77	4.40 ± 2.04
Preferred	17.6 ± 23.83	65 ± 41.37	47 ± 39.20	4.15 ± 3.77
Student's *t*	4.62	2.13	1.56	0.23
df	9	9	9	9
$p <$	0.001	0.05	NS	NS

*P_2–N_3 and P_3–N_3 amplitude measures are represented in arbitrary units (10 μV correspond to 16 average units).

[25, 28, 31, 32]. Pharmacological studies, lesions in different brain structures and behavioral studies [3, 4, 24, 25, 32] demonstrate that there is an inverse relationship between the amplitude of the SNW, the SAD duration and behavioral reactivity and activity. It was also suggested that SNW-SAD decrease as a function of the intensity of voluntary non-appetitive locomotor activity [25,32]. Rats with prolonged SAD and facilitated SNW were shown to require more trials to establish the washing conditioned reflex, and in rats with brain lesions which stabilized high amplitude and prolonged SADs remarkable learning deficits were observed [25].

SNW seems to be a universal component of many cortical stimulus-related events. Prominent slow negative waves paralleled by inhibition of motor activity ("arrest reaction") can be elicited by electrical stimulation of the non-specific medial thalamus [2, 20, 29] or mesencephalon [38] with a frequency of about 3 Hz. A similar effect defined as "inaktivierungssyndrom" was found during low frequency stimulation of the caudate nucleus [1,6].

Caudate stimulation also evokes a slow negative secondary wave which is correlated with inhibition of the performance of a learned response [7,19]. Krauthamer and Albe-Fessard [23] demonstrated an inhibitory influence of the striopallidum on multisensory potentials in the association cortex. This inhibition extended over 150–350 msec and was blocked by strychnine, suggesting that it is of postsynaptic origin. Long lasting IPSPs have been recorded in cortical neurons after a shock delivered to the caudate [7,19] and intralaminar thalamus [29]. A microelectrophysiological analysis conducted in the visual cortex in rabbits and rats proved that the intracellular correlate of the SNW of the VEP are similar long lasting hyperpolarizing potentials (IPSP) synchronously generated on, or near, soma of pyramid cells [25]. Disinhibitory (arousing) stimuli shorten or abolish IPSP in cortical cells, and correspondingly suppress slow waves of any origin [25]. It is possible that with a greater inhibition of one hemisphere, the brain experiences a sort of "partial (unilateral) arrest" behavior. In this situation the less inhibited, i.e., more active side, determines the direction of the postural asymmetry and rotation behavior.

Angyan *et al.* [2] report that during unilateral thalamic stimulation animals exhibited a postural asymmetry "tilting" towards the side of stimulation, i.e., away from the side with smaller SNW. This postural asymmetry mimics the neostriatal involvement. A similar "tilting" can be reproduced by the electrical stimulation of the caudate nucleus [40], and in the normal state an intrinsic activity of the caudate can serve as a vehicle channeling exploratory locomotion into a consistent side preference. Pycock and Marsden [30] recently marshalled experimental and theoretical evidence favoring the view that rotation behavior has at least two component control systems. The nigrostriatal dopamine imbalance causes a postural asymmetry while a mesolimbic dopamine system creates locomotion and circling. A failure to observe an increment in the SNW asymmetry after amphetamine administration, which should have been revealed if the electrophysiological asymmetry reflected that of the locomotion, conforms to this hypothesis. Although direct evidence on the variation of the dopamine level and the corresponding changes of the SNW amplitudes and motor behavior is lacking, when all the evidence presented above is considered together, it becomes very difficult to escape the conclusion that the unilateral decrease of the slow negativity of the VEP represents a correlate of the relative depression of striatal inhibitory activity ("inhibition of inhibition") due to homolateral increase in the concentration of dopamine [13].

Electrical stimulation of the caudate nucleus and other basal ganglia (putamen, globus pallidus) was effective in inducing synchronized spindle waves in cats and monkeys [10, 18, 22]. Electrical stimulation of the caudate nucleus in man has been shown to induce sleep [17], pleasant light intoxication and confusion [39]. Local injection of dopamine into the caudate nucleus has been shown to induce slow wave and spindles on the ECoG in cats [16]. Polysensory associational areas, as defined by Thompson, Smith and Bliss [33] were particularly involved in spindle activity which is consistent with the findings of Krauthamer and Albe-Fessard [23] mentioned above. The development of frontal spindles homolateral to synchronized activity in the occiput, suggests that the striopallidal system may be responsible for creating the electrographic picture of an idling hemisphere. This synchronization may be achieved by the complex circuit involving putamen-pallidum-thalamus and cortex [11]. Since the substantia nigra acts as a major relay regulating the flow of impulses to the striatum, it is important to add that the nigrostriatal dopamine system sets the asymmetrical tone of the caudate. It is tempting to speculate that the recently described asymmetry of sleep spindles in human subjects [26,27] and that observed in the present study are phenomena of a similar nature. Both may be associated with the asymmetry of reactivity of the nigrostriatal system.

REFERENCES

1. Akert, K. and B. Anderson. Experimenteller beitrag zur Physiologie des nucleus caudatus. *Acta physiol. scand.* **22:** 281–298, 1951.
2. Angyan, L., P. Kajtar and E. Sik. Correlation between thalamic-induced cortical spike and wave activity and behavior in unrestrained cats. *Acta physiol. hung.* **32:** 291–306, 1967.
3. Bigler, E. D., D. E. Fleming and D. E. Shearer. Stabilization of photically evoked after-discharge activity: Control procedures and effects of classical trace conditioning. *Behav. Biol.* **16:** 425–437, 1976.
4. Bigler, E. D., D. E. Fleming and D. E. Shearer. Metrazol potentiated after-discharges: Dose-response relationships and effects of selective lesions. *Pharmac. Biochem. Behav.* **5:** 423–429, 1976.
5. Bloom, F. E., E. Costa and G. C. Salmoiraghi. Anesthesia and responsiveness of individual neurons of the caudate nucleus of the cat to acetylcholine, norepinephrine and dopamine administered by microelectrophoresis. *J. Pharmac. exp. Ther.* **150:** 244, 252, 1965.
6. Buchwald, N. A., E. J. Wyers, C. W. Lauprecht and G. Heuser. The "Caudate Spindle," IV. A behavioral index of caudate-induced inhibition. *Electroenceph. clin. Neurophysiol.* **13:** 531–537, 1961.
7. Buchwald, N. A., C. D. Hull and M. G. Trachtenberg. Concomitant behavioral and neural inhibition and disinhibition in response to subcortical stimulation. *Expl Brain Res.* **4:** 58–72, 1967.
8. Costall, L. B. and R. J. Naylor. Specific asymmetry behavior induced by the direct chemical stimulation of neostriatal dopaminergic mechanisms. *Naunyn-Schmiedebergs Arch. exp. Path. Pharmak.* **285:** 83–98, 1974.
9. Creel, D. J., R. E. Dustman and E. C. Beck. Differences in visually evoked responses in albino versus hooded rats. *Expl Neurol.* **29:** 298–309, 1970.
10. Dieckmann, G. Cortical synchronized and desynchronized responses evoked by stimulation of the putamen and pallidum in cats. *J. Neurol. Sci.* **7:** 385–391, 1968.
11. Dieckmann, G. and K. Sasaki. Recruiting responses in the cerebral cortex produced by putamen and pallidum stimulation. *Brain Res.* **10:** 236–250, 1970.
12. Ernst, A. M. Mode of action of apomorphine and dextamphetamine on gnawing compulsion in rats. *Psychopharmacology* **10:** 316–323, 1967.
13. Glick, S. D., T. P. Jerussi, D. H. Waters and J. P. Green. Amphetamine-induced changes in striatal dopamine and acetylcholine and relationship to rotation (circling behavior) in rats. *Biochem. Pharmac.* **23:** 3223–3225, 1974.
14. Glick, S. D., T. P. Jerussi and L. N. Fleisher. Turning in circles: The neuropharmacology of rotation. *Life Sci.* **18:** 889–896, 1976.
15. Glowinski, J. and J. Axelrod. Effects of drugs on the uptake, release and metabolism of ^{3}H-norepinephrine in the rat brain. *J. Pharmac. exp. Ther.* **149:** 43–49, 1965.
16. Hall, R. C. and P. E. Keane. Dopaminergic and cholinergic interaction in the caudate nucleus in relation to the induction of sleep in the cat. *Br. J. Pharmac.* **54:** 247P–248P, 1975.
17. Heath, R. G. and R. Hodes. Induction of sleep by stimulation of the caudate nucleus in macaqus rhesus and man. *Trans. Am. Neurol. Ass.* **77:** 204–210, 1952.
18. Horvath, F. E., S. Soltysik and N. A. Buchwald. Spindles elicited by stimulation of the caudate nucleus and internal capsule. *Electroenceph. clin. Neurophysiol.* **17:** 670–676, 1964.
19. Hull, C. D., N. A. Buchwald and J. B. Vieth. Cortical intracellular analyses of responses to inhibitory and disinhibitory stimuli. *Brain Res.* **6:** 12–21, 1967.
20. Hunter, J. and H. H. Jasper. Effects of thalamic stimulation in unanesthetized animals. *Electroenceph. clin. Neurophysiol.* **1:** 305–324, 1949.
21. Jerussi, T. P. and S. D. Glick. Amphetamine-induced rotation in rats without lesions. *Neuropharmacology* **13:** 283–286, 1974.
22. Kitsikis, A., F. E. Horvath and A. Rougeul. Synchronized spindle activity elicited in the cortex of the monkey by basal ganglia stimulation. *Electroenceph. clin. Neurophysiol.* **25:** 160–169, 1968.
23. Krauthamer, G. and D. Albe-Fessard. Inhibition of nonspecific sensory activities following striopallidal and capsular stimulation. *J. Neurophysiol.* **28:** 100–124, 1965.
24. Mello, W. F. and J. S. Schwartzbaum. Effects of scopolamine upon behavioral reactivity and visually evoked potential to flashes in rats. *J. comp. physiol. Psychol.* **85:** 469–478, 1973.
25. Myslobodsky, M. *Petit mal epilepsy: A Search for the Precursors of Wave-Spike Activity*. New York: Academic Press, 1976.
26. Myslobodsky, M., V. Ben-Mayor, B. Yedid-Levi and M. Mintz. Interhemispheric asymmetry of electrical activity of the brain in sleep and cerebral dominance. *Bull. Psychon. Soc.* **7:** 465–467, 1976.
27. Myslobodsky, M., M. Mintz, B. Yedid-Levi and V. Ben-Mayor. Electrophysiological evidence of hemispheric asymmetry in non-REM sleep. Proc. IXth Internat. Congress of *Electroenceph. clin. Neurophysiol.* **43:** 460, 1977.
28. Pickenhain, L. and F. Klinberg. Behavioral and electrophysiological changes during avoidance conditioning to light flashes in the rat. *Electroenceph. clin. Neurophysiol.* **18:** 464–476, 1965.
29. Pollen, D. A. Intracellular studies of cortical neurons during thalamic induced wave and spike. *Electroenceph. clin. Neurophysiol.* **17:** 398–404, 1964.
30. Pycock, C. J. and C. D. Marsden. The rotating rodent: A two component system? *Eur. J. Pharmac.* **47:** 167–175, 1978.
31. Schwartzbaum, J. S., C. J. Kreinick and J. W. Gustafson. Cortical evoked potentials and behavioral reactivity to photic stimuli in freely moving rats. *Brain Res.* **27:** 295–307, 1971.
32. Schwartzbaum, J. S. and C. J. Kreinick. Interrelationships of hippocampal electroencephalogram, visually evoked response, and behavioral reactivity to photic stimuli in rats. *J. comp. physiol. Psychol.* **85:** 479–490, 1973.
33. Thompson, R. F., H. E. Smith and D. Bliss. Auditory, somatic sensory and visual response interaction and interrelations in association and primary cortical fields of the cat. *J. Neurophysiol.* **26:** 365–378, 1963.
34. Ungerstedt, U. Striatal dopamine release after amphetamine or nerve degeneration revealed by rotational behavior. *Acta physiol. scand. suppl.* **367:** 49–68, 1971.
35. Ungerstedt, U. Postsynaptic supersensitivity after 6-hydroxy-dopamine induced degeneration of the nigro-striatal dopamine system. *Acta physiol. scand. suppl.* **367:** 69–93, 1971.
36. Ungerstedt, U. Brain dopamine neurons and behavior. In: *The Neurosciences: Third Study Program*, edited by F. O. Schmidtt and F. G. Worden. Cambridge, Mass.: The MIT Press, 1974, p. 695.
37. Ungerstedt, U. and G. W. Arbuthnott. Quantitative recording of rotational behavior in rats after 6-hydroxy-dopamine lesions of the nigrostriatal dopamine system. *Brain Res.* **24:** 485–493, 1970.
38. Weir, B. and P. G. Sie. Extracellular unit activity in cat cortex during the spike-wave complex. *Epilepsia (Amst.)* **7:** 30–43, 1966.
39. Wood, J. H., C. R. Lake, M. G. Ziegler and J. M. Van Buren. Neurophysiological and neurochemical alterations during electrical stimulation of human caudate nucleus. *J. Neurosurg.* **46:** 361–368, 1977.
40. Zimmerberg, B. and S. D. Glick. Rotation and stereotypy during electrical stimulation of the caudate nucleus. *Res. communs chem. pathol. Pharmac.* **8:** 195–197, 1974.