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Slow Potentials and Interferences in Evaluation of Psychotropic Drugs^a

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Although slow potentials would generally be regarded as good measures for evaluating behavior, it is not known if they are nonspecifically related to brain activation or selectively related to brain information processing and cognitive strategies.

For a methodological approach, we have previously shown the importance of a control of the "endogenous conditions," which are relevant to interindividual variability and are evaluated by usual psychometric scales, and of the "external conditions," which are relevant to cues and intraindividual changes (Paty *et al.*, 1979).

Since psychotropic drugs are commonly used in experiments on human behavior as a means of changing internal conditions, it is important to appreciate the effects of such drugs on cortical activities. Changes of EEG spontaneous rhythms have been classically described and have good descriptive and predictive value for psychotropic drugs. The EEG is, however, not very useful for an explanation of drug action (Fink, 1974).

The human contingent negative variation (CNV) has been shown to be sensitive to pharmacological manipulations (Dongier, 1973), but the results are quite variable. No consistent data have been reported that might be relevant to psychological and biological drug effects (Rebert, 1980). No good model has been proposed for describing the relation between event-related potentials (ERPs) and behavior, or psychotropic drug action.

Thus, our purpose in this paper is to define external and internal interactions occurring when two drugs have the same disinhibitory psychological activity, but different neurobiological modes of action.

METHOD

We studied two drugs: Carpipramine, a combination of a neuroleptic and a tricyclic, which is regarded as an antistress and disinhibitor agent (Denicker *et al.*, 1977) and Minaprine (chloride) an original compound which has been developed for its catecholaminergic stimulant ability (Laborit, *et al.*, 1972). Both drugs had been proposed for their disinhibiting effects in depressed patients.

In two experiments with paid volunteers we compared the effects of drug against placebo by a double-blind procedure. A preselection of subjects was performed by psychological test. The criteria included no psychiatric antecedent or psychotropic

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drug intake and cluster notes on the Wittenborn test of less than 4. Electrophysiological criteria included normal alpha rhythm and well-developed CNV.

Carpipramine (150 mg per day) was taken for 30 days by 16 subjects (7 men and 9 women, 26 to 49 years of age). Minaprine (150 mg per day) was taken for 60 days by 12 subjects (26 to 49 years of age). In both cases a crossover procedure was used. Recordings were taken at baseline prior to drug intake (T0), then at day 8 (T8) and day 15 (T15) for the Carpipramine subjects, and at day 30 (T30) and 60 (T60) for the Minaprine subjects.

The subject was comfortably seated in a sound isolated and dark room. A usual CNV S_1 - S_2 paradigm was used. Paired stimuli were randomly delivered every 20 to 25 seconds. S_1 was a filtered click (1200 Hz, 70 dB) followed 2 seconds later by S_2 , a series of flashes to which the subject responded. Reaction time was measured at each trial. After amplification (6 sec time constant) and magnetic tape recording (Schlum-

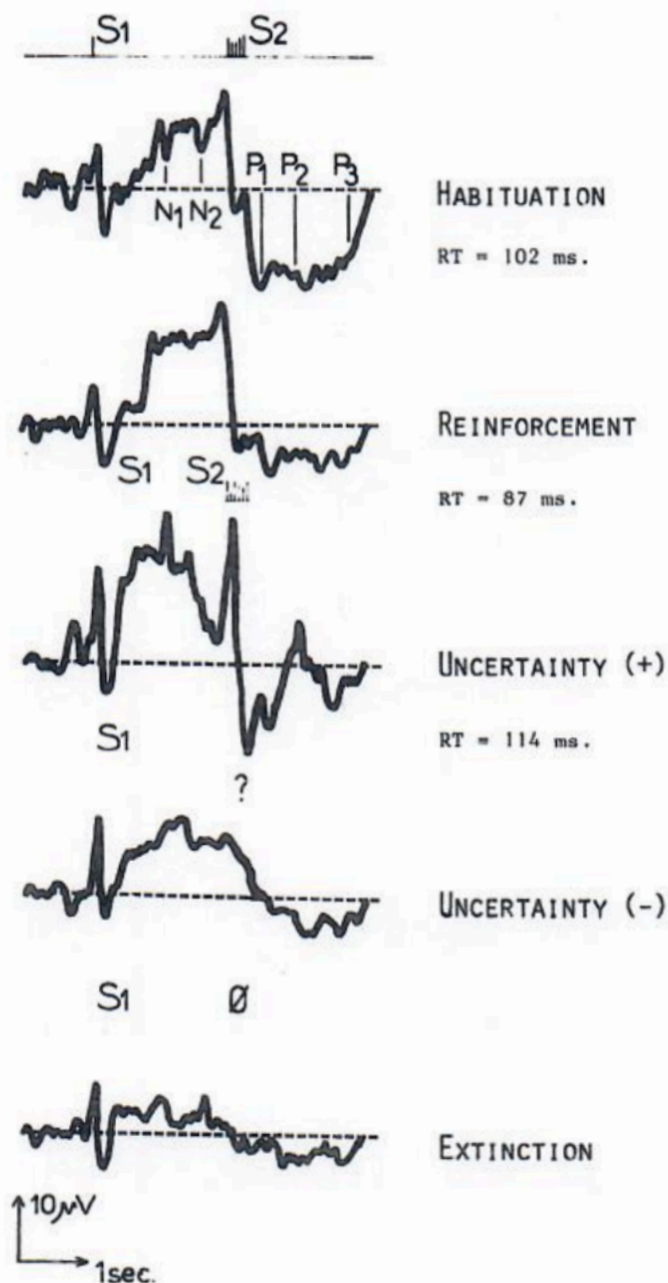


FIGURE 1. Averaged CNV in each situation for one subject.

TABLE 1. Differential Changes in CNV Amplitude with Antidepressant Drugs. Values of CNV Amplitude (ΔNb) in Each Condition and Δ Values of the Condition Index Expressed as Percent Difference between Placebo and Drug

Situation	Δ Carpipramine $n = 12$	Δ Minaprine Chloride $n = 16$
Habituation	+ 29.8%	+ 212% ^a
Reinforcement	+ 16.1%	0%
Uncertainty (+)	+ 42.5%	+ 15%
Uncertainty (-)	+ 33.6%	+ 46%
Extinction	+ 130% ^a	+ 50%
Condition Index $\frac{\sigma Nb}{m Nb}$	- 37.4%	- 27%

^a $p < 0.05$

berger MMP 5521), CNV were averaged for 10 sweeps (200 Hz sample frequency), with an automatic rejection of artifact (eye movement, amplitudes more than 100 μV , reaction time more than 400 ms), by using a Plurimat's computer.

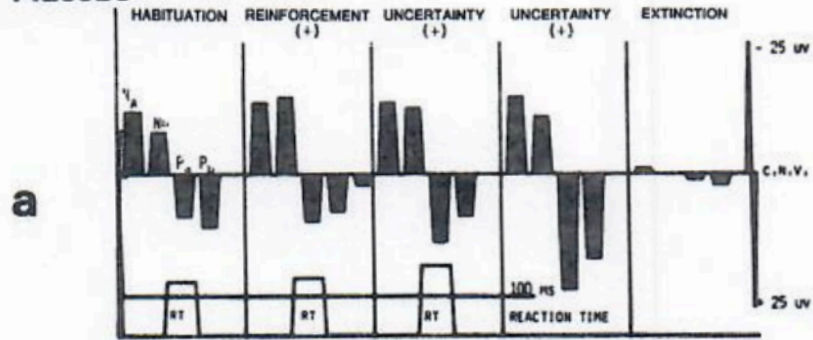
There were five conditions: (1) *Acquisition*. Random presentation of paired S_1 - S_2 trials every 20 to 25 seconds. (2) *Habituation*. Last 10 trials of 40 trials. (3) *Reinforcement*. Giving feedback on reaction time and warning the subject to give the best performance. (4) *Uncertainty*. Random omission of S_2 without warning the subject. Separate averages were made for complete (uncertainty +) and incomplete (uncertainty -) sequences. (5) *Extinction*. Complete omission of S_2 .

Five amplitude measurements were made with reference to the baseline (mean EEG amplitude 1 sec prior to S_1). N_a is the mean amplitude for 500 to 800 ms after S_1 . N_b is the mean amplitude for 1500 to 1800 ms after S_1 , P_a for 200 to 700 ms after S_2 , P_b for 1500 to 1800 ms after S_2 , and P_c for 1800 to 2000 ms after S_2 . Schematic drawings of the CNV using the 5 measures were made. Furthermore, for the N_b wave, two other measures were computed for each subject: (1) ΔNb amplitude, the ratio N_b (drug) minus N_b (placebo) divided by N_b (placebo) times 100, and (2) condition index, the ratio σ / m where m equals the average and σ equals the standard deviation of N_b amplitudes in the five conditions. Drugs effects were statistically analyzed with the nonparametric Fisher's C1 test. The condition index shows intraindividual variability across the conditions.

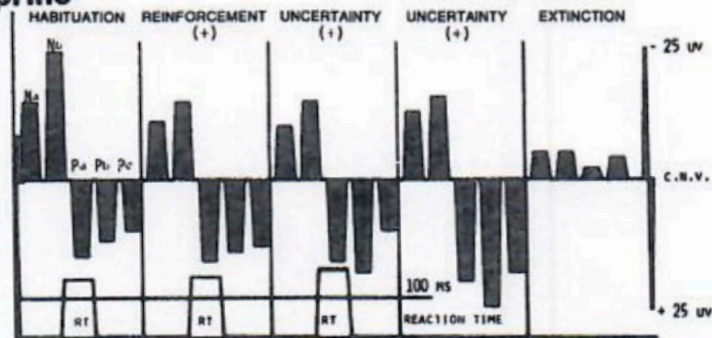
RESULTS

There were significant increases of N_b amplitudes with both drugs, but no significant change in reaction times ($\Delta Nb > 0$). An increase in N_b amplitude was observed in all the conditions, and consequently the condition effect, observed under placebo, was smoothed under both drugs. Changes in N_b amplitude were quite different under Minaprine and Carpipramine. With Carpipramine, N_b amplitude remained higher after suppression of S_2 , which shows that there was a delayed extinction ($p < 0.05$). With Minaprine, N_b amplitude was not decreased after repetition of the paired stimuli, *i.e.* there was less habituation than under placebo ($p < 0.05$).

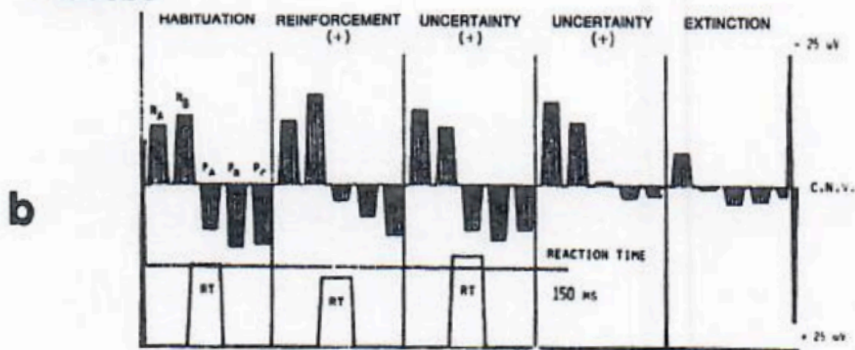
Placebo



Minaprime



Placebo



Carpipramine

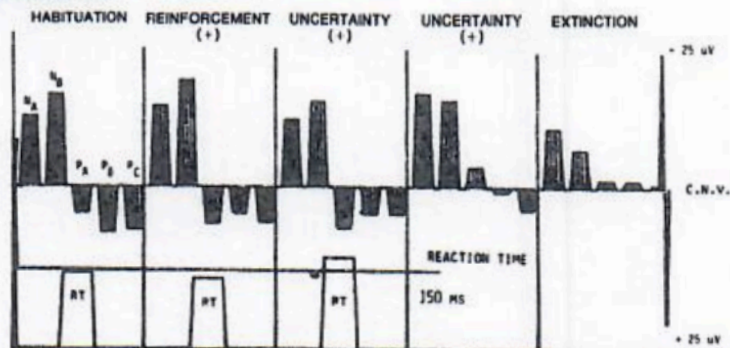


FIGURE 2. Multiparametric outlines for a comparison between placebo and drugs are computed on five parameters of averaged CNV amplitudes (Na, Nb, Pa, Pb, Pc) and reaction times in each situation. (a) Minaprime: 16 cases. (b) Carpipramine: 15 cases.

DISCUSSION

We observed not only CNV morphological or amplitude changes in subjects treated with psychotropic drugs, but also dynamic changes which may be related to a condition effect (shown by an intraindividual variability index), and by effects specific to selective conditions (extinction with Carpipramine, habituation with Minaprine). These data have theoretical implications and also clinical, or pathophysiological CNV applications.

It has been theorized that CNV might be the summation of a sensory evoked potential and a motor potential (Rohrbaugh *et al.*, 1980). With such a model it is not possible to understand how a "condition effect" could be observed, as in our experiment. Thus, the existence of endogenous components of the CNV which depend on the psychological features of the task is clearly implied.

In previous reports of CNV changes after psychotropic drug intake, no consistent changes were observed (*cf.* Dongier, 1973, Rebert, 1980). But in these observations, only CNV amplitudes were studied, and not dynamic changes. Jansen *et al.* (1978) have reported some differences in habituation under amphetamine drugs, related to intraindividual psychological characteristics (extraversion or introversion). We have also reported CNV changes with benzodiazepines which are only observed in reinforcing conditions (Paty *et al.*, 1978). Standardization for looking at dynamic parameters of CNV would be fruitful for psychotropic drug screening for descriptive and predictive purposes. It appears that with some drugs there is a global, nonselective effect: decreased CNV amplitudes with morphine, increased amplitudes with chlorpromazine (Paty *et al.*, 1978). With other drugs there are more selective effects, as with minor tranquilizers like benzodiazepines (reinforcement) and with stimulant drugs (habituation or extinction).

Actually, it is not possible to have consistent data for an explicative model of electrocortical parameters of behavior. As a matter of fact, we can conclude that: (a) mechanisms of psychotropic drug action are hypothetical; even if neuroleptics mainly target dopaminergic systems and antidepressants mainly target catecholaminergic and serotonergic systems, we know that in humans, psychotropic drugs act on several targets and effects are interactive (Usdin *et al.*, Barchas, 1977), (b) neurochemical brain mediators which might be involved in mental illness are, to a great extent, unknown (Zarifian, 1979), and (c) psychotropic drug effects seem to be more relevant to their psychological action than to their neurochemical actions (Pirch, 1977).

Thus, there is a need for better heuristic models for describing electrocortical activity. It is not a good idea to insulate CNV from other electrocortical parameters. For instance, Zappoli *et al.* (1980) have shown that neurobiological mechanisms of brain activation of alpha rhythms and CNV amplitudes are quite different. Averaging is not the only way to analyze phenomena observed in the CNV paradigm. Cortical rhythms, which are mixed with slow potentials, trial by trial changes, topographic differences, and the duality of pre- and postimperative CNV, must not be ignored (Klorman and Bentsen, 1975).

As a first step a two-dimensional linear model including static and dynamic parameters for interpreting CNV can be proposed. The DC baseline appears to be relevant to individual endogenous components of behavior, which may be described as "genetic" parameters (*cf.* Claverie *et al.*, this volume). The initial level can be changed by psychotropic drug action and it may be indirectly measured by dynamic plasticity (or condition effect) in several test conditions. The transient DC shift activated by a warning stimulus and cue responding appears to be related to external conditions and the "actual" conditions of behavior. It may be measured by static parameters (like

CNV amplitudes). More precision may hopefully be obtained by further development of signal analyses. Computerized CNV may prove as useful as frequency analysis of EEG, especially if it is studied in reference to baseline (defined on the preimperative EEG) and computed so as to measure the segments over time.

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