Event-Related Brain Research (EEG Suppl. 42)
Editors: C.H.M. Brunia, G. Mulder and M.N. Verbaten

Contingent negative variation (CNV) in psychopharmacology

M. Timsit-Berthier

Laboratoire de Neurophysiologie Clinique et de Psychopathologie, University of Liège, 4000 Liège (Belgium)

Introduction

Since the discovery of 'expectancy wave' 25 years ago (Walter et al. 1964), the relationship between contingent negative variation (CNV) and psychotropic drugs has been extensively studied. The results obtained are complex and often difficult to interpret because of uncertainty about physiological and psychological processes underlying CNV and also because of numerous methodological problems due in part to the interindividual variability of response to drug. However, this paper attempts to study this question by viewing the field both pharmacologically and clinically.

The *pharmacological studies* are centred on drug characteristics and have 2 aims: the first is to detect drug central effects and to specify their latency and duration and the second is to define their 'electrophysiological profile' in order to classify them and predict their pharmacological action. All studies need to be carried out on a homogeneous population. The subjects should be young, healthy and conform to predetermined electroencephalographic statistical tests. After appropriate control measurement, the test drug is administered; it is important to establish that a dose-response relationship exists between the drug dose used and the electrophysiological effects observed. Thus, pharmacological experiments involving the CNV need to be carefully designed so that precisely formulated questions are asked that will produce clear-cut answers.

By contrast, *clinical studies* are centred on the patient and have 2 aims: the first is to measure objectively the therapeutic effects of drugs and to assess the 'normalisation' of abnormal electrophysiological measures associated with a particular pathological condition and the second is to select 'responders' to a given drug. The latter can be an extremely useful approach to overcome the wide variation of individual responses and the imprecise diagnostic criteria available in psychiatry. The population under study is necessarily heterogeneous because it is composed of patients. Furthermore, under clinical conditions, drugs are administered chronically, and this is likely to produce effects that are substantially different from the action of a single acute dose of the same drug. Finally, under these conditions, it is difficult to study systematically the effects of a single drug and also to establish a dose-response relationship.

We shall develop successively these 2 sections starting with a discussion of methodological problems and then a review of the main trends in relevant literature, illustrating them by reference to our own research.

Correspondence to: Dr. M. Timsit-Berthier, Laboratoire de Neurophysiologie Clinique et de Psychopathologie, University of Liège, 154 Rue Principale, 4000 Liège, Belgium.

Pharmacological studies

Methodological problems

The use of CNV in psychopharmacology raises many methodological problems that we do not attempt to review extensively; instead, we will focus on the more critical problems related to the selection of subjects and to the choice of experimental paradigm.

Selection of subjects. The experimental design most often consists of double-blind crossover studies that require 2 matched groups of subjects, one of which receives placebo and the other an active substance. Thus, the 2 groups must be homogeneous with regard to age, height, weight, sex and phase of the menstrual cycle (Abramovitz and Dubrovsky 1980). Howard et al. (1982) showed very stable CNV in male subjects, contrasting with systematic variations of those recorded in females along their menstrual cycle. In addition, subjects should be selected taking into account personality data since a considerable body of physiological, behavioural and pharmacological evidence supports Eysenck's hypothesis (1969) that introverts, who are characterized by a greater intrinsic activity in arousal systems than extraverts, display differential responses to psychotropic drugs (review in Ashton 1987). Moreover, there would be a non-linear, inverted U-shaped relationship between CNV amplitude and central arousal levels (Tecce 1972). Thus, combined with Eysenck's theory of personality, this model predicts that stimulant drugs would enhance CNV amplitude preferentially in extravert subjects. In fact, psychopharmacological studies which have taken personality traits into account have, in part, confirmed these hypotheses (Ashton et al. 1981; Binnie and Commer 1978; Münte et al. 1984; Rizzo et al. 1985; O'Connor 1986). However, we need to investigate with more accurate measures the different psychophysiological levels of arousal to demonstrate clearly these theories which appear as an oversimplification of the complex adjustment of cerebral resources to output (Hockey and Hamilton 1983).

The selection must also be based on electrophysiological criteria like amplitude, duration and shape of CNV, at least when it is recorded with standard protocol with a short inter-stimuli interval (ISI). Thus matched groups must be constituted with equal proportions of subjects belonging to the different categories (i.e., low vs. high amplitude CNV; fast vs. gradual rise time CNV). This implies that CNV will be recorded at least once before the pharmacological experiment, which has the advantage of rubbing out the effect of the first session.

As for the experimental session, the following points must be carefully checked: quality of sleep the night before the experiment, smoking and drinking habits, and meal time; breakfast and lunch must be standardized. Moreover, during the course of the experiment, psychological changes must be studied by means of visual analogue scales (VAS), and changes in task performances must be analysed in recording not only responses speed but also the rate of error in responding (Wesnes et al. 1987).

Choice of CNV paradigm. The second methodological difficulty lies in the choice of a relevant CNV paradigm. Numerous studies used the standard CNV protocol which consists of a warning stimulus (S1) followed 1 or 2 sec later by an imperative stimulus (S2) which induces a simple, undivided attention set for motor response (review in Tecce et al. 1978). Over the past 10 years, however, this paradigm has been challenged by several researchers because it is unable to display the different CNV components (Fehm-Wolfsdorf et al. 1981; Rockstroh et al. 1981; Münte et al. 1984; Rösler et al. 1985). In fact, by lengthening the ISI beyond 3 sec, at least 2 distinct CNV components have been demonstrated: the first one (early or initial CNV), with a predominantly frontal distribution, appears in response to S1 and is assumed to be associated with orienting attention or with processing stimulus input; the second one (late or terminal CNV) occurs in anticipation of motor response and of S2 with a maximum at the vertex and is thought to reflect expectancy, preparation or response-directed attention (review in Rohrbaugh and Gaillard 1983; Brunia and Damen 1988). Thus, it is of interest to specify the exact CNV component which might be sensitive to a specific drug by lengthening the ISI and by using topographical mapping.

In addition, in comparison to standard CNV protocol, the CNV task can be complicated and subjects

may be required either to divide their attention between 2 simultaneous tasks (as in the 'distraction paradigm' of Tecce et al. 1983) or to shift their attention from one task to another (go/no go paradigm: aversive/neutral stimulus; mixed ISI). Finally, several different event-related potentials (ERPs) may be studied either separately or simultaneously as in the 'double priming paradigm' (Rösler et al. 1985): a succession of visual stimuli was presented, which transmitted different information on how to classify the terminal stimulus in a sequence. Within a long recording epoch, the authors identified several P300a and b and early and late CNV components.

Ideally, the experimental paradigm must be based on the psychophysiological constructs which are thought to be related to the hypothetical actions of the drug under study. However, to date there is not enough experimental evidence to indicate clearly the best experimental paradigm to be chosen to test a particular psychotropic drug, and one approach to overcome this problem might be to establish a standardized battery of ERPs which would be systematically used in psychopharmacological studies in addition to more specific protocols. It would also be of interest that ERP studies were always associated with EEG power spectrum analysis and with ECG recording.

Finally, the way to analyse data deserves some comment. In addition to the usual descriptive statistics on group means and variances, single case studies have to be performed, as strong drug-induced effects can be masked by the opposed trends of some of the subjects. Another aspect of data analysis should be the description of several index covariations (i.e., reaction time and CNV amplitude; EEG spectrum reactivity and CNV parameters). Some covariations concurrent and concomitant under baseline conditions may become reciprocal and successive due to drug effect, and such changes may reflect not only quantitative alteration in ERPs but also modification in organizational characteristics of the CNS.

Data from the literature

The effects of psychotropic drugs upon CNV parameters have been extensively reviewed by Tecce et al. (1978) and by Thompson et al. (1986). Generally speaking, when recorded with standard paradigm with short ISI (< 3 sec), CNV amplitude decreases with sedative drugs whereas it increases with stimulants; these effects were not clearly observed with longer ISI (Münte et al. 1986). With the 'double priming paradigm,' Rösler et al. (1985) found a significant reduction of late CNV after flupentixol intake (2 mg) and this CNV change occurs while no subjective effect is reported; such a study may be useful for detecting infraclinic side effects. Anticonvulsant benzodiazepines (BZD), carbamazepine (CBZ) and clonazepam, were studied with a 2-stimulus reaction time paradigm which mixed 2 and 6 sec ISIs (Rockstroh et al. 1987, 1991). These 2 drugs similarly dampened the late CNV but had a different effect on the early CNV component with a fronto-central reduction under clonazepam and a centro-parietal decrease under CBZ. Such data might indicate differential drug effects on specific brain regions.

Only a few studies have evaluated the effects of dysleptic drugs on CNV parameters and all used paradigms with short ISIs. Lysergic acid diethylamide (LSD) enhanced CNV amplitude (Walter et al. 1964) while acute or prolonged THC use reduced CNV amplitude and post-S2 positivity (Kopell et al. 1972; Herning et al. 1979). Nitrous oxide ('laughing gas') did not decrease CNV amplitude in spite of attentional deficit (Fenwick et al. 1979) but induced the occurrence of post-S2 negativity component (PINV) associated with derealization state (Timsit-Berthier et al. 1987a).

Peptide hormones may represent a privileged class of substances to be screened by ERPs and CNV recordings because they are not detected by quantitative EEG and also because their receptors are often located in frontal, central and limbic areas which are involved in ERP genesis. However, neither the luteinizing hormone releasing factor (LH-RH) nor the growth hormone releasing factor (GH-RH) were shown to induce any change in CNV amplitude (Ashton et al. 1976). ACTH analogues ($ACTH_{1-24}$ and $ACTH_{4-10}$) have been extensively studied, but the results obtained are contradictory; no significant action on CNV (recorded with a go/no-go paradigm with a 4 sec ISI) was found by Miller et al. (1974) while significant results were described by other authors. Thus, $ACTH_{4-10}$

shortened reaction time and decreased the late component of CNV when the subject's attention was required for a simple attention task (ISI: 6 sec) (Gaillard and Varey 1979; Rockstroh et al. 1981); but it slowed reaction time and prevented the habituation of the early CNV component when the task was more effortful (attention shift between neutral and aversive stimuli; ISI: 6 sec; Fehm-Wolfsdorf et al. 1981). The results of these studies taken together suggest that $ACTH_{4-10}$ facilitates the fixation of an 'attentional set,' then allowing rapid habituation of the late CNV but makes difficult the shift between different attentional sets, impairing performance in spite of more resource mobilisation as attested by the lack of early CNV habituation. Whatever the interpretation of these results, such data stress the importance of the choice of relevant CNV paradigm to show the central effect of peptides.

Neurohypophyseal hormone assessment

In addition to their peripheral action, the 2 neurohypophyseal peptides appear to modulate learning and memory at least in animals, and their effects appear to operate in opposite directions (review in De Wied and Versteeg 1979). In studies in humans results obtained using psychometric tests are more controversial; it would be of interest to detect and specify their effects on CSN using an electrophysiological method. Unfortunately, EEG spectrum was not modified by vasopressin (Vp) (Timsit-Berthier et al. 1978). The early component of CNV which is able to habituate could reflect an elementary form of learning and appears to be a good tool for testing these peptides. Using a standard CNV paradigm (S1-S2 motor response with ISI = 1 sec), we tested the CNV habituation rate induced by Vp (Timsit-Berthier et al. 1982) and by oxytocin (OT) (Geenen et al. 1988).

The OT study illustrates some of the methodological points previously developed. It was conducted double blind on 2 groups of 14 males selected by means of present state examination (Wing et al. 1981) and using CNV features; 8 subjects were rejected because of slight psychological disorders or CNVs outside the normal range. Finally, on the basis of their individual CNV profiles, 2 matched groups each having 10 subjects were made; group I received OT, and group II received placebo (Pb). Moreover to control interindividual variability of the data better, each subject was compared to himself in a 3 part experimental design; A and B recordings were performed on the same day and the C recording was made 1 week later. In A, both groups received an intravenous infusion of 0.9% saline (Pb) for 45 min starting at 09.30 h; at the end of the infusion, CNV was recorded (CNV-A). Then group I was infused with OT for 45 min (84 m IU/min leading to a total dose of 3.780 m IU OT). Group II once more received Pb infusion (0.9% saline); another CNV was recorded at the end of the infusion (CNV-B) and, 1 week later, a third CNV was recorded at 11.00 h (CNV-C). The CNV amplitude was measured as the area under the curve between 500 and 1000 msec after S1. The results are displayed in Figs. 1 and 2: compared to CNV-A, the amplitude of CNV-B was reduced after OT infusion and this short-term effect was statistically significant only at Cz (Fig. 1). No subjective effect was reported and only some light alteration of memory performance was observed after OT infusion (Rey PRM test). Moreover, no significant changes occurred at the level of EEG power spectrum nor at the level of autonomic function (heart rate, blood

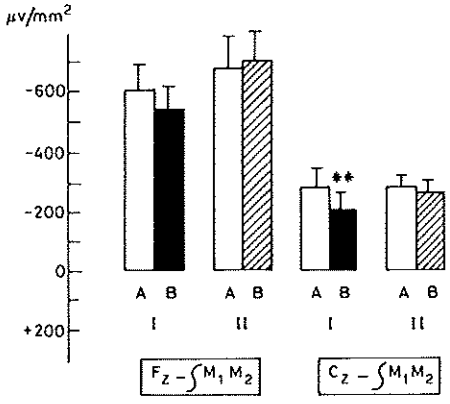

Fig. 1. Short-term effect of oxytocin on the amplitude of CNV (measured as area under the curve). Each histogram represents the amplitude of CNV (mean + S.D.). Two recording conditions: (i) Fz-linked mastoids, results shown in 2 left-hand pairs of histograms; (ii) Cz-linked mastoids, results shown in 2 right-hand pairs of histograms. Groups I and II both received placebo after which group I was infused with oxytocin (black) whereas group II received placebo again (hatched). Note reduced CNV amplitude following oxytocin given in session B which was statistically significant at Cz ($P < 0.01$) but not at Fz. (From Geenen et al. 1988.)

pressure). A long-term OT effect was supported by CNV-C results: a significant decrease of CNV amplitude persisted but was mainly evident at Fz (Fig. 2). This effect is surprising since OT has a half-time of only a few minutes. It is interesting to compare these results with those obtained in previous research on the effects of lysine-vasopressin (LVP) on CNV (Timsit-Berthier et al. 1982). In a group of 26 young male volunteers, LVP administered by nasal spray prevented the spontaneous decrease of CNV amplitude normally observed upon long recordings and repetitive sessions and thus delayed the course of 'habituation.' This effect appears to oppose that of OT which accelerates the spontaneous decrease of CNV amplitude over recording sessions. Therefore, these studies provide additional arguments in favour of opposite central action of OT and VP in humans.

In conclusion, we may state that, in spite of many methodological problems, CNV is already useful to detect and analyse the central effect of drugs, especially when quantitative EEG is not relevant.

Clinical use of CNV

Compared with studies on normal healthy volunteers, clinical studies are characterised by several differences. First, clinical populations are necessarily heterogeneous and used to taking drugs chronically; CNV patients often display abnormal

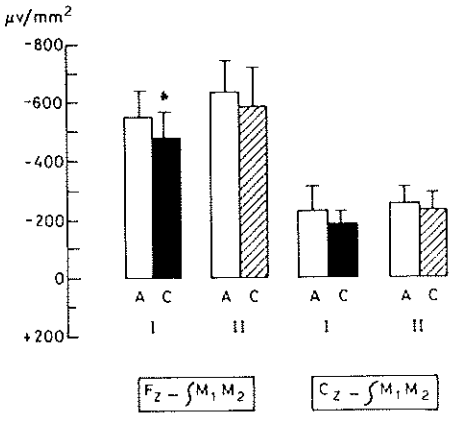

Fig. 2. Long-term effect of oxytocin on CNV amplitude (see legend of Fig. 1 for key). Session C was recorded 1 week following infusion. Note reduced CNV amplitude at Fz ($P < 0.05$). (From Geenen et al. 1988.)

features with too high or low amplitudes followed by PINV (review in Roth et al. 1986). Moreover, many psychotropic drugs, in particular the antidepressants, have anticholinergic effects which can affect CNV independent of their other pharmacological actions. Finally, CNV parameters measured after drug intake must be considered to be the result of interactions between the clinical state and neurobiological drug effect, and it is difficult to disentangle these 2 factors.

Methodological problems

CNV paradigm. It is difficult to apply complex experimental paradigms for eliciting CNV in patients who often have a limited attention span and are unable to cooperate. Thus, in most clinical studies, a simple CNV paradigm with a S1-S2 interval not exceeding 2 or 3 sec is adopted. A go/no-go paradigm wiht longer ISI also was used (Pierson et al. in press) and it seems interesting to detect 'responders' to new antidepressants.

Subject selection. Based on clinical criteria, groups of patients are formed according to criteria of standard methods of psychiatric classification (PSE, DSM III, RDC, etc.). Although a requisite for any clinical research, this principle of selection does not prevent ambiguity; patients belonging to the same nosological group often present a wide neurobiological heterogeneity, leading to different, even opposite, reactivities to similar drugs. Therefore, the selection should include, in addition to diagnostic criteria, neurobiological and psychological tests which could help to classify patients from a trans-nosological and functional point of view (Van Praag et al. 1987).

Washout period. Each clinical trial is usually preceded by a washout period of at least 1 week before dispensing the drug under study. Such a practice raises not only ethical but also neurobiological problems. A well known example is given by BZD abrupt washout which may reduce the electroconvulsive threshold and increase CNV amplitude since an enhancement of negative slow cortical potentials would indicate a high risk for seizure to develop (Elbert et al. 1990).

Control group. The choice of control group is a delicate problem; ideally, one may deal with healthy matched subjects recorded at the same interval as the patients (Giedke et al. 1987). However, we have to be aware that this experimental design is difficult to perform in practice. Another method is to compare the experimental group with patients receiving Pb, often in a double-blind design. However, if giving placebo to Alzheimer patients will not substantially modify the course of their degeneration and does not raise ethical problems, this is not the case when the mental illness may endanger the patient if no therapy is dispensed (cf., major depressive disorder or schizophrenia). Finally, it would be more advisable to give the patients serving as controls a standard medication of which the effects are well known.

Experimental conditions. The control of experimental conditions is hardly checked as well as in control subjects. In particular, variables such as quality of sleep or cigarette consumption are nearly impossible to control. The rhythm at which re-test recording sessions should be scheduled must take into account not only the pharmacological constraints but also the clinical criteria for treatment efficacy. For example, in the testing of patients with Alzheimer-type dementia, 3 month intervals were chosen by Tecce et al. (1983), while 12 month intervals were used by Zappoli et al. (1988). At variance, most antidepressant studies had test-retest intervals ranging from 2 to 4 weeks (Giedke et al. 1987; Ashton et al. 1988; Pierson et al. in press). Our opinion is that, because of the slow time course of mental illness, CNV retest must be recorded with an interval of at least 45 days.

Data analysis. Data analysis must be carefully conducted; before analysing group data, individual data must be scanned in order to discriminate subjects showing opposite modifications under drugs, thus inducing non-significant differences in group averages. Also drop-out subjects must be taken into account; for example, we noticed that CNV amplitude of depressive patients, who did not tolerate tricyclic antidepressants and dropped out of our pharmacological study (13 subjects), was significantly higher than that of patients who completed the study (51 subjects).

Data of literature

The effect of drugs on CNV has been studied less extensively in pathophysiological population than in control subjects and the results so far obtained are only partial. In general, the experiments were designed in agreement with the CNV neurochemical model developed by Marczynski (1978) and by Libet (1978) who emphasised the role of cholinergic and catecholaminergic systems in the modulation of negative components of the CNV.

Parkinson's disease. As Parkinson's disease is related to dopamine (DA) deficiency in caudate nucleus and in putamen and is often associated with low CNV amplitude, it was postulated that DA agonist treatment would enhance CNV amplitude and induce PINV. In fact, Zappoli et al. (1972) and Amabile et al. (1986) who recorded CNV in parkinsonians before and after treatment by L-DOPA and/or bromocriptine (DA agonist) noticed the occurrence of PINV, frequently associated with an increase in CNV amplitude. These results are consistent with the CNV neurochemical model.

Dementia. Alzheimer dementia is a multisymptom disease, and cerebral cholinergic system deficit is certainly one of a wide range of neurotransmitter abnormalities underlying its clinical feature. Early CNV component decrease (recorded with a standard CNV paradigm with ISI = 2 sec) was observed in the early stages of presenile idiopathic mental deterioration (Zappoli 1988). Hydergine and nicergolide which are drugs known to improve the functioning of the cholinergic system are not very efficient when there is severe clinical degeneration, but they may be efficient at the early stage of the disease. These drugs are able to modify CNV amplitude in demented or predemented patients. Thus, Tecce et al. (1983) observed that the 'CNV rebound effect,' recorded with a CNV distraction paradigm which induced divided attention, was significantly increased in Alzheimer patients receiving hydergine for a period of 3 months. However, this electrophysiological drug effect was not correlated with clinical improvement. Zappoli et al. (1988), using a standard CNV paradigm with a 2 sec ISI (the optimal ISI length for facilitating preparation in normal elderly people), noticed an increase of CNV amplitude in patients with presenile Alzhei-

mer-type dementia receiving nicergolide treatment for 12 months and also pointed out slight clinical improvement after treatment. These results are consistent with the view that drugs which stimulate the cholinergic system also increase CNV amplitude. They also prove that CNV may be a useful discriminator for early detection of presenile mental decline. This early detection is crucial if therapeutic advances are to be made, since potential therapies need to be introduced at a time when brain dysfunction can be reversed or arrested.

Headache. Headache is a frequent disease with a large body of aetiology. Hyperactivation of catecholaminergic systems was assumed in migraine and, in agreement with this hypothesis, we identified an electrophysiological pattern which characterises migraine vs. tension headache. This pattern is constituted by high amplitude CNV with no habituation during the experimental session, associated with high level of alpha blocking (Timsit et al. 1986).

In a pathophysiological study, a group of 28 subjects (17 migraineurs and 11 tension headache sufferers, classified in accordance with the Ad Hoc Committee (1962)), was studied to correlate CNV amplitude with plasma levels of noradrenaline (NA), adrenaline (A) and DA. The subjects were free from attacks for at least 7 days before examination and were not receiving any prophylactic treatment. Their results are shown in Fig. 3. Tension headache sufferers displayed a significant lower NA plasmatic level than migraineurs, but there was a good positive correlation between CNV amplitude and NA plasma level regardless of the type of headache ($r = 0.59$; $P < 0.01$ Spearman's test). No difference between groups, and no correlations were found for A and DA.

In a prospective therapeutic study, another group of 25 migraineurs was recorded before and after a 5 month treatment with beta-blockers (BB; metoprolol, 110 mg/day). The clinical efficacy of the drug was evaluated by a global severity score, taking into account the number of attacks and their duration. The treatment significantly reduced the severity score, the CNV amplitude and NA plasma level in a striking comparison. Moreover, CNV amplitude provided a significant index to predict the therapeutic efficacy of BB: the higher the CNV amplitude, the better the response to treatment in terms of severity score reduction (Fig. 4). This CNV pharmacological approach of headache validated CNV as a tool to predict the response to a specific therapeutic strategy, and this application has now been run as routine in our laboratory. Thus, about 12 headache sufferers are recorded each week with a standard CNV paradigm (ISI = 1 sec) associated with an EEG spectrum analysis (Timsit et al. 1986). The results are quickly obtained, as for any other examination in medical practice, and integrated into the clinical data in order to aid therapeutic decision making (i.e., the occurrence of high amplitude CNV

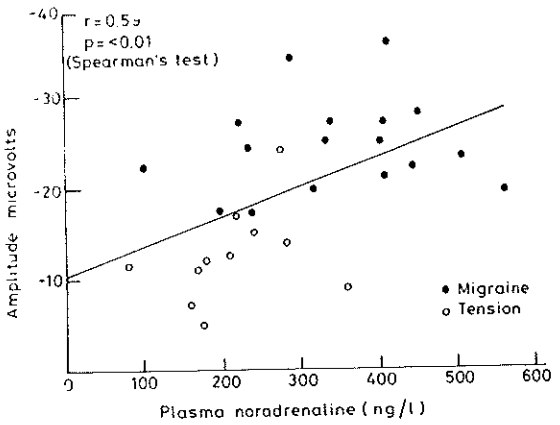

Fig. 3. Correlation between CNV amplitude (ordinate) and plasma concentration of noradrenaline (abscissae) in headache sufferers. (From Timsit et al. 1986.)

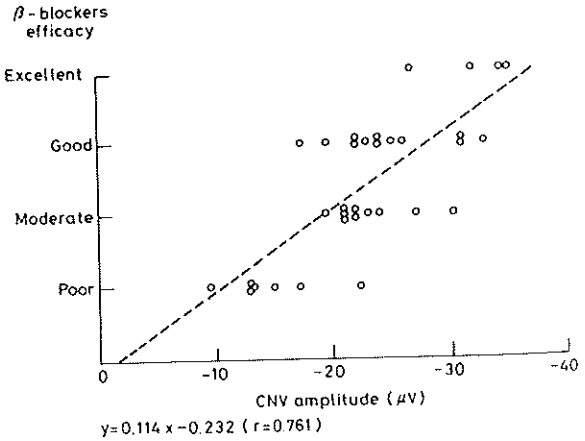

Fig. 4. Effect of treatment with beta-adrenoceptor blocking drugs on CNV amplitude in migraineurs. (From Timsit et al. 1986.)

associated with high EEG reactivity is an argument for prescribing BB).

Depression. The biochemical approach to depression is extremely complex. Central disturbances in catecholaminergic and cholinergic systems as well as in the serotoninergic system are encountered (review in Van Praag 1982). A small CNV amplitude is consistent with theories postulating reduced levels of monoaminergic activities in depression. However, high as well as low amplitude CNV have been described in this disease (Timsit-Berthier et al. 1987b). The relationship between these CNV changes and the biochemical depression mechanism is not clear. In order to bring light to this problem, we recorded CNV with standard paradigm (ISI = 1 sec) in 56 patients with major depressive episode (as defined by the DSM-III criteria), and in order to assess the disturbances of their catecholaminergic systems, we performed 2 neuroendocrine challenge tests which allow appreciation of DA and NA reactivity. Thus, these patients were submitted to a washout period of 2 weeks and then were injected with a single dose of clonidine and 2 days later with apomorphine. Growth hormone (GH) response to both these substances indirectly reflects the functional reactivity of NA and DA systems. Finally, in measuring the relationship between CNV amplitude and GH response to clonidine and apomorphine, we noticed: (1) a lack of correlation between CNV and GH response to clonidine which may be explained by the great occurrence of no reactive ('blunted') clonidine test in depressive patients (Ansseau et al. 1988); (2) a significant positive correlation between CNV and GH response to apomorphine (r +0.44; P <0.001): the higher the CNV, the higher the reactivity of DA receptors (Fig. 5). This relationship which held independent of the influence of age is of theoretical interest since it highlights the role of the DA system in the modulation of CNV, a role which has received little attention among the contributions to this congress (Skinner (1989) and Pineda et al. (1989) mainly pointed out the NA system). In addition it provides immediate practical interest because it allows definition of the subjects who will respond to antidepressants; indeed, Ansseau et al. (1988) showed that patients with no reactive apomorphine test are

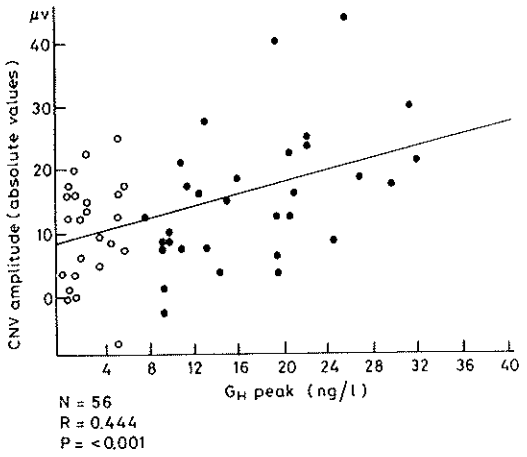

Fig. 5. Correlation between peak growth hormone (GH) level achieved during apomorphine test and CNV amplitude in depressed patients. White circles refer to 'blunted' tests.

more likely to respond to substances activating the catecholaminergic system. Thus, it may be assumed that subjects with low CNV amplitude would be the best 'responders' to DA and NA antidepressant agonists while patients with high amplitude CNV would better respond to serotoninergic drugs. This hypothesis is consistent with the results obtained by Timsit-Berthier and Timsit (1981) who recorded standard CNV (ISI = 1 sec) in 13 depressed patients before and after treatment by DA and NA reuptake inhibitors; they noticed clinical improvement associated with an increase of CNV amplitude in 11 out of 13 patients after 3 months of drug treatment. It also is in agreement with the study of Pierson et al. (in press) who showed a rather selective action of fluoxetine HCl (a pure serotoninergic agonist drug) in depressive patients displaying high amplitude CNV in a go/no-go paradigm (ISI = 4 sec).

However, this hypothesis is somewhat overshadowed by other results. Thus, Ashton et al. (1988) recorded 32 depressive patients at approximately 1, 3 and 6 weeks after the start of antidepressant therapy (amitriptyline, 22 patients; other tricyclic antidepressants, 6 patients; lithium carbonate, 1 patient; monoamineoxidase inhibitor, 1 patient; combination of drugs, 2 patients). CNV was obtained with standard paradigm and 2 different ISI intervals (1.25 and 4 sec). There was a highly significant correlation between long and

short CNVs ($r = 0.6$; $P < 0.001$). Before treatment, CNV amplitude correlated negatively with severity of depression regardless of diagnostic category. In patients with initially small CNV, there was an increase in magnitude over time but, in those with larger CNVs, there was little change or even a decrease. Using a standard CNV paradigm with ISI = 1.9 sec, Giedke et al. (1987) recorded 59 depressive patients before and after 4 week double-blind treatment with either amitriptyline (AT) or oxaprotiline (OT). At the same times, 30 healthy subjects were investigated 3 times in identical intervals of 2 weeks. In the AT group, clinical improvement and drug plasma levels of nortriptyline (the principal metabolite of AT) were positively related to an increase of CNV area. In the OT group, the reverse was true; increase in CNV area was related to smaller OT plasma levels and less favourable outcome. There was no individual CNV analysis in these last 2 studies.

Finally, the use of CNV in clinical pharmacological study brought clearer results with neurological diseases (as Parkinson's disease and headache) than in depression. However, compared with the other biological markers of depression, only few ERPs studies were already performed in this field. Hopefully further CNV studies in depressive patients associated with refined clinical and biochemical assessments should lead to a better understanding of the meaning of CNV parameter changes in the evolution of depression under specific drugs.

References

Abramovitz, M. and Dubrovsky, B. CNV characteristics throughout the normal menstrual cycle. In: H.H. Kornhuber and L. Deecke (Eds.), *Motivation, Motor and Sensory Process of the Brain. Prog. Brain Res., Vol. 54.* Elsevier, Amsterdam, 1980: 441 – 447.

Ad Hoc Committee. Classification of headache, *JAMA*, 1962, 179: 717 – 718.

Amabile, G., Fattaposta, F., Pozzessere, P., Albani, G., Sanarelli, L., Rizzo, P.A. and Morocutti, C. Parkinson's disease: electrophysiological (CNV) analysis related to pharmacological treatment. *Electroenceph. clin. Neurophysiol.*, 1986, 64: 521 – 524.

Ansseau, M., Von Frenckell, R., Maassen, D., Cerfontaine, J.L., Papart, P., Timsit-Berthier, M., Legros, J.J. and Franck, G. Prediction of treatment response to selective antidepressants from clonidine and apomorphine neuroendocrine challenges. In: M. Briley and G. Fillion (Eds.), *New Concepts in Depression. Pierre Fabre Monogr. Series, Vol. 2.* MacMillan Press, London, 1988: 269 – 276.

Ashton, H. *Brain Systems, Disorders and Psychotropic Drugs.* Oxford Univ. Press, Oxford, 1987: 547 pp.

Ashton, H., Millman, J.E., Telford, R. and Thompson, J.W. An electroencephalographic investigation of short-term effect of three hypothalamic hormones (TRH, LH/FSH-RH, GH-RIH) in normal subjects. *Br. J. Clin. Pharmacol.*, 1976, 3: 523 – 531.

Ashton, H., Golding, J.F., Marsh, V.R., Millman, J.E. and Thompson, J.W. The seed and the soil: effect of dosage, personality and starting state on the response to tetrahydrocannabinol in petit mal. *Br. J. Clin. Pharmacol.*, 1981, 12: 705 – 720.

Ashton, H., Golding, J.F., Marsh, V.R., Thompson, J.W., Hassanyeh, F. and Tyrer, S.P. Cortical evoked potentials and clinical rating scales as measures of depressive illness. *Psychol. Med.*, 1988, 18: 305 – 317.

Binnie, C.D. and Comer, A.K. The effect of cigarette smoking on the contingent negative variation (CNV) and eye movement. In: R.E. Thornton (Ed.), *Smoking Behavior: Physiological and Psychological Influences.* Churchill Livingstone, Edinburgh, 1978: 69 – 75.

Brunia, C.H.M. and Damen, E.J.P. Distribution of slow potentials related to motor preparation and stimulus anticipation in a time estimation task. *Electroenceph. clin. Neurophysiol.*, 1988, 69: 234 – 243.

De Wied, D. and Versteeg, D.H.G. Neurohypophyseal principles and memory. *Fed. Proc.*, 1979, 38: 2348 – 2354.

Elbert, T., Rockstroh, B., Birbaumer, N., Canavan, A. and Bulow, I. Self regulation of slow cortical potentials and its role in epileptogenesis. In: J.G. Carlson and R. Serfert (Eds.), *Biobehavioral Self-regulation and Health.* Plenum Press, New York, 1990.

Eysenck, H.J. *The Biological Basis of Personality.* Thomas, Springfield, IL, 1967.

Fehm-Wolfsdorf, G., Elbert, T., Lutzenberger, W., Rockstroh, B., Birbaumer, N. and Fehm, H. Effect of an ACTH 4 – 10 analog on human cortical evoked potentials in a two-stimulus reaction-time paradigm. *Psychoneuroendocrinology*, 1981, 6: 311 – 320.

Fenwick, P., Bushman, J., Howard, R., Perry, I. and Gamble, T. Contingent negative variation and evoked potential amplitude as a function of inspired nitrous oxide concentration. *Electroenceph. clin. Neurophysiol.*, 1979, 47: 473 – 482.

Gaillard, A.W.K. and Varey, C.E. Some effects of an ACTH 4 – 9 analog (Org. 2766) on human performance. *Physiol. Behav.*, 1979, 23: 79 – 84.

Geenen, V., Adam, F., Baro, V., Mantanus, H., Ansseau, M., Timsit-Berthier, M. and Legros, J.J. Inhibitory influence of oxytonic infusion on contingent negative variation and some memory tasks in normal men. *Psychoneuroendocrinology*, 1988, 13: 367 – 375.

Giedke, H., Heiman, H. and Rein, W. La modification des potentiels évoqués lents chez les déprimés sous amitriptyline et oxaprotiline. *Rev. EEG Neurophysiol. Clin.*, 1987, 17: 279 – 287.

Herning, R., Jones, R.T. and Peltzman, D.J. Changes in human event-related potentials with prolonged delta-9-tetrahydrocannabinol (THC) use. *Electroenceph. clin. Neurophysiol.*, 1979, 47: 556 – 570.

Hockey, R. and Hamilton, P. The cognitive patterning of stress states. In: R. Hockey (Ed.), *Stress and Fatigue in Human Performance.* Wiley, Chichester, 1983: 331 – 362.

Howard, R., Gifford, M. and Lumsden, J. Changes in an electro-cortical measure of impulsivity during the menstrual cycle. *Pers. Individ. Diff.*, 1988, 9: 917 – 918.

Kopell, B.S., Tinklenberg, J.R. and Hollister, L.E. Contingent negative variation: marijuana and alcohol. *Arch. Gen. Psychiat.*, 1972, 27: 809 – 811.

Libet, B. Slow post-synaptic responses of sympathetic ganglion cells as models for slow potential changes in the brain. In: D.A. Otto (Ed.), *Multidisciplinary Perspectives in Event-Related Brain Potential Research.* U.S. Govt. Printing Office, Washington, DC, 1978: 12 – 19.

Marczynski, T.J. 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. Govt. Printing Office, Washington, DC, 1978: 25 – 35.

Miller, L., Kastin, A., Sandman, C., Finck, M. and Van Veen, W. Polypeptide influences on attention, memory and anxiety in man. *Pharmacol. Biochem. Behav.*, 1974, 2: 663 – 668.

Münte, T.F., Heinze, H.J., Künkel, H. and Scholz, M. Personality traits influence the effects of diazepam and caffeine on CNV magnitude. *Neuropsychobiology*, 1984, 12: 60 – 67.

Münte, T.F., Heinze, H.J. and Künkel, H. Use of endogenous event-related potentials (ERPs) in the evaluation of psychotropic substances: toward an ERP profile of drug effects. *Neuropsychobiology*, 1986, 16: 135 – 145.

O'Connor, K. The effects of smoking and personality on slow cortical potentials recorded within a signal detection paradigm. *Physiol. Psychol.*, 1986, 14: 49 – 62.

Pierson, A., Dodin, V. and Lesèvre, N. A pilot study of the treatment of major depressive disorders with fluoxetine HCl according to their subtypes: retarded or agitated. In press.

Pineda, J.A., Snick, D. and Foote, S.L. The role of noradrenergic and cholinergic systems in the generation of P300-like potentials. *This volume*, 1991: Ch. 14.

Rizzo, P.A., Pierelli, F., Pozzessere, G., Pattaposta, F., Sanarelli, L. and Morocutti, C. Pain, anxiety and CNV: a clinical and pharmacological study. *Biol. Psychiat.*, 1985, 20: 1297 – 1302.

Rockstroh, B., Elbert, T., Lutzenberger, W., Birbaumer, N., Fehm, L. and Voigt, K. Effect of an ACTH 4 – 9 analog on human cortical evoked potentials in a constant foreperiod reaction time paradigm. *Psychoneuroendocrinology*, 1981, 6: 301 – 310.

Rockstroh, B., Elbert, T., Lutzenberger, W., Altenmüller, E., Diener, H., Birbaumer, N. and Dichgans, J. Effects of the anticonvulsant carbamazepine on event-related brain potentials in man. In: C. Barber and T. Blum (Eds.), *Evoked Potentials, III.* Butterworth, London, 1987: 361 – 369.

Rockstroh, B., Elbert, T., Lutzenberger, W. and Altenmüller, E. Effects of the anticonvulsant benzodiazepine clonazepam on event-related brain potentials in humans. *Electroenceph. clin. Neurophysiol.*, 1991, 78: 142 – 149.

Rohrbaugh, J.W. and Gaillard, A.W.K. Sensory and motor aspects of the contingent negative variation. In: A.W.K. Gaillard and D.W. Ritter (Eds.), *Tutorials in Event Related Potentials Research: Endogeneous Components. Advances in Psychobiology, Vol. 10.* North-Holland Publ., Amsterdam, 1983: 269 – 310.

Rösler, F., Manzey, D., Sojka, B. and Stieglitz, R.-D. Delineation of pharmacological effects by means of endogenous event-related brain potentials: an examplification with flupentixol. *Neuropsychobiology*, 1985, 13: 81 – 92.

Roth, W., Duncan, C., Pfefferbaum, A. and Timsit-Berthier, M. Application of cognitive ERPs in psychiatric patients. In: W.G. McCallum, R. Zappoli and F. Denoth (Eds.), *Cerebral Psychophysiology: Studies in Event-Related Potentials. Electroenceph. clin. Neurophysiol., Suppl. 38.* Elsevier, Amsterdam, 1986: 419 – 439.

Schoenen, J., Maertens de Noordhout, A., Timsit-Berthier, M. and Timsit, M. Contingent negative variation and efficacy of beta-blocking agents in migraine. *Cephalalgia*, 1986, 4: 229 – 233.

Skinner, J.E. The event-related slow potential: biological function and genesis. *This volume*, 1991: Ch. 23.

Tecce, J.J., Savignano-Bowman, J. and Cole, J.O. Drug effects on contingent negative variation and eyeblinks: the distraction-arousal hypothesis. In: M.A. Lipton (Ed.), *Psychopharmacology: a Generation of Progress.* Raven Press, New York, 1978: 745 – 758.

Tecce, J.J., Cole, J.O., Mayer, J. and Lewis, D.C. Methadone effect on brain functioning and types A and B CNV shapes. *Psychopharmacology (Berl.)*, 1979, 65: 21 – 25.

Tecce, J.J., Cattanach, L., Boehner-Davis, M., Branconnier, R.J. and Cole, J.O. Etude neuropsychologique de la baisse de l'attention et traitement médicamenteux chez les malades atteints de la maladie d'Alzheimer. *Presse Méd.*, 1983, 12: 3155 – 3162.

Thompson, J.W., Ashton, H., Golding, J.F. and Marsh, V.R. Pharmacology of event-related potentials in humans. In: W.C. McCallum, R. Zappoli and F. Denoth (Eds.), *Cerebral Psychophysiology: Studies in Event-Related Potentials. EEG Suppl. 38.* Elsevier, Amsterdam, 1986: 374 – 383.

Timsit-Berthier, M. and Timsit, M. Toward a neurochemical interpretation of CNV in psychiatry: some preliminary results in depressive patients. In: D. Kemali and C. Perris (Eds.), *Advances in Biological Psychiatry, Vol. 6.* Karger, Basel, 1981: 165 – 172.

Timsit-Berthier, M., Audibert, A. and Moeglen, J.M. Influence de la lysine vasopressine sur l'EEG chez l'homme: résultats préliminaires. *Neuropsychobiology*, 1978, 4: 129 – 139.

Timsit-Berthier, M., Mantanus, H., Devos, J.E. and Spiegel, R. Action of lysine-vasopressin on human electroencephalo-

graphic activity. *Neuropsychobiology,* 1982, 8: 248 – 258.

Timsit, M., Timsit-Berthier, M., Schoenen, J. and Maertens de Noordhout, A. Contingent negative variation and EEG power spectrum in headache. In: C. Barber and T. Blum (Eds.), *Evoked Potentials: 3rd Int. Symposium.* Butterworth, London, 1986: 370 – 374.

Timsit-Berthier, M., De Thier, D. and Timsit, M. Electrophysiological and psychological aspects of the derealization state induced by nitrous oxide in nine control subjects. In: J. Mendlewicz and H. Van Praag (Eds.), *Advances in Biological Psychiatry, Vol. 16.* Karger, Basel, 1987a: 90 – 101.

Timsit-Berthier, M., Mantanus, H., Ansseau, M., Devoitille, J.M., Dal Mas, A. and Legros, J.J. Contingent negative variation in major depressive patients. In: R. Johnson, Jr., J.W. Rohrbaugh and R. Parasuraman (Eds.), *Current Trends in Event-Related Potential Research. EEG Suppl. 40.* Elsevier, Amsterdam, 1987b: 762 – 771.

Van Praag, H. Neurotransmitters and CNS disease: depression. *Lancet,* 1982, ii: 1259 – 1264.

Van Praag, H., Kahn, R.S., Asnis, G., Wetzler, S., Brown, S., Bleich, A. and Korn, M. Denosologization of biological psychiatry. *J. Affect. Dis.,* 1987, 13: 1 – 8.

Walter, W.G., Cooper, R., Aldridge, V.J., McCallum, W.C. and Winter, A.L. Contingent negative variation: an electrical sign of sensory association and expectancy in the human brain. *Nature,* 1964, 203: 380 – 384.

Wesnes, K., Simpson, P. and Christmas, L. The assessment of human information – processing abilities in psychopharmacology. In: I. Hindmarch and P.D. Stonier (Eds.), *Advances in Psychopharmacology.* Wiley, Chichester, 1987: 79 – 91.

Wing, J.K., Cooper, J. and Sartorius, N. *The Measurement and Classification of Psychiatric Symptoms.* Translation in French by M. Timsit-Berthier and A. Bragard-Ledent. Mardaga, Liège, 1981.

Zappoli, R. Event-related potential changes in the normal presenium and in patients with presenile idiopathic cognitive decline. In: *The EEG of Mental Activities – the Dementias.* Karger, New York, 1988: 1 – 25.

Zappoli, R., Versari, A., Paganini, M., Arnetoli, G., Battaglia, A., Ardia, A. and Maniero, A. Effect of long-term nicergoline treatment in contingent negative variation activity and clinical status of patients with presenile idiopathic mental deterioration: preliminary studies. In: *Ergot Alkaloids and Aging Brain: an Uptake on Nicergoline.* Excerpta Medica, Amsterdam, 1988: 72 – 83.