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Contingent Negative Variation in Major Depressive Patients

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Depression constitutes a frequent but very heterogenous disease that may involve disturbances of various neurochemical substances such as noradrenaline (NA), dopamine (DA), serotonine, and acetylcholine (ACh). Among other evidence, these neurochemical hypotheses are supported by the occurrence of blunted growth hormone (GH) response to clonidine and apomorphine in endogenous depression (Ansseau et al. 1986) and by the shortening of rapid eye movement (REM) latency related to hypercholinergic activity (Sitaram et al. 1976). Moreover, there is growing evidence that these neurochemical disorders may be secondary to uncontrollable stress and coping failure (Anisman and Zacharo 1982), and that stressful events may contribute to the provocation or exacerbation of depressive symptoms. For studying the depressed brain state, a rigid separation of the environmental and the biological factors has little empirical justification since there are numerous interactions between these different domains. In such a context, the study of the Contingent Negative Variation (CNV) is of interest, since the CNV has been shown to be responsive both the neurochemical factors such as acetylcholine and catecholamine (Libet 1978; Marczynski 1978) and to psychological factors, such as subject's evaluation and control of stress (Rockstroh et al. 1982). In depressive patients, several authors have reported low CNV amplitude with the appearance of a Post-Imperative Negative Variation (PINV) (review in Roth et al. 1986), but these findings were not obtained by all authors (Elton 1984).

The present study was designed to describe better the CNV aspects in major depressive patients, with an attempt to assess the interactions between neurophysiological, psychological and biological processes in this disease.

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METHODS

The total sample comprised 61 depressive inpatients, 10 males and 51 females, with ages ranging from 26 to 65, (mean: 46 ± 11). All of them met the Research Diagnostic Criteria (Spitzer et al. 1978) for definite major depressive disorders, and their total scores on the Hamilton Psychiatric Rating Scale for Depression was at least 23. Diagnosis was made by psychiatrists not aware of the biological results of the patients. Patients showing signs or symptoms of endocrine disease or substance abuse, or with brain organic symptoms were excluded. They were all right-handed. The electrophysiological recordings, and the neuroendocrine challenge test were performed after a drug-free period of 2 weeks.

The Present State Evaluation (PSE) of Wing et al. (1964), translated into French by Timsit-Berthier and Bragard-Ledent (1980), was administered to the 61 patients. It is a structured interview designed to identify the nature and the severity of the psychiatric dysfunction. The psychopathological characteristics of the group were described in terms of 140 separate items, 4 syndrome scores, and the CATEGO subclasses.

In order to study the CNV, the EEG signals were recorded on an EEG apparatus using amplifiers modified to provide a 5 sec time constant from 3 leads: Fz-A1 (left earlobe), Cz-A1 and Pz-A1. Ag/AgCl electrodes were used. In addition, an electro-oculogram (EOG) was recorded from above and below the left eye to check for EOG artefacts.

The CNV paradigm consisted of a highly compatible, simple reaction time (RT) task. A warning stimulus (S1, 1000 Hz, 60 dB, 50 msec duration tone), delivered through a speaker, was followed 1 sec later by an imperative stimulus (S2, series of 1800 cd, 18 Hz squared light flashes) delivered by a photic stimulator, that the subject had to stop by pressing a button with the right hand. The intertrial interval was pseudo-randomized from 10 to 30 sec. The CNV was obtained by averaging 48 artefact-free trials, as determined by visual inspection of EOG tracings, on-line for each individual trial (manual rejection). The signals were analyzed with a sampling rate of 64 Hz.

CNV amplitude (pre-imperative variation) was measured from the averaged curves recorded on Cz-A1 as the voltage difference between the average during the 1 sec baseline preceding S1 and the average during the 200 msec preceding S2. According to the normative data obtained in control subjects recorded from 3 different laboratories (Timsit-Berthier et al. 1984) we distinguished 3 classes of CNV amplitudes: low CNV ($< 12\ \mu V$); normal CNV (between 12 and 22 μV) and high CNV (higher than 22 μV).

PINV was measured as the voltage difference between the 200 msec baseline preceding S2 and the 500 − 700 msec period following S2. In the absence of a PINV this value should be positive. The criterion of PINV occurrence (abnormal CNV duration) was a ratio of Post-Imperative Variation/Pre-Imperative Variation < -0.69, as estimated on the basis of the above mentioned normative data.

The RT was measured from S2 to the occurrence of the motor response (flash switch-off).

The auditory evoked potential (AEP) evoked by S1, was analyzed separately in order to score amplitude and latency of N1 and P300 components. The averaging epoch

covered a 180 msec baseline before S1 and a 500 msec post-S1 interval. The sampling rate was 256 Hz.

The first negative component N1 was identified as the negative peak occurring within the latency range 100 – 150 msec following S1, and the positive component P3 as the positive peak within the 280 – 460 msec range. The latency of each component was calculated, and its amplitude was measured with reference to pre-S1 baseline.

In the neuroendocrine challenge tests, the hormonal responses to a specific stimulus were measured thus giving a physiological assessment of hypothalamic function. This hormonal response is related to the same neurotransmitters that are presumed to be involved in psychiatric disorders. The clonidine test evaluated noradrenergic receptor sensitivity, as clonidine is an alpha 2 adrenoreceptor agonist. The apomorphine test evaluated dopaminergic receptor sensitivity because apomorphine is considered a specific agonist, directly acting on DA post-synaptic receptors.

Clonidine and apomorphine challenge tests were performed in this order according to the same procedure with at least a 2 day interval:

At 7 a.m., after an overnight fast, an indwelling catheter was inserted in a forearm vein. Blood samples of 10 ml were collected every 20 min for 40 min before and 120 min after injection at 8 a.m. of either clonidine 0.15 mg diluted in saline to obtain 20 ml intravenously in 10 min; or apomorphine 0.5 mg diluted in saline to obtain 0.5 ml subcutaneously.

GH was measured by radioimmunoassay, with intra- and inter-assay coefficients of variation of respectively 13.3 ± 4.7 and 14.8 ± 9.6%.

GH responses following clonidine and apomorphine were assessed by GH peak values following injection and by the difference between baseline (T0) and peak values.

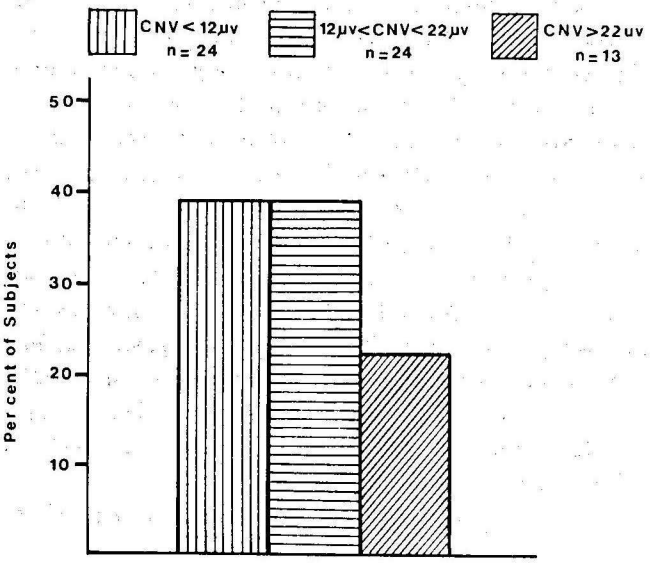

Fig. 1. CNV amplitude in depressive patients. Percentage of depressive patients in the 3 different CNV amplitude classes (low, normal and high CNV).

Subjects with a GH baseline level higher than 5 ng/ml were excluded. Thus, only 40 among our 61 depressive patients were retained for this study (36 with clonidine test, 39 with apomorphine test, 35 with both tests).

The data were analyzed statistically with BMDP software.

RESULTS

ERP data

Mean CNV amplitude in depressive patients was 14.5 ± 10.2 μV but this average value does not reflect the extreme heterogeneity of our data. To describe better the patients' CNVs, we repartitioned them according to the 3 different amplitude classes (CNV less than 12 μV, CNV between 12 and 22 μV, and CNV greater than 22 μV). Fig. 1 shows the distribution of CNV amplitude, which was normal in 24 patients, according to the normative data obtained in a former study (Timsit-Berthier et al. 1984), abnormally low in 24 patients and elevated in 13 patients. It is worth emphasizing that the high-amplitude CNV subgroup, estimated as 22% of our sample, has never been described in the literature.

PINV occurred in 38 out of our 61 depressive patients (62%) and the remaining 23 patients showed normal CNV duration (38%). When studying the occurrence and amplitude of the PINV according to the 3 amplitude subgroups (see Table I), we obtained a significant difference: the high-amplitude CNV subgroup more often displayed PINVs and had a higher average PINV amplitude than the two other subgroups.

RT was also faster in this high-amplitude CNV group (Table I).

The mean amplitude of the N1 component evoked by S1 was −14.0 ± 9.9 μV, and the mean amplitude of the P300 component was 5.2 ± 9.9 μV. Because of the large variance, the data were also analyzed according to the distribution of the 3 CNV amplitudes. Fig. 2 shows that the high CNV amplitude group exhibited the highest amplitude of the N1 component and the lowest amplitude of the P300 component. This low-amplitude P300 (which often attained a reversed polarity in patients with high

TABLE I

OCCURRENCE AND MEAN VALUES AND STANDARD DEVIATION OF POST-IMPERATIVE NEGATIVE VARIATION (PINV) AND REACTION TIME (RT) ACCORDING TO THE 3 SUBGROUPS OF CNV CLASSIFIED ACCORDING TO THEIR AMPLITUDE

	CNV < 12 μV (n = 24)	12 μV < CNV < 22 μV (n = 24)	CNV > 22 μV (n = 13)
PINV occurrence	6	20	12
PINV amplitude (μV)	−1.6 ± 5.9	−9.3 ± 5.4	−14.6* ± 9.7
RT (msec)	458 ± 181	415 ± 157	296* ± 115

* Significantly different at the 0.01 level, when compared to the low-amplitude group (Student's *t* with Bonferroni correction).

amplitude CNV) is illustrated by Fig. 3 which displays data from a depressive woman aged 28. Upon relief of depression, CNV amplitude decreased and P300 amplitude increased. Such data, frequently encountered when we retest our subjects for CNV amplitude modification, raises the problem of knowing whether there is really in fact CNV with excessively high amplitude or whether instead there is only a normal amplitude CNV developing from a heightened baseline (see the problem of the 'Loveless Baseline,' discussed by Verhey et al. 1984).

Correlation with clinical assessment

CNV parameters were not related to a specific CATEGO class. Table II displays the distribution of the CATEGO classes according to the 3 CNV amplitude groups. Four CATEGO classes were found: (1) D+ (Depressive Psychoses) with, as main symptoms, depressed mood and depressive delusions or hallucinations. This form of depression was only found in low CNV amplitude group. (2) R+ (Retarded Depression) with, as

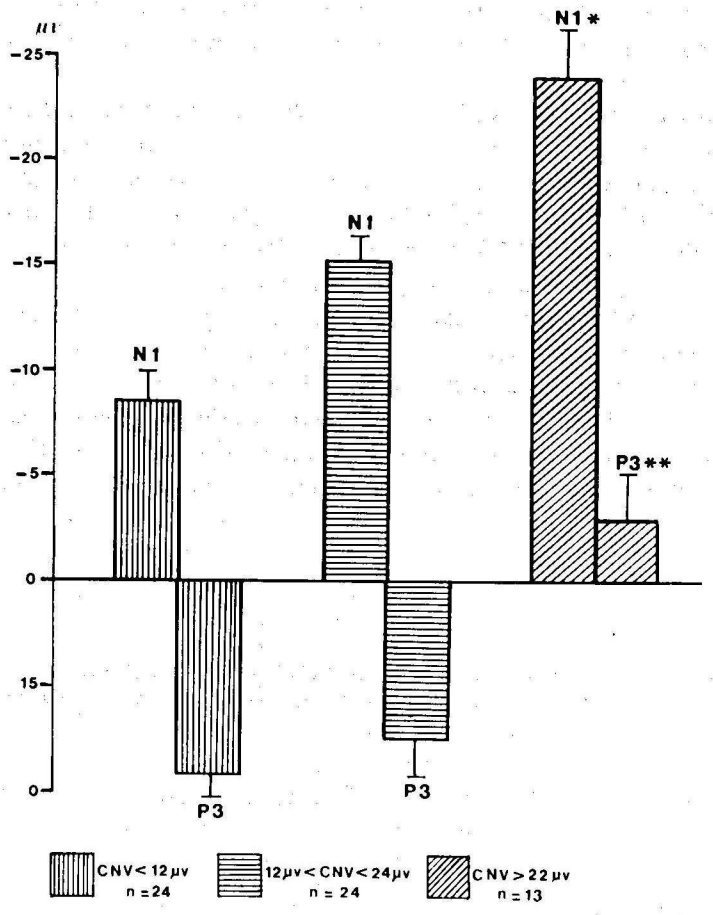

Fig. 2. Mean amplitude and (SE) of N1 and P3 components evoked by the warning stimulus of the CNV, in the 3 different CNV amplitude classes (low, normal and high CNV). *$P < 0.05$; **$P < 0.005$.

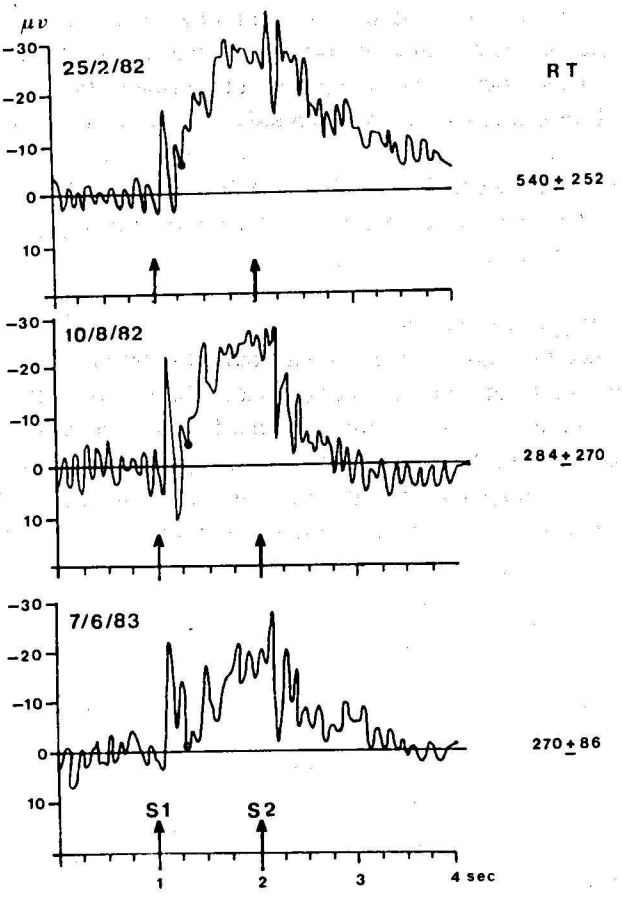

Fig. 3. Example of high-amplitude CNV recording in a depressive patient, recorded during a severe episode of major depression (25/2/82) and during progressive recovery. • indicates the P300 component evoked by S1.

TABLE II

REPARTITION OF CATEGO SUBCLASSES ACCORDING TO THE 3 SUBGROUPS OF CNV CLASSIFIED ACCORDING TO THEIR AMPLITUDE

Catego subclasses	CNV < 12 μV (n = 24)	12 μV < CNV < 22 μV (n = 24)	CNV > 22 μV (n = 13)
Depressive psychoses	2	1	0
Retarded depression	10	7	4
Neurotic depression	8	16	6
Anxiety state	4	0	3

main symptoms, depressed mood, retardation, guilt and sometimes agitation. (3) N+ (Neurotic Depression) with depressed mood and anxiety. (4) A+ (Anxiety States) with subjective or observed anxiety, where depressive symptoms are present but not predominant. The last 3 forms of depression were about equally distributed over all CNV subgroups.

However, we found a significant difference in the distribution of the PSE symptoms: item 1 (bad subjective evaluation of physical health) and item 5 (tension pain) scored higher in subjects with high CNV amplitude.

Correlations with the neuroendocrine challenge tests

When compared to the data obtained in control subjects (Timsit-Berthier et al. 1987), the GH responses to clonidine as well as apomorphine appeared globally reduced in depressive subjects. Following clonidine, the mean value of the GH peak was 5.7 ± 8.7 ng/ml (vs. 18.9 ± 15.8 in controls) and the mean value of GH response difference was 3.6 ± 7 ng/ml. Following the apomorphine challenge test, the mean value of the GH peak was 15.7 ± 16.6 ng/ml (vs. 27.2 ± 10 in controls) and the mean difference

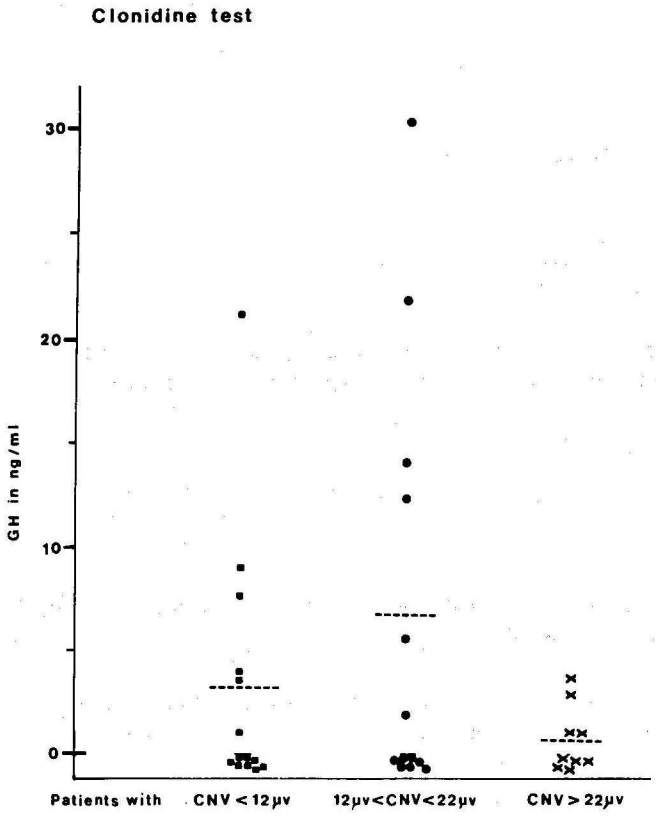

Fig. 4. GH response following clonidine injection (GH peak − GH baseline) in 3 subgroups of depressive patients classified according to their CNV amplitude. The high CNV group displayed significantly more blunted tests ($P < 0.05$).

was 13.9 ± 16.4 ng/ml. In agreement with our previous findings (Ansseau et al. 1986), the present results support noradrenergic as well as dopaminergic neurotransmitter dysfunction in major depression.

With the aim of looking for relationships between specific NA and/or DA dysfunction and CNV amplitude, we compared the GH response differences after clonidine (Fig. 4) and after apomorphine (Fig. 5) in the 3 subgroups of depressive patients classified according to CNV amplitude. Fig. 4 shows that in high CNV amplitude subjects the number of blunted GH responses following clonidine is significantly higher. None of the subjects with high CNV (and PINV) presented a normal reactivity to the clonidine test. These results suggest a noradrenergic disturbance associated with the increase of CNV amplitude. Fig. 5 shows that the GH response following apomorphine does not differentiate between the 3 CNV subgroups. We can only observe that the high-amplitude CNV group displayed rather few blunted apomorphine tests (only 2 subjects vs. 5 subjects with normal CNV amplitude and 3 subjects with low CNV amplitude).

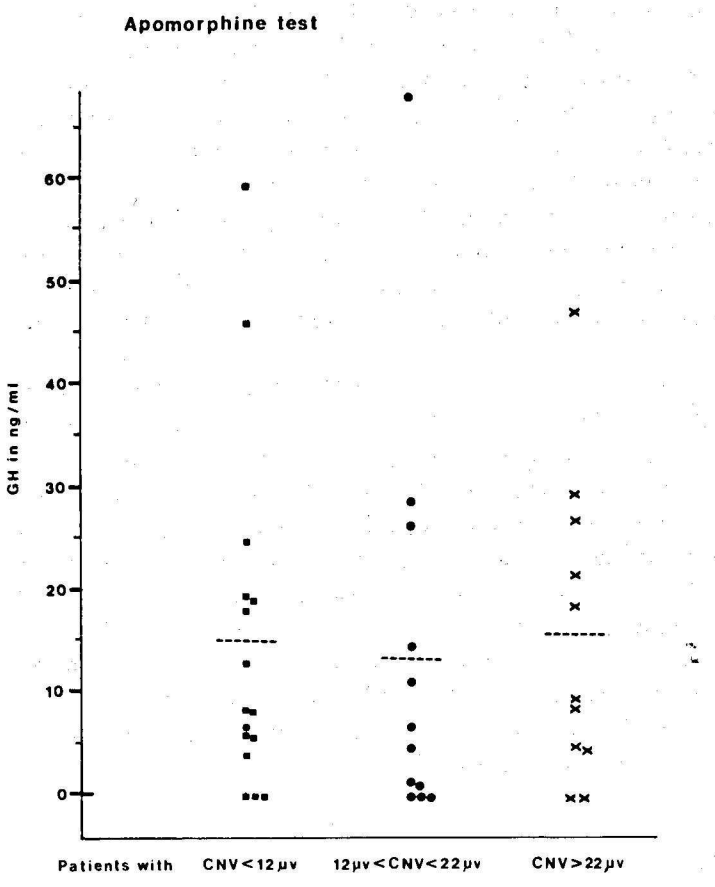

Fig. 5. GH response following apomorphine injection (GH peak – GH baseline) in 3 subgroups of depressive patients classified according to their CNV amplitude. No difference exists between the 3 groups.

DISCUSSION

The literature has usually reported low CNV amplitude in depressive patients (see review by Roth et al. 1986). Such results seem to be due to a tendency to focus on CNV amplitude average measures, which hide the occurrence of a high-amplitude subgroup behind a high value of standard deviation. The point of interest of the present study was the identification of a subgroup of depressive patients (13 among 61) with abnormally high CNV amplitude ($>22\ \mu V$), high PINV, low amplitude of the P300 following the warning stimulus of the CNV and relatively fast RT. This particular subgroup does not display any specific clinical syndrome, but it exhibits tension pains atypically often. It is interesting to compare these results with those obtained from migraine patients who also present high CNV amplitude with no habituation, high degree of alpha blocking and high NA plasma level (Timsit et al. 1987).

At variance with these results, the neuroendocrine challenge test results from high amplitude CNV patients, suggested a low NA receptor reactivity contrasting with a normal or subnormal DA receptor reactivity. To explain the occurrence of such a subgroup of depressive patients, it would also be possible to evoke cholinergic overactivity already described in depression (Sitaram et al. 1976). This hypothesis is in line with the results published by Ansseau et al. (1985) which showed close correlations between rapid eye movement (REM) sleep latency and CNV amplitude, suggesting that both parameters may depend on the same cholinergic mechanism: thus, the higher the CNV amplitude, the shorter the REM latency and the higher the cholinergic activity.

Whatever is the neurochemical interpretation of the high-amplitude CNVs observed in a subgroup of our depressive patients, a major factor of our results is to emphasize the neurophysiological heterogeneity of clinical depressions. This heterogeneity may, in part, reflect neurochemical heterogeneity and thus contribute to the conflicting results obtained when depressed subjects are viewed as a homogeneous population. Moreover, it would be interesting to compare these CNV data with the model of depression presented by Gilbert (1984) who assumed that the brain is programmed to exhibit and experience two types of depressive response patterns in relation to abandonment, separation, and stress. The first one, which may be termed a 'protest state' is ignited by the perception of loss or frustration, with focusing of attention on the lost object, coupled with heightened activity designed to increase the probability of reunion. The second one, which may be termed a 'despair state' is associated with a turning-in on the self and a reduced and retarded activity. In this perspective, the CNV parameters would reflect, in part, the type of depressive response patterns and, in particular, the high-amplitude CNV associated with high PINV and fast RT would index the 'protest' state. Further studies are needed to test the different hypotheses related to the functional meaning of the CNV modifications in depressive states.

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