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CEREBRAL PSYCHOPHYSIOLOGY OF DEPRESSION: PRELIMINARY RESULTS

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ABSTRACT

Some features of psychophysiological research are discussed on the basis of preliminary data derived from vertex slow potentials (contingent negative variation, CNV) recorded during reaction-time paradigms in normal subjects and depressive patients. Peak amplitude and area failed to discriminate between "neurotic" and "endogenous" depressives defined according to clinical criteria, although a trend toward higher amplitudes was evidenced in the endogenous group. The need for a more accurate description at the behavioural level is emphasized, along with some suggestions for further research resting upon a multivariate approach to psychiatric electrophysiology.

INTRODUCTION

Psychophysiological research implies the measurement of physiological effects of psychological manipulations (42). From a more general standpoint, however, it may be said that psychophysiology extends the observational field to those covert processes that may be relevant to psychic states (1) and thus contribute to their description. Since psychophysiology deals with overt behaviour and its somatic counterparts, the two major problems most frequently encountered concern, on the one hand,

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an accurate taxonomy of the behavioural domain and the selection of appropriate physiological indicators on the other.

Psychophysiological indicators are deemed to be relevant for clinical purposes when they are either synchronic with the behavioural processes under study or may be related to the biological systems mediating them. A further requisite is that they be measurable with minimal disruption of the process studied.

Both of these strategies have been employed in the biological study of affective illnesses. Due to their periodic character they are amenable to time-series analyses of psychometric and physiologic data on the basis of which meaningful relationships between variables may emerge (25, 28). This approach can help discover predictable regularities in longitudinal studies and be of prognostic value in the assessment of treatment outcome.

Although not disagreeing with this approach, other workers concentrate on indicators obtained at definite points in time. The relevance of these indicators is postulated on theoretical grounds or on the basis of their previously established association with physiological systems subserving the behaviour under consideration. In general, the aim of these studies is the definition of homogeneous groups of subjects within a population and the establishment of physiologically-based diagnostic categories. Aside from being objective criteria for the assessment of depressive conditions, physiological and biochemical indicators may provide clues regarding their etiology and management (16).

When the behaviourally relevant variables are sought for in the functioning of the central nervous system (CNS) –as opposed to visceral or peripheral autonomic physiology– the approach may be termed "cerebral psychophysiology" (8). Within this framework, reliance may be placed upon indicators derived from the electrical activity of the brain. Our own work has been aimed at establishing their operational validity in psychophysiological personality research (22), in basic studies of information-processing and associative performances of animals and humans (5, 24, 27), in clinical psychosomatics (23) and in the assessment of the effects of experimental manipulations of CNS excitability (18, 21). The last point deserves emphasis, for one of the basic assumptions underlying the use of brain electrophysiological indicators is that behavioural changes are paralleled by modifications of the excitability level within the CNS. A second assumption is that this level may be reflected in the parameters derived from brain electrical activity by means of scalp electrodes (in a noninvasive way) and appropriate computational devices.

As it has been stated elsewhere (19) such way of studying the CNS-

behaviour-relationship has proved to be reliable enough in the evaluation of long-term organismic variables (traits) and psychopharmacological testing provided appropriate indicators are used. It is well known that few significant and useful relationships have been established between conventional electroencephalographic (EEG) phenomena and psychological states, apart from quantitative variations along the sleep-wakefulness continuum and early attempts to educe properties of personality at different age levels, given the "psychological" correlates of different waveforms (17, 44, 45). The inaccuracy of such an approach can be attributed to its reliance upon visual inspection of neuroelectric recordings, partly overcome since the advent of quantitative electroencephalography (frequency and amplitude analysis) and more sophisticated data-reduction techniques (9, 11, 32).

Despite the increased efficiency of data-handling procedures in EEG analysis, their results in terms of behavioural relevance are largely superseded by other approach to the study of brain electrical activity based upon the analysis of time-locked signals. In contrast with spontaneous, background rhythms (EEG), a large and heterogeneous group of brain electrophysiological signals collectively known as event-related potentials (ERP) explore brain function on the basis of its temporal association with "events" (sensory stimuli, motor action, etc.). Largely dependent upon computer technology for their succesful recording (enhancement of signal-to-noise ratio and control of artifacts) ERP bear consistent relationships to the anatomical and physiological integrity of sensory and motor pathways within the CNS and certain parameters derived from them yield data concerning neural information-processing and psychological phenomena. The contention that cognitive performances, intelligence and personality variables as well as the interaction between environmental and organismic aspects of biological information processing may be reflected in ERP has been amply documented in recent years and has led to wide applications to psychiatric research (6, 15, 31, 34).

The bulk of our work has concentrated upon the behavioural relevance of a class of ERP, known as slow potentials (event-related slow brain potentials, ERSP). "Slow" refers not to a slowing in frequency of recurrent EEG waves, but to an identifiable amplitude pattern of electrical potential which is not itself a spontaneously recurring wave train or oscillatory pattern and can be described as a time-locked, event-related "baseline shift" of the EEG. Hence the designation "steady potential shifts" or "baseline shifts" often found in the literature (24). The conditions under which such slow potentials are generated resemble those which also produce "activation" of EEG records (i.e. electrographic desynchronization or low-voltage fast activity) (7, 30). Some of these

conditions are behaviorally relevant and describable in terms of psychological constructs. During the interval between a warning and an imperative stimulus demanding a response from the subject, a slow shift termed "contingent negative variation" by Walter and associates (46) seems to reflected expectancy, arousal, and attention involved in the associative performance required by the task (reaction-time task) (43).

Depressive illness has been studied by means of electrocortical indicators by a number of workers. Early attempts involving conventional EEG recordings yielded contradictory results, although in some cases a differentiation between manic and depressive phases was possible (3, 4, 13, 16, 47). Using paced, cumulative intravenous doses of barbiturate and a rather complex EEG criterion of the point at which "sedation" occurred, Shagass and his co-workers reported discrimination between neurotic and psychotic depression (16, 35), although some authors have reported difficulties in using these criteria (26). The recovery cycle of cerebral evoked potentials has been also proposed as a useful electrocortical indicator in psychotic depression (34, 36) and this technique, or modifications of it, has been used to assess the effects of antidepressant medication and lithium compounds (37). Paulson and Gottlieb (29) found and elevated threshold for responding to environmental stimulation measuring alpha blocking in the EEG. Other reports suggest a heightened arousal response in depressed patients on the basis of EEG changes to auditory stimulation (49). Using the recovery cycle of the auditory evoked response, Satterfield (33) distinguished between depressives with overactive excitatory mechanisms and depressives with overactive inhibitory mechanisms. Heninger (12) found a decrease in the amplitude of a late component of the evoked response associated with improvement in a withdrawn-retarded rating-scale factor. Using the **relationship** between EEG and evoked response measures a diagnostic specificity for its patterning has been suggested (38). Slow potentials recorded during reaction-time paradigms (CNV, contingent negative variation), widely employed for psychiatric diagnostic purposes, have been studied in relation to depressive illness by Small and Small and their associates (39, 40, 41), among others, indicating the possibility of differentiating between patients and normals.

This report concentrates on preliminary data gathered at our laboratory using contingent negative variation as possible adjunct criterion to the diagnosis of different forms of affective illness. It stems from our previous research in this field and its rationale was to establish a set of standard procedures that might be later utilized by clinical workers. Although at the outset this work was planned as a contribution to neurophysiological nosological description, we wish to emphasize the main

limitations and constraints that might pervade its conclusions and put forward some suggestions for further research.

MATERIAL AND METHODS

Twenty-six subjects took part in the preliminary phase of this study (15 women, 11 men). Their ages ranged from 19 to 49 years, with an overall mean of 35.2. Seven of these subjects (4 women, three men, mean age 31.5 ± 9.2) were not psychiatric patients, but controls. A practising psychiatrist was in charge of a preliminary classification of the subjects as "neurotic depressives" (DN) and "endogenous depressives" (DE), based on a clinical interview. His diagnostic criteria were not made available to the experimenters. Mean age for the DN group was 35.6 years with a SD of 10.6, and for the DE group 38.5 with a SD of 12.3. All these subjects were administered the Eysenck Personality Inventory (EPI) form A for an evaluation of Neuroticism and Extraversion, and those with a high score on the Lie (L) scale were discarded. An independent assessment of depressive symptomatology was obtained by means of self-rating depression inventories (Beck and Zung) (2, 48).

The experimental situations (Table I) were implemented by means of a LINC computer. Each subject attended two sessions, the order of which was counterbalanced within each group. Three basic situations were employed; in one of them ($S_1 - S_2$) the subject was exposed to a warning (S_1) and to an imperative (S_2) stimulus, but no instruction to respond was given. In the other two situations, employed about seven days apart, the subjects were instructed to respond "as fast as possible" after S_2 presentation by depressing a telegraph key situated on the right-hand side of the armchair on which the subject was seated. This situation (fixed foreperiod reaction time task) was implemented in two ways, either employing a repetitive S_2 (S_r in Table I) or a single S_2 (S_s). S_1 was of auditory modality (100 msec, 1000 Hz tone), while S_2 consisted of a single (S_s) or repetitive (S_r) flash 100 msec in duration. In the repetitive condition the subject's motor response terminated the train of flashes.

Throughout the experimental session, the subject was in a sound-attenuated, dimly-illuminated chamber, comfortably seated in an armchair and provided with earphones for the delivery of S_1. Flash (S_r or S_s) was presented about 1.5 m in front of the subject, the interstimulus interval (ISI) being Isec.

Brain electrical activity was recorded using a Beckman type T electroencephalograph (input time constant 5 sec) from a vertex-mastoid derivation. Ag-AgCl electrodes stable enough for the recording of slow shifts,

were positioned at CZ (10-20 system) and right mastoid process using collodion-impregnated gauze patches. Electrooculogram (EOG) was continously monitored from supra and infraorbital right electrodes, the subject being instructed to fixate the gaze in front and to refrain from blinking during stimuli presentation. Computer sampling of EEG was accomplished using 8 msec dwell time, and was started about 1000 msec before S_1 presentation in order to obtain an appropriate baseline. Uncontaminated slow potentials during the ISI (foreperiod) were averaged off-line and yielded curves based upon 18 or 20 individual trials. These were quantified in terms of amplitude, area under the curve and other measures.

Further procedural details have been presented elsewhere (20, 22, 23).

TABLE I

EXPERIMENTAL SITUATIONS FOR EACH SUBJECT

Blocks	Session I	Session II
1	$S - S_s$	$S - S_s$
2	$S - S_s - R$	$S - S_r - R$
3	$S - S_s - R$	$S - S_r - R$
4	$S - S_s - R$	$S - S_r - R$
5	$S - S_s$	$S - S_s$

S_s = Single imperative stimulus; S_r = Repetitive imperative stimulus; R = motor response. Subjects were counterbalanced accross both sessions using a cross-over design.

RESULTS

Schematic waveforms obtained are depicted in Fig. 1. These are reconstructions of the actual computer displays based on average points taken every 100 msec during the foreperiod (ISI). Amplitude values refer to the 1000 msec baseline prior to S_1 (not depicted), which was normalized as to constitute a "true" baseline for comparison. In each of the waveforms shown, two parts can be discerned, corresponding to the evoked potential elicited by S_1 and to the late surface-negative slow shift (contingent negative variation) which extends to S_2. The evoked potential elicited by S_2 has been omitted.

These reconstructed waveforms correspond to the response conditions ($S_1 - S_s - R$ and $S_1 - S_r - R$, A and B). In the non-response condition ($S_1 - S_2$) the contingent negative variation is scarcely seen. As shown in this Figure, no major differences between "neurotic" (N) and "endogenous" (E) depressives are apparent, although a trend toward higher amplitudes in the CNV of the E group may be suggested.

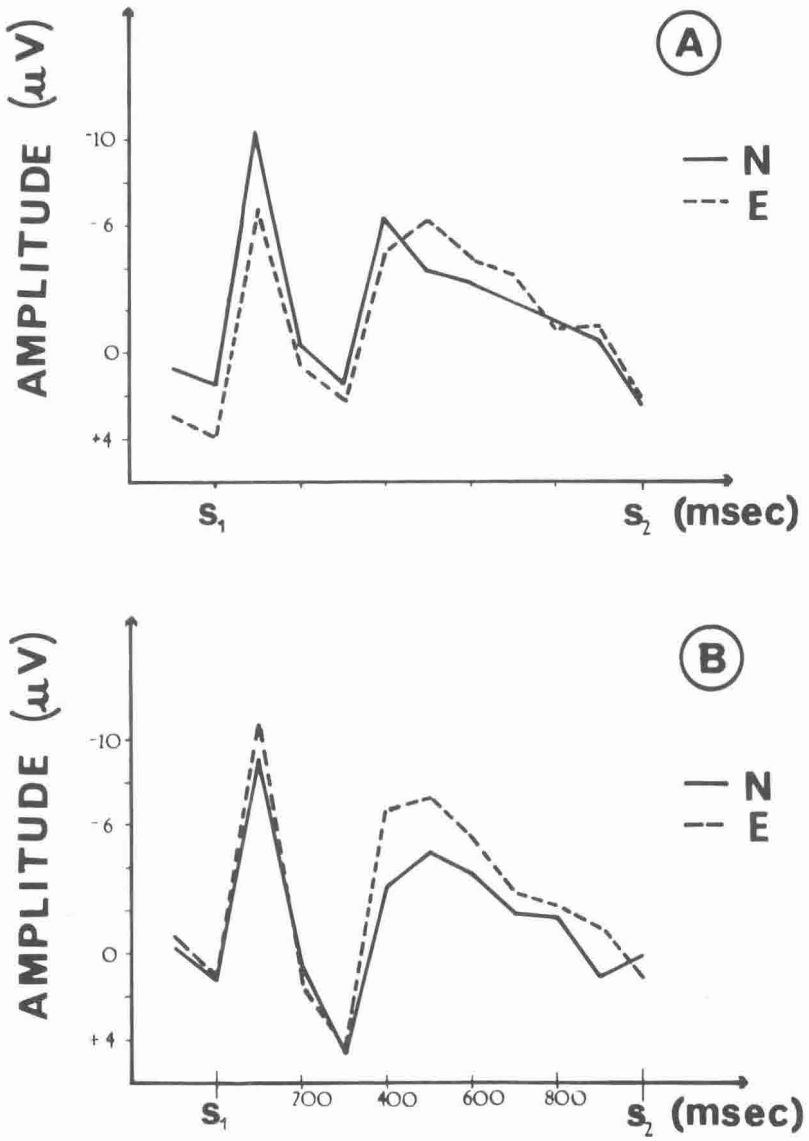

Fig. 1.– Average vertex potentials during reaction-time paradigms in neurotic (N) and endogenous (E) depressives. Waveforms reconstructed taking mean values for 20 trials every 100 msec during the interval between S_1 (warning stimulus) and S_2 (imperative stimulus). The latter was either single (A) or repetitive (B) flash. Negativity upwards.

Table II shows mean values of peak amplitudes (CNV_{max}), area and reaction time for the three groups clinically defined. Peak amplitude corresponds to the maximum amplitude found within the ISI, excluding evoked potential to S_1. Area refers to the integral value cumulatively obtained per time unit between the limits indicated in the Table; it does not include evoked potential to S_1 and the last 100 msec of the ISI. Reaction time, defined as the $S_2 - R$ interval, is automatically computed and displayed after each trial, whenever a response is made. It is interesting to observe that although no clear-cut differentiation between groups or testing conditions can be made on the basis of these figures, "neurotic" depressives show a trend toward smaller peak amplitudes and longer reaction times under both testing conditions (single and repetitive S_2) when compared to controls and "endogenous" depressives.

TABLE II

PEAK AMPLITUDE, AREA, AND REACTION TIME FOR DIFFERENT GROUPS OF SUBJECTS

	N	CNV max (uV)		CNV area (uVsec)*		Reaction time (msec)	
		Single S_2	Repetitive S_2	Single S_2	Repetitive S_2	Single S_2	Repetitive S_2
Controls	7	7.57 ± 1.78	6.13 ± 0.85	1.327 ± 0.27	1.027 ± 0.34	268.45 ± 29.6	204.86 ± 16.36
Depressives Endogenous	11	6.36 ± 2.00	6.55 ± 1.99	1.077 ± 0.35	1.080 ± 0.47	253.59 ± 37.13	240.81 ± 37.10
Neurotic	8	5.82 ± 1.86	5.54 ± 1.51	1.060 ± 0.49	1.042 ± 0.37	290.43 ± 42.09	250.70 ± 65.80

* Total negative area between 350 and 900 msec after S_1

An analysis of variance performed on the peak amplitude and area data yielded non-significant F ratios, either for the distinction between clinically-defined groups or between experimental conditions (Table III).

TABLE III

ANALYSES OF VARIANCE FOR SLOW POTENTIAL PEAK AMPLITUDE AND UREA VALUES

Source of variation	d. f.	Peak amplitude Mean squares	F	Area* Mean squares	F
Groups (diagnosis)	2	6.723	2.04	0.069	0.358
Conditions (single vs repetitive	1	4.500	1.36	0.099	0.513
Interaction	2	1.678	0.51	0.106	0.549
Residual	46	3.302		0.193	
Total	51				

* Total negative area between 350 and 900 msec after S_1

Beck scores correlated highly with Zung scores for the whole group ($r = 0.7233$; $p < 0.01$). A second step in the analysis consisted in disregarding the clinical impression and defining groups entirely on the basis of psychometric data derived from the Zung inventory. An arbitrary cut-off point of 54 was used taking into consideration both Zung's suggestion and our own parametric estimates in a larger sample. Combining this information with that derived from Eysenck's Neuroticism dimension, four groups could be defined (high neuroticism – low depression; high neuroticism – high depression; low neuroticism – low depression; low neuroticism – high depression). Cut-off point for neuroticism was a score of 14, close to the median of the N distribution in larger populations. Comparison between all these groups yielded non significant results, when parametric (t) and non-parametric (Mann-Whitney) tests were used, and taking into consideration peak amplitude as well as area measures. Further analyses of this kind were prevented by the fact that only two subjects fell within the high neuroticism-low depression group. No clear-cut trend was evinced for Eysenck's Extraversion dimension.

DISCUSSION

Despite its apparent lack of significance, an appraisal of these preliminary data may illustrate the main problems of psychophysiological research. The specific question posed has been the possibility of differentiating between groups of subjects previously classified on the basis of clinical and behavioral criteria. Dependent variables have been derived from the contingent negative variation (CNV), a frontally recorded slow potential shift thought to reflect the operation of a cerebral system concerned both with energizing non-informative aspects of behavior (arousal) and with directional and informationally relevant factors (attention) (43). Its usefulness in diagnostic psychiatric research rests upon this association with psychological constructs (22, 31, 46). The experimental situation in which CNV is reliably recorded (reaction time task) presupposes an active engagement on the part of the subject and in this regard it may be considered as "psychological provocation method" disclosing the "reactivity" of the subject to environmental challenges.

The strategy of CNV-behavior relationships illustrated here has developed within the context of a straightforward clinical investigation. The notion entertained has been that information derived from CNV in this experimental condition may serve as a source of relevant diagnostic data. This is actually the lead followed in most clinical studies. Starting off from the assumption of an isomorphic dimensionality between CNV parameters and clinical criteria, we find that this does not hold true for the present sample of normals and depressives - at least not in a simple fashion.

Part of the problem resides in the ambiguity of the diagnostic terms used. Individual clinicians vary considerably in their use of psychiatric terminology and any group of individuals diagnosed as "depressed" is probably heterogeneous. Clinical judgment often implies prognostic as well as diagnostic elements and the criteria are difficult to specify. One reason for adopting one of the many classificatory schemata in common use is precisely their independent validation by means of quantitative and physiologically-based techniques. In the present case, both set of criteria do not overlap to any significant degree.

This point deserves emphasis, for in the majority of the "correlative" approaches often found in the psychiatric literature, any prospect of meaningful replication of results rests upon an accurate taxonomy of the behavioral domain. By this we mean to imply the reduction of clinical data to units of description amenable to biochemical or physiological analysis.

Although inappropriate, the correlative approach is often the best way of conducting preliminary research and posing the relevant questions for further scrutiny. In the present case, the heuristic validity of the psychological constructs of arousal and attention and their relevance to research on depression may, if not ascertained, at least suggested on the basis of some trends present in the results. The trend toward smaller amplitudes in the "N" group is in accord with previous studies which have led to the conclusion that high anxiety may be associated with smaller amplitude of the CNV. Even considering that our present sample may be heterogeneous in many respects, this trend is worth considering in further studies in which this factor be specifically isolated (22). The variables studied here, however, do not lend direct support to the notion of a heightened arousal in endogenous depression (47, 49) although other aspects deserve mention. Among these, the most important one seems to be the selection of an appropriate indicator at the physiological level. Brain electrical activity, for instance, may be evaluated not only in terms of amplitude or latency of event-related potentials. Topography may be decisive, especially in psychiatric studies taking into account the different processing capabilities of both cerebral hemispheres. Another approach that may be used to enhance reliability is multiple testing by means of different challenges and study of the relationships between measures (15, 38, 40). It is thus critical to specify both operationally and conceptually the physiological dimension under consideration.

Apart from these considerations, two additional comments may be made. Both will require further testing. The first is that even assuming an appropriate framework, CNV correlates lack relevance to a physiological

study of depression. An examination of this possibility would lead necessarily to a multivariate approach. A second point is that CNV may be inappropriate for evaluating changes in the **state** of the subject, although its efficacy in discriminating on the basis of enduring **traits** seems to be demonstrated. Any given subject may possess a way of responding to the experimental situation that may obscure slight changes caused by psychological malfunction. The diagnostic usefulness of CNV would be limited to those psychophysical and characteristic response patterns which constitute the basic psychological make-up, but would be blind to their transient changes. Both these possibilities require further experimental analysis.

The issues raised here against the clinical correlative approach should not lead to its abandonment. Were the diagnosis of psychiatric conditions to be based solely upon laboratory data, its meaningfulness could be seriously questioned. As in other branches of medicine, the task of research in psychophysiology must include comprehensive strategies of study available both to the researcher and the practitioner.

RESUMEN

Psicofisiología cerebral de la depresión. resultados preliminares. *Lolas F, De la Parra G (Departamento de Fisiología y Biofísica, Universidad de Chile, Casilla 6524, Santiago 7, Chile).* **Invest. Clín.** *20 (1): 33-47, 1979.* – Se discute algunas características de la investigación psicofisiológica en base a datos preliminares derivados de potenciales lentos del vertex (variación contingente negativa, CNV) registrados en sujetos normales y pacientes depresivos durante paradigmas de tiempo de reacción. La amplitud máxima y el área no discriminaron entre depresivos "endógenos" y "reactivos" definidos según criterios clínicos, aunque se evidenció una tendencia a una mayor amplitud del potencial en el grupo endógeno. Se enfatiza la necesidad de una más acuciosa descripción a nivel conductal, junto con sugerencias para ulteriores estudios basadas en una aproximación multivariada a la electrofisiología psiquiátrica.

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