

PINV (Gauthier and Gottesman 1976). In fact, under such conditions, the stress (pain) appears to interfere with the subject's conative attention, and therefore, S_2 diminishes in significance as an imperative stimulus. Moreover, the stress situation may contribute to a deterioration of the subject's performance, as evidenced by a higher frequency of errors during pain episodes, especially when observed among the more anxious subjects.

The influence of anxiety in painful conditions seems to be further confirmed by the results obtained after anxiolytic treatment of the more anxious group with respect to baseline recordings: a less evident reduction of CNV area, a decrease in PINV appearance, and a lower percentage of errors. Conversely, the less anxious group did not demonstrate so noticeable a change after pharmacological therapy.

In conclusion, our pharmacological and electrophysiological study confirms the utility of a multimodal approach in the investigation of affective components involved in pain in humans.

References

- Chouinard G, Annable L, Dubrosky B, Dongier M (1975): Postimperative negative variation (PINV) in ambulatory schizophrenic patients. *Compr Psychiatry* 16:457-460.
- Gauthier P, Gottesman C (1976): Etude de la variation contingente négative et de l'onde post-impérative en présence d'interférences. *Electroenceph Clin Neurophysiol* 40:143-152.
- Irwin DA, Knott JR, McAdam DW, Rebert CS (1966): Motivational determinants of the contingent negative variation. *Electroenceph Clin Neurophysiol* 21:538-543.
- Knott JR, Irwin DA (1968): Anxiety, stress and the contingent negative variation. *Electroenceph Clin Neurophysiol* 24:286-287.
- Knott JR, Irwin DA (1973): Anxiety, stress and the contingent negative variation. *Arch Gen Psychiatry* 29:538-541.
- Low MD, Coats AC, Retting GM, McSherry JW (1967): Anxiety, attentiveness-alertness: Phenomenological study of the CNV. *Neuropsychologia* 5:379-384.
- Low MD, McSherry JW (1968): Further observations of psychological factors involved in CNV genesis. *Electroenceph Clin Neurophysiol* 25:203-207.
- McCallum WG, Walter WG (1968): The effects of attention and distraction on the contingent negative variation in normal and neurotic subjects. *Electroenceph Clin Neurophysiol* 25:319-329.
- Price DD, Barrel JJ, Grocely RH (1980): A psychophysical analysis of experiential factors that selectively influence the affective dimension of pain. *Pain* 8:137-149.
- Rizzo PA, Albani GF, Pierelli F, Pozzessere G, Morocutti C (1982): Further observations on experimental pain influence on brain preparatory sets. *Phronesis* 3:15-19.
- Rizzo PA, Caporali M, Pierelli F, Spadaro M, Zanasi M, Morocutti C, Albani G (1984): Pain influence on brain preparatory sets. *Ann NY Acad Sci* 425:676-680.
- Tecce JJ (1972): Contingent negative variation (CNV) and psychological processes in man. *Psychol Bull* 77:73-108.
- Tecce JJ, Hamilton BT (1973): CNV reduction by sustained cognitive activity (distraction). In McCallum WC, Knott SJ (eds), *Event-related Slow Potentials of the Brain: Their Relations to Behaviour* (Electroenceph Clin Neurophysiol Suppl 33) Amsterdam: Elsevier.
- Walter WG, Cooper R, Aldridge VJ, McCallum WC, Winter AL (1964): Contingent negative variation: An electric sign of sensorimotor association and expectancy in the human brain. *Nature* (London) 203:380-384.

REM Sleep Latency and Contingent Negative Variation in Endogenous Depression Suggestion for a Common Cholinergic Mechanism

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In a sample of 13 endogenous depressive inpatients, REM (rapid eye movement) latency (recorded over 4 consecutive nights after 2 habituation nights) and contingent negative variation amplitude showed significant relationship, suggesting that both parameters may depend on the same mechanisms, possibly cholinergic.

Introduction

Major depression is associated with various sleep abnormalities: decrease in sleep efficiency and delta sleep, shortening of REM (rapid eye movement) latency, and increased REM activity (Kupfer 1976). Among those parameters, shortened REM latency seems to be the most specific feature, leading some investigators to test its possible use as a biological marker of depression (review in Ansseau et al. 1985). REM latency has been related to cholinergic mechanisms (Sitaram et al. 1976, 1978), and shortened REM latency could reflect a cholinergic overactivity that is associated with major depression (Sitaram et al. 1982).

Contingent negative variation (CNV) is a slow potential shift that develops during a simple experimental situation in which stimuli and responses are serially organized (Walter et al. 1964). CNV studies in psychiatric patients have shown abnormalities in both amplitude and duration (Timsit-Berthier et al. 1984). CNV amplitude has been related to psychological constructs, such as attention, motivation, and conation (Howard et al. 1982). Recently, Marczynski (1978a,b) developed a neurochemical model of CNV based on animal data, suggesting that CNV negativity is mediated via cholinergic receptors and is modulated via catecholaminergic influences.

The purpose of the present study was, therefore, to test a possible relationship between REM latency and CNV negativity in depressive patients; indeed, similar cholinergic processes may be involved in the regulation of these two electrophysiological indexes.

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Methods

The study was performed in 13 depressive inpatients who met Research Diagnostic Criteria (Spitzer et al. 1978) for definite major depressive disorder, endogenous subtype, and had a score of at least 6 on the Newcastle Scale (Carney et al. 1965) and of at least 24 on the Hamilton Depression Scale. Diagnoses were made by two independent psychiatrists who were blind to biological results. Patients were nine men and four women, ranging in age from 34 to 62 years, with a mean age (SD) of 49.4 years (11.6). All patients were free of medical illness and gave informed consent.

After a drug-free period of at least 2 weeks, sleep recordings were obtained for 6 consecutive nights and were scored according to the criteria of Rechtschaffen and Kales (1968). Sleep onset was defined by the first epoch (30 sec) of stage II and REM latency by the time between sleep onset and first REM period (3 min); intermediate wakefulness was not excluded. Individual REM latencies were calculated as the mean of the last 4 nights, the 2 first recording nights being considered as habituation nights.

CNV was recorded according to a procedure described previously (Timsit-Berthier et al. 1983). Briefly, the CNV paradigm was obtained by a warning stimulus (S1: 1000 Hz, 50-msec duration tone) generated from a loud speaker 1 m in front of the subjects, followed 1 sec later by an imperative stimulus (S2: 18/sec flashing light). The duration of S2 was 1 sec, unless it was terminated by the subject applying pressure to a pear-shaped bell push. Six block of eight trials completed the CNV phase, with pseudorandomized intertrial intervals ranging from 7 to 25 sec.

CNV amplitude was measured on the averaged 48 trials by the voltage difference between a 1-sec pre-S1 baseline and the 800-1000 msec after S1 level (Timsit-Berthier et al. 1984).

The relationship between REM latency and CNV amplitude was assessed by the Pearson correlation coefficient. As REM latency tends to be log-normally distributed, the data were analyzed using a log transformation.

Results

Individual mean REM latency and CNV amplitude are presented in Table 1. REM latency showed a large interpatient variability, ranging from 34.0 min to 228.6 min, with a mean (SD) of 83.3 min (58.1). CNV amplitude also presented a large interpatient variability, ranging from -3.0 to -39.6 μ V, with a mean (SD) of -18.6 μ V (10.4). REM latency showed a significant relationship with CNV amplitude ($r = -0.76$, $p < 0.001$), which is displayed in Figure 1.

Discussion

The present study shows a significant relationship between REM latency and CNV amplitude, which may suggest that these two neurophysiological parameters are controlled by common biochemical mechanisms.

The main neurotransmitter involved in both indexes could be acetylcholine. Indeed, on one hand, Sitaram et al. (1976, 1978) demonstrated the role of acetylcholine in REM sleep induction by shortening REM latency with physostigmine (a cholinesterase inhibitor) or arecoline (a muscarinic agonist) infused during the preceding non-REM period. How-

Table 1. Sample of Endogenous Depressives and Individual Results

Patient number	Sex	Age (years)	Mean REM latency (min)	CNV amplitude (μ V)
1	F	57	34.0	-29.0
2	F	34	34.2	-19.0
3	M	62	38.2	-24.1
4	F	61	42.8	-39.6
5	M	50	47.7	-18.5
6	M	56	57.5	-23.3
7	M	54	62.3	-21.3
8	M	28	67.5	-25.9
9	M	57	72.9	-9.4
10	F	36	119.5	-3.0
11	M	39	121.6	-15.5
12	M	47	156.2	-7.5
13	M	61	228.6	-5.2
Mean		49.4	83.3	-18.6
SD		11.5	58.1	10.4

ever, other neurotransmitter systems are also implicated in the control of REM sleep (e.g., norepinephrine or serotonin) (review in Koella 1981). On the other hand, Libet (1978) elaborated a neurochemical model of CNV based on the study of slow postsynaptic response of rabbit sympathetic ganglion cells, which was independently confirmed by pharmacological studies in cats (Marczynski et al. 1978a,b). In this model, the negative part of CNV depends on the activity of the cholinergic system and can be modulated by catecholaminergic influences, whereas the positive part would result from a slackening in the tonus of catecholamines, which allows the action of GABAergic hyperpolarizing circuits. We previously verified the role of the dopaminergic system in CNV modulation by showing a high correlation between CNV amplitude and growth hor-

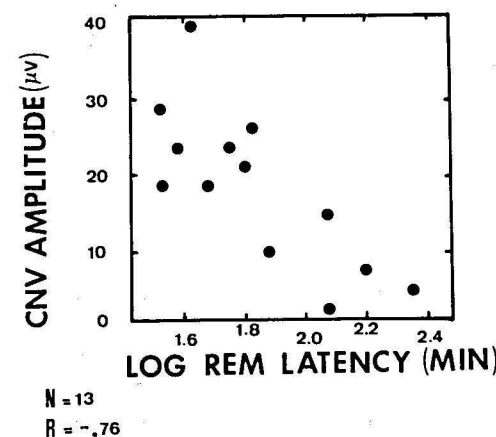


Figure 1. Relationship between REM latency and CNV amplitude in 13 endogenous depressive patients.

mone response following apomorphine in a sample of psychiatric patients (Timsit-Berthier et al. 1983). Thus, the cholinergic hypothesis suggested by the present preliminary results must be developed in a more global context of balance between different neurotransmitter systems.

This study also shows a wide range of individual values among the group of endogenous depressive patients. Mean REM latency for the whole group is in the normal range, which is in contrast to the hypothesis of Kupfer (1976) of a specific shortening of REM latency among endogenous depressive patients. These discrepancies may result from different definitions of sleep onset, as well as of REM latency: e.g., intermediate awakening is included in our definition of REM latency, whereas it is excluded in Kupfer's group definition.

Finally, this wide range of individual values suggests that a single neurobiological mechanism (such as a cholinergic hypersensitivity) may be difficult to reconcile with a general explanation of depressive disorders. Depression rather appears to include heterogeneous groups of illnesses from a biological point of view.

These promising preliminary findings obviously need to be confirmed in a larger sample of depressive patients as well as in normal subjects.

References

- Ansseau M, Kupfer DJ, Reynolds CF III (1985): Internight variability of REM latency in major depression: Implications for the use of REM latency as a biological correlate. *Biol Psychiatry* 20:489-505.
- Carney MWP, Roth M, Garside RF (1965): The diagnosis of depressive syndromes and the prediction of ECT response. *Br J Psychiatry* 111:659-674.
- Howard RC, Fenton GW, Fenwick PBC (1982): *Event-Related Brain Potentials in Personality and Psychopathology: A Pavlovian Approach*. Chichester: John Wiley.
- Koella WP (1981): Neurotransmitters and sleep. In Wheatley D (ed), *Psychopharmacology of Sleep*. New York: Raven Press, pp 31-51.
- Kupfer DJ (1976): REM latency: A psychobiological marker for primary depressive disease. *Biol Psychiatry* 11:159-174.
- Libet B (1978): Slow postsynaptic responses of sympathetic ganglion cells as models for slow potential changes in the brain. In Otto D (ed), *Multidisciplinary Perspectives in Event Related Brain Potential Research*. Washington, DC: U.S. Government Printing Office, pp 12-19.
- Marczynski TJ (1978a): Neurochemical mechanisms in the genesis of slow potentials: A review and some clinical implications. In Otto D (ed), *Multidisciplinary Perspectives in Event Related Brain Potential Research*. Washington, DC: U.S. Government Printing Office, pp 25-35.
- Marczynski TJ (1978b): A parsimonious model of mammalian brain and event related slow potentials. In Otto D (ed), *Multidisciplinary Perspectives in Event Related Brain Potential Research*. Washington, DC: U.S. Government Printing Office, pp 626-634.
- Rechtschaffen A, Kales AA (1968): *A Manual of Standardized Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects*. Washington, DC: Public Health Service, U.S. Government Printing Office.
- Sitaram N, Wyatt RJ, Dawson S, Gillin JC (1976): REM sleep induction by physostigmine infusion during sleep. *Science* 191:1281-1283.
- Sitaram N, Moore AM, Gillin JC (1978): Induction and resetting of REM sleep rhythm in normal man by arecoline: Blockade by scopolamine. *Sleep* 1:83-90.
- Sitaram N, Kaye WM, Nurnberger JI, Ebert M, Gershon ES, Gillin JC (1982): Cholinergic REM sleep induction: A trait marker of affective illness? In Usdin E, Hanin I (eds), *Biological Markers in Psychiatry and Neurology*. Oxford: Pergamon Press, pp 397-404.
- Spitzer RL, Endicott J, Robins E (1978): Research Diagnostic Criteria: Rationale and reliability. *Arch Gen Psychiatry* 34:773-778.
- Timsit-Berthier M, Mantanus H, Ansseau M, Doumont A, Legros JJ (1983): Methodological problems raised by contingent negative variation interpretation in psychopathological conditions. In Perris C, Kemali D, Koukkou-Lehmann M (eds), *Neurophysiological Correlates of Normal Cognition and Psychopathology*. Basel: Karger, pp 80-92.
- Timsit-Berthier M, Geronio A, Rousseau JC, Mantanus H, Abraham P, Verhey FHM, Lamers T, Emonds P (1984): An international pilot study of CNV in mental illness. Second report. *Ann NY Acad Sci* 425:629-637.
- Walter WG, Cooper R, Aldridge VJ, McCallum WC, Winter AL (1964): Contingent negative variation: An electric sign of sensory-motor association and expectancy in the human brain. *Nature* 203:380-384.