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Contingent negative variation in epilepsy

MILES E. DRAKE JR, STEVEN J. WEATE & SHARON A. NEWELL

Division of Epilepsy and Clinical Neurophysiology, Departments of Neurology and Psychiatry, The Ohio State University Medical Center, Columbus, Ohio, USA

The contingent negative variation (CNV) is a long-latency event-related potential elicited by paired or associated stimuli. We recorded contingent negative variation in 50 patients with complex partial and secondarily generalized seizures and in 20 neurologically and psychiatrically normal unmedicated controls.

CNV was recorded from Fz, Cz, and Pz. A 2000 Hz tone was followed after 1.5 s by 1000 microsecond light flash, at which a button press was to be executed. Filter band pass was 0.1–20 Hz, analysis time was 10 s and 10 responses were replicated.

Patients with complex partial seizures with and without secondary generalization had lower measurements of area under the CNV curve (AUC) than did controls, and CNV amplitude was significantly reduced. Patients with interictal behavioural symptoms had significantly smaller AUC and lower amplitude. No significant difference was found between depressed and non-depressed seizure patients with respect to AUC, but amplitude was significantly lower in depressed patients. Seizure patients with psychosis had significantly lower AUC but did not differ from non-psychotic patients in CNV amplitude. No differences were found between seizure patients with and without personality disorder with respect to CNV AUC or amplitude. Post-imperative negative variation was significantly more common in seizure patients than in controls and among patients with epilepsy, was significantly increased in those with inter-ictal behaviour disturbance generally and psychosis particularly. No specific effect of anticonvulsant monotherapy on AUC or amplitude was identified.

These findings suggest that CNV may differ between partial epilepsy patients and controls, and that inter-ictal behaviour disturbance may particularly affect CNV measures. They also agree with previous evidence for a frontal lobe generator for the CNV, and a possible role for central dopaminergic pathways in the production of PINV.

Key words: epilepsy; seizures; contingent negative variation; evoked potentials; event-related potentials.

INTRODUCTION

The contingent negative variation (CNV) is a long-latency event-related potential related to the association or contingency between two stimuli[1]. It has been extensively studied in the psychophysiological literature[2]. Although many studies have been undertaken in psychiatric disorders[3], relatively few neurological applications have been investigated[4]. CNV has not been systematically applied to date in the evaluation of epilepsy patients.

The CNV may nevertheless be useful in assessment of epilepsy and neurobehavioural disorders. Recordings in patients who have had psychosurgery[5] and magnetoencephalographical evidence[6] suggest a frontal lobe origin for at least some CNV components. The CNV has been shown to reflect central dopaminergical activity[7,8], and the post-imperative negative variation (PINV) may, in particular, reflect the influence of dopamine. These associations might make the CNV useful in assessment of epilepsy, particularly seizures of frontal lobe origin, and in the further characterization of inter-ictal neuropsychiatric symptoms and possibly medication effects.

We compared CNV in patients with complex partial seizures with and without secondary generalization, satisfactorily controlled with anticonvulsant monotherapy, with responses recorded in neurologically and psychiatrically intact unmedicated controls.

METHODS

A group of 50 consecutive patients, approximately equally divided between male and female,

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were selected during outpatient evaluation in the Epilepsy Center. They had complex partial seizures with and without secondary generalization, diagnosed clinically or by EEG monitoring. Eighteen channel sleep-deprived EEGs had previously been abnormal, with focal slowing, epileptiform activity, or recorded seizures, but EEG background was otherwise normal. Computed tomographic or magnetic resonance imaging tests had been negative with respect to causative structural lesions, although volumetric MRI measurements were not done. Of the patients, 23 were taking carbamazepine monotherapy, 17 were on phenytoin alone and 10 patients were treated only with valproate. All had therapeutic anticonvulsant levels without toxic symptoms.

The 50 patients were healthy except for epilepsy, but 30 had documented symptoms involving inter-ictal behaviour or personality, for which they had received psychiatric treatment, sought psychological counselling, or become involved in support groups of the Epilepsy Association of Central Ohio. Sixteen patients had previously received diagnosis of a depressive disorder or reaction, five patients had been psychiatrically hospitalized for psychosis, and 25 patients had had behavioural or personality disturbance other than psychosis. Psychiatric or psychological evaluation had yielded diagnoses of personality disorder in nine patients. Seizure patients were compared to 20 control subjects, aged 20–40 years, equally divided between males and females, and taking no medications at the time of study.

The CNV was recorded from silver-silver chloride electrodes placed at the Fz, Cz, and Pz positions of the International 10:20 electrode placement. Responses were recorded from Fz with linked ear reference, the Cz and Pz positions serving to assist in peak identification. Additional electrodes were placed at the outer canthi of both eyes, and ocular artefact was excluded by bipolar recording. A 2000 Hz tone, delivered at 76 dB SL binaurally through shielded headphones, was followed after 1.5 s by a 100 μs light flash, at which the patient or subject had been instructed to press a button. The amplitude and area under the curve (AUC) of the frontal CNV were measured in patients and controls, as was the occurrence of post-imperative negative variation (PINV).

RESULTS

CNV recordings in control subjects, seizure patients without inter-ictal behavioural symptoms, and epileptics with inter-ictal psychosis, personality disorder, or depression, are exemplified in the Figs. 1–3. AUC and amplitude measurements and frequency of PINV in each of the groups are summarized in Table 1.

Patients with complex partial seizures with and without secondary generalization had significantly smaller AUC than did controls. They also had a significant reduction in CNV amplitude. Patients with inter-ictal behaviour symptoms had significantly smaller AUC and lower amplitude. Depressed individuals did not differ from non-depressed patients with regard to AUC, but had significantly smaller CNV amplitude. Conversely, patients with seizures and psychosis had significantly larger AUC than patients without psychosis, but amplitudes were not significantly different. No significant differences in AUC or amplitude were found in complex partial seizure patients felt to have personality disorders and seizure patients without personality disorder. PINV was significantly more common in the seizure patients than in the controls, and patients groups with and without inter-ictal behaviour symptoms, and with and without psychosis, differed significantly, although no significant differences were found between depressed and non-depressed patients and patients with and without personality disorder.

No differences were found evident between therapeutic levels of carbamazepine, phenytoin, and valproate on monotherapy CNV amplitude or AUC. The depressed and psychotic patients

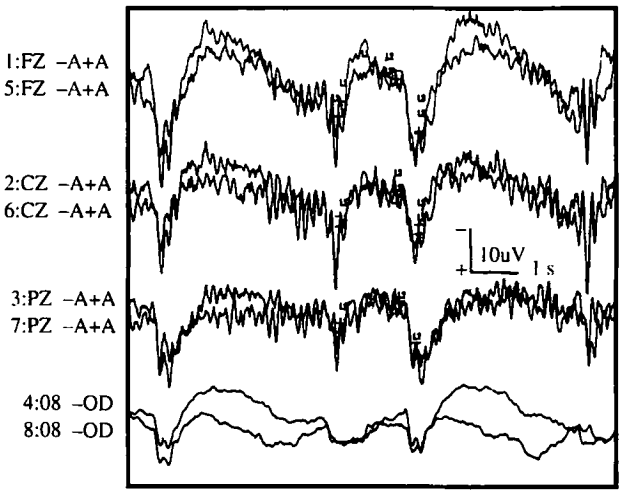

Fig. 1: Contingent negative variation recorded as described in the Methods section in a control subject. A reproducible negative potential develops between the warning ('L1') and imperatrice ('L2') stimuli, followed by a brief period of negativity and then return of the EEG to baseline. The fourth channel represents electro-oculogram, recorded between linked electrodes at the outer canthi.

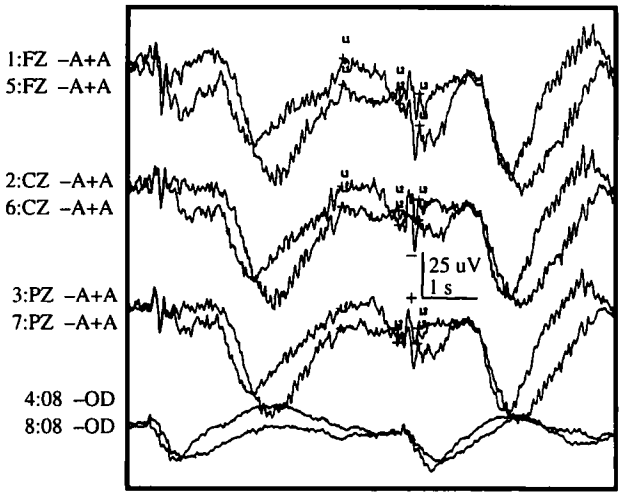

Fig. 2: CNV in a patient with complex partial seizures unattended by inter-ictal cognitive or behavioural symptoms. The response has similar morphology but reduced amplitude.

were not taking antidepressant or antipsychotic drugs at the time of their evaluation, although some had been on medications for these problems within a week before the study. No other prescription medications were reported, but the use of over-the-counter medications or other substances was not addressed.

DISCUSSION

The CNV is attenuated by psychosurgical procedures on the frontal lobes and may therefore have, at least in part, a frontal generator[5]. The early component of the magnetic contingent negative variation (CMV) has shown to arise in the occipital region, while the later component has a frontal generator[6]. CNV has been shown to be closely modulated by noradrenergic[7] and dopaminergic[8] systems, and some application has been shown in some neurological disorders of central catecholamine metabolism, such as migraine[9], Parkinson's disease[10], and Tourette's syndrome[11]. The response has been less well studied in epilepsy, with attenuation of frontal CNV in centrenecephalic epilepsy and also during epileptiform discharges of temporal lobe origin[12]. These earlier studies predated present epilepsy classification, and did not relate CNV measures to antiepileptic drug treatment or any specific clinical features.

Our findings suggest that epilepsy patients generally had CNV attenuation compared to normal controls. This may suggest some involvement by temporal lobe or limbic structures in CNV generation, in addition to the frontal generators previously suggested, or may reflect the prominence of frontal lobe epilepsy in a tertiary referral population of partial seizure patients. CNV attenuation in patients with inter-ictal disturbance of behaviour or personality could reflect the role that frontal lobe dysfunction plays in such symptoms, and might also make the CNV useful in the evaluation of inter-ictal behaviour in epilepsy.

We found no anticonvulsant-specific CNV effects, although amplitude reduction has been shown with carbamazepine[13] and clonazepam[14] in previous studies. This discrepancy may reflect the fact that earlier studies of drug effect on CNV utilized acute administration of high doses to normal volunteers, while we measured CNV in chronically medicated individuals and did not otherwise assess anticonvulsant status except to exclude patients with toxic anticonvulsant levels.

Patients with inter-ictal behaviour symptoms involving psychosis had CNV enhancement as measured by AUC, although amplitudes did not differ significantly from controls. Patients with psychosis were also more likely to have PINV, which has been correlated with psychotic illness and possibly with central dopaminergic state[2], and has been shown to arise during treatment of Parkinson's disease[10] and to be more frequent in patients with Tourette's syndrome, which is a disorder of dopamine excess[11]. This suggests that CNV enhancement or the development of PINV might indicate susceptibility to inter-ictal behavioural symptoms generally and psychosis

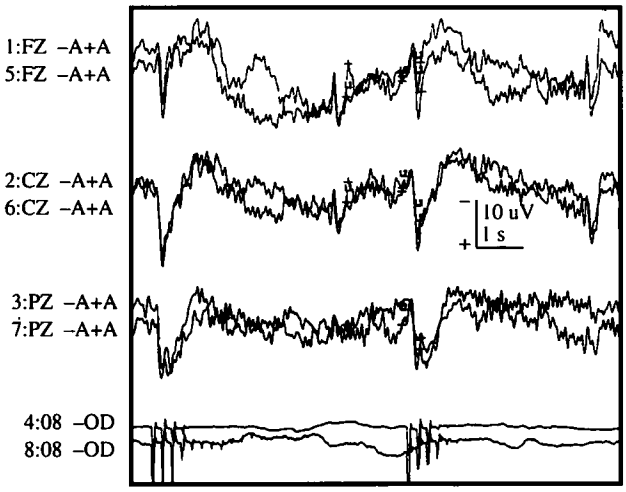

Fig. 3: CNV in a patient with poorly controlled complex partial and secondarily generalized seizures attended by personality disorder. The response is attenuated in amplitude and followed at 'L3' by a prolonged negative potential (post-imperative negative variation).

Table 1: CNV measurements in seizure patients and controls

	n	Area under curve (uV^2 + sd)	Amplitude (uV + sd)	PINV
Complex partial seizures	50	5.4 + 3.14	5.98 + 3.44[a]	11[a]
Control	20	13.8 + 11.5	2.81 + 3.44	2
Inter-ictal behavioural symptoms	30	4.23 + 3.13[a]	4.68 + 3.10[a]	11[a]
No inter-ictal behavioural symptoms	20	7.15 + 2.16	8.01 + 3.05	2
Depressed	16	4.91 + 4.45	3.07 + 0.21[a]	5
Non-depressed	34	5.63 + 2.80	7.39 + 3.70	5
Psychotic	5	9.17 + 5.29[b]	7.48 + 6.29	3
Non-psychotic	25	3.24 + 1.13	4.11 + 1.78	2
Personality disorder	9	2.86 + 0.88	4.68 + 2.35	3
No personality disorder	21	5.92 + 4.48	4.11 + 3.39	2

[a] $P < 0.001$.
[b] $P < 0.05$.

particularly, and may be of value in the periodic assessment of refractory seizure patients.

Our patients with epilepsy and depression had no difference in CNV AUC, but reduced amplitude compared to controls and non-depressed patients. Such amplitude attenuation has been described in various depressive disorders, along with amplitude increase during treatment with antidepressants which augment central catecholamine levels[2]. CNV amplitude reduction may therefore be relevant to development or progression of depressive symptoms in seizure patients, and might be a measure of antidepressant efficacy of anticonvulsant or other medication regimens.

CNV can easily be recorded with evoked potential instrumentation or in some cases on EEG instruments. Monitoring of patient state and ocular artefact is mandatory, as are means of delivering two associated or contingent stimuli, preferably with a motor task afterward which increases CNV amplitude. The utility of CNV recording in epilepsy evaluation may be clarified by prospective studies comparing patients with and without secondarily generalized seizures, and investigating the influence on CNV of the presumed sites of origin of partial seizures. Comparison of antiepileptic drug monotherapy and polypharmacy and correlation of CNV amplitude and latency with anticonvulsant level is also appropriate. More specific correlations of CNV measures with psychometric test variables and quantitative measures of psychiatric symptomatology would also be appropriate, and may indicate the extent to which CNV changes in these patients are determined by epilepsy on the one hand or neuropsychiatric symptoms on the other.

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