Preprogramming motor dysfunction in paroxysmal kinesigenic choreoathetosis

Francesco Fattapposta
Filomena My
Donatella Valente*
Rodolfo Quadrini
Carmelo D’Alessio**
Giuseppe Amabile

Department of Neurology and Otalaryngology and
*Department of Child Neurology and Psychiatry,
University “La Sapienza”, Rome;
**IRCCS Neuromed, Pozzilli (IS), Italy

Reprint requests to: Prof. Francesco Fattapposta,
Dipartimento di Neurologia e Otorinolaringoiatria,
Viale dell’Università 30, 00185 Rome, Italy
E-mail: francesco.fattapposta@uniroma1.it

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Summary

Paroxysmal kinesigenic choreoathetosis (PKC) is characterized by abnormal involuntary movements precipitated by sudden movement. As a result, a possible impairment of cerebral organization of voluntary motor activity is hypothesized in PKC.

We examined a 14-year-old boy affected by a sporadic form of PKC, adopting a multimodal psychophysiological approach, including P300, contingent negative variation (CNV) and a specific paradigm for the study of movement related potentials (MRPs). Recordings were made before and after phenobarbital therapy.

No changes were observed in the non-motor parameters (P300 and early wave of the CNV), whereas the premotor CNV component and the electrophysiological components, reflecting the preprogramming activity of a voluntary motor act, showed selective modifications induced by the anticonvulsant therapy.

Our PKC patient presents a disorder of temporal organization of a voluntary motor response to a stimulus. Both a clinical improvement and normalization of motor-related electrophysiological anomalies were observed during phenobarbital (PB) therapy.

KEY WORDS: CNV, MRPs, P300, PB therapy, PKC.

Introduction

Paroxysmal kinesigenic choreoathetosis (PKC) is a familial or sporadic movement disorder characterized by the recurrence of brief paroxysms of choreoathetosis, dystonic posturing or ballismus, in most cases precipitated by sudden voluntary movements (1-4). The attacks last less than five minutes (usually from 10 to 30 seconds), occur with a frequency ranging from one a month up to 100 a day, and may involve the limbs, head, neck or trunk, although without impairment of consciousness. Commonly, the attacks are preceded by sensory prodroma consisting of paraesthesias or feelings of tightness involving the affected limbs, and a refractory period can almost always be observed (5,6).

The aetiology and pathophysiology of PKC are still unclear. The induction of attacks by movement, the frequent occurrence of a sensory aura, and the good response of this disorder to anticonvulsant therapy are suggestive of a form of reflex epilepsy involving the basal ganglia (7-10). A non-epileptic disturbance of the basal ganglia function has, however, also been hypothesized in view of the type of movement disorder (9) and the good response to levodopa in many cases (11,12). As PKC attacks usually begin in childhood or in early adolescence, their frequent disappearance with increasing age has led some authors (1,11) to regard PKC as a manifestation of delayed maturation of the extrapyramidal system. Hence, Lance (3) stated that any disturbance in the cortical control of the neostriatum and its thalamic connections can induce a PKC attack. The pathophysiology of PKC has consequently been the focus of much debate. Moreover, laboratory investigations and autopsy studies have failed to reveal specific abnormalities in this disorder (4).

Given that the factors which provoke PKC attacks are anticipated or sudden voluntary movements (e.g., standing up to speak in public, carrying out sudden commands, crossing the road when a car unexpectedly appears around the corner), some authors (5,6,13) have investigated the underlying psychophysiological aspects of PKC using specific paradigms resembling the situations in which affected patients tend to experience attacks. This psychophysiological approach (event-related potentials-ERPs) has been used successfully to detect specific electrophysiological abnormalities in PKC.

Over the last fifteen years, examination of the two-paired stimuli paradigm (contingent negative variation-CNV) (5,6) and of a motor P300 paradigm (6) has, in fact, yielded very interesting results. P300 is one of the endogenous ERPs with maximal parietal representation, accurately reflecting the evaluation and categorization of a significant stimulus. More recently, it has been suggested that P300 reflects a cerebral process associated with the updating of representations in working memory (14). Busard et al. (6), employing a paradigm involving the process of integration and evaluation of an information stimulus related...
to the preparation of motor activity (a P300 motor paradigm), revealed aberrant data in their patient whose condition improved following treatment with valproic acid.

The CNV is a slow event-related potential which develops in the interval between two stimuli: the first stimulus (S1) serves as a warning that prepares the subject to expect the second, imperative stimulus (S2), which instead requires a decision or a motor response (15). It has been suggested that CNV is not a unitary phenomenon but consists of at least three components, each related to specific psychophysiological aspects: the slow positive wave (SPW), found in the parietal association cortex, is thought to reflect the outcome of an evaluation of the stimulus; the slow negative wave (SNW), showing bilateral frontal predominance, reflects continued information processing in the frontal cortex, possibly related to subsequent motor output processes; lastly, the late or terminal-CN V (ICNV), has been related to preparatory processes, and in particular to motor preparation (16,17). Since the CNV paradigm involves a series of complex processes in the preparation of a motor response, Franssen et al. (5) explored, for the first time, CNV changes in a case of sporadic PKC: they reported an increased amplitude of the SPW and SNW, components which returned to normal after treatment with phenytoin sodium. Similarly, Busard et al. (6) reported a CNV amplitude increase in a case of familial PKC and in the patient’s asymptomatic brother, and a complete disappearance of the electrophysiological anomalies after therapy with valproic acid.

All these data suggest a disturbance in stimulus-related motor act processing. An investigation of the literature on the factors that provoke PKC attacks reveals that some psychophysiological aspects of motor behaviour, such as planning a self-paced motor act, are not selectively explored by the classic CNV paradigm or by the motor P300 evaluation.

In particular, voluntary motor activity, whether externally or internally cued, requires a series of preparatory processes (18) and precise temporal processing (19) before the final motor outcome.

Movement related potentials (MRPs) provide the most information on the preparatory processes involved in an internally guided movement, reflected in the Bereitschaftspotential (BP). Houser et al. (13), recorded the BP in two patients with PKC and both showed reduced amplitude of the early negativity and a relatively steep late negativity with delayed onset.

The skilled perceptual task (SPT), through analysis of MRPs in the context of an interactive paradigm (20), permits the investigation of cerebral processes related to preprogramming activity and to the appraisal of a performance result, represented by a post-motor brain activity called skilled performance positivity (SPP).

Thus, this paradigm could specifically reveal possible abnormalities in the movement programming, execution and control phases in patients suffering from PKC.

Our aim was to evaluate the influence of movement preprogramming and control activities on the psychophysiological genesis of PKC by using both motor (CNV, MRPs) and non-motor (P300 acoustic) paradigms. We studied a patient affected by sporadic PKC before and after anticonvulsant therapy.

Materials and methods

A 14-year-old boy, with an unremarkable family history, was admitted to our hospital because of recurrent brief attacks of paroxysmal dystonic movements in the neck, trunk and limbs, which were prevalent on the right side and lasted a few seconds. The attacks had begun at the age of 8 years and occurred with a frequency of 10-15 a day; they were induced by sudden movements, such as quickly getting up from a chair to answer the telephone or going to the blackboard on a teacher’s request. The attack frequency was increased by emotional stress and attacks never occurred during sleep. The patient reported that the attacks were sometimes preceded by a vague dysesthetic sensation in the calf area, and that he was able to prevent an attack by adopting specific strategies, such as ‘moving the limbs like a dancer warming up’. The paroxysms were never associated with a loss or clouding of consciousness or with incontinence.

During the neurological examination, the request to perform a quick gait acceleration provoked a brief dystonic attack characterized by dorsal flexion of the right foot and flexion of the carpus and fingers of the right hand. The remainder of the clinical examination was normal.

No abnormalities were found in a complete routine haematological analysis. Metabolic, endocrinological, immunological, toxic and infectious aetiologies were ruled out by means of specific biochemical screening. CSF study, brain CT, EEG, visual (VEP) and somatosensory (SEP) evoked potentials were normal. The paroxysms decreased in frequency and eventually disappeared after four weeks of therapy with phenobarbital (PB) 100 mg/day.

Electrophysiological recordings

P300, CNV and MRPs were recorded before and after four weeks of PB therapy (100 mg per day). Electrophysiological and behavioural data were compared with the normative data from our laboratory. During recordings, the subject was seated in a comfortable chair in a faradized room with attenuated sound and dimmed lights. The electrophysiological signals were recorded by means of Ag/AgCl electrodes fixed with collodion to the scalp. Active electrodes were placed according to the 10-20 International System and referred to linked mastoids. Electrode resistance was kept constant at below 3 Ω. Bipolar electro-oculogram (EOG) was recorded from above and below the left eye to monitor blinking and eye movements (bandpass: 0.02-30 Hz). All artifact-contaminated trials were rejected. The patient did not experience any dystonic paroxysms during the recording sessions.

P300

We used the acoustic oddball paradigm. For P300 recording, two different tones (2000 Hz and 500 Hz) of 200 ms duration and an intensity of 70 dB SPL, and with a 0.5 ms rise/decay time, were administered binaurally via earphones. The stimuli (20% of which were 2000 Hz tones) were randomly presented. The subject had to count mentally only the 2000 Hz tones (target
Psychophysiological study in PKC

CNV

CNV was recorded by means of a choice-reaction motor task for paired stimuli: the first stimulus served as a warning (S1) to prepare the subject to expect the second, imperative stimulus (S2), which required a motor response. S1 consisted of a flash (100 µs, 1.5 J) emitted by a strobe lamp at a distance of 30 cm from the subject’s face, while S2 consisted of a tone of 250 or 2000 Hz (200 ms in duration and 70 dB SPL) delivered binaurally via earphones. The occurrence of a 2000 Hz tone (target tone), was randomized with a probability of around 20%. The subject, in his right hand, a special handle-grip equipped with a button that he had to press as quickly as possible upon hearing the target tone, in order to stop it. The CNV recording was preceded by a brief training period to prepare the subject properly.

Two different interstimulus intervals (ISIs) were used: 1.5 s and 2.5 s, and an intertrial period that varied randomly between 6 and 12 s. The analysis time was 4 s. A passband of 0.016-15 Hz was used. Active electrodes were placed on Fz, Cz, C3, and C4 and referenced to the linked mastoids.

The CNV area for both ISIs was calculated: from 200 ms to 1499 ms post S1 for the shorter ISI (1500 ms), and from 200 to 2499 ms for the longer ISI (2500 ms). The use of a longer ISI (2.5 s) allowed us, as reported in the literature (21), to evaluate the three main components of the CNV (SPW, SNW and tCNV), each of which has specific psychophysiological value. We measured them during intervals of 200 ms after S1 (SPW), and of 500-700 ms after S1 (SNW), as well as in the 200 ms immediately preceding S2 (tCNV).

MRPs

The SPT paradigm was used to record MRPs. The subject, holding in each hand a handle-grip equipped with a button, faced the 10-cm screen of an oscilloscope, placed at a distance of 80 cm. The subject was required to start the oscilloscope sweep by pressing, with his left index finger, the button on the handle-grip held in that hand and to stop it (in a time interval of 40-60 ms from the sweep start) within a defined target area by pressing, this time with his right index finger, the button on the other handle-grip. For the purposes of this study, stopping the sweep within the target area constituted a “correct performance”. Owing to the small time interval of the target area (20 ms) and the high sweep velocity (1 m/s), the subject had to pre-program the entire motor sequence in advance and update motor strategies according to the results achieved. The recording was started only when the patient had clearly understood the verbal explanation of what the task required and was able to execute it correctly. Active electrodes were placed at Fpz, Fz, Cz,

P300

No variation was observed before or during treatment in P300 latency (Table I), which fell within the normal age-

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MRPs

The recording was started only when the patient had clearly understood the verbal explanation of what the task required and was able to execute it correctly. Active electrodes were placed at Fpz, Fz, Cz,

Pz, P4, P3, and at RPC (right precentral) and LPC (left precentral). The last two leads were located on each hemisphere 2 cm anterior to a point 5 cm from the midline on a line extending from 2 cm behind the vertex to each auditory meatus (19). The surface electromyogram (EMG) was recorded from the left and right fore-arm flexor muscles with a bandpass filter of 0.2 Hz-3 kHz, which was rectified to identify the onset of muscular activity. One hundred artifact-free trials were averaged.

The BP onset (latency value in relation to the EMG onset) and BP amplitude (average of the 200 ms before EMG onset), SPP latency (value measured from the trigger pulse) and SPP amplitude (averaged value, from the baseline, over 200 ms centred around the main positive peak value in the latency band between 350 and 650 ms after triggering), and percentage of correct performances were calculated.

For further details of the experimental techniques and procedures see: Amabile et al. for CNV (21), Stanzione et al. for P300 (22) and Fattapposta et al. for BP (23).

Results

Abbreviations: CNV: contingent negative variation; ISI: interstimulus interval; SPW: slow positive wave; SNW: slow negative wave; tCNV: terminal CNV; MRPs: movement related potentials; BP: B ereitschaftspotential; SPP: skilled performance positivity.

Cz

BP amplitude (µV) | 5 | 5 |
BP onset (ms) | 266 | 1170 |
BP area (µV × ms) | 1565 | 6167 |
Pz

SPP amplitude (µV) | 21 | 19 |
SPP latency (ms) | 552 | 570 |

Correct performances (%) | 28 | 30 |

Correct performances (%) | 28 | 30 |
matched range (331.3±28.2), nor in the amplitude and scalp distribution (Fig. 1). Neither the N100-P200 complex, which reflects the early stages of information processing, nor the physical features of the stimulus varied during PB treatment.

**CNV**

Before PB administration, the CNV waveform during the short ISI (1.5 s) underwent a unitary shift, which did not return to baseline after delivery of S2, a phenomenon known as post-imperative negative variation (PINV). In the longer ISI (2.5 s), the CNV appeared as a multiphasic, sharply rising wave, which did not return to baseline after task completion. In the latter case, it was not possible to define a PINV owing to the short analysis time we employed.

During therapy, the PINV disappeared during the 1.5 s ISI and the post-S2 negativity observed during the 2.5 s ISI was reduced (Fig. 1). Moreover, with clinical improvement the total CNV area presented a decrease of 35.5% and 35.6% during the 1.5 s and 2.5 s ISIs, respectively. Notably, by analysing the CNV recorded during the on-therapy 2.5 s ISI, it was possible to detect selective changes in the SNV and tCNV areas, which decreased when compared with those obtained during the symptomatic period (by 55.6% and 52.6%, respectively). By contrast, the SPW component remained unchanged (Table I).

**MRPs**

The BP was symmetrically distributed over the precentral-centro-parietal regions, with the maximum amplitude and its onset on the vertex (Cz), and minimal representation over the frontal sides. The BP amplitude did not change after treatment with phenobarbital. By contrast, BP onset occurred earlier and the BP area increased markedly in concomitance with clinical improvement after one month of therapy (Fig. 2, Table I). SPP was mainly detectable on Pz, with a symmetrical distribution over the lateral parietal sites and an ill-defined waveform over the central and precentral sites. After therapy, SPP amplitude decreased slightly while the latency was substantially unmodified (Fig. 2) (Table I).

The percentage of correct performances did not vary markedly (30% and 28% correct hits ratio before and after therapy, respectively) (Table I).

**Discussion**

The electrophysiological recordings obtained in relation to selective paradigms are able to measure, unobtrusively and in real time, the modifications of brain electrical activity specifically related to the different phases underlying the information processing and preparatory aspects of a motor response. Not all of the ERPs recorded changed. Those that did were the electrophysiological components that reflect the electrical cerebral activity correlated with the movement (BP), the temporal processing (SNW component of CNV) and the motor adjustment process (tCNV). On the contrary, the electrophysiological components that did not change were the ones not correlated with motor activity (P300 and SPW component of CNV).

We would like to point out that barbiturate therapy did not affect the subject’s attentional level, as demonstrated by the unchanged P300 and the good quality of psychomotor performance in the SPT paradigm during therapy.

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*Fig. 1 - P300 and CNV waveforms before therapy (A) and on-therapy (B) recorded at Pz and Cz, respectively. S1 indicates warning stimulus; S2 indicates imperative stimulus requiring motor response. In the 1.5 s ISI, note, during therapy, the marked reduction in the CNV area together with the disappearance of PINV. In the 2.5 s ISI, the SNW and tCNV components also decreased during therapy, as did the lasting negativity beyond the S2.*
Two electrophysiological parameters, the SPW component of CNV and the P300, which reflect the outcome of an evaluation of the stimulus material and the stimulus discrimination (24) respectively, did not change during therapy. This suggests that stimulus evaluation, when not requiring a sudden motor response, was unimpaired in our patient, which raises the hypothesis of an abnormality in the motor output processes.

Conversely, the on-therapy reduction in SNW, a CNV component related to the temporal processing of the stimulus contingency (25), suggests a basal dysfunction in the timing processing required for a correct execution of a motor act. This hypothesis is confirmed by the finding of a lasting negativity after S2 during both the ISIs, which is regarded as a sign of an ongoing contingency evaluation beyond the imperative stimulus (S2) (26). Furthermore, the increased negativity, before therapy, of the ICNV, considered as a combination of motor and temporal preparation (25), lends further support to the presumed abnormal temporal programming and control activity of externally guided motor acts in PKC.

MRP data provide further psychophysiological information. BP negativity usually begins about 1-2 s before the EMG onset and is divided into two portions, the first (early BP) being commonly related to preparation and the second (late BP) being related more specifically to movement and its characteristics (27).

The delayed BP onset in our patient in the basal condition denotes the absence of the early BP component, i.e., of the early stages of cerebral motor preparation. In the presence of a drug-induced clinical improvement, BP onset occurred earlier and the BP area consequently increased. The modified data point to the recovery of the early BP component, i.e., of a correctly timed motor preparation for internally cued motor acts. The SPP component, related to appraisal of the performance result, was substantially unchanged.

All these electrophysiological data have led to the concept, in PKC, of abnormal temporal processing in the preparation of a motor act, whether externally or internally cued. The temporal organization of sequential self-paced movements is co-ordinated by internal cues generated within the basal ganglia and projected to the supplementary motor area (SMA), which is believed to be the main generator of the early component of BP (28). The selective dependence of pre-movement SMA activity on temporal parameters of movement indicates that the SMA plays a crucial role in the temporal organization of sequential movements rather than the programming of specific movements (28).

Likewise, the normal timing processing that precedes an externally cued voluntary motor output is thought to entail a complex interaction between the basal ganglia and frontal lobes (29,30).

According to Fuster (29), the prefrontal cortex (dorsolateral part) is involved in the temporal integration of motor behaviour, which is accomplished with the assistance of two mutually complementary and interrelated functions: a retrospective function of temporary memory for recent events and a prospective function of preparation for coming events, effectively explored by the CNV. This multimodal electrophysiological approach in our PKC patient revealed the presence of a dysfunction of the temporal organization of a voluntary motor response to a stimulus, whether internal or external. In view of the specific role played by the SMA and basal ganglia in temporal motor processing, the aforementioned findings could lend further support to the hypothesis, in PKC, of selective impairment of these intricately linked structures (31).

Our data do not, for several reasons, contrast with the hypothesis that PKC is a peculiar form of epilepsy: first, central mechanisms related to the elaboration of movement, rather than proprioceptive afference, may be critical in initiating reflex seizures (32); second, invasive monitoring in a girl with PKC recorded an ictal discharge from the supplementary motor cortex, with a concomitant discharge within the ipsilateral caudate nucleus, which did not spread to other neocortical areas (33); finally, anticonvulsant therapy is, as also observed in our patient, effective in PKC.

References