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Preparatory visuo-motor cortical network of the contingent negative variation estimated by current density

C.M. Gómez,[a] J. Marco,[b] and C. Grau[b,*]

[a] *Psychobiology Laboratory, Department of Experimental Psychology, University of Sevilla, Spain*
[b] *Neurodynamics Laboratory, Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Catalonia, Spain*

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Abstract

The present report studied the intracerebral current density of the contingent negative variation (CNV) during a visuo-manual task using the gap paradigm. The CNV is usually obtained during preparatory periods for perception and action. In this experiment right-hand responses were required. The CNV potential was obtained during the preparatory period from electrodes placed at 58 scalp sites. The CNV showed an early and a late phase. Scalp voltage and source current density maps showed that the early phase was focused on frontal midline sites. The late phase had two foci, one overlying the primary motor cortex and one over occipital sites. When analyzed by low-resolution tomography, the early phase of the CNV showed activations in the supplementary motor area (SMA), the anterior cingulate cortex (ACC), and some posterior areas. The late phase had anterior activations in the left prefrontal cortex, middle frontal cortex, primary motor cortex, ACC, and SMA; and several posterior activations including those in the medial occipital cortex, middle inferior occipital cortex, posterior cingulate cortex, and temporal and parietal areas. Results from the activated areas and their temporal dynamics during the preparatory period suggest that the ACC and the SMA areas recruit the action- and perception-related areas needed to process the expected subsequent imperative task.

Keywords: Contingent negative variation (CNV); Source current density; LORETA; Frontal activation; Cingulated cortex

Introduction

When two subsequent stimuli S1-S2 are presented, the preparation for an imperative stimulus (the S2) induced by the warning stimulus (S1) generates the contingent negative variation (CNV) (Walter et al., 1964; Rockstroh et al., 1982). CNV is not only relevant in basic neurobiological terms, but has proved sensitive to various neural disorders such as attention-deficit/hyperactivity disorder (Perchet et al., 2001), schizophrenia (Heimberg et al., 1999; Klein et al., 2000), depression (Heimberg et al., 1999), and anorexia nervosa (Torigoe et al., 1999).

From a functional perspective it has been proposed that the S1 acts as a warning stimulus that triggers the activation of areas needed for the subsequent processing of the S2 stimulus (Gómez et al., 2001). Traditionally, use of event-related potentials (ERPs) has led to the suggestion that the CNV has at least two phases: an early one relating to orientation and induced by the warning stimulus (Weerts and Lang, 1973), and the late phase relating to the motor preparation for the response (Loveless and Sanford, 1974). In the above-mentioned studies the early phase has a frontal bilateral distribution. Different ERPs and lesion studies suggest that the supplementary motor area (SMA) and the anterior cingulate cortex (ACC) are the sources for this component of the CNV (Cui et al., 2000; Zappoli et al., 2000; Gómez et al., 2001). In addition, it has been proposed that the early phase of the CNV during time-estimation tasks has its origin in the SMA and plays a major role in timing processes (Vidal et al., 1995; Macar et al., 1999).

The late CNV phase is contralateral to the hand to be

* Corresponding author. Neurodynamics Laboratory, Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Passeig de la Vall d'Hebron 171, 08035 Barcelona, Catalonia, Spain. Fax: +934034424.

E-mail address: cgrau@psi.ub.es (C. Grau).

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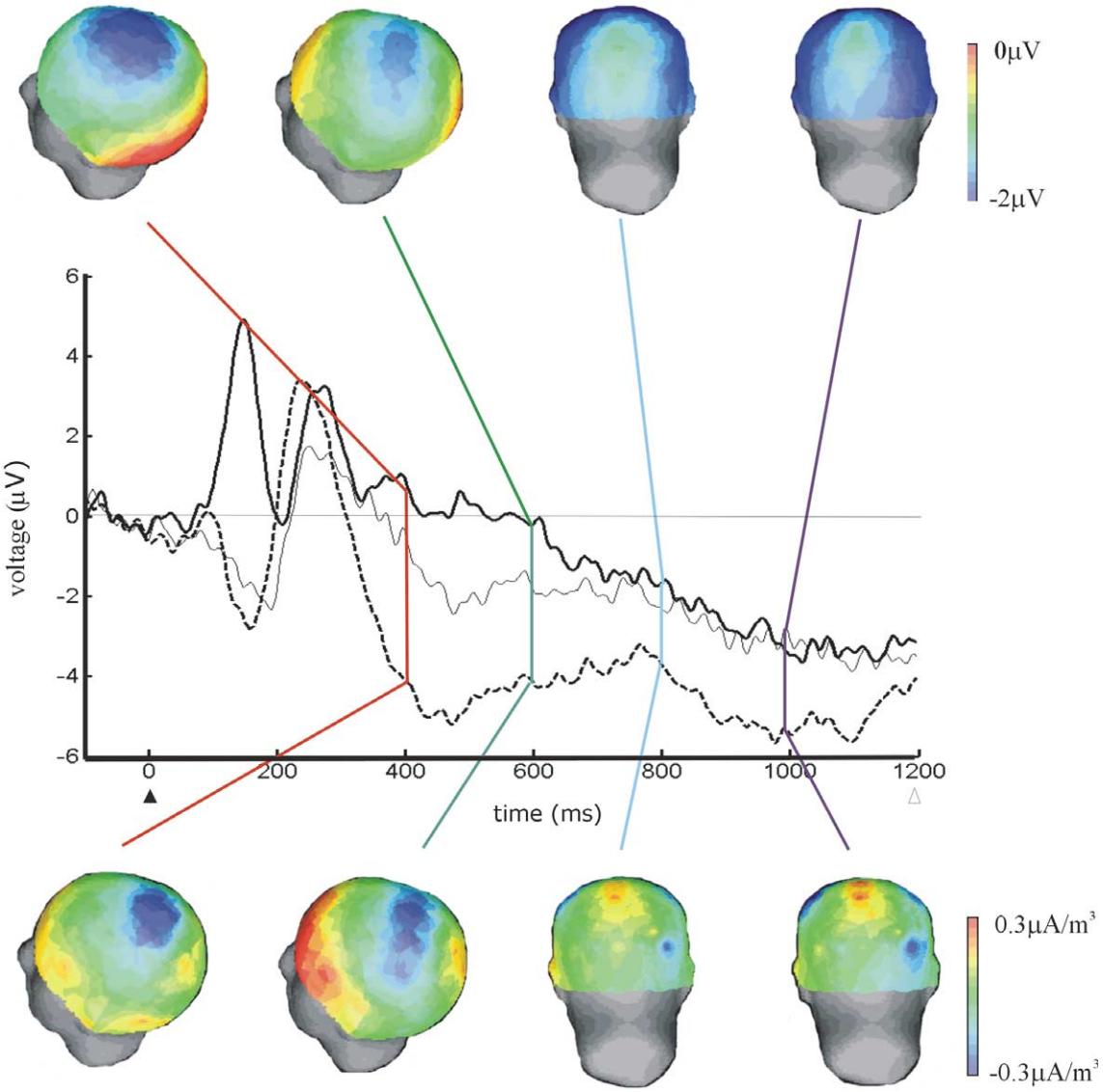

Fig. 1. Visual ERPs produced by the warning visual stimulus and during the preparatory period. The ERPs corresponding to the electrodes C3 (thin line), CZ (dashed line), and Oz (thick line) are displayed. The voltage and SCD maps of a time window of 100 ms around the vertical bars in the brain waves are shown in the upper and lower parts of the figure, respectively. The warning stimulus arrival is marked with a black arrow (0 ms) and the imperative stimulus is marked with an open arrow (1200 ms). Note the presence of visual ERPs to the warning, and the appearance of a CNV during the preparatory period.

used for responses, and seems to be associated with motor responses (Loveless and Sanford, 1974). According to Gaillard (1978) it reflects preparation for optimal, effective motor responses. Some controversy has arisen about whether the CNV can be equated to the Bereitschafts potential (BP) or not (Kornhuber and Deecke, 1965). A generally accepted view is that the late phase of the CNV represents motor preparation processes very similar to those indexed by the BP component (reviewed in Rockstroh et al., 1982). Recently Cui and Deecke (1999), using self-paced autogenerated movements, proposed the existence of three subsequent negativities relating to motor preparation and execution. It was suggested that the first of these is an initial phase called BP1, with possible origin in SMA and cingulate motor areas, which helps organize sequential movements and bimanual coordination. The second, BP2, is contralateral to the hand to be moved with a possible origin in the primary motor cortex (M1) and prepares the M1 contralateral to the subsequent response. Finally, BP2 is followed by the motor negative potential 60 ms before the first electromyography activity, and reflects activation of the motor cortex during generation of the pyramidal tract volley.

In addition to these frontal sources for the early and late phases of the CNV, some reports suggest that posterior sites could also contribute to the generation of the late phase of the CNV (Brunia and van Boxtel, 2001; Gómez et al., 2001). In fact, what is known as the stimulus preceding negativity, which could reflect anticipatory attention for an upcoming stimulus, shows sources in perceptually related

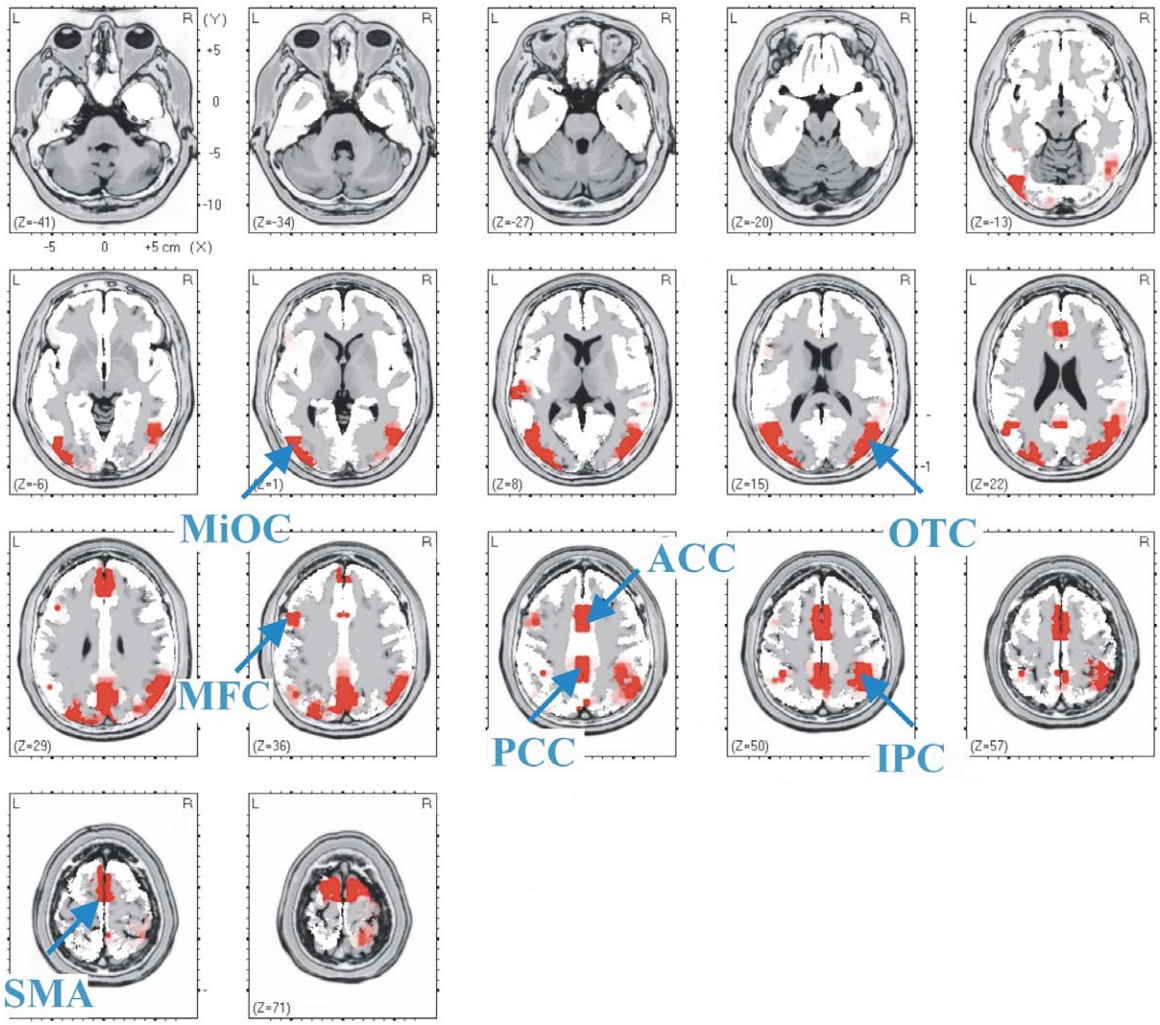

Fig. 2. Current density of the early CNV (400 to 800 ms after warning stimulus), calculated with LORETA. Red areas are significant activated in this period ($P < 0.05$) compared with baseline: ACC, anterior cingulate cortex; IPC, inferior parietal cortex; MFC, middle frontal cortex; MiOC, middle occipital cortex; OTC, occipito-temporal cortex; PCC, posterior cingulate cortex; SMA, supplementary motor area.

posterior brain areas (Brunia and van Boxtel, 2001). Other possible sources of the CNV, such as thalamic (Rektor et al., 2001) and basal ganglia activities, have been found recently through implanted electrodes (Bares and Rektor, 2001).

From a functional perspective, negativities present in the preparatory periods are interpreted by the "threshold regulation theory" (Birbaumer et al., 1990; Rockstroh et al., 1993). This theory proposes that preparatory negativities, including CNV, recorded over the scalp reflect increased activation due to depolarization in the apical dendrites of pyramidal neurons. In this view, negativities over the M1 cortex (Cui et al., 2000) and posterior negativities (Gómez et al., 2001) reflect the preparation of the motor and sensory areas, respectively, which are going to be needed to process the next imperative stimulus in the visuo-motor task.

A few studies have addressed the question of the neural generators of the CNV using dipole localization techniques. Activity in different areas of the frontal cortex, such as the prefrontal, anterior cingulate, and motor cortex, has been obtained in a variety of preparatory tasks by means of electroencephalography (EEG) (Pouthas et al., 2000; Ferrandez and Pouthas, 2001), and magnetoencephalography (Basile et al., 1994, 1997; Hultin et al., 1996). The contribution of posterior sites to the CNV is much rarer (Ionnides et al., 1994; Gómez et al., 2001). Elbert et al. (1994) described a magnetic counterpart of the CNV that could involve an important contribution from the temporal cortex. Several studies using electrophysiological recordings of single neurons in animals (Luck et al., 1997) and functional magnetic resonance imaging (fMRI) in humans (Kastner et al., 1999) also support the activation of frontal and posterior sites during preparatory periods.

An alternative to dipole localization in order to obtain noninvasively the activated areas is low-resolution electromagnetic tomography (LORETA) (Pascual-Marqui et al., 1994). This method based on scalp current density computes one single unique solution for the 3-D intracerebral sources and imposes the constraint of the smoothest source

configuration as the valid solution. This constraint is physiologically justified by the higher contribution to the scalp voltages of adjacent synchronized neural areas than of the nonsynchronized areas. The relation of LORETA solutions to brain activity has received support from the correlation between the human cerebral glucose metabolism measured through positron emission tomography, and the intracerebral brain activity measured by the LORETA method (Dierks et al., 2000). One of the main advantages of this method is that, by establishing tomographic brain imaging with the excellent time resolution of the EEG method, it enables brain dynamics in the subsecond range to be studied.

The goal of the present study was to obtain the brain sources of the CNV in a visuo-motor task: the manual gap paradigm. As the LORETA method gives a dynamic picture of the different areas involved in a given behavioral or cognitive task, the sequence of activation of the brain areas can be established. The spatio-temporal information obtained could improve the understanding of neurocognitive activity during anticipatory motor intention and perceptual attention.

Materials and methods

Subjects

Eleven subjects (seven female, right-handed) between 18 and 27 years old took part in the experiment. The experiments were conducted with the informed consent of each subject.

Behavioral paradigm

Participants were seated 50 cm in front of a computer screen. They were instructed to fix their eyes on a green square (0.91° of visual angle) which would appear in the center of the screen, and to press one button of the mouse as soon as a target (also a green square) appeared peripherally to the first square. The central stimulus was the warning stimulus, and the peripheral stimulus the imperative one. The eccentricity of the target was 11.4° from the fixation point in the left or right visual field of the horizontal meridian. The left button of the mouse had to be pressed when the target appeared in the left visual field, and the right one when the target appeared in the right visual field. Both responses were made with the right hand, using the index finger for left responses and the middle one for right responses. Each subject was given 500 trials.

Stimulus presentation was computer-controlled (Stim system, Neuroscan). The event sequence within a trial was as follows: the central fixation point was on for 1 s, a temporal gap (200 ms) followed the offset of the fixation stimulus, and then the peripheral target was on for 1 s. The intertrial interval was also 2 s. As the focus of this report is the CNV, only pretarget results are given here.

Recording and analyses

Vertical and horizontal eye movements were recorded by electro-oculography (EOG). The electrodes were placed on the external canthi of both eyes for recording horizontal movements, and on the inferior and superior areas of the ocular orbit for recording vertical eye movements. EEG data were collected from 58 scalp sites of an extended version of the International 10–20 system, using tin electrodes mounted in an electrode cap. All the electrodes were referred to the left mastoid. Impedance was maintained below 5000 ohms. Data were filtered using a bandpass of 0.01–100 Hz (1/2 amplitude low- and high-frequency cutoffs); the amplification gain was 30,000 (Synamps, Neuroscan). Recordings were notch-filtered at 50 Hz. They were acquired at a sampling rate of 500 Hz, using a commercial AD acquisition and analysis board (Scan). Recordings were averaged off-line using an artifact-rejection protocol based on voltage amplitude. All the epochs for which the EEG or EOG exceeded 50 μv were automatically discarded. For each subject ERPs were obtained by averaging the EEG, using the switching on of the central fixation as trigger. The algebraically linked mastoids were computed off-line and used as reference for purposes of analysis. Repeated-measures ANOVA was performed to the voltage data. The factors were electrodes (FZ, OZ, CZ, and C3) and condition (activation vs baseline), for four intervals (350–450 ms, 550–650 ms, 750–850 ms, 950–1050 ms after the warning stimulus). Baseline was the 100-ms interval before warning stimulus. *P* values were calculated using the Greenhouse–Geisser correction when appropriate.

To obtain the scalp activations of the brain potentials generated during the preparatory phase, first the spatial voltage maps and source current density (SCD) maps of the experimental data were computed using the Hjorth (1975) method.

LORETA (Pascual-Marqui, 1999; Pascual-Marqui et al., 1994) was used to find intracerebral sources of the CNV. The LORETA version employed in this study uses 2394 voxels that take account of gray matter and hippocampus in the Talairach digitized human brain. In order to determine whether a source was activated or not during the CNV at a given time point, pairwise comparisons between sources of CNV and baseline (100 ms before stimuli) were performed, using the nonparametric method as described by Holmes et al. (1996). This method uses the pseudo-randomization *t* test and is corrected from multiple comparisons problem. Areas with $P < 0.05$ or less were accepted as being activated.

Results

Fig. 1 shows the ERPs to the warning stimulus and during the preparatory period before the arrival of the imperative stimulus. The upper part of Fig. 1 displays voltage 3-D maps, and the lower part the corresponding SCD maps.

After the visual ERPs evoked by the warning stimulus, a clear CNV can be observed. The earliest CNV negative activity appears 400 ms after the warning stimulus, and presents maximum activity in the frontocentral sites (activation vs baseline $F(1,10) = 19.301$, $P < 0.009$), as can be appreciated on both voltage and SCD maps. Around 600 ms after the warning stimulus, negativity spreads over the C3 and adjacent electrodes ($F(1,10) = 16.9$, $P < 0.002$). Around 800 ms after the warning stimulus a broad negativity appears in the occipito-temporal sites, as can be observed on the voltage and SCD maps ($F(1,10) = 22.461$, $P < 0.001$), and continues until the end of the expectancy period (around 1000 ms, $F(1,10) = 27.445$, $P < 0.0009$).

Fig. 2 indicates in a color code the source current density from 400 to 800 ms (early CNV); and Fig. 3, the activated areas from 800 to 1200 ms (late CNV). All colored areas have statistically significant activity compared with the base line ($P < 0.05$ in Holmes nonparametric method; see Materials and methods). Regions activated are shown in the digitized Talairach atlas. In frontal cortex bilateral SMA (area 6), bilateral ACC (area 24), and left middle frontal cortex (MFC) (area 9) were activated in early CNV, and the left prefrontal cortex (PFC) (area 45), left M1 (area 4), left MFC (area 9), bilateral ACC (area 24), and bilateral SMA (area 6) were activated in late CNV. In posterior sites activity appeared in both early and late CNV in middle inferior occipital cortex (MiOC) (area 19), posterior cingulate cortex (PCC) (area 31), and parietal area (IPC) (area 40), whereas there was activation only in early CNV in right, occipito-temporal cortex (OTC) (area 37). In addition, for the late CNV there was statistically significant activity in medial occipital cortex (MeOC) (area 17).

The corresponding temporal dynamics of these areas are shown in Fig. 4. Fig. 4A shows the activity of SMA and the ACC. ACC and SMA show enhanced activity that matches in time the early frontally distributed scalp CNV (Fig. 1). The activity of ACC decreases from 400 to 800 ms, and stabilizes until the arrival of the imperative stimulus (S2), whereas activity of SMA is almost constant throughout the entire CNV range. From 600 ms there is slowly rising activity in the left PFC and left MFC (Fig. 4B) and in the left primary motor cortex (M1) (Fig. 4C). It should be noted that M1 activity does not increase on the right side, which has been incorporated for comparison purposes.

In posterior areas (Fig. 4D), LORETA finds an initial burst of activity whose latency corresponds to the visual ERPs, and then MeOC, and MiOC shows a sustained activity throughout the CNV. However activity in MeOC is not significant ($P > 0.05$) in the early CNV. PCC and IPC (Fig. 4E) show sustained increase of activation from 400 ms to the arrival of imperative stimulus. OTC (Fig. 4F) contributes only to the first part of early CNV. Finally, it should be noted that the dynamics of the activity in the PFC (Fig. 4B) resembles the activity of the left M1 (Fig. 4C), PCC, and IPC (Fig. 4E).

Discussion

During the preparatory period a clear CNV potential appeared (Fig. 1). The scalp voltage and SCD maps show that this potential has at least three different components: two in anterior areas and one in posterior sites. This result is in line with the classic proposal of the contribution of anterior components in CNV, one early component with a frontal distribution that has been associated with an orienting response (Weerts and Lang, 1973), and the late CNV component placed contralaterally to the hand to be used for responses, which seems to be related to motor responses (Loveless and Sanford, 1974). The anterior CNV components may be associated with BP1 and BP2 of BP in self-paced movements (Kornhuber and Deecke, 1965; Cui and Deecke, 1999). Previous studies of voltage and SCD distribution led to the suggestion that the early phase of CNV had its origin in the SMA and ACC areas and had a major function in programming processes but not in response execution. The late phase of CNV would be accounted for by M1, and be related to the response execution (Vidal et al., 1995; Macar et al., 1999; Gómez et al., 2001). One fMRI study, using a paradigm similar to that used for obtaining CNV, supports previous findings based on electrophysiological techniques, showing activation of ACC and SMA in the preparatory periods and of M1 in the executive response (Lee et al., 1999).

All the above-mentioned areas are activated in the LORETA solution obtained in the present experiment. These results corroborate both the validity of the methodological approach used in this study and the previously reported involvement of these specific areas in CNV production. The dynamic analysis of neural activity (Fig. 4) shows that SMA and ACC activate before other areas. The fact that the earliest negativity in the CNV scalp potential coincides in time with the peak of the ACC and the first activation of SMA in LORETA supports a simultaneous contribution of these areas to the first phase of CNV. This confirms the observation of Lee et al. (1999) that observed the coactivation of ACC and SMA areas using a similar paradigm.

After the activation of the SMA/ACC, there is an activation of left M1, PCC, right IPC, left PFC, and left MFC areas. The M1 area has been proposed as the origin of the motor-related late component of the CNV (Rockstroh et al., 1982; Gómez et al., 2001). Present results support this view, and interestingly activation of the left M1 area grows steadily in the preparatory period as the arrival time of the executive stimuli approaches, favoring greater activity of the left than of the right M1 (Fig. 4C).

The left PFC and left MFC follow a dynamic pattern that is similar to left M1 activation. The PFC has been proposed as the neural substrate of the working memory and motor attention (Fuster, 2000; Goldman-Rakic, 1995). Moreover, Frith (2001) suggested that anticipatory attention tasks, such as CNV, require the working memory process in order to

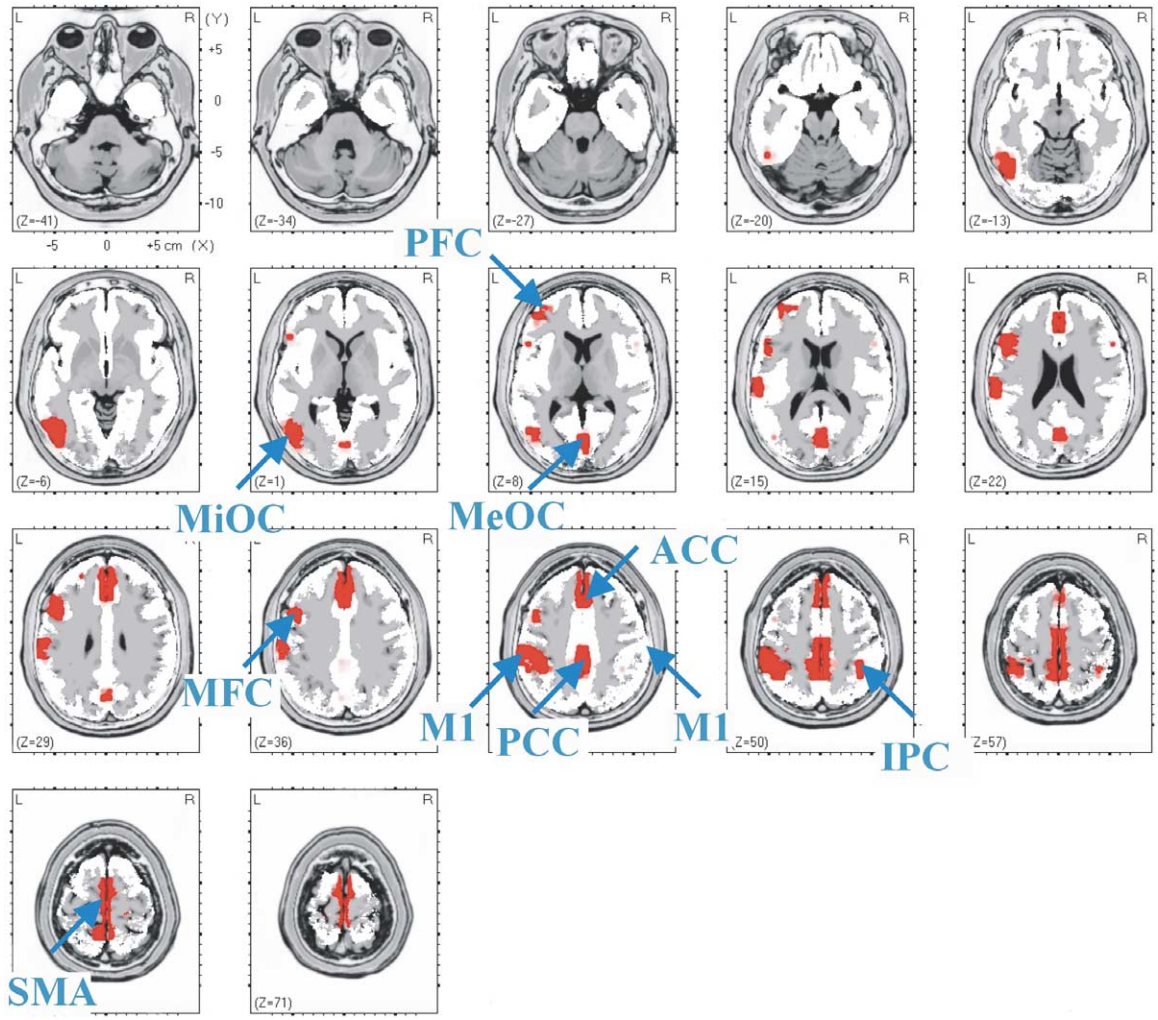

Fig. 3. Current density of the late CNV (800 to 1200 ms after warning stimulus), calculated with LORETA. Red areas are significant activated in this period ($P < 0.05$) compared with baseline: ACC, anterior cingulate cortex; IPC, inferior parietal cortex; MeOC, medial occipital cortex; MFC, middle frontal cortex; MiOC, middle occipital cortex; PCC, posterior cingulate cortex; PFC, prefrontal cortex; M1, primary motor area; SMA, supplementary motor area (right M1 has been selected for comparative purposes).

ensure that the neural representations of the expected stimuli and responses needed are active during the preparatory period, proposing a functional overlapping between executive attention and working memory processes.

The initial activation of SMA and ACC is compatible with an organizational function of these areas in the subsecond chain of activations and supports their possible involvement in the executive attention processes (Posner and Rothbart, 1998). The sequential dynamics of SMA/ACC and PFC/MFC suggest that they cooperate in solving the task, but may participate in a different time framing.

Present results show that scalp voltage and SCD maps have posterior topography for late CNV. The idea that negativities associated with the upcoming sensory stimulus could be recorded during the last preparatory phase of CNV has already been put forward (Brunia and Damen, 1988; Brunia and van Boxtel, 2001; Gómez et al., 2001). The similar topography of the posterior CNV with respect to the P1 and N1 components supports a function in anticipatory perceptual attention for the late component of CNV (Gómez et al., 1994; Hillyard and Anllo-Vento, 1998). Animal and fMRI studies suggest that there is a baseline shift in the visual cortex during attentional conditions (Luck et al., 1997). fMRI shows an activation of extrastriate and striate cortex during the preparatory periods (Kastner et al., 1999). The present experiment found a tonic increase of neural activity in several posterior areas (Figs. 4D and E). The results suggest that the recorded posterior CNV could be the electrophysiological counterpart of the posterior tonic activities obtained in electrophysiological recordings of extracellular activity and in metabolic fMRI studies during perceptually related anticipatory attention.

The sequence of activations obtained suggests that SMA and ACC start the process of preparation for action and perception. These areas might be able to recruit the specific sensory and motor cortex activation (Gómez et al., 2001)

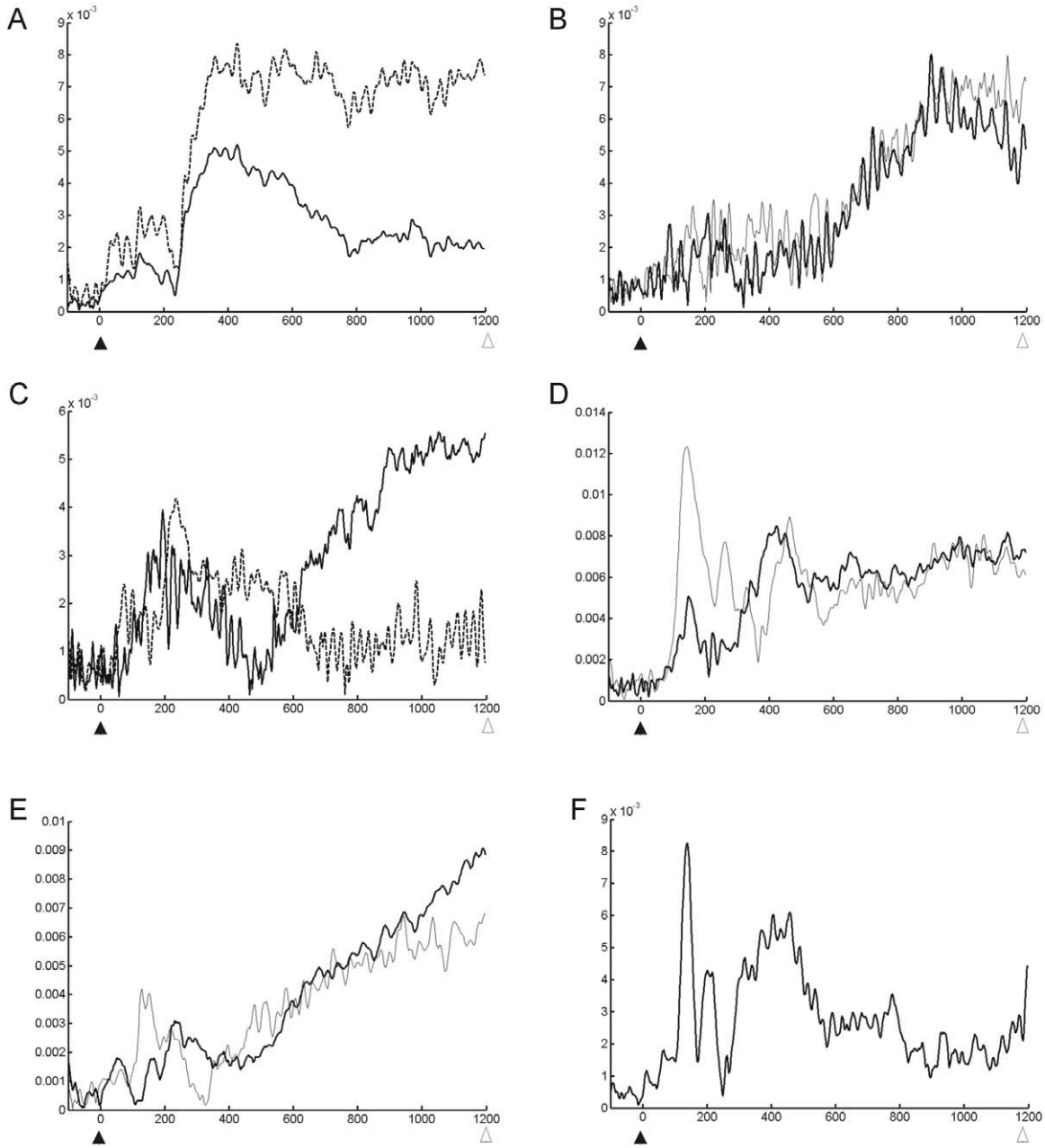

Fig. 4. Dynamics of the areas marked in Figs. 2 and 3. The activation shown corresponds to the source current density from 100 ms before the warning stimulus to 1200 ms after it. Warning stimulus is marked with a black arrow, and imperative stimulus is marked with an open arrow. Units of vertical axis are proportional to $\mu A^2/mm^4$. (A) Activity of SMA (area 6, dashed line) and ACC (area 24, solid line) is shown. (B) Activity in the left PFC (area 45, thick line) and left MFC (area 9, thin line). (C) Activity in the left (solid line) and right (dashed line) M1 area (area 4). Note the steady increase in the task-related M1 area (left side), unlike in the nonrequired area (right side). (D) Activity in posterior areas MeOC (area 17, thin line) and left MiOC (area 19, thick line). (E) Activity in posterior cingulate (area 31, thick line) and right IPC (area 40, thin line). (F) Activity in the right OTC (area 39).

needed for the sensory and motor processing of the imperative stimulus (Lee et al., 1999; Kastner et al., 1999). The function of the PFC/MFC could be to sustain activation in the sensory and motor cortices (see Figs. 4B–E). The mechanism for this would lie in reciprocal interactions between PFC/MFC with both: M1 and posterior visual areas, in a manner similar to that which occurs in working memory experiments such as delayed matching-to-sample tasks in monkeys (Fuster, 2000). However, given the motor, cognitive, and arousal functions proposed for the ACC and the correlational nature of ERP studies, the possible functional role of the ACC cannot be completely determined with present results (Paus, 2001).

The preparation for action and perception mediated by the frontal cortex suggested by the results of the present experiment adds evidence for links of the frontal cortex to gating in sensory and motor systems (Knight et al., 1999; Barceló et al., 2000). In conclusion, the activated frontal

areas may organize the timing of the neural activities of the different cortical areas involved in the attentional and intentional preparatory period.

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