Cortical excitability and rest activity properties in patients with depression

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Objective: Results of recent studies suggest a link between neuronal excitatory or inhibitory unbalance and depression. To investigate this relation, we studied the rest activity and the cortical excitability of the cerebral areas dedicated to hand control in 12 patients with depression. Methods: Brain activity was recorded from the Rolandic region in both hemispheres of 12 depression patients and 11 control subjects by means of magnetoencephalography. We studied cortical excitability by focusing on the M20 and M30 components of the magnetic fields evoked by a stimulation of the median nerve. Results: Parietal rest rhythms showed greater total power in patients than in control subjects. In particular, the patient’s parietal alpha was higher in the right than in the left hemisphere. Primary sensory cortex excitability, expressed by the M20, appeared significantly reduced in patients with depression, but was still higher in the right than in the left hemisphere. The M30 also appeared reduced, and this reduction was significantly correlated with both depression severity and global illness. Conclusions: The patients studied were not completely drug free. For this reason, it is impossible to rule out the possibility that our results are an effect of drug assumption. Nevertheless, since all patients were well below the drugs’ steady state levels when the data were recorded, the behaviour of M20 and M30 and their relation with the patients’ clinical pictures suggest that an unbalance of the excitatory or inhibitory cortical activity, and especially a potentiation of the parietal afferent to the motor cortex, may be significant hallmarks of depression.

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Introduction

There is extensive evidence that abnormal hemispheric asymmetries of cerebral activity are linked to depression. Early experiments performed on college students, during which depression and euphoria were transiently induced, showed that the depressed phase was characterized by an above-average electroencephalogram (EEG) activity in the right frontal region. The same was found by Schaffer and colleagues, who measured rest EEG from the frontal regions of depression patients and related the EEG amplitudes to the patients’ scores on the Beck Depression Inventory. Early studies, though, used the word “activation” in a rather confusing way, not detailing the difference between rest activity and evoked activation. An insight into this fundamental difference came from frequency-targeted EEG studies of patients with a history of past and present depression, which showed increased alpha power in the left frontal areas. Because cerebral activation was long known to produce alpha suppression, this asymmetry was interpreted as a sign that people with depression have an increased activation, rather than activity, in their right frontal areas and at the same time, a decreased activation in their left frontal areas. On the basis of these and many other studies, Davidson proposed a famous theory, according to which an increased right frontal activation capability would be associated with a generalized “withdrawal” (negative) personal attitude, whereas an increased left frontal activity would be associated with an “approach” (positive) attitude. Further confirmation of an increased right frontal activation in adults with depression has come from positron emission tomography (PET) studies of cerebral blood flow (CBF) and glucose metabolism. The frontal asymmetry pattern has also been observed in newborns and young infants of mothers with depression, suggesting that this type of abnormality could be a predictive mark of depression.

In parietal areas, depression patients have been reported to have more alpha activity in the right hemisphere than control subjects (i.e., a pattern opposite to the frontal areas). In a review of single photon emission CT (SPECT) studies of CBF in depression, Bolwig described patients with unipolar depression as having below average flow in the right parietal and temporal lobes. Bruder and colleagues also found that offspring with both parents with major depression show relatively more alpha (i.e., less activation) over right central and parietal regions, compared with offspring with only 1 or no parent with major depression.

The occipital and temporal areas do not seem to exhibit asymmetries associated with depression that are as strong as those in the frontal and parietal areas. However, some authors have reported that depression patients normally show a decrease of the right occipital alpha power consistent with behavioural impairments of half-field vision, dichotic listening and visuo-spatial performance. Also, temporal delta alterations were found in agreement with dichotic listening abnormalities.

Although there is much literature on the issue of asymmetries in people with depression and their link to alterations of the natural rhythms, it seems that minimal attention has been paid to the relation between rest activity and cortical activation in the same pathological subject. The literature is almost entirely devoted to separate analyses of the 2 states. Despite evidence that rest activity and cortical excitability are somehow related, no well-defined relation between them has been found either in people with depression or in healthy subjects.

In this study, we aimed to investigate the 2 states in people with depression and in healthy individuals. The parietal cortex, which has been neglected in favour of the frontal areas, represents a perfect target for an investigation of that relation, since its response to external stimulation is very stable, relatively noiseless and well documented. For this reason, we investigated both rest and excitability properties of the Rolandic areas devoted to hand control and their relation to pathological traits.

The motor function in depression has not been widely investigated, but interest is growing because clinical and experimental observations are now evidencing similarities between Parkinsonian symptoms and depression. Signs of bradykinesia in idiopathic Parkinson’s disease are virtually indistinguishable from those in major depression, and some investigators have hypothesized a common neurobiological mechanism.

Some information on the cortical activation in people with depression and, in particular, on the role of inhibitory structures on the pyramidal neurons excitability comes from Transcranial Magnetic Stimulation (TMS) studies of the motor threshold, paired-pulse excitability and silent periods. Altogether, depression patients seem to have structural and functional motor cortex asymmetries characterized by lower and higher right pyramidal neuron excitability.

In this paper, we define cortical excitability as the cortex responsiveness to galvanic stimulation of the contralateral median nerve. Brain rest rhythms were instead evaluated (subject at rest with eyes open) by analyzing the spectral power within the delta, theta, alpha, beta and gamma bands and as total power in the whole range 2–45 Hz. We studied the cortical excitability and rest rhythms’ of spectral properties both in terms of their absolute values in the left and right hemispheres and their interhemispheric differences with respect to a group of healthy control subjects.

Methods

We included 12 patients in the study (2 men, 10 women, aged 54.6 [standard deviation (SD) 14.0] yr), after they signed a written informed consent. We excluded patients with a history of alcoholism, psychotropic drug abuse or mental retardation. All of the included patients had been admitted to the Psychiatric Emergency Service of the San Giovanni Calibita – Fatebenefratelli Hospital for a recurrent major depressive episode: the diagnosis was assessed by clinical interview on the basis of the Diagnostic and statistical manual of mental disorders, 4th ed., text revision (DSM-IV-TR) criteria. The experimental protocol was approved by the San Giovanni Calibita Fatebenefratelli Hospital ethics committee.

All patients enrolled had reached the hospital after volun-
tary suspension of their previous therapy and consequent mood degradation. A new therapy had been immediately initiated. All our measurements were performed within the first 5 days of admission (median 2 d); thus, we assumed the administered drugs were still well below their steady state levels, which are normally reached after 10–15 days, concurrently with their clinical efficacy.

Patients’ severity of illness was rated according to the Clinical Global Impression Scale (CGI–item 1); the severity of depression was scored according to the Montgomery–Asberg Depression Rating Scale (MADRS). Our patients were affected by a medium-to-severe level of major depression as scored by the MADRS for depression severity and CGI-item 1 for severity of illness (Table 1). One patient refused the median nerve stimulation but accepted to have the rest activity measured by the MEG apparatus. Consequently, results presented in this paper include 12 patients, when describing rest activity and 11 patients when describing evoked activation. Eleven healthy subjects, similar to the patient group in sex (2 men, 9 women) and age (average age 54.1 [SD 14.3] yr), were enrolled in the study as control subjects.

**MEG investigation**

**Recordings**

Brain magnetic fields were recorded with a 28-channel system (16 internal axial gradiometers and 9 peripheral magnetometers, 3 balancing magnetometer devoted to noise reduction, covering a scalp area of about 180 cm². The entire system is located inside a magnetically shielded room (Vacuum-umschmelze GMBH), which drastically reduces both magnetic and radiofrequency interferences.

Cerebral magnetic activity was recorded from the Rolandic region of both hemispheres by positioning the system in such a way that its central sensor was centred first over C3 and then over C4 of the International 10–20 Electroencephalographic System. Subjects laid comfortably on a nonmagnetic hospital bed and were asked to keep their eyes open to reduce the effects of occipital rest activity. Usually a physician would sit inside the shielded room to make the patients feel safe and relaxed.

Brain activity was recorded both at rest and during electrical stimulation of the contralateral median nerve for 3 minutes and separately for each hemisphere; electrical stimuli were 0.2 ms long electric pulses (cathode proximal), with a 631 ms interstimulus interval delivered to the wrist via surface disks; stimulus intensities were individually set slightly above the value, inducing a painless thumb twitch.

All signals were first analogically filtered between 0.48 Hz and 250 Hz, then sampled at 1 kHz and processed off-line. The entire recording procedure lasted about 30 minutes.

**Rest activity analysis**

After visual inspection of the recorded data, a semiautomatic artifact rejection procedure was applied to minimize the contribution of spurious sources (e.g., heart, eyes, muscles), whose frequencies overlap with the cerebral ones. The Power Spectral Density (PSD) was estimated for each MEG channel by the Welch procedure (2048 ms duration, Hanning window, 60% overlap, about 180 artifact-free trials used). The total PSD (tPSD) was calculated as the mean of the PSD obtained by the 16 inner channels covering a circular area of about 12 cm in diameter. Total signal power was obtained by integrating the tPSD in the 2–44 Hz frequency interval. Spectral properties were investigated in the following frequency bands (IFSECN 1974): 2–3.5 Hz (delta), 4–7.5 Hz (theta), 8–12.5 Hz (alpha), 13–23 Hz (beta-1), 23.5–33 Hz (beta-2), 33.5–44 Hz (gamma). Similarly, the relative PSD (rPSD) was obtained as the ratio of the PSD to the total power. We also defined a hemispheric individual alpha frequency (IAF) as the frequency with maximal PSD in the 6–13.5 Hz band in each hemisphere.

**Cortical excitability**

We studied the M20 and M30 components of the somatosen-

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*MADRS = Montgomery–Asberg Depression Rating Scale; CGI = Clinical Global Impression Scale; BZD = benzodiazepine.
*Mean 29.9 (SD [standard deviation] 6.7).
†Mean 4.1 (SD [standard deviation] 0.9).
Note: Duration of illness and pharmacological treatment before hospital admission are missing for P11, since her was the first depressive episode.
sory magnetic fields evoked by the stimulation of the contralateral median nerve. M20 reflects the responsiveness of the primary sensory Brodmann area (BA) 3b, while M30 reflects intracortical connectivity from BA3b and BA4. Also, they have been proven to be stable and repeatable and are both unaffected by the subject’s attention level.

Somatosensory Evoked Fields (SEF) were obtained by averaging about 280 artifact-free trials after bandpass filtering the data 2–150 Hz. The signal amplitude was defined with respect to a baseline chosen as the mean of the 10–15 ms post-stimulus epoch.

Equivalent current dipole (ECD) characteristics (spatial coordinates, orientation and strength) were calculated at 1 ms intervals in the 15–50 ms poststimulus window, using the model of a moving dipole inside a homogeneously conducting sphere. Localization results were accepted only if the variance explained was above 90% (i.e., the influence of adjunctive dipoles was < 10%). Coordinates were expressed in the individual coordinates system, defined as follows: the positive Y axis passed through the nasion and perpendicular to the plane which includes the vertex and the 2 preauricular points; the positive Z axis passed through the vertex and the positive X axis was, thus, directed to the right. When comparing the ECD positions and orientations in the 2 hemispheres, the X coordinate of the position was considered positive for both hemispheres.

Statistical analysis

We performed a statistical analysis of the absolute ECD parameters (latency, position and strength) and of the spectral rest characteristics (total and absolute band power, IAF) to identify differences between control subjects and patients with depression; data were first log-transformed to better fit a Gaussian distribution, whenever the Kolmogorov–Smirnov test resulted in \( p < 0.05 \). An analysis of variance (ANOVA) design for repeated measures was applied for each set of values, with group (patients, control subjects) as the between-subjects factor; hemisphere (right hemisphere, left hemisphere) was included as the within-subjects factor, to take into account possible interhemispheric differences of absolute parameters.

Results

Rest activity

Rolandic total power at rest was higher in patients than in control subjects (group factor: \( F_{1,18} = 7.49; p = 0.014 \) ) (Fig. 1A). Table 2 shows the absolute and relative Rolandic power in the classic frequency bands. In the alpha band in particular (Fig. 1B), patients showed a significant asymmetry of the relative power (group \( \times \) hemisphere interaction \( F_{1,18} = 4.95; p = 0.039 \)), with greater power in the right than in the left hemisphere (2-tail paired \( t \) test; \( t = -1.928, df = 11; p = 0.080 \)). We observed a slight alpha asymmetry also in control subjects, but the result was not significant (\( t = 1.124, df = 10; p = 0.287 \)). All asymmetries in the beta, theta and gamma bands were statistically not significant.

Evoked activity

No anomaly was observed in either location or latency of the
M20 and M30 ECDs. Patients showed a generalized amplitude reduction of both components when compared with control subjects (Fig. 2), but this reduction was statistically significant only for the M20, not for the M30. In fact, ANOVA for repeated measures of the M20 ECD strength delivered a significant group effect ($F_{1,18} = 5.28, p = 0.030$). ANOVA also showed a group × hemisphere effect ($F_{1,18} = 7.38, p = 0.014$), indicating that, while the response from the control subjects was higher in the left than in the right hemisphere (paired $t$ test $t = 2.611$, $df = 10; p = 0.026$), this was not the case for depression patients ($t = -0.985, df = 10, p = 0.348$). When comparing patients with control subjects separately in the 2 hemispheres, a smaller response in patients with respect to control subjects was found only in the left hemisphere (2-tailed $t$ test; $t = 3.405, df = 20; p = 0.003$ and $t = 1.013, df = 20; p = 0.323$ in the right hemisphere).

A box diagram of M20 asymmetry is shown in Figure 3.

The same analysis for the M30 ECD strength did not show any statistically significant effect. Also, no effect was observed for the ratio between M30 and M20 ECD strengths.

### Neurophysiological clinical relation

Table 3 summarizes the relation between neurophysiological parameters and the patients’ clinical pictures: a positive cor-

| Table 2: Spontaneous rhythms in patients and control subjects |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Frequency band  | Absolute power; log(FT) (and SD) | Relative power; log(FT) (and SD) |
|                 | Patients        | Control subjects | Patients        | Control subjects |
| Left hemisphere |                 |                 |                 |                 |
| delta           | 3.10 (0.16)     | 3.04 (0.06)     | 0.11 (0.09)     | 0.08 (0.03)     |
| theta           | 3.10 (0.12)     | 3.05 (0.11)     | 0.10 (0.05)     | 0.09 (0.03)     |
| alpha           | 3.37 (0.15)     | 3.32 (0.11)     | 0.33 (0.13)     | 0.31 (0.09)     |
| beta1           | 3.36 (0.14)     | 3.33 (0.11)     | 0.31 (0.12)     | 0.33 (0.08)     |
| beta2           | 3.14 (0.09)     | 3.13 (0.12)     | 0.11 (0.05)     | 0.14 (0.06)     |
| gamma           | 2.91 (0.08)     | 2.90 (0.08)     | 0.04 (0.02)     | 0.05 (0.01)     |
| Right hemisphere|                 |                 |                 |                 |
| delta           | 3.12 (0.11)     | 3.03 (0.08)     | 0.11 (0.06)     | 0.09 (0.03)     |
| theta           | 3.11 (0.12)     | 3.04 (0.12)     | 0.10 (0.04)     | 0.09 (0.03)     |
| alpha           | 3.39 (0.18)     | 3.30 (0.13)     | 0.36 (0.16)     | 0.29 (0.08)     |
| beta1           | 3.36 (0.15)     | 3.35 (0.14)     | 0.29 (0.09)     | 0.36 (0.09)     |
| beta2           | 3.14 (0.14)     | 3.13 (0.13)     | 0.12 (0.09)     | 0.14 (0.06)     |
| gamma           | 2.89 (0.07)     | 2.89 (0.09)     | 0.03 (0.02)     | 0.04 (0.01)     |

SD = standard deviation.

| Table 3: Neurophysiological and clinical pictures relation |
|---------------------------------|-----------------|-----------------|
|                                | Score; Spearman’s rho $p$ value (and Pearson’s $r$ $p$ value) |
|                                | CGI | MADRS |
| Left hemisphere                |     |       |
| M30*                           | 0.875 (0.001) | 0.722 (0.018) |
| M30/M20†                       | 0.753 (0.012) | 0.702 (0.024) |
| Theta relative power‡          | 0.672 (0.024) | (> 0.200) |
| Right hemisphere               |     |       |
| M30*                           | 0.753 (0.012) | 0.671 (0.034) |
| M30/M20†                       | 0.774 (0.009) | 0.748 (0.013) |
| Theta relative power‡          | 0.852 (0.001) | (> 0.200) |

CGI = Clinical Global Impression Scale; MADRS = Montgomery–Asberg Depression Rating Scale.

* $n = 11$.
† $n = 12$.
‡ $n = 12$.

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Fig. 2: Comparison between the somatosensory evoked fields (SEFs) of representative patients and control subjects. Superimposition of SEFs from all channels positioned over the Rolandic region contralateral to the stimulated side in 2 control cases (C1, male, aged 56 years; C2, female, aged 43 years) and 2 representative patients (S1, male aged 60 years; S2 female, aged 46 years).
relation was found between M30 ECD strength bilaterally and both severity of depression (MADRS score) and severity of illness (CGI-item 1 score). These relations with the clinical state were confirmed also after normalizing the M30 to the M20s ECD strength. Relative theta power correlated with CGI. Figure 4 shows the scatter plot of the normalized M30 strength (M30/M20) in both hemispheres versus the patients’ depression severity. The IAF correlated negatively with the MADRS scores (12 patients, Pearson’s $r = -0.662; p = 0.032$) in the left hemisphere. No correlation was found in the right hemisphere. The total power did not show any relation with clinical parameters.

Taking into account that the M20 strength increases with age (57 control subjects, Pearson’s $r = 0.34$ and $0.38; p = 0.004$ and $p = 0.008$, respectively, for the left and right hemisphere), the correlation between M20 ECD strength with disease duration was corrected for age dependence. A significant correlation appeared in both hemispheres (partial correlation coefficient 0.775, $df = 7; p = 0.015$ in the left hemisphere and 0.731, $df = 7; p = 0.026$ in the right).

**Discussion**

The major evidence of our investigation is that the M30 increases when the clinical status worsens (Fig. 4), which seems to go against common sense. How can we explain this phenomenon?

About 20 ms after the stimulus, the thalamic input reaches the somatosensory BA3b pyramidal cells and triggers an excitatory postsynaptic potential (EPSP) along the pyramidal cells’ dendrites, still unopposed by the inhibitory action of the local stellate cells; the M20 reflects this current. In about 10 ms, the stellate cells reach enough inhibitory action to turn the direction of the pyramidal dendritic current, producing an inhibitory postsynaptic potentials (IPSP) along it; concurrently, an EPSP is generated on the dendrites of BA4 pyramidal cells. The currents associated with the BA3b IPSPs and the BA4 EPSPs contribute in the same direction to the magnetic signal, and their sum is represented by the magnetic M30.

Thus an M30 increase can be the result of an increase of either the inhibitory efficacy in BA3b or of the excitatory efficacy in BA4, or both. A bulk of literature consistently reports reduced gamma-aminobutyric acid (GABA) levels in subjects with depression, corresponding to a reduced inhibitory efficacy. Because less inhibition in sensory BA3b contributes to decrease the M30, it is reasonable to believe that the M30 increase comes primarily from a prevailing contribution of the motor BA4 area. This is in line with the TMS studies mentioned, which have found lower thresholds in the right motor responses of depression subjects, indicating a higher excitability of their motor neurons.

This higher right excitability is also reported by Fitzgerald and colleagues to be associated with the severity of the condition; this is confirmed in Figure 4, which shows that the M30 certainly increases with increasing MADRS in the right hemisphere. When we removed the sickest patient from the computation, the relation in the right hemisphere remained significant ($p = 0.042$), while the correlation decreased below significance in the left hemisphere ($p = 0.375$). However, it is unlikely that the increase of the BA4 contribution to the M30 is exclusively due to a dysfunction of the motor inhibitory structures; this would be at least partly compensated for by an equally effective (and opposing) contribution from the
less-inhibited sensory BA3b. Thus, we believe that the effect is due to a stronger contribution of other projections that impinge to BA4. Because we know that afferent neurons impinging on BA4 have almost exclusively a parietal origin,\textsuperscript{16,22} we speculate that lower inhibition in sensory BA3b results in a potentiation of the fibers that project into the motor BA4, after travelling around the Rolandic fissure. Whether this potentiation is triggered directly by the sensory stellate cells or indirectly by the sensory pyramidal cells remains unclear.

These conclusions certainly do not imply that an unbalance of the GABAergic neurotransmission has an insignificant role in depression. Many studies have shown that antidepressant and mood-stabilizing treatments targeting GABA systems give good results.\textsuperscript{49–52}

Our results showed changes in the natural brain rhythms in agreement with what has been published in the literature. However, regarding the alpha band in particular, published studies do not seem to agree on the strength of the hemispheric asymmetry, although they all agree on its direction. Works published by the same groups at different times report quite different figures. The subjects with depression in our study showed an above normal Rolandic alpha power, and this power resulted higher in the right than in the left hemisphere. We could not draw conclusions on beta, delta and gamma bands because our results did not reach statistical significance.

Because our patients were not completely drug free, we cannot rule out the possibility that the findings described are actually an effect of the drugs. Conversely, MEG was recorded when the drug presence in the patients’ system was still well below the steady state level, the reaching of which generally marks the beginning of clinical efficacy. For this reason, we believe that the behaviour of M20 and M30 and their relation with clinical severity and disease duration suggests that an unbalance of the excitatory–inhibitory cortical activity, especially a potentiation of the parietal afferent to the motor cortex, may be significant hallmarks of depression.

**Competing interests:** None declared.

**Contributors:** Drs. Salustri, Tecchio, Squitti and Rossini designed the study. Drs. Bevacqua, Fontana and Milazzo and Ms. Ercolani acquired the data, which Zappasodi analyzed. Salustri wrote the article. Drs. Bevacqua, Fontana and Milazzo and Ms. Ercolani ac-

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