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Discriminative Power of EEG-Based Biomarkers in Major Depressive Disorder: A Systematic Review

CLAUDIA GRECO[1], OLIMPIA MATARAZZO[1], GENNARO CORDASCO[1,2], ALESSANDRO VINCIARELLI[3], ZORAIDA CALLEJAS[4], (Member, IEEE), AND ANNA ESPOSITO[1,2]

[1]Department of Psychology, Università della Campania Luigi Vanvitelli, 81100 Caserta, Italy
[2]International Institute for Advanced Scientific Studies (IIASS), 84019 Vietri sul Mare, Italy
[3]School of Computing Science, University of Glasgow, Glasgow G12 8QQ, U.K.
[4]Department of Languages and Computer Systems, Universidad de Granada, 18011 Granada, Spain

Corresponding author: Claudia Greco (claudia.greco@unicampania.it)

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ABSTRACT Currently, the diagnosis of major depressive disorder (MDD) and its subtypes is mainly based on subjective assessments and self-reported measures. However, objective criteria as Electroencephalography (EEG) features would be helpful in detecting depressive states at early stages to prevent the worsening of the symptoms. Scientific community has widely investigated the effectiveness of EEG-based measures to discriminate between depressed and healthy subjects, with the aim to better understand the mechanisms behind the disorder and find biomarkers useful for diagnosis. This work offers a comprehensive review of the extant literature concerning the EEG-based biomarkers for MDD and its subtypes, and identify possible future directions for this line of research. Scopus, PubMed and Web of Science databases were researched following PRISMA's guidelines. The initial papers' screening was based on titles and abstracts; then full texts of the identified articles were examined, and a synthesis of findings was developed using tables and thematic analysis. After screening 1871 articles, 76 studies were identified as relevant and included in the systematic review. Reviewed markers include EEG frequency bands power, EEG asymmetry, ERP components, non-linear and functional connectivity measures. Results were discussed in relations to the different EEG measures assessed in the studies. Findings confirmed the effectiveness of those measures in discriminating between healthy and depressed subjects. However, the review highlights that the causal link between EEG measures and depressive subtypes needs to be further investigated and points out that some methodological issues need to be solved to enhance future research in this field.

INDEX TERMS Biomarkers, cognitive science, depressive subtypes, early detection, electroencephalography (EEG), EEG measures, major depressive disorder (MDD).

I. INTRODUCTION

Major depressive disorder (MDD) is one of the most important challenges in global mental health and the leading cause of disability worldwide. Globally, depression affects more than 300 million people and the prevalence rates by gender report that it occurs more commonly among females (5.1%) than males (3.6%). Major depression significantly impacts work or school life, sleeping, eating habits and general physical health [1]. Indeed, MDD has been associated with other physical conditions as cardiac problems and cancer [2]. Besides physical impairments, MDD also generates social disabilities, as deficits in emotional expression recognition and in personal relationships, causing isolation and pauperization of individuals' quality of life [3].

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TABLE 1. Description of symptom-based subtypes of MDD, according to DSM-5 (American Psychiatric Association, 2013).

Depression with	Characteristics
Melancholic features	Characterized by features that are not attributable to any external or environmental factors. Symptoms include anhedonia, lack of mood reactivity (i.e. mood does not improve in response to positive events), depression worse in the morning, terminal insomnia, psychomotor disturbance, weight loss and excessive guilty thoughts.
Atypical features	Symptoms include mood reactivity, weight gain or increased appetite, hypersomnia, leaden paralysis (i.e., heaviness feeling in the arms or legs movements) and interpersonal sensitivity (i.e. *the individual hypersensitivity to perceived self-deficiencies concerning others*)
Psychotic features	Characterized by delusions or hallucinations whose contents are usually mood-congruent and include typical depressive themes of guilt, disease, death, or punishment. The psychotic features could also be mood-incongruent and do not include the typical depressive themes.
Anxious distress	Symptoms include feeling keyed up or tense, unusual restlessness, difficulty to concentrate because of worry, constant feeling that something awful might happen, feeling to lose control of the self.
Mixed features	During the depressive episode, at least three of the subsequent symptoms should occur: expansive mood, characterized by unrestrained emotional expression; enhanced self-esteem; increased energy; increased frequency of speech; intrusive and persistent thoughts and reduced need for sleep.
Catatonic features	Characterized by a considerable psychomotor alteration, which could imply a diminished motor activity or a peculiar motor activity (e.g., echolalia or echopraxia) and a poor involvement during the clinical interview.

The MDD symptomatology consists of core and secondary symptoms. Core symptoms include depressed mood and anhedonia (i.e., loss of interest or pleasure). Secondary symptoms include appetite and weight changes, sleep disturbances (insomnia or hypersomnia), psychomotor agitation or retardation, fatigue or loss of energy, diminished ability to concentrate, feelings of worthlessness or excessive guilt and suicidal thoughts. The diagnosis of major depressive disorder requires that five or more symptoms, including at least one of the two core symptoms, have to be present within a 2-week period [4].

Although MDD symptoms are broadly accepted and recognized by clinicians, many scholars agree on the polythetic nature of depression, which can impede the successful diagnosis and choice of the proper treatment [5]. To this regard, Østergaard [6] pointed out that, according to the DSM criteria in force at the time, more than 1400 possible combinations of symptoms can result in the diagnosis of MDD. Moreover, depressive symptomatology overlaps with comorbid disorders or syndromes, increasing the diagnostic heterogeneity [7]. An attempt to overcome the heterogeneous MDD symptomatology's traits and facilitate the disorder's detection was to distinguish, within MDD, homogenous subgroups characterized by specific clusters of differing depressive symptoms. To this regard, the latest edition of DSM (DSM-V) [4] includes six specifiers based on clusters of different symptoms, which can further define the MDD's diagnosis and allow clinicians to carry out more specific treatments. The six specifiers are the following: melancholia, atypical depression, psychotic depression, depression with anxious distress, depression with mixed features and depression with catatonic features, and are detailed in Table 1.

The detection of depression can favor the promotion of prevention programs and increase the likelihood of obtaining positive care's outcomes [8]. However, even with this added knowledge, successful diagnoses, interventions and therapies are hindered by lack of resources and trained health providers.

The major reason for untreated cases relies on the absence of accepted objective biomarkers for MDD. Indeed, most of the diagnoses are based on patients' subjective description of their symptoms obtained during clinical interviews and self-reported questionnaires. Objective biomarkers can provide impartial criteria to detect depression at early stages and prevent the worsening of the symptoms. Nevertheless, biomarkers are not currently accounted for in the diagnosis of any psychiatric disorder, including MDD [9].

Unbiased information for supporting the MDD diagnosis can be obtained by changes in the electroencephalography (EEG) features. Indeed, EEG's measures can be considered successful biomarkers of depressive symptoms, being at the same time easily available and cost-effective [10].

EEG is an electrophysiological method for recording the electrical activity of the brain with a temporal resolution on a millisecond time scale. The brain activity, generated

TABLE 2. Classification of brain waves.

Brain waves	Characteristics
Delta waves	They range between 0.5 and 4 Hz and they are associated with the deepest levels of relaxation and restorative sleep.
Theta waves	They range between 4 and 8 Hz and indicate deep relaxation. They are present during deep meditation or daydreaming, and are associated with creativity and psychological well-being.
Alpha waves	They have a frequency range between 8 and 12 Hz. They are are mainly found in daydreaming, inability to focus or resting-state with eyes closed.
Beta waves	Their frequency range is between 12 and 35 Hz. They are observed in awaken state and are involved in conscious thought and logical thinking.
Gamma waves	They are considered to be the fastest brain activity (>35 Hz). These waves are associated with processes of heightened perception, learning, and problem-solving tasks when different parts of the brain are involved in the information processing.

when neurons are triggered by synaptic activation, is captured by metal electrodes positioned on the surface of the scalp. An EEG signal between electrodes consists of neural oscillations, or brain waves, produced by synchronized electrical pulses from neurons communicating with each other. The most frequently used method to classify brainwaves is by their frequency: EEG signals can be decomposed into delta, theta, alpha, beta and gamma oscillations measured in hertz and their sub-bands (cycles per second, Hz). Table 2 reports the classification of brain waves into five categories as described by Abhang and colleagues [11].

Various combinations of the features (frequency's power, ratio, and amplitude) of EEG frequency bands are expected during certain psychological states and considered informative of cognitive processes, as those concerning motivation, attention or emotional feelings [12].

Neuronal activity can also be assessed by the time-locked EEG activity, or event-related potentials (ERPs), which are very small voltages generated in the brain structures in response to specific events or stimuli [13]. ERPs can be elicited by a wide variety of sensory, cognitive and/or motor tasks and they represent a valuable methodology for examining the aspect of both normal and abnormal cognitive processes [14]. Since ERPs provide a continuous measure of processing between a stimulus and a response, they can detect the brain activity at the exact moment in which a specific experimental manipulation occurs (e.g., the presentation of a sound, a word, a picture). Such temporal precision makes ERPs an effective measure to examine the mental operations involved in cognitive processes as perception, attention, memory or language processing [15].

Frequency domain features and ERPs are routinely used for clinical and diagnostic purposes [16]. However, these measures may not be informative of the EEG dynamic variations, which are nonlinear and non-stationary in nature. To overcome these limitations, several non-linear measures from information theory, chaos theory and random fractal theory have been proposed to analyze the EEG data [17], such as the Higuchi fractal dimension (HFD), the Lempel-Ziv complexity (LZC), the Sample Entropy (SampEn).

Hence, the exploitation of EEG signals in clinical research has moved from the simple visual inspection of the shape and/or power of the measured signals in specific frequency bands to a more detailed and complex analysis of the temporal and spatial characteristics of the EEG signals. Nevertheless, the spatial resolution of neuronal activities identified from EEG waves may be altered by *volume conduction*, due to holes, lesions, ventricles or anisotropic conductivity of the skull. Volume conduction is the term used to describe the effects of recording electrical potentials at a distance from their source generator [18]. These effects can produce misleading information about the spatial localization of the brain activities and generate spurious connections between cerebral areas [19]. To overcome the EEGs poor spatial resolution and to reliably localize sources of brain activities, EEG measurements have been combined with data describing head and brain anatomy. Brain source localization algorithms exploiting biophysical models of highly spatially sampled density, such as the low-resolution electromagnetic tomography (LORETA) and its variants [20], have been developed to infer information about the brain functional connectivity, and reconstruct the brain activity in the source space [21]. Functional connectivity is defined as the temporal correlation, in terms of statistically significant dependence between spatially remote brain areas, of the activity of different neural groups [22].

Abnormalities in the typical electrophysiology of neurocognitive processes have been found in MDD patients when compared with healthy controls. These abnormalities could concern the power in distinct frequency bands, EEG activation of the left and right hemisphere, amplitudes or intensities of the ERPs components, non-linear features of

the EEG signal, and functional connectivity between brain regions. Therefore, EEG may help to provide objective criteria for the early detection of depression as suggested by the several studies reporting significant differences in the features extracted from EEG signals of healthy subjects and MDD patients [9], [23].

Nevertheless, to the best of our knowledge no previous work has provided a comprehensive review of the literature concerning this topic. In an attempt to overcome this gap, a summary of the current knowledge about the relationship between EEG-based measures and MDD is presented. The primary aim is to assess the discriminative power of EEG-based features, recorded both at resting-state and during tasks' execution, to identify objective criteria to facilitate the early detection of the disorder. The second aim is to evaluate whether specific clusters of depressive symptoms are associated with specific EEG characteristics. Finally, this review aims to identify the aspects that have not been exhaustively investigated in the EEG-based studies and to suggest future research directions in this field.

II. METHODS

A. SEARCH STRATEGY AND STUDY SELECTION

The present study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) methodology [24]. The electronic literature search was carried out from June 2020 to May 2021 through Scopus, Web of Science and PubMed databases. The first group of key search terms consisted of ''Electroencephalogram'' OR ''EEG''. The second group of key terms consisted of ''Major depressive disorder'' OR ''depressive subtypes'' OR ''depressive subgroups'' OR ''Major depressive episode'' OR ''Major depression''. The focus was on studies published between the 2010-2021 temporal interval in order to avoid the inclusion of outdated methods and technologies.

In the first stage of the selection process, duplicates (the specific number of identified papers during the selection process will be given in the section A of Results) across databases were removed. After that, titles and abstracts were screened to avoid the inclusion of research not relevant for the topic of the review. The full text of remaining publications was examined to identify relevant information for the review. Fig. 1 illustrates the study selection process.

B. ELIGIBILITY CRITERIA

The literature concerning the assessment of cerebral activity in MDD patients consists of a large number of studies. The reason is that the relationship between EEG signals and MDD has been investigated in several research fields and with numerous techniques. Therefore, the inclusion and exclusion criteria were developed in order to decrease the heterogeneity among the studies and, thus, make reliable comparisons between the findings. The inclusion criteria were the following:

- Studies in which the cerebral activity was assessed only with EEG.
- Studies in which the sample consisted of adult participants of any gender, and the experimental session was performed in a community or clinical setting.
- Quasi-experimental and observational studies.
- Studies involving participants with a primary diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM IV or later versions), and/or the International Classification of Diseases (ICD-9 or ICD-10).
- Year of publication: between 2010 and 2021.

Exclusion criteria were:

- Studies focusing on mood disorders other than MDD.
- Pharmacological and machine learning studies.
- Studies in which EEG signals were recorded only during sleep.
- Studies in which cerebral activity was altered by using techniques as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS).
- Studies in which statistical analyses were not specifically performed on EEG parameters.
- Studies which did not report statistical comparisons between the clinical sample and healthy participants.
- Case report, letter to the editor, editorials, dissertation, book chapter, personal opinions or commentary, review.
- Papers not written in English.
- Papers whose full text was not available through institutional access nor by searching in the web for free.

III. RESULTS

A. STUDY SELECTION

The first phase of the electronic search identified 1871 studies. After duplicates were removed, 1201 records remained, of which 601 were excluded because the title or the abstract had no pertinence to the review topic. Of the remaining 600 papers, 520 were excluded based on the basis of the following reasons: types of publications other than research article or conference paper; sample features did not meet the inclusion criteria listed above; no primary clinical diagnosis of MDD; no involvement of EEG metrics; methodologies involving techniques other than EEG or pharmacological testing. Finally, four papers were excluded due to full-text unavailability. The remaining 76 studies encountered the inclusion criteria and were included in the review. Data extraction included the sample characteristics (number of participants, sample composition, diagnosis, gender, age), the type of feature extracted from EEG signal, the study characteristics (setting, study design, experimental paradigm), and the summary of the main findings.

B. SUMMARY OF MAIN FINDINGS

The 76 selected records are quite heterogeneous in terms of the methodology adopted and the features extracted from the EEG signal. In order to make reliable comparisons among the results and identify possible depression markers able to discriminate between MDD patients and healthy subjects, the summary of the main findings is divided into 5 sections based

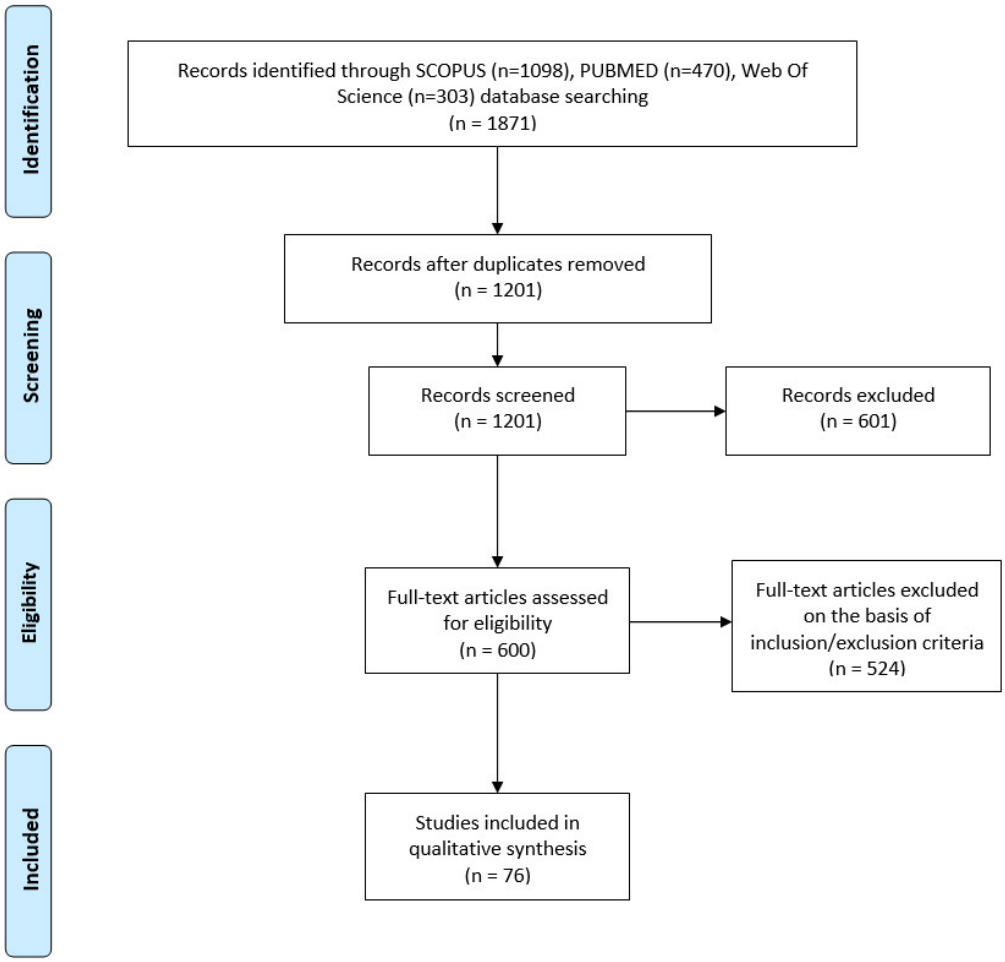

FIGURE 1. Flowchart of the literature search strategy.

on the different EEG measures considered by the selected studies. In addition, for a better understanding of the results, a brief description of the adopted measures is provided in each section. A summary of the results discussed in each section is reported in Table 1 of supplementary material for each study.

1) EEG FREQUENCY BANDS

The EEG signal consists of brainwaves characterized by different frequencies. The most used analysis method for decomposing and quantifying their oscillatory activity is the spectral analysis [25]. Spectral analysis provides information about power, spatial distribution, or event-related temporal change of frequency of interest trough several methods. The most common methods include Fourier transform method, which creates a representation of the signal in the frequency domain, or the Wavelet transform method, which creates a representation of the signal in both the time and frequency domains (for a review see [26]).

Among the spectral measures, power spectral density is the most used, since the power spectrum of a time series describes the distribution of power among the frequency components of the signal [27].

Many studies involving EEG signal investigated whether putative differences between healthy and depressed subjects, can be observed among EEG frequency bands' power. In this context, Jaworska and colleagues [28] found that depressed patients display greater alpha power than controls at resting state. Segrave *et al.* [29], compared MDD and healthy measurements of the event related synchronization (ERS), which refers to the percentage increase in a specific band during a test interval compared to a reference one and is calculated using the formula (Test- Reference)/ Reference) x 100) [30]. In this study, alpha band power was firstly assessed at resting-state and then alpha band ERS was calculated during a Stenberg verbal working memory task [31]. This task consists in an encoding phase in which a set of letters is presented, followed by a maintenance phase in which the letters disappear from the screen. After that, participants observe a single letter and have to indicate whether it was present in the previous set (i.e., response phase). ERS was calculated by considering a 600 ms reference interval within

a pause period between the offset of a fixation point and the onset of the encoding phase, and a 2000 ms test interval after the maintenance phase. Results showed that MDD patients displayed greater alpha ERS than controls during the test interval; suggesting the need for MDD of additional neuronal resources to achieve performance comparable to healthy participants. The same experimental paradigm was used by Murphy *et al.* [32] to calculate ERS on the whole scalp for upper alpha ($\backsim$10–13 Hz), theta and gamma frequency bands during working memory (WM) encoding and maintenance. Results showed that, when compared to healthy controls, depressed patients exhibited increased occipital upper alpha power and decreased frontal-midline theta power during the WM encoding phase. Moreover, they showed reduced frontal-midline theta power and occipital gamma and upper alpha during the WM maintenance phase. Kane *et al.* [33] also used a memory task to investigate theta power in MDD patients and healthy subjects. During encoding phase, participants viewed neutral words occurring at different position of the screen and had to categorize them as living/non-living or mobile/immobile. In the subsequent retrieval phase, participants responded to some questions about words previously presented (e.g., in which position the word occurred; whether the word was a number or not; how they categorized them). EEG on the whole scalp was only recorded during the retrieval phase. Theta power analysis showed that it was reduced in depressed patients relative to healthy subjects during retrieval process, suggesting that abnormal theta activity may contribute to memory deficits in MDD.

Siegle *et al.* [34] investigated the elaboration of emotional stimuli in MDD by using an emotional word valence identification task. They found that depressed patients exhibited a sustained and increased gamma power activity (all over the 20 electrodes used to record the EEG activity) after the presentation of negative words compared to neutral ones, whereas the control group did not show such gamma power differences due to the emotional valence of the presented words. These results were further supported by Martin *et al.* [35] which used the same experimental paradigm and found that the MDD group showed greater gamma power activity after the presentation of positive words, compared to the control group, but also ''reliable increased [gamma power activity] to negative compared to positive [words]'' (Martin *et al.* [35], p. 7). Ding *et al.* [36] investigated the power activity of the full EEG bands (theta, delta, alpha, beta and gamma), measured in the prefrontal cortex rather than the whole brain area, during the presentation of 8 video clips (3 positive, 3 dysphoric and 2 neutral) with different emotional valence. They observed a decrease of the MDD full EEG power bands activity compared to controls.

Cook *et al.* [37] examined resting-state absolute (i.e., the amount of power in a frequency band at a given electrode) and relative (i.e., the percentage of power contained in a frequency band relative to the total spectrum) power and cordance in theta band at midline and prefrontal sites. Cordance is a measure of regional brain activity that combines the information from absolute and relative power of EEG spectra [38]. Results showed that depressed patients were associated with higher values of cordance at midline frontal site (Fpz electrode), compared to healthy subjects. No differences between groups were observed in absolute and relative theta power. Cordance values in MDD patients at frontal site were further examined by Chen *et al.* [39]. The authors analyzed absolute, relative power and cordance values in delta, theta, alpha and beta bands over the whole scalp both at resting-state and during the test of variables of attention (TOVA, [40]) in which participants had to respond or not to target and nontarget stimuli according to specific criteria. Results showed that theta cordance values were greater in MDD patients at the left frontal site, regardless the condition (resting state, target, and nontarget stimuli).

Starting from the frequency bands analysis, it is possible to collect information about EEG vigilance stages by using an algorithm indicating the different levels of brain arousal during waking state, ranging from high wakefulness to sleep onset [41]. In a recent study [42] such algorithm was used to process continuous EEG data acquired from MDD patients and healthy subjects at resting-state. EEG recordings were divided in segments and classified into 5 different EEG-vigilance states (A1, A2, A3, B1 and B2/3) in order to obtain two arousal indices indicating the arousal decline from high vigilance stages to lower ones (i.e. arousal stability index) and the relative amount of each EEG-vigilance stages in percentage (i.e., arousal level). Results showed that depressed patients switched less between stages and remained longer in A stages than healthy controls, confirming the authors' hypothesis that MDD is associated with a hyperstable arousal regulation and higher level of brain arousal than healthy subjects. Another recent study [43] used the same algorithm to compute the vigilance-analysis between MDD patients and healthy subjects at resting-state. The authors found that MDD patients spent significantly more times at stages B2/B3 and less time at stages A2/A3, compared to controls.

Most of the above-mentioned studies support the hypothesis that frequency bands measures can be considered potential biomarkers of MDD. Depressed patients are characterized by frequency bands activity different from healthy subjects, such as greater alpha power at resting-state, higher gamma activity in response to emotional stimuli, and higher theta cordance values both at resting-state and during task execution. However, univocal conclusions are hard to be drawn due to the heterogeneity of the studies in terms of methodology and procedure. Many variables hinder comparisons between findings. Some of them concern the experimental paradigms (resting-state or task execution), the type of task or whether or not experiments involve emotional stimuli. Other aspects concerned the EEG recording procedure, as the location of the electrodes and the electrodes number, the pre-processing procedure of EEG data and/or the length of recordings. Since findings seem to depend on such variables, future research

should focus on more coherent experimental paradigm and recording procedures in order to test the discriminative power of frequency bands measures between depressed and non-depressed individuals in more replicable conditions.

2) EEG ASYMMETRY

Human brain consists of two hemispheres, which have been known to not be completely symmetrical for what concerns both structural and functional aspects [44]. Abnormalities in right-left asymmetry have been widely associated with MDD and most of the findings come from EEG studies which have investigated alpha band activity, usually at frontal regions [45]. Following the assumption that alpha power is inversely related to regional brain activity, meaning that decreased alpha power values indicate an increase in cortical or hemispherical activation [46] it is assumed that MDD is characterized by hyperactivity of the right prefrontal cortex and hypoactivity of the left prefrontal one. According to Henriques and Davidson [47], the decreased left-sided frontal activation would be ascribed to a deficit in the approach system that is responsible of active and goal-seeking behaviors. On the other hand, the right-side frontal activation would be related to withdrawal system which 'facilitates the withdrawal of an organism from sources of aversive stimulation and generates certain forms of negative affect' (Davidson [48], page 608).

Empirical evidence supporting this hypothesis comes from studies which have calculated alpha asymmetry from EEG recorded both at resting-state and during tasks. To compute asymmetry, the alpha power at any given site is firstly natural log transformed. Then a difference score is calculated by subtracting the natural log of left hemisphere alpha power from the natural log of right hemisphere alpha power (ln[right]-ln[left]) for each homologous pair of electrodes [46]. This calculation results in an asymmetry score, according to which positive values reflect greater right alpha power, and thus decreased relative right cortical activity, and negative values reflect the opposite.

For what concerns frontal alpha asymmetry, some studies investigating alpha activity at resting-state found that MDD exhibited lower asymmetry scores, which reflect less left hemispheric frontal activity compared to healthy individuals [43], [49]–[51]. However, Gollan *et al.* [52] observed higher positive alpha asymmetry scores at frontal electrodes in MDD patients compared to healthy subjects, indicating greater relative left than right frontal activation.

Jaworska and colleagues [28] calculated resting-state alpha asymmetry scores at both frontal and parietal sites in MDD patients and healthy subjects. Asymmetry scores were calculated for alpha band (8–13 Hz), alpha1 (8–10.5 Hz) and alpha2(10.5–13 Hz) sub-bands. MDD group reported negative frontal asymmetry score for the alpha2 sub-band, reflecting a decreased relative left fronto-cortical activity, whereas control group reported a positive score. Analyses on parietal alpha asymmetry revealed significant results only for female participants: MDD females exhibited a relative left parietotemporal hypoactivity while control females exhibited the opposite pattern. Koo *et al.* [43] examined frontal and parietal EEG asymmetry in all frequency bands, finding that MDD patients showed greater right-than-left frontal activity compared to control group.

Kemp *et al.* [53] compared frontal and parietotemporal alpha asymmetry scores in MDD patients, post-traumatic stress disorder (PTDS) patients and healthy controls. Results of frontal asymmetry showed that the MDD group was significantly right-lateralized compared to control, which did not differ from PTSD group. Concerning the parietotemporal asymmetry, no significant differences were found between groups.

A recent study [54] investigated the neural sources of alpha asymmetry with a technique called exact low resolution brain electromagnetic tomography (eLORETA [20]) that localizes the electrical activity in the brain based on scalp potential from multiple-channel EEG recording. Results from the study showed that depressed patients were characterized by less left than right activity in the precentral and midfrontal gyrus.

Roh *et al.* [55] investigated frontal alpha asymmetry in MDD patients with and without suicidal ideation (SI) and healthy controls. Increased alpha power at the left frontal region was found in the MDD groups compared to the control one. Moreover, MDD patients with SI exhibited reduced alpha power at the left frontal region compared to MDD patients without SI.

Other studies examined differences in EEG asymmetry between MDD patients and healthy subjects during the task performance. Beeney *et al.* [56] compared frontal alpha asymmetry scores of individuals suffering from MDD, Borderline personality disorder (BPD) and healthy subjects. EEG data were recorded before and during a computerized rejection task called Cyberball task [57]. Participants were provided with an avatar playing a virtual ball-throwing game with two others, and the task was programmed in such a way that the participant's avatar was either included in ball-throwing or excluded from it. Compared to the other two groups, MDD patients exhibited a greater right-frontal cortical activation both at baseline and following rejection, suggesting that MDD is associated with a particular way to deal with social stress that involves withdrawal behaviors.

Stewart *et al.* [58] presented MDD patients and healthy subjects with a facial emotion task where they were required to move their facial muscles into certain configurations representing approach-related emotions (happiness, anger) and withdrawal-related emotions (fear, sadness). Frontal alpha asymmetry scores were calculated both at resting-state and during the task execution. Analyses showed that MDD group displayed relatively less left than right frontal activity than controls during the task but not during the rest phase. According to the authors, these results suggest that emotional tasks would be more powerful in detecting individual differences than resting-state. Similar conclusions were reached by Kustubayeva *et al.* [59], which investigated brain asymmetry

analyzing left and right alpha power and ERPs amplitudes at frontal, central, parietal, occipital sites both at resting-state and during a decisional task entailing positive or negative feedback. Results showed that depressed patients were characterized by a lack of left dominance at resting-state, whereas during the task baseline and the following decision-making process they exhibited a larger right dominance compared to healthy subjects.

Gheza *et al.* [60] examined frontal alpha asymmetry differences between MDD patients and healthy subjects during reward processing and reinforcement learning. Participants were presented with a probabilistic learning task where they had to learn, by trial and error, hidden stimulus-response associations. A feedback was given after every response and each trial was associated with a different probability of a positive (reward) and negative outcome. Analyses on frontal alpha asymmetry scores in response to feedback revealed that MDD group expressed a negative asymmetry index, whereas the control group showed the opposite trend.

Although the previous findings confirmed the hypothesis that MDD was characterized by right-lateralization, other authors failed to find significant differences between groups or report a reduced or a lack of EEG asymmetry in depressed patients [61], [62]. No significant differences were also found in Jang *et al.* [63] in which depressed patients' frontal alpha asymmetry scores were compared with those of schizophrenic and healthy subjects.

EEG alpha asymmetry was also assessed in order to discriminate between healthy subjects and patients with different depressive subtypes. To this regard, Quinn *et al.* [64] investigated alpha asymmetry in melancholic, non-melancholic and healthy subjects at resting-state. They hypothesized a difference between control and melancholic groups. On the contrary, they found that non-melancholic patients significantly differed from control group by showing a relative global left-hemispheric activation (across frontal and parieto-temporal regions). Differently, a more recent study [65] found that melancholic symptoms were associated with reduced left-than-right frontal activity during a computerized slot machine paradigm, used to measure reward sensitivity. Melancholic symptoms were measured both dimensionally and categorically. Significant results were only obtained when melancholic symptoms were inserted in the regression analysis as a continuous variable. On the contrary, when melancholia was defined as a categorical variable, no significant group effect was found.

A large body of literature has been dedicated to EEG asymmetry in MDD, often concerning the alpha band power at frontal regions. As reported by experimental findings, this measure can discriminate between MDD and healthy subjects and be considered a promising biomarker of depression. More specifically, the majority of studies reported that MDD is associated with a reduced left than right frontal cortical activity. However, most of the findings are obtained from EEG recorded at resting-state, whereas few studies examined EEG asymmetry during tasks execution and even less of them analyzed asymmetry during the processing of emotional information. Yet, as suggested by Stewart *et al.* [58], which investigated frontal alpha asymmetry both at resting-state and during an emotional task, this measure seems to have more discriminative power when emotional material is involved compared to the resting-state. Hence, this research line may be strengthened by increasing the number of studies using emotional tasks and by extending the investigation of EEG asymmetry concerning other frequency bands and brain regions.

3) ERP COMPONENTS

When an individual experiences a stimulus, the brain waves deflect in some specific ways. These specific responses are called event-related responses (ERPs). An ERP component indicates a specific part of the more complex ERP waveform. ERP components are classified by their polarity, timing, scalp distribution, sensitivity to stimuli type and task manipulation [66]. The nomenclatures of ERP components derive from different aspects of such defining characteristics. For example, ERP components that occur at the time of 100, 200, 300 milliseconds from the stimulus onset are called N100/P100, N200/P200 and N300/P300, respectively, where P and N indicate whether the deflection is Positive or Negative [67]. P300 is generated if the stimulus is different from the previous ones; otherwise, other components (e.g., N100, P200, N200) can be observed [16]. Moreover, different types of stimuli could elicit specific ERP components as the mismatch negativity (MMN), which arises in response to an odd stimulus in a sequence of standard ones. For instance, in the case of auditory stimuli, the MMN arises after an infrequent change in a repetitive sequence of sounds (*oddball paradigm*, [68]). Likewise, the Late Positive Component (LPC) is an ERP component whose modulation depends on whether the stimulus is new or previously experienced. This is a positive-going ERP component, particularly considered in studies of explicit recognition memory since it is thought to reflect the reactivation of memory representation [69]. The LPC, also termed P600, follows, or even includes, the P300 component and it is larger for old stimuli than for new ones [70]. Differently, the Late Positive Potential (LPP) is a positive deflection, modulated by the emotional intensity of a stimulus. Emotional stimuli of either a positive or negative valence elicit a larger LPP than neutral stimuli and more arousing neutral pictures elicit a larger LPP than less arousing neutral pictures [71].

Other ERPs components are the contingent negative variation (CNV), the error-related negativity (ERN) and correct-related negativity (CRN). The first is a slow negative potential occurring prior to the onset of a stimulus which requires a motor response or decision from the subject [72]. The ERN component consists in a negative deflection occurring approximately 80-150 ms after an individual responds incorrectly during a task or responds when a response should be withheld. The CRN appears at the same latency as the ERN, but it is usually smaller and occurs after the

individual correctly responds to a trial task [73]. A variant of the ERN is the Feedback error-related negativity (FRN), which occurs approximately 250 ms after an individual receives external feedback indicating that the performance is worse than expected [74]. These components are elicited when the experimental paradigm involves a feedback of the task performance, as reinforcement learning paradigms (e.g., *Eriksen flanker task*, [75]).

ERP components have been investigated in clinical research and proposed as diagnostic markers of MDD. Several studies have examined such a hypothesis in order to test ERPs discriminative power. Shestyuk and Deldin [76] assessed the P200 and LPC amplitudes of current MDD patients, remitted patients and healthy subjects during an identification word task in which they had to indicate whether positive and negative words can be used to describe themselves and former US president Bill Clinton (self-referential vs other-referential conditions). Analysis of EEG data revealed that in the self-referential condition both MDD groups exhibited greater P200 amplitudes in response to negative than positive words, whereas control group exhibited the opposite results. In the self-referential condition, greater amplitudes of LPC were observed after negative words compared to positive ones only in current MDD patients, whereas healthy subjects showed greater amplitudes in response to positive words than negative ones. Fogelson *et al.* [77] elicited P300 component by presenting MDD and healthy subjects with sequences of standard and target stimuli appearing in random or predicted order. In the predictive sequence the standard stimuli preceding the target always followed the same presentation order. Results showed that, compared to controls, MDD patients exhibited smaller P300 amplitudes for all the experimental trials, and longer P300 latencies in response to target stimuli in the predicted sequences. No group differences in P300 latency following the target stimuli in the random sequences were found.

To elicit P300 component, Mumtaz *et al.* [78] used a visual oddball paradigm, consisting in the presentation of standard stimuli infrequently interrupted by a deviant one. They observed smaller P300 amplitudes and longer latencies in MDD group, compared to control one. Oddball paradigm but with auditory stimuli was used by van Dinteren *et al.* [79] that found smaller amplitudes of P300 at frontal and parietal sites in MDD compared to healthy subjects, whereas the same group effect for N100 amplitudes was limited only to young MDD patients (<46 years). The same task was used by Chen and colleagues [80] that compared the P300 amplitudes and latencies at central, frontal and temporal sites in individuals with a MDD first-episode, recurrent MDD, and healthy controls. Compared to control and first-episode groups, smaller amplitudes and longer latencies in the recurrent MDD group were observed.

A different procedure was used by Favrod *et al.* [81] which compared the global field power (GFP) of depressed, schizophrenic and healthy subjects' EEG, during a visual backward masking task. GFP quantifies the amount of activity at each time point in the field by considering the data from all electrodes simultaneously [82]. Results showed that GFP N100 amplitudes of depressed patients were lower compared to controls, and higher compared to schizophrenic patients. Yin *et al.* [83] assessed the amplitudes of N170 component of MDD and healthy subjects during a task involving the presentation of visual stimuli (human faces, tables and butterflies) in different position (upright vs inverted). They found that MDD patients exhibited increased N170 amplitudes when presented with face stimuli, but not with the other categories. These results suggest that perceptual processes involved in the early stages of face processing are impaired in MDD.

Zhu *et al.* [84] assessed the amplitudes and latencies of N450 and P300 components in MDD and control groups, using a face-word Stroop task. Participants were presented with sad and happy face stimuli with the words happy or sad superimposed on them in incongruent and congruent ways and had to indicate the emotion expressed by the face, ignoring the word. Results showed that, compared to control group, MDD was characterized by shorter N450 latencies after happy incongruent trials (i.e., happy face with the word sad superimposed) than happy congruent ones. P300 amplitude following sad incongruent stimuli was higher than sad congruent ones in healthy subjects, whereas this difference was not found in MDD patients.

Palmwood *et al.* [85] investigated inhibitory control in depression through a Go/NoGo task. Larger P300 amplitudes during successful NoGo trials relative to unsuccessful NoGo ones in healthy subjects were observed, whereas MDD patients showed no differences due to trial type. A similar Go/NoGo task with visual emotional stimuli was used by Camfield *et al.* [86] to compare ERPs amplitudes in MDD and healthy subjects. Results showed that N200 component following NoGo trials was less negative with positive stimuli compared to neutral ones, while the P300 component in response to NoGo trials was reduced for positive and negative stimuli compared to neutral ones. This effect was found to be enhanced in depressed patients compared to controls.

For what concerns the MMN ERP component, the findings are quite mixed. All the selected studies assessing this component used a visual or auditory oddball paradigm. Pang *et al.* [87] instructed participants to watch a silent movie while words pronounced with different emotional prosodies were presented. They found that MMN for sad vocal stimuli was absent in patients with MDD, whereas MMN components of angry and happy stimuli were similar across groups. Chen *et al.* [80] presented neutral standard and deviant tones while first-episode MDD patients, recurrent depression patients, and healthy controls watched a silent movie. They found that first-episode patients had lower MMN amplitudes compared to healthy controls, while no differences were found between the recurrent and first-episode groups. A similar experimental procedure was used by Bissonnette *et al.* [88] to compare MMN amplitudes between MDD patients and healthy subjects. They used 5 deviant tones

varying from the standard ones in intensity, pitch, duration, perceived location, or continuity. Results showed that, compared to controls, MDD group reported higher MMN amplitudes following tones deviating in intensity and location, and greater latencies following tones deviating in the pitch, suggesting that the auditory change detection process is altered in MDD but only for certain types of auditory stimuli. In support of this hypothesis, Restuccia and colleagues [89] recorded acoustic MMN in MDD patients and healthy subjects at 2 different stimulus intensities (70 dB and 90 dB) while they were reading a novel. Shorter latency and increased amplitudes of MMN in MDD group were observed, but in response to 90 dB acoustic stimuli only. In a recent study, Kim *et al.* [90] compared amplitudes and source activity of MMN in major depression, bipolar depression (BD) patients and healthy subjects during an auditory oddball paradigm. Results from source analysis showed that MMN at left anterior cingulate cortex, inferior and middle frontal gyrus was significantly increased in the bipolar group compared to the MDD. However, MDD and BD groups did not significantly differ from healthy subjects.

Auditory stimulation with different sound intensities was also used in Kim *et al.* [91] to elicit the Loudness dependence of auditory evoked potentials (LDAEP) in in MDD patients with and without Attention deficit hyperactivity disorder (ADHD) and healthy subjects. LDAEP assesses changes in the amplitude of N100-P200 component in response to different auditory stimulus intensities [92]. Results reported that comorbid patients had lower LDAEP levels compared to MDD without ADHD symptoms and healthy subjects. However, differences in the LDAEPs between only depressed patients and healthy subjects were not statistically significant.

Regarding the LPP component, known to be involved in emotional processing, Benau *et al.* [93] presented depressed and non-depressed participants with sentences ending with a negative, positive or neutral word. Results showed that LPP amplitudes following negative stimuli were larger in the MDD group, compared to healthy subjects. LPP amplitudes in response to positive and neutral stimuli did not differ between groups. Kettle and Allen [94] examined LPP amplitudes across central, frontal and parietal sites presenting to MDD patients, psychotic patients and healthy subjects facial expressions with different valences. Regardless of the emotional valence of stimuli, MDD patients and healthy subjects showed lower LPP amplitudes compared to psychotic subjects. However, no significant differences between MDD and control group were observed.

Emotional stimuli were used also to elicit CNV component [95]. Participants viewed faces expressing different emotions and non-facial objects followed by a target stimulus. They had to respond to the target only after face stimuli and inhibit the response when non-facial objects appeared. The onset of CNV component was calculated and results showed that CNV appeared significantly later in MDD group compared to healthy subjects, suggesting that disengaging from emotional facial stimuli took longer in MDD.

Deficits in attention inhibition toward specific stimuli were also investigated by Vanderhasselt *et al.* [96]. They conducted a topographical analysis on ERP data registered in order to identify electric field configurations over the whole scalp. Duration (Global Field Power, GFP) of scalp topographies and neural sources associated with them were examined. ERP data were registered during a Cued Emotional conflict task in which participants had to categorize happy and sad facial expressions as the same or the opposite of their actual valence. Results showed that MDD patients exhibited longer duration of a topography characterized by a positive component over centro-parietal electrodes, followed by a left-lateralized negative component over frontal/pre-frontal ones, only in response to sad stimuli categorized as happy. Source analysis revealed that they showed a stronger activity in the bilateral dorsal anterior cingulate cortex, which reflects anomalous control when they had to inhibit attention towards negative stimuli.

Besides attentional bias, MDD has also been associated with increased sensitivity for negative performance feedback, as reported in various studies which have observed enhanced ERN and FRN amplitudes compared to healthy subjects [97]–[99]. However, other studies drew different conclusions. Bakic *et al.* [100] examined ERN and FRN components by using a probabilistic learning task. Results revealed that while FRN mean amplitudes in healthy subjects were inversely proportional to the reward probability, MDD patients did not show FRN variations depending on reward probability. In addition, ERN mean amplitudes did not differ between groups. No significant differences were observed by Muir *et al.* [101] that compared ERN and CRN amplitudes at fronto-central electrodes in MDD, generalized anxiety disorder, comorbid patients and healthy subjects by using a modified version of the Eriksen Flanker test.

Regarding findings related to depressive subtypes, ERPs were uniquely examined in melancholia. Kerr *et al.* [102] compared auditory ERPs of patients with melancholic and non-melancholic major depression, subclinical depressed mood and healthy controls during an auditory oddball task by using the technique of deconvolution of target waveforms into overlapping standards [103]. Deconvolution expresses the difference between standard and target waveforms using the entire waveform and not the isolated points. Deconvolution waveform usually contains two peaks: the first peak corresponds to N100 and P200 features of the target waveform, and the second one corresponds to N200 and P300 components. Deconvolution measures consist in the peak area and the latency. The latency of a deconvolution peak corresponds to the relative response latency between standard and targets, and the peak area corresponds to relative response amplitude. Results of Kerr and colleagues' study showed that the amplitude of relative responses to targets versus standard stimuli at parietal sites decreased significantly in patients

with major depression compared to healthy controls, with more pronounced decreases in melancholics.

Quinn *et al.* [104] compared N200, P200 and P300 components recorded at frontal and midline location in melancholics, non-melancholics and healthy subjects during the execution of Go/No-go task. Statistical analyses were performed on the ERP averages following correct response to the No-Go stimuli. Results revealed no significant differences between groups for any of the ERP components. Chen *et al.* [105] analyzed the mean peak amplitudes of whole scalp ERP data while melancholic patients and healthy subjects performed a mental rotation task with different stimuli (hand vs letter). Compared to control group, melancholic patients showed lower mean peak amplitudes for both type of stimuli and longer latencies only in response to hand stimuli at parietal site, which may suggest an impairment concerning the processing of this specific type of stimuli in melancholia. Finally, Weinberg *et al.* [106] calculated the difference between ERN and CRN (i.e., ΔERN), acquired during a modified version of Eriksen Flanker Test in remitted melancholic, remitted non-melancholic and healthy subjects. Results revealed that melancholic group showed smaller ΔERN compared to the remitted non-melancholic and control ones, which did not differ from each other, suggesting that blunted ERN may be a marker for melancholia.

Several studies investigating the differences in ERP components between depressed and non-depressed individuals have been carried out. Findings in the literature suggest that MDD patients are characterized by ERPs activity different from healthy individuals. However, two issues emerged: on one hand, results are not always consistent, which makes it difficult to identify solid conclusions. On the other hand, the discriminative power of ERPs is strictly related to the task and the type of stimuli used to elicit them, which may impede comparisons between findings and their generalizability. Therefore, further investigations may be necessary to consider evoked potentials as reliable biomarkers of MDD.

4) EEG COMPLEXITY METRICS

A complex system is a system composed of many components interacting with each other. The massive number of neuronal connections and its staggering computing power makes the human brain the best example of a complex system [107]. Complex systems as the brain cannot be fully understood by decomposing them into simpler components. For this reason, in the last decade, the investigation of brain dynamics through EEG has borrowed several concepts and techniques from the Nonlinear Dynamical Systems theory, which can describe the fluctuations within the signal better than analysis of frequency bands [108]. Due to the huge amount of information generated within it, the brain is characterized by non-linear dynamical process (i.e., nonlinearity is defined as the lack of proportionality between a stimulus and the system's response to that stimulus) and unpredictability.

The difficulty to predict a system's future behavior depends on the amount of information generated within it. In information theory, the rate of generation of new information is called entropy. Entropy-related measures are the Approximate Entropy (ApEn) [109] and the Sample Entropy (SampEn), which quantify the regularity degree in time-series data by examining their similar epochs: more frequent and more similar epochs lead to lower values of entropy [110].

Closely related to entropy measures, the Lempel-Ziv Complexity (LZC) quantify the uncertainty contained in time series data. LZC assesses the number of distinct segments and their occurrence in a specific signal [111]. Other complexity metrics regard the fractal properties of time series. The analysis of fractal dimension (FD) aims to quantify the self-similarity of time series data, which refers to how many times a pattern in the time-series is repeated. Katz fractal dimension (KFD) [112] and Higuchi's fractal dimension (HFD) [113] algorithms assess FD directly in the time domain.

Complexity metrics have been applied to analyze EEG data and to the study of depressive disorders, in order to identify potential nonlinear markers of MDD. Hence, many studies tested the hypothesis that individuals diagnosed with MDD and healthy controls exhibit differences in complexity metrics.

Ahmadlou *et al.* [114] studied the fractal properties of frontal EEG oscillations in alpha, beta, delta and gamma bands in MDD patients and healthy subjects at resting-state. KFD and HFD were computed at right, left and overall frontal electrodes. Results showed that HFD values in beta and gamma bands in MDD group were greater than control. This means that frontal activity in MDD is characterized by higher fractality compared to non-MDD participants. Similar group differences, at resting-state, in HFD and KFD values in beta and gamma bands at frontal and parietal regions were reported by Akar *et al.* [115]. The same authors further investigated KFD, HFD and LZC values in depressed and non-depressed individuals during emotional processing [116]. EEG was recorded both at resting-state and during the listening of music and noise aimed to elicit positive and negative emotional states, respectively. Compared to resting-state, LZC and KDF values of patients increased in the frontal region in response to music and noise stimuli, whereas controls showed the opposite pattern in response to music stimuli. Moreover, MDD patients had the largest KFD increase during the noise period compared to baseline state at frontal region. Greater resting-state values of LZC on the whole scalp in MDD patients were also observed by Bachmann *et al.* [117]. Wolff *et al.* [118] analyzed LZC values from EEG recorded during an auditory oddball paradigm, finding that LZC changes after stimulus onset were significantly lower in MDD group, but for deviant stimuli only.

Cukic *et al.* [119] compared the HFD and SampEn values at resting-state in patients suffering from acute depressive episode, patients in remission and healthy participants. Regardless of the course of illness, depressed patients had higher HFD and SampEn values compared to healthy subjects at frontal and centro-parietal regions. Counterintuitively,

patients in remission reported higher values of both metrics at frontal and parietal regions, compared to the acute-episode group.

Higher SampEn values in depressed patients were also reported by Lin *et al.* [120]. SampEn analysis of 10 minutes EEG recordings at resting-state revealed that MDD group had higher values of this index at frontal, posterior temporal and occipital sites, compared to healthy controls.

Finally, the recent study of Chen and colleagues [39], previously described, extracted ApEn values from EEG recorded at resting-state and during TOVA, finding an increase in MDD group compared to control group in response to target and nontarget stimuli, whereas no group differences were observed at resting-state.

According to the above-mentioned studies, nonlinear features are potentially effective methods to discriminate between depressed and non-depressed individuals. Empirical findings suggest that EEG dynamics of depressive patients are associated with higher values of non-linear parameters, compared to healthy controls. Future research should further investigate their discriminative power and pay particular attention to two topics. On one hand, the discriminative power of nonlinear parameters should be further tested during task execution. It would be interesting to examine whether differences in complexity metrics between healthy subjects and depressed patients occur when they are engaged in experimental paradigms aimed to assess attentional, emotional recognition or memory processes. Indeed, as Chen *et al.* [39] showed, nonlinear parameters seem to be more informative markers of depression during task execution than at resting-state. On the other hand, analysis of nonlinear parameters should be adopted also for the detection of depressive subtypes. As the electronic search showed, currently no studies have investigated these measures in the attempt to discriminate between different types of depression.

5) EEG FUNCTIONAL CONNECTIVITY MEASURES

Brain activity can also be examined through the interactions among different brain regions. Neuronal activity acquired through EEG electrodes can provide information about the brain network structure and the connections within it. In mathematics, a network is a graphic representation of a complex system, described by connections between nodes and edges. In a cerebral network, the nodes usually represent the brain regions and the edges represent the connections between them. Brain connectivity can be structural or functional [22]. Structural connectivity refers to the physical connections between different cerebral areas. Functional connectivity is defined as statistical dependencies among remote neurophysiological events. Therefore, the analysis of functional connectivity provides information about temporal correlations in activity occurring between different areas, which are not necessary structurally connected with each other [121].

The functional analysis involves various metrics to assess connectivity between regions. One of the most used is the coherence metric. Coherence measures linear dependencies between two electrode signals recorded at distinct locations at a specific frequency domain. This method is based on the assumption that inter-regional synchronization of neuronal oscillations is one of the mechanisms that enables the exchange of information between various brain areas [122]. However, this functional connectivity measure simply indicates that a specific area is linked with another, without specifying the direction of influence [123]. Another measure of synchronization is the Phase Synchronization Index (PSI), also called phase-locking value, which quantifies the synchrony of same-frequency oscillations extracted from a pair of signals, especially when the interaction between areas is too weak to be detected by other measures [124].

Functional connectivity of brain networks using EEG signals has also been assessed with measures associated with graph theoretical approach. Graph theory is a branch of mathematics, describing the relationship among the network's elements. By applying the graph theory measures to EEG data, it is possible to configure an architecture of the brain network (known as ''topology'') both at global and nodal levels [125]. Some of the main network metrics adopted in EEG studies to assess functional connectivity are summarized in table 3.

The investigation of functional connectivity between brain regions has been applied to the study of depressive disorders in order to improve knowledge about their pathophysiology [131]. In the last decade, functional connectivity metrics have been adopted to test whether they can detect differences between depressed patients and healthy subjects.

Olbrich and colleagues [132] performed EEG connectivity analysis using eLORETA technique. Resting-state EEG was recorded in depressed and healthy subjects and the PSI of delta, theta, alpha and beta bands at prefrontal areas was computed. Compared to healthy subjects, MDD patients revealed increased connectivity at alpha frequency between subgenual prefrontal cortex and the left dorsolateral and left medial prefrontal cortex. A study of Li *et al.* [133] computed the PSI of delta, theta, alpha and beta frequencies in MDD and control subjects during a visual oddball task, by using event-related phase coherence, which is a method to analyze the dynamic coupling between different brain regions in response to specific motor, sensory or cognitive events [134]. In response to deviant stimuli, MDD patients showed a decreased PSI at delta frequency between frontal and parietal/temporal/occipital sites and increased frontal and prefrontal PSI of theta, alpha and beta band activities.

Differences in functional connectivity of delta and beta bands between depressed and non-depressed subjects were also observed in Liu *et al.* [135]. They recorded EEG during music perception and calculated the phase synchronization for all channels pairs at all frequency bands through Phase Lag Index method (PLI) [136]. PLI is an asymmetry index assessing the distribution of phase differences and can vary between 0 (=no coupling) and 1 (= true coupling strength between pairs of channels). Results showed that in

TABLE 3. Description of the main network metrics adopted in EEG studies.

Network Metrics	Description
Strength	The degree of connection strength in the network. Higher values of strength correspond to a strongly connected brain.
Clustering Coefficient (CC)	The degree to which a node is clustered with its adjacent neighbors. This measure assesses the functional segregation, which is the property of the brain to manage specialized processes through specific nodes groups highly interconnected with each other, within the network [126].
Path length (PL)	A measure of functional integration, which reflects the brain's capability to process information originating from different network areas. PL corresponds to the sum of the lengths between two nodes. A shorted path means that the network is well-integrated [126].
Small-worldness (S)	A measure of both functional segregation and integration, based on the trade-off between high local clustering and short path length. In small-word networks most nodes are not neighbors of one another, but the neighbors of any given node are likely to be neighbors of each other and most nodes can be reached from every other node by a small number of steps [126]. Small-world networks are different from random networks. Random networks are generated by starting with a disconnected set of nodes that are then paired with a uniform probability. These types of networks have low heterogeneity, since most nodes have the same number of connections, and are characterized by short average path and low clustering [127].
Efficiency	A measure assessing the effectiveness of information processing in the brain. Low efficiency corresponds to poorer performance of the network. Local efficiency indicates how effectively information is integrated between the immediate neighbors of a given network node, whereas Global efficiency indicates how effectively information is integrated across the entirety of the network [128].
Eigenvector centrality (EC)	The influencing power of hubs, which are nodes with a pivotal role in the control of information within the network [129]
Betweenness Centrality (BC)	It is defined as the fraction of all shortest paths in the network that pass through a given node. Nodes with high values of betweenness centrality participate in a large number of shortest paths. BC is also applied to edges (Edge betweenness centrality, EBC) [130].

the MDD group, connectivity strength increased for the delta band and decreased for the beta band, compared to control group. The authors also calculated the degree of each node (i.e., the number of links connected to a node) in delta and beta bands for both groups, and observed the same results of phase synchronization analysis.

Li *et al.* [137] investigated EEG coherence between each possible pairs of 72 channels in theta, alpha and beta frequency bands in MDD and healthy subjects. Results showed that compared to controls, global coherence of MDD group was higher in theta band, but not in the other two frequency bands. Further analysis on theta coherence showed that depressed group had significantly higher coherence in the left hemisphere of the brain, especially in parietal and temporal regions, compared with healthy controls. Theta coherence was also investigated by Ahn *et al.* [138] among frontal, parietal and temporal regions in MDD patients, Somatic symptom disorder (SSD) patients, and healthy participants. Results showed decreased theta coherence in SSD and MDD groups compared to controls within temporoparietal junction. However, theta coherence in frontotemporal area was lower in the SSD group than MDD and healthy controls, which did not differ from each other.

Guo *et al.* [139] examined N100, P200, N200, P300 and N450 components in MDD and healthy individuals to identify functional connected regions during a Face-word Stroop test. Results showed that during N450 component, after the occurrence of incongruent stimuli, for healthy subjects functional connectivity was observed over left frontal and central lobes, whereas for depressed patients, the functional connected regions involved not only the left frontal and central lobe but also the right frontal one.

An alternative synchronization measure to examine functional connectivity was used by Fingelkurts and Fingelkurts [140]. They investigated the self-referential brain network in MDD patients and healthy subjects. This network is responsible for those processes resulting in the awareness of oneself, which is suggested to be abnormal in MDD [141]. In Fingelkurts & Fingelkurts' study [140], EEG electrodes were used to estimate the operational synchrony within the network modules, which provides information about discrete brain operations occurring simultaneously in different cortical areas [142]. A significant increase in the strength of EEG operational synchrony within all the modules was observed in MDD group compared to control.

Orgo *et al.* [143] analyzed coherence values in delta, theta, alpha, beta, gamma and total frequency band of EEG recorded

at resting-state in depressed and non-depressed individuals. In addition, CC, PL, and S graph metrics were computed. Results showed that MDD subjects had increased coherence and decreased CC, PL and S values, revealing a more randomized brain network compared to healthy subjects.

Shim *et al.* [144] extracted various graph measures from the resting-state EEG recordings of MDD patients and healthy participants. Network analysis showed that strength, CC and efficiency significantly decreased in MDD group in theta and alpha bands, whereas the PL in the alpha band was significantly enhanced compared to control group. Zhang *et al.* [145] found lower CC, PL and local efficiency but increased global efficiency in MDD patients, compared to controls. A recent study by the same authors [146] further investigated the brain networks dynamics in MDD and control groups. Network metrics were extracted from resting-state EEG data. Results showed that NBC in left temporal region, CC in left frontal and left central regions, and local efficiency at left parietal-occipital region decreased in MDD group in theta band. However, MDD group showed increased PL in the left central region. For the alpha2 band (9–10.9 Hz), the PL increased in left frontal and right temporal regions and the CC decreased in the left temporal region.

Decreased CC at left central and frontal regions and lower PL value at left central region in theta band were observed by Sun *et al.* [147] in depressed patients, compared to healthy subjects. Furthermore, they found that MDD group showed lower EBC and NBC values at right temporal region in alpha band, compared to control group, suggesting a more randomized network structure. As well, analysis from a recent study [148], in which several graph metrics were compared between MDD and healthy subjects, revealed that MDD was associated with a more random network configuration.

Fogelson *et al.* [149] extracted various graph measures from the EEG signal recorded during a target detection task, previously described (see [77]). Results showed that the CC and local efficiency values in the beta frequency band were greater in patients compared to controls during the processing of standard stimuli preceding the target in the predicted sequence, suggesting an increased structured network organization.

Finally, a recent study [150] used a method called microstate analysis [151] to study network activity in MDD. This method consists of examining electrical microstates in the brain, which are defined as subsequent short time periods during which the configuration of the potential field on the scalp stays semi-stable, suggesting the synchronism of activity among the nodes of a network. These microstates persist for tens of microseconds and then transit to a different topography [152]. The analysis of microstates revealed that the proportion of the microstate involving the parietal and left insular cortex (i.e., microstate D) was reduced in MDD patients and remitted MDD patients, compared to healthy controls. Moreover, the duration and the occurrence of microstate D were decreased in MDD group compared to the control one.

The number of studies on functional connectivity in MDD has increased during the last decade. Empirical evidence revealed that MDD is associated with neurophysiological characteristics different from healthy individuals. Indeed, findings suggest that functional connectivity metrics extracted from EEG recordings can discriminate depressed from non-depressed subjects. However, results are heterogeneous. This can be ascribed to the different EEG measures adopted to assess functional connectivity, the methods used to analyze EEG data and the cerebral areas investigated. To reduce the variance of results and make reliable comparisons between them, experimental conditions should be unified regarding the regions of interest and methods for modeling connectivity. Moreover, most of the studies assessed these metrics at resting-state and only some of them investigated the discriminative power of functional connectivity metrics during task execution. Future research should be conducted in these directions. As well, this line of research should explore the possibility to use functional connectivity metrics to discriminate between depressive subtypes. Therefore, further studies are still necessary in order to consider these metrics as effective markers of MDD.

IV. DISCUSSION

The review shows that the effectiveness of EEG measures for detecting MDD has been widely investigated. According to the selected studies, many EEG measures are efficient in discriminating between MDD patients and healthy subjects.

Significant differences in frequency bands power between depressed and non-depressed individuals have been reported. However, it is quite complicated to identify a trend, even between studies investigating the same frequency band, since the findings are quite mixed. More consistent results are obtained on EEG alpha asymmetry. Indeed, much empirical evidence corroborates the hypothesis that MDD is associated with a hyper-activation of the right prefrontal cortex, which is considered related to withdrawal behaviors [47]. Among the ERP components, findings suggest a trend for time-related features of the ERP responses. MDD patients show lower amplitudes or shorter latency of these components compared to healthy controls. ERPs components related to the type of stimuli and feedback also succeed to detect significant differences between MDD patients and controls; however, the results are less univocal. For what concerns complexity metrics, studies suggest that MDD is characterized by higher values of nonlinear parameters, which reflects the fractality and unpredictability properties of the time-series data. MDD patients are also associated with increased EEG coherence, reflecting increased neurophysiologic connectivity, and abnormal graph properties, suggesting a random brain network configuration.

Taken together, the current findings support EEG measures' discriminative power to separate depressed patients from healthy subjects. However, results do not always point

in the same direction and the brain regions associated with changes in the typical EEG activity are still unclear and open to further investigation.

The major issue in identifying standardized and consistent biomarkers relies on the fact that the studies are conducted with very different techniques and methodologies. The present review attempts to downsize this barrier and present more comparable results by describing the findings as a function of the features extracted from EEG data. Nevertheless, heterogeneity remains a characteristic of EEG-based studies' results. In agreement with other works [9], [23], [153], the present review ascribes these inconsistencies to several factors. The first of them is the variety of experimental paradigms and stimulus content: for example, analyses performed on EEG data recorded at resting-state or during the execution of a task involving different cognitive processes led to different results which cannot be compared with each other. Second, differences in electrode positioning and reference can affect the discriminative power of the EEG metrics. Another difference concerns the sampling rate of EEG acquisition, i.e., the rate at which the waveform data is sampled in order to convert it into a numerical format. As well, studies differ in pre-processing procedures (e.g. correction or removal of artefact segments) and analysis procedures to extract the features from the EEG signals, especially for what concerns the methods to model functional connectivity [154]. Moreover, the reviewed studies differ in sample sizes and composition and this can impact the statistical significance of results. Therefore, solving these issues becomes fundamental to establish the usage of biomarkers in the diagnostic process of MDD.

Suggestions for future research concern at least two aspects: focusing on more consistent experimental paradigms and materials, and choosing a common EEG reference at the time of data acquisition, such as sharing one of the international electrode positioning systems. As Chella *et al.* [155] argue, these aspects matter and influence the results. Moreover, to improve the validity of EEG biomarker research, future studies may consider combinations of EEG-based and non-EEG markers in order to identify more defined criteria. In addition, the research of MDD biomarkers should enhance the interest towards specific clusters of differing depressive symptoms. Few studies have investigated the discriminative power of EEG features in depressive subtypes and all of them were focused on melancholic symptoms. This line of research should be strengthened, especially for what concerns EEG nonlinear or connectivity metrics. Future works should extend the use of these measures to investigate whether they could detect depressive subtypes.

The current review has some inherent limitations that should be acknowledged. For example, some methodological aspects were not taken into account in the inclusion/exclusion criteria of the studies, such as the length of EEG recordings, the order in which EEG is collected, the pre-processing procedure or the gender distribution in the studies' samples. Moreover, since the pharmacological treatment of patients was not always specified in the studies, such information was not extracted in the present review. However, omitting the studies that did not report the type of medical treatment would have led to a decrease of findings that are instead useful to shed light on the discriminative power of EEG-based markers for depression. Furthermore, papers comparing only the effect of treatments on EEG data were excluded by the selection criteria, even though they should be studied in further systematic reviews. Another limitation is represented by the low number of empirical findings about the subtypes of depression, which are currently examined only through linear measures of EEG. Indeed, to the best of our knowledge, the only studies that have investigated the discriminative power of EEG features in depressive subtypes are those concerning depression with melancholic features. There are no studies devoted to establishing a possible link between EEG features and other depressive subtypes, as psychotic or atypical depression.

Maybe, the scarcity of these types of studies could be ascribed to the inherent difficulty to identify the depression subtypes themselves, which are characterized by overlaps across symptoms, aetiologies, and time of onset (as pointed out by other works [156] Harald & Gordon, 2012; [5] Ulbricht *et al.*, 2013]. Consequently, building a sample composed of homogenous subgroups identified by specific clusters of differing depressive symptoms becomes challenging. However, this gap needs to be filled to strengthen the line of research interested in the search of biomarkers for depressive disorders.

Finally, the present review did not consider the studies which have used machine learning (or deep learning) approaches to classify depressed patients and healthy subjects based on EEG features. This decision relied on the fact that the studies based on machine learning approaches usually utilized several combinations of features and models which may generate confusion in the reading and an overload of information. However, it is worth noting that recent reviews are specifically dedicated to this field of research [9], [157] and suggest that these approaches would be a useful methodology to implement in the MDD diagnosis process. As pointed out by some authors [158], [159], the use of both machine and deep learning techniques can provide valuable biomarkers in discriminating MDD from other mood disorders, and can also be adapted to the computer-aided diagnosis of depression.

Overall, the present work has also some strengths. To the best of our knowledge, there are no systematic reviews in the field of psychology which have investigated the body of literature concerning the EEG-based biomarkers aimed to discriminate between depressed and non-depressed individuals. Moreover, for a matter of clarity and to better comprehend the findings, the review provides information about the linear, non-linear and connectivity EEG measures which are usually assumed to be acknowledged.

V. CONCLUSION

The review offers a comprehensive assessment of the extant literature concerning the EEG-based biomarkers for MDD and identifies possible future directions for this line of research. The current findings support the discriminative power of such biomarkers to separate depressed patients from healthy subjects. In addition to the promising results, the non-invasiveness and feasibility of the electroencephalogram should increase the usage of EEG-based biomarkers for the detection and diagnosis of major depressive disorder. However, some methodological issues previously addressed need to be solved in order to establish clinically useful and valid MDD biomarkers.

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CLAUDIA GRECO received the Laurea degree *(cum laude)* in cognitive psychology from the University of Campania Luigi Vanvitelli, Italy, in February 2015, and the Ph.D. degree from the University of Campania Luigi Vanvitelli, in January 2020. Her Ph.D. thesis was on the moral behavior in competitive interaction contexts. From 2016 to 2019, she attended the Ph.D. course "Sciences of mind" at the University of Campania Luigi Vanvitelli. From February 2019 to June 2019, she was a Visiting Research-Scholar with the Social Evolution and Behaviour Laboratory, Department of Experimental Psychology, University College London (UCL), London, U.K. From May 2020 to April 2021, she was a Postdoctoral Fellow (Assegnista di Ricerca) with the Psychology Department, University of Campania Luigi Vanvitelli. During her Postdoctoral Fellowship she participated in the AutoNomous DiscoveRy Of depressIve Disorder Signs (ANDROIDS) Project. She is currently cooperating in the research activity with the Behaving Cognitive Systems 2020 Laboratory (BeCogSys) at the University of Campania Luigi Vanvitelli.

OLIMPIA MATARAZZO received the Laurea degree *(cum laude)* in philosophy and the Ph.D. degree in relational sciences from the University of Naples "Federico II," in 1979 and 1991, respectively. She has been a Full Professor of general psychology with the University of Campania Luigi Vanvitelli, since 2005. Her research interests include deductive reasoning, deontic rules representation and deontic reasoning, emotion regulation, strategic interactions and fairness, emotion influence and cognitive distortions in decision-making, moral reasoning, and decision-making.

GENNARO CORDASCO received the Laurea degree *(cum laude)* in informatica (computer science) from the University of Salerno, Italy, in 2002, discussing a thesis in distributed algorithms whose title is: Un algoritmo di mapping ottimale per alberi binari completi su memorie parallele (An optimal mapping algorithm for complete binary trees to parallel memories), and the Ph.D. degree, in April 2006, discussing a thesis on peer to peer systems whose title is: On Designing Overlay Networks for Peer to Peer Systems. The thesis was supervised by Prof. Alberto Negro. The thesis was supervised by Prof. Alberto Negro and Prof. Vittorio Scarano. From 2002 to 2006, he attended the Ph.D. Program in computer science with the Dipartimento di Informatica ed Applicazioni, University of Salerno, (Advisor: Prof. Alberto Negro). He is currently an Associate Professor with the Dipartimento di Psicologia, Facoltà di Psicologia, Università degli studi della Campania Luigi Vanvitelli, Italy, and an Affiliate of the International Institute for Advanced Scientific Studies, Vietri sul Mare, Italy. From March 2005 to November 2005, he was a Research-Scholar with the Theoretical Aspect of Parallel and Distributed Systems (TAPADS) Laboratory, Department of Computer Science, University of Massachusetts at Amherst, Amherst, MA, USA, doing research activity under the supervision of Distinguished Prof. Arnold L. Rosenberg. From May 2006 to March 2011, he was a Postdoctoral Fellow (Assegnista di Ricerca) with the Dipartimento di Informatica, University of Salerno, cooperating in the research activity of the ISISLab Laboratory.

ALESSANDRO VINCIARELLI is currently a Full Professor with the School of Computing Science and Associate Academic, Institute of Neuroscience and Psychology—www.dcs.gla.ac.uk/vincia/, University of Glasgow. Overall, he has published more than 130 works, including one authored book, and more than 35 journal articles. His main research interest includes social signal processing, the domain aimed at modeling analysis and synthesis of nonverbal behavior in social interactions. He was the General Chair of the IEEE International Conference on Social Computing, in 2012, and the ACM International Conference on Multimodal Interaction, in 2017. Furthermore, he has initiated and chaired a large number of international workshops, including the Social Signal Processing Workshop and the International Workshop on Socially Intelligence Surveillance and Monitoring. He is or has been a Principal Investigator of several national and international projects, including the UKRI Centre for Doctoral Training in Socially Intelligent Artificial Agents—http://www.social-cdt.org/, a European Network of Excellence (the SSPNet—www.sspnet.eu/), and more than ten projects funded by the Swiss National Science Foundation and the U.K. Engineering and Physical Sciences Research Council. Last, but not least, he is also the Co-Founder of Klewel—www.klewel.com/, a knowledge management company recognized with national and international awards.

ZORAIDA CALLEJAS (Member, IEEE) received the Ph.D. degree in computer science from the University of Granada, Spain, in 2008. She is currently a tenured Associate Professor with the Software Engineering Department, University of Granada. She has been a Visiting Researcher with the Technical University of Liberec (Czech Republic), the University of Trento (Italy), Ulster University (U.K.), the Technical University of Berlin (Germany), Ulm University (Germany), and Télécom ParisTech (France), among others. She also coordinates the EU H2020 MSCA-RISE Project MENHIR about the use of conversational technologies for mental health. She is also coordinating the Andalusian I+d+i Project BonAppPetit related to the use of conversational systems to foster healthy eating in children. Her research interests include dialogue systems, conversational systems, emotion processing, affective computing, and user modeling.

ANNA ESPOSITO received the Laurea degree *(summa cum laude)* from the University of Salerno, with a thesis published on complex system, in 1992, and the Ph.D. degree in applied mathematics and computer science from the University of Naples Federico II, with a Ph.D. thesis published on phonetica, in 2002, and developed at MIT, RLE Laboratory, Cambridge, MA, USA. She has been a Postdoctoral Researcher with the International Institute for Advanced Scientific Studies (IIASS), and an Assistant Professor with the Department of Physics, University of Salerno, where she taught cybernetics, neural networks, and speech processing, from 1996 to 2000. She held a Research Professor position at the Department of Computer Science and Engineering, Wright State University, Dayton, OH, USA, from 2000 to 2002. She has been a Full Professor in computer science with Università della Campania Luigi Vanvitelli (UVA), since 2003, teaching cognitive and algorithmic issues of multimodal communication, social networks dynamics, cognitive economy, and decision making. She is the author of more than 250 peer-reviewed publications and an editor/coeditor of more than 30 international books. She is also the Head of the Behaving Cognitive Systems Laboratory (BeCogSys), UVA. The lab is participating to the H2020 funded projects: 1) Empathic, 2) Menhir, 3) SIROBOTICS, and 4) ANDROIDS.