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Review article

Depression biomarkers using non-invasive EEG: A review

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ABSTRACT

Depression is a serious neurological disorder characterized by strong loss of interest, possibly leading to suicide. According to the World Health Organization, more than 300 million people worldwide suffer from this disorder, being the leading cause of disability. The advancements in electroencephalography (EEG) make it a powerful tool for non-invasive studies on neurological disorders including depression. Scientific community has used EEG to better understand the mechanisms behind the disorder and find biomarkers, which are characteristics that can be precisely measured in order to identify or diagnose a disorder. This work presents a systematic mapping of recent studies ranging from 2014 to the end of 2018 which use non-invasive EEG to detect depression biomarkers. Our research has analyzed more than 250 articles and we discuss the findings and promising biomarkers of 42 studies, finding that the depressed brain appear to have a more random network structure, also finding promising features for diagnostic, such as, gamma band and signal complexity; among others which may detect specific depression-related symptoms such as suicidal ideation.

1. Introduction

Depression is the leading cause of burden worldwide (Friedrich, 2017), it is characterized by lack of motivation, difficult to experiment pleasure, impacting on daily lives activities and, in extreme cases, leading to suicide (World Health Organization, 2017). With the further development in non-invasive electroencephalography (EEG), scientists have used it as a tool to investigate the brain. Neurological diseases are hard to diagnose precisely because of the lack of known biomarkers and the subjectivity of the patient to answer the psychological evaluation questionnaires. A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indication of normal biologic processes, pathogenic processes, or pharmacological responses to a therapeutic intervention" (Group et al., 2001). With that in mind, studies have explored the use of non-invasive EEG to find biomarkers either for diagnostic purposes or treatment prediction (Mahato and Paul, 2019; Kas et al., 2019; Olbrich and Arns, 2013).

Finding non-invasive EEG biomarkers for depression is important because it may help to diagnose the disorder in a more objective way, since it is often diagnosed through the use of questionnaires which are prone to professional's and patient's subjectivity. But it is also difficult because depression presents heterogeneous symptoms (Nelson et al., 2018) and has high comorbidity, specially with anxiety (Nusslock et al., 2018), leading to inconsistent biomarker findings in literature.

Given the complexity of depression it is important to know the state-of-the-art findings in depression biomarkers. This work aims to provide a wider view on depression biomarkers in the last years, highlighting some gaps and difficulties, also briefly presenting each of these works so the reader can detect gaps, consensus, important references and other information that aid future research. With this objective a systematic mapping was conducted, reviewing articles concerning non-invasive EEG depression biomarkers from 2014 to 2018.

2. Review methodology

A systematic mapping (SM) consists in a formal methodology to improve the efficiency of literature search, by setting the scope of the search (Kitchenham, 2004). In this section we briefly discuss important aspects of our methodology; for a detailed explanation please refer to our supplementary material (Supplementary Material, 2019).

Our focus was to bring a better understanding of recent works related to depression biomarker detection and diagnosis using non-invasive EEG, therefore we generated the following research questions:

- **Q1:** Is non-invasive EEG a reliable tool to detect depression?
- **Q2:** What are the best biomarkers to detect and understand depression using only non-invasive EEG?

In order to find articles we applied search strings in two great databases: PubMed (Pubmed, 2019) which comprises millions of citations

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for biomedical literature and IEEE (IEEE Xplore Library, 2019) which comprises literature from computer science contributing with more algorithmic approaches to depression biomarkers. Both datasets may contain grey literature, which was not filtered out in our review, since it may bring important contributions to a systematic review (Paez, 2017). To search for papers the following search string was used:

- ((depress*) **AND** (electroencephalog* **OR** eeg **OR** qeeg) **AND** (biomarker **OR** "bio marker" **OR** diagnos* **OR** detection* **OR** classification))

Selection criteria can be found at the supplementary material (Supplementary Material, 2019).

2.1. Data extraction

The conducting phase of this review was done following the protocol in Kitchenham (2004) aided by Parsifal tool (Parsifal systematic review tool, 2019), reading each article found individually. 258 papers were selected, being 220 from PubMed, 35 from IEEE and 3 added manually; after reading all articles only 42 fit all criteria and were accepted, being 30 from PubMed, 9 from IEEE plus 3 that we added manually.

The 42 articles reviewed on this work are presented in Table 7 and also available online under the link "Accepted Articles References" at our supplementary material (Supplementary Material, 2019), which also contains summarized information, the data extraction form, some charts and also the *BibTex* of accepted articles. It is worth to notice that we found another literature review work from August 2018 by Mahato and Paul (2019) which has a smaller number of studies and can complement the findings reported in our work.

3. Findings and discussion

The literature presents many works in the scope of this review, some study specific biomarkers, others present literature reviews and others present computational approaches to depression diagnostic. This section is structured by biomarker types (see Fig. 1 for biomarker distribution), with a brief explanation of each biomarker and the conclusions that the articles read had achieved, alongside with a summary table (see Tables 1–6). Lastly, the research questions and some research barriers will be discussed.

3.1. Band power (spectral analysis)

One direct information obtained by EEG is band power, since the signal can be described in frequency domain and the principal EEG bands are well known (Rao, 2013; Freeman and Quian-Quiroga, 2012) it is easy to analyze the power amplitudes for each band. Each band is associated with some mechanisms in the brain; the bands related to depression are stated below:

- **Alpha:** reflects inactivity in the brain and relaxation (Rao, 2013; Freeman and Quian-Quiroga, 2012), asymmetry in brain activity is related to the approach-withdraw model (Coan and Allen, 2004; Davidson, 1995);
- **Beta:** related to expectancy (Freeman and Quian-Quiroga, 2012), anxiety and introverted concentration (Abhang et al., 2016);
- **Theta:** related to emotional processing (Aftanas and Golocheikine, 2001; Aftanas et al., 2002);
- **Gamma:** related to attention and sensory systems (Freeman and Quian-Quiroga, 2012) and may be related to mood swings (Fitzgerald and Watson, 2018);
- **Delta:** related to deep sleep (Freeman and Quian-Quiroga, 2012).

One way to explore biomarkers is to apply classification algorithms and try to predict the diagnostic using a set of features (Mohammadi et al., 2015; Cai et al., 2017; Hosseinifard et al., 2013); if a given feature gives high prediction accuracy it may be an important biomarker. Some classification algorithms may give information about the features, e.g. increased alpha amplitude predicts depression, others may only indicate which features are important, e.g. alpha based features provide high accuracy in classification. Using this approach, an early study in 2013 (Hosseinifard et al., 2013) with 90 subjects presented evidence that alpha and theta bands are good discriminators between depressed and healthy controls, in agreement with previous research which related these bands to emotional processing (Aftanas and Golocheikine, 2001; Aftanas et al., 2002). Later, Mohammadi et al. (2015) selecting EEG channels and band power features from 96 subjects in an automated way, achieved higher accuracy for delta and high-alpha bands corroborating with early group studies such as Alhaj et al. (2011). These findings may be related to alpha asymmetry (discussed in Section 3.2), specially in Hosseinifard et al. (2013) which finds that the information given by the electrodes in the left hemisphere are more suitable for prediction, less can be inferred in Mohammadi et al. (2015) because the authors do not provide any information about the positions (electrodes) or the values of the band powers.

Still regarding alpha band, a recent work (Lee et al., 2018) reports higher alpha at the left side of the brain for depressed compared to euthymic (emotional stable) subjects, which is the same region of interest in Hosseinifard et al. (2013), and also reports reduced beta waves in the central-left side of the brain for depressed. Lastly, Dolsen et al. (2017) report increased alpha activity during whole night sleep for depressed subjects with suicidal ideation compared to the ones with low suicidal ideation.

On the other hand, two recent and independent conference papers (Cai et al., 2017; Shen et al., 2017) conducted with 178 and 170 subjects respectively and only 3 electrodes at the forehead, found different results with respect to alpha band, which was outperformed by features derived from other bands, specially beta band which achieved the best results in both studies. These differences may be explained by electrode setup, since all other studies cited above use electrodes in the entire head scalp, for instance Hosseinifard et al. (2013) found little prediction capability at electrodes in the forehead.

Liu et al. (2017), using a working memory task which the subjects should remember faces presented in forward order or backward order,

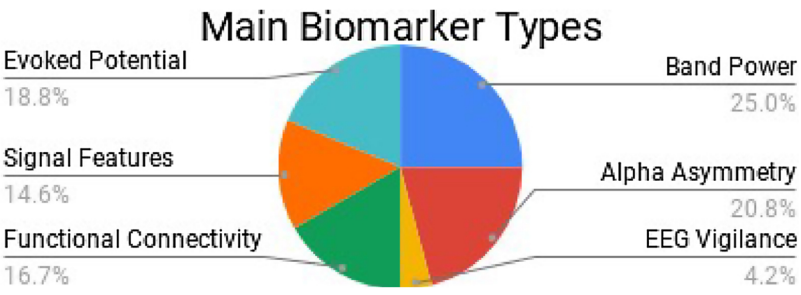

Fig. 1. Biomarker approaches distribution. Some articles present more than one biomarker.

find larger slow wave (theta and delta) amplitudes for remitted depressed compared to controls at the central parietal and lateral electrodes for negative targets in the backwards trial.

A review from Fitzgerald et al. in 2018 regarding gamma band (Fitzgerald and Watson, 2018), reports many studies relating increased gamma power in monopolar depressed compared to healthy controls, concludes that gamma may be related to mood swings, by the means that there is a good amount of gamma power to provide mood equilibrium, even relating it to treatment prediction, this review also presents a discussion regarding inconsistencies in gamma findings and standards to be used in experiments.

Lastly, it is worth to notice the study conducted by Grin-Yatsenko et al. (2010) in 2010 which had a total of 637 subjects, 111 depressed and 526 healthy subjects, being the largest study in this review regarding the number of subjects. The authors find increased activity in theta, alpha and beta bands at occipital and parietal areas of the brain of depressed subjects. They also compare the findings with previous works, being a good review work for articles prior to 2010.

It is important to notice that each study reported here had it own focus, some simply wanted to automate the diagnosis, e.g. Mohammadi et al. (2015) and Hosseinifard et al. (2013), others are more focused in diagnosis with little and comfortable equipment, e.g. Cai et al. (2017) and Shen et al. (2017), while others were preoccupied with overall differences in brain, e.g. Lee et al. (2018) and Dolsen et al. (2017), this brings differences at experimentation that may impact the findings regarding biomarkers.

3.2. Alpha asymmetry and brain laterality

Another common studied biomarker is alpha asymmetry, which measures the relative alpha band activity between the brain hemispheres, specially at frontal electrodes. It can be related to the approach-withdraw model (Coan and Allen, 2004; Davidson, 1995) which posits that left side frontal brain activity is related to approach behavior whereas the right frontal side is related to withdraw behaviors. Such model helps to explain some results reported in the previous subsection

Table 1
Summary of findings regarding band power.

Article	Frequency bands	Findings
Hosseinifard et al. (2013)	Alpha, Theta	Using the accuracy of a classifier, it finds that alpha and theta bands, specially at the left hemisphere, are good features to discriminate depressed from healthy controls.
Mohammadi et al. (2015)	Delta, High-Alpha	Using the accuracy of a classifier, it finds that high-alpha and delta bands are good features to discriminate depressed from healthy controls. Does not indicate any region of interest.
Cai et al. (2017) and Shen et al. (2017)	Alpha, Beta, Theta, Gamma	Both studies independently and using a pervasive electrode setting (3 electrodes at the forehead), it finds that alpha-based features had less prediction power than beta, theta and gamma based features.
Lee et al. (2018)	Alpha, Beta	Increased high-alpha power at the left hemisphere of the brain and reduced beta power in the central-left side of the brain of depressed compared to euthymic patients.
Dolsen et al. (2017)	Alpha	Correlates increased alpha activity during whole night sleep to increased suicide ideation in depressed subjects.
Fitzgerald and Watson (2018)	Gamma	Increased gamma power in monopolar depressed compared to healthy controls. Also, concludes that there is a good amount of gamma power that provides mood equilibrium.
Liu et al. (2017)	Delta, Theta	Increased amplitude in theta and delta waves for remitted depressed at the central parietal and lateral areas.
Grin-Yatsenko et al. (2010)	Alpha, Beta, Theta	Increased activity in alpha, beta and theta bands at occipital and parietal areas of the brain of depressed subjects.

Band power is widely studied and easily applied to classifiers that differentiate depressive from healthy subjects. Regarding this, there is some evidence indicating that monopolar depressed subjects have increased gamma activity as reviewed by Fitzgerald in a high impact study (Fitzgerald and Watson, 2018). As for alpha activity there are diverging results, even though some studies report that alpha is a good discriminant for depression or its symptoms (Lee et al., 2018; Dolsen et al., 2017; Mohammadi et al., 2015; Hosseinifard et al., 2013), there are some studies which disagree (Cai et al., 2017; Shen et al., 2017). These differences may be related to the areas of the brain studied, for instance in Hosseinifard et al. (2013) and Lee et al. (2018) the authors report increased alpha at the left hemisphere, while the works which report alpha as a not-so-good discriminator use three electrodes positioned at the forehead (Cai et al., 2017; Shen et al., 2017). Regarding delta and theta waves they appear to be worthy of attention (Liu et al., 2017; Mohammadi et al., 2015) although more studies are needed for a better understanding of the impact of these waves in depression.

That said, we find that gamma band should be studied since it is related to mood regulation (Fitzgerald and Watson, 2018), also increased alpha band in sleep seems to be related to suicidal ideation (Dolsen et al., 2017), alpha band seems to be better understood by the means of other features, such as alpha asymmetry (related to approach-withdraw model) or EEG vigilance (wake to deep sleep transition), and may be a predictor for specific symptoms. As for theta, it seems to be good feature in diagnostic tools (Hosseinifard et al., 2013; Cai et al., 2017; Shen et al., 2017), but there is still little information about the mechanisms related to it. And for beta wave, it seems more related to anxiety and ruminating thinking which are common in depressive patients, but may not be so important for specific diagnostic.

regarding alpha band at left side hemisphere in depressed, since alpha is related to *lack* of activity in the brain, increased alpha at the left side of the brain indicates lower activity and therefore may indicate lack of approach behavior.

Related studies report alpha asymmetry in various ways that may confuse the reader, for the sake of clarity and simplicity we will refer to asymmetry by the means of increased left alpha activity (meaning lower brain activity at left side), therefore *high asymmetry* refers to increased left hemisphere alpha activity, associated with lack of approach behavior.

Some studies presented in the previous subsection already indicate that alpha activity may happen more at the left side of the brain for depressed subjects, e.g. Lee et al. (2018), although these studies do not compare directly with the activity at the right side of the brain, there are some recent studies focused on alpha asymmetry. For instance van der Vinne et al. (2017) present a review study regarding only alpha asymmetry and concluded that alpha asymmetry may not be a good biomarker for depression diagnosis, being more suitable for a prognostic biomarker as it can be related to treatment response. The lack of trust in frontal alpha asymmetry for diagnostic purposes relies in many studies which failed to find such asymmetry in depressed patients compared to healthy controls, and also indicative that are needed many subjects to find statistical effect for alpha asymmetry (van der Vinne et al., 2017).

Another review presented by Bruder et al. (2017) has many information regarding alpha asymmetry and brain laterality, it also has some information regarding the comorbidity of depression with other disorders, such as anxiety. The authors conclude that it is important to analyze alpha asymmetry (not only frontal) taking into consideration

other features such as gender, age, and comorbid disorders. Nusslock et al. (2015) present a literature review, comparing unipolar and bipolar depression with regard to alpha asymmetry and concludes that the risk for unipolar depression is related to an increased left side alpha activation relating to decrease in motivation, although for bipolar depression the opposite happens, there is lower alpha activity increasing approach behavior, this disequilibrium in alpha activity impacts on depression. Another work from Nusslock et al. (2018) finds that anxious apprehension masks the relationship between depression and prefrontal alpha asymmetry.

In a work presented in 2017, Jesulola et al. (2017) conclude that frontal alpha asymmetry is related to depression only in females, finding no significance for males. Later, Smith et al. (2018) find no difference between genders with regard to alpha asymmetry and find that subjects with lifetime Major Depressive Disorder (MDD) presented increased left alpha activity mostly at frontal and central-parietal locations. Agreeing with Smith, Koo et al. (2018) find higher alpha activity at the left hemisphere for MDD subjects when compared to healthy controls. Acharya et al. (2018) conclude that the EEG signals from the right hemisphere are more suitable for depression diagnosis than the EEG signals obtained from the left hemisphere when using deep learning classification. Cai et al. (2017) could not classify depressed versus healthy using asymmetry.

Lastly, a work presented by Nelson et al. (2018) relates alpha asymmetry to dysphoria and lassitude symptoms, concluding that depression symptoms are related to motivation disturbances rather than affective disturbances.

Table 2
Summary of findings regarding alpha asymmetry.

Article	Findings
Lee et al. (2018) and Hosseinifard et al. (2013)	Left alpha activity is a good predictor for depression diagnosis.
van der Vinne et al. (2017)	Review study concludes that alpha asymmetry may be suitable for treatment prediction, but not for diagnosis.
Bruder et al. (2017)	Brain laterality review, concludes that other features, such as gender and comorbidity play a role in alpha asymmetry.
Nusslock et al. (2018)	Anxious apprehension masks the relationship between depression and prefrontal alpha asymmetry.
Nusslock et al. (2015)	Relates alpha asymmetry to unipolar (lack of approach motivation) and bipolar (excess of approach motivation) depressive disorders.
Jesulola et al. (2017)	Frontal alpha asymmetry is related to depression only in females, finding no significance for males.
Smith et al. (2018)	No gender impact on alpha asymmetry. Also increased left alpha activity mostly at frontal and central-parietal locations for lifetime MDD.
Koo et al. (2018)	Higher alpha activity at the left hemisphere for MDD subjects when compared to healthy controls.
Acharya et al. (2018)	EEG signals from the right hemisphere are more suitable for depression diagnosis than the EEG signals from the left hemisphere when using deep learning classification.
Cai et al. (2017)	Could not classify depressed versus healthy using asymmetry.
Nelson et al. (2018)	Relates alpha asymmetry to dysphoria and lassitude symptoms.

There is strong evidence that alpha asymmetry may predict specific symptoms and treatment outcome (van der Vinne et al., 2017; Nusslock et al., 2015; Nelson et al., 2018), although for diagnostic purposes it may not be suitable (van der Vinne et al., 2017) since there are many conflicting findings in literature, which may be explained by the unknown impact of gender in alpha asymmetry (Bruder et al., 2017), where some authors find gender impact (Jesulola et al., 2017) and others do not (Smith et al., 2018). Also, anxiety may alter alpha asymmetry making it difficult to diagnose depression (Nusslock et al., 2018).

Alpha asymmetry seem to be an efficient biomarker for specific symptoms, as dysphoria and lassitude (Nelson et al., 2018) and to differ unipolar from bipolar depression (Nusslock et al., 2015), but has little diagnostic power given its sensibility to other factors specially anxiety, future studies should explore its sensibility to other external factors before using it for diagnostic prediction.

3.3. Signal based features

Some features that quantify EEG signal characteristics may be studied as biomarkers; for the sake of clarity a short description is provided below, please refer to cited papers for more information:

- **Alpha Power Variation (APV):** proposed in Bachmann et al. (2018), measures the power and frequency variations in alpha band;
- **C0-Complexity (C0-C):** proposed in Fang et al. (1998), measures the randomness of a signal (Cai et al., 2017, 2018);
- **Correlation Dimension (CD):** indicates the degree of freedom of a signal, lower values indicate smaller randomness of the signal (Shen et al., 2017; Cai et al., 2018);
- **Detrended Fluctuation Analysis (DFA):** introduced by Peng et al. (1994), indicates long-time correlations of the signal (Mahato and Paul, 2019; Bachmann et al., 2017);
- **Higuchi's Fractal Dimension (HFD):** introduced by Higuchi (1988), indicates the fractal dimension of a signal (Mahato and Paul, 2019; Bachmann et al., 2018);
- **Lempel–Ziv Complexity (LZC):** introduced in Lempel and Ziv (1976), it measures the complexity of a signal (Zhang et al., 2001; Bachmann et al., 2018);
- **Maximum Lyapunov Exponent (MLE):** measures the randomness of a signal (Hosseinifard et al., 2013);
- **Relative Gamma Power (RGP):** also introduced in Bachmann et al. (2018), measures the relative gamma power compared to all spectrum;
- **Spectral Asymmetry Index (SASI):** introduced in Hinrikus et al. (2009), calculates the relative asymmetry between higher and lower frequency bands (Mahato and Paul, 2019; Bachmann et al., 2017, 2018).

The work presented by Hosseinifard et al. (2013) and discussed in Section 3.1 also use some non-linear features, such as DFA, to train a classifier and differentiate healthy from depressed subjects, being CD one that best help to distinguish between these classes, and the use of all studied features, band power and signal based, achieved 90% accuracy, indicating that the use of both features can contribute to depression biomarker studies. Mumtaz et al. (2015) using DFA, achieves similar results to Hosseinifard et al. (2013).

Bachmann et al. (2017) find significant lower DFA and increased SASI in depressed compared to healthy subjects at Pz channel. Although a subsequent work from the same authors in the next year (Bachmann et al., 2018) finds no difference in SASI or LZC, maybe due to a change in the reference electrode used, beside that, authors find significant higher values for DFA, HFD, RGP and APV.

Hou et al. (2017) compare depressed and non-depressed brains with unilateral basal ganglia infarctions and healthy controls and find that only the patients with right lesions could be differentiated from healthy controls using long-range temporal correlations, measured using DFA,

in EEG signal.

Regarding LZC, Kalev et al. (2015) find overall lower LZC for depressed when using a multi-scale approach, except near 40 Hz where the opposite is found. Specifically at electrode F3 similarly lower LZC up to 18.2 Hz and higher LZC above 22 Hz for depression, no difference found in between frequencies.

Cai et al. (2017) when using the signal from 3 frontal electrodes, find that CD, C0-Complexity and RGP are not good features, providing accuracy slightly better than chance (accuracy near 60%) for depression diagnosis.

Table 3
Summary of findings regarding signal based features.

Article	Feature	Findings
Mahato and Paul (2019)	DFA, SASI, HFD	Increased HFD, significant lower DFA for depression. For SASI the same findings as Bachmann et al. (2018, 2017).
Bachmann et al. (2017)	DFA, SASI	At channel Pz, significant decreased DFA and increased SASI in depressed when compared to healthy controls.
Bachmann et al. (2018)	SASI, DFA, LZC, HFD, RGP, APV	No difference in SASI or LZC. Higher HFD, DFA, RGP and APV in depressed.
Mumtaz et al. (2015)	DFA	DFA is a good feature to diagnose depression.
Hou et al. (2017)	DFA	Only the patients with right lesions could be differentiated from healthy controls using long-range temporal correlations in EEG signal.
Kalev et al. (2015)	LZC (multiscale approach)	Overall lower LZC in depressed, except near 40 Hz where the opposite is find. And at F3 lower LZC up to 18.2 Hz and higher LZC above 22 Hz for depression, no difference found in between frequencies.
Hosseinifard et al. (2013)	DFA, CD, HFD, MLE	Non-linear features classified depressed from healthy controls better than linear features (band power). Being CD the one which provided more accuracy.
Cai et al. (2017)	CD, RGP, C0-C	Using 3 electrodes at forehead, CD (60.59%), RGP (59.41) and C0-C (58.24%) provide classification slightly better than chance.

Relevant studies present DFA as a discriminant feature (Mahato and Paul, 2019; Bachmann et al., 2018; Mumtaz et al., 2015; Hosseinifard et al., 2013), specially in Bachmann et al. (2017) which not only find significant decreased DFA in depressed but also uses only one electrode (Pz) making it a good candidate for depression biomarker, although conflicting results were found by the same authors (Bachmann et al., 2018). As for SASI, even promising results were found, in Bachmann et al. (2017) the authors have found no difference in SASI in a subsequent study a year after (Bachmann et al., 2018), therefore further studies should be addressed at SASI and DFA as biomarkers for depression.

Considering signal complexity, HFD appears to be higher in depressed brains (Mahato and Paul, 2019; Bachmann et al., 2018) indicating a complex signal in agreement with decreased DFA findings, also CD appears to be a good discriminant (Hosseinifard et al., 2013; Cai et al., 2017) but no information about the value was provided, we assume a higher CD indicating a chaotic signal agreeing with the findings using DFA and HFD. As for LZC, it appears that the methodology may bias the results since Bachmann et al. (2018) found no difference and in Kalev et al. (2015) the authors using a multiscale approach found different results depending on the frequency. For MLE and C0-Complexity only two studies (Cai et al., 2017; Kalev et al., 2015) covered these features and further study should be done in order to better understand the impact of these features as biomarkers for depression.

Lastly, higher RGP and APV were found in depressed (Bachmann et al., 2018) but RGP was a relatively weak feature in Cai et al. (2017), which may be explained by the different electrode positioning between these studies. These features should be studied more in the context of depression biomarker.

Therefore we advise the use of HFD as other signal complexity measures for depression diagnostic, specially together with linear features (as in Hosseinifard et al., 2013). As for SASI, RGP, DFA, APV we advise further investigation.

3.4. Network based features

EEG electrodes capture the activity of populations of neurons (Rao, 2013), using this information it is possible to analyze brain activity by the interactions among different brain regions and study its network structure. Many researchers study network features in the brain and associate them to depression. As in the previous sections, we describe shortly the features discussed here and invite the reader to read the cited papers for more information:

- **Alpha Wave Spread (AWS):** indicates inactivity in many areas of the brain (Lee et al., 2018; Rao, 2013; Freeman and Quian-Quiroga, 2012);
- **Cluster Coefficient (CC):** when a neighbor node is directly connected to another neighbor it forms a cluster, cluster coefficient measures the density of these connections, random networks tend to have low average CC opposed by complex networks which have higher CC (Liu et al., 2018; Bullmore and Sporns, 2009; Sporns, 2010);
- **Coherence (Coh):** coherence measures linear dependencies between signals, indicating synchronous oscillations for a band (Li et al., 2016; Kay, 2019);
- **Functional Connectivity (FC):** generic term to indicate connection among areas in the brain, can be measured in many ways for instance using coherence to indicate synchronous activity among brain regions (Orgo et al., 2017);
- **Path-Length (PL):** the smaller amount of nodes between two different nodes, random or complex networks tend to have smaller paths than regular ones (Bullmore and Sporns, 2009; Sporns, 2010);
- **Phase Synchronization (PS):** Similar to coherence, indicates the synchronization of oscillations of the same frequency (Li et al., 2017);
- **Small-Worldness (SW):** the human brain naturally presents a small world structure, i.e. small highly interconnected regions linked to each other by a few hubs (Sporns, 2010; Sporns and Zwi, 2004).

Li et al. (2016) analyze many bands with respect to coherence, the authors find that, during an emotional face presentation task, only gamma wave coherence could differentiate between depressed and healthy subjects, mild depressed showing lower gamma coherence only at the right hemisphere, no significant difference was found for the left side of the brain. Also using coherence, Fingelkurts and Fingelkurts (2017) present a work in 2017 relating three brain operational modules to self-consciousness, hypersynchrony in all three modules are related to depressive symptoms, contributing to excessive self-focus, rumination, and body tension.

Using path length, Shim et al. (2018) find longer PL for alpha and theta, also decreased CC. Guo et al. (2018) find weaker FC and longer PL at depressed brains, mainly on left hemisphere. On the other hand, Liu et al. (2018) find shorter PL and also decreased CC in depressed.

Orgo et al. (2017) find decreased small-worldness in depressed

indicating a more random network in the brain and also find increased FC, meaning that many neurons (or regions) activated synchronously. Lee et al. (2018) find that alpha wave is more spread through depressed brains.

In another work, Li et al. (2017) present abnormally enhanced beta phase synchronization containing more short-range frontal connections and interhemispheric temporal-parietal connections, for a n-back (memory) task, concluding the possibility that to compensate eventual memory impairment in depression other pathways are generated in the brain.

Table 4
Summary of findings regarding network based features.

Article	Feature	Findings
Lee et al. (2018)	AWS	Alpha wave is more spread in depressed brains.
Li et al. (2016)	Coh	During an emotional face presentation, mild depressed showed lower gamma coherence only at the right hemisphere, no difference was found in other bands.
Li et al. (2017)	PS	Enhanced beta phase synchronization containing more short-range frontal connections and interhemispheric temporal-parietal connections.
Orgo et al. (2017)	SW, FC	Decreased SW and increased FC in depressed compared to healthy controls.
Guo et al. (2018)	FC, PL	Decreased FC and longer PL in depressed compared to healthy controls.
Shim et al. (2018)	PL, CC	Decreased CC and increased PL for alpha and theta bands in depressed.
Liu et al. (2018)	PL, CC	Decreased PL and decreased CC in depressed.
Fingelkurts and Fingelkurts (2017)	Coh	Relates three modules in brain to self-awareness and relates the hypersynchrony in all three modules to depressive symptoms, such as rumination and body tension.

Regarding brain network structure, there are studies which present relations with specific brain regions, such as Fingelkurts and Fingelkurts (2017), others, study in a broader view of the brain, e.g. Shim et al. (2018) and Liu et al. (2018). The presented works seem to agree regarding the randomness of depressed brain networks, but for functional connectivity some studies find stronger connections for healthy (Guo et al., 2018) other for depressed (Orgo et al., 2017) subjects. It is possible that the task imposed to the study subjects had impact, since in Guo et al. (2018) the subjects do a face-word Stroop task and in Orgo et al. (2017) the EEG is collected from resting state.

There is no consensus regarding path lengths also, since two studies from 2018 found conflicting path lengths, in Liu et al. (2018) the authors found decreased path lengths; and in Shim et al. (2018) the authors found increased path lengths for depressed compared to healthy controls. Such conflict may be due to sample size since Shim et al. (2018) study more subjects, 87 depressed and 58 healthy, compared to Liu et al. (2018), which collected data from 13 depressed and 13 healthy subjects.

Many authors study depression by means of brain network and this approach helps to better understand the brain functionality, although there are lots of conflicting findings, therefore further studies are still necessary, specially with suitable sample sizes and aiming to evaluate the impact that the task imposed to the subject has in brain network functionality.

3.5. Evoked potentials

When an individual is subject to some stimuli, e.g. a different noise (Ruohonen and Astikainen, 2017), the brain waves deflect in some specific ways, they usually are named after their direction and latency; evoked potentials are studied using many different tasks such as emotional face presentation (Burkhouse et al., 2017) or working memory (Liu et al., 2017) and may reflect differences in brain functioning between depressed and healthy subjects. The discussed evoked potentials are summarized below:

- **Late Positive Potential (LPP):** it is a late (300 ms-600 ms) positive deflection, usually precedes emotional processing (Grunewald et al., 2019; Ibanez et al., 2012), and it is associated with encoding processing for word-evoked stimuli (Xie et al., 2018);
- **N1:** is a negative deflection that occurs about 150 ms after visual or auditory cue presentation, is related to stimulus encoding (Näätänen, 1990) and is modulated by emotional salience (Ibanez et al., 2012);
- **N200:** is a negative deflection at approximately 200 ms after the stimulus (Rao, 2013) and is related to conflict monitoring (Iannaccone et al., 2015);
- **P100 or P1:** is a positive deflection that occurs around 100 ms after cue presentation, may be related to severity of delusional thoughts (Bedwell et al., 2013, 2018) and is also modulated by emotional salience (Ibanez et al., 2012);
- **P200 or P2:** is a positive deflection that occurs around 200 ms after the stimulus and is related to selective attention (Ibanez et al., 2012);
- **P300 or P3:** is a positive deflection at approximately 300 ms after some odd stimulus is presented, e.g. a special beep (Rao, 2013);

Mumtaz et al. (2016) find increased latency in P300 for depressed subjects using a visual oddball task, where pictures were presented randomly and the subjects should pay attention to a specific one, also found decreased amplitudes for P300 in depressed. In another posterior study, Liu et al. (2017) using a working memory task, where the subjects should remember faces presented in forward order or backward order, also find increased latency in P300 for depressed, but contrary to Mumtaz et al. (2016) they find increased amplitudes. Still using a memory related task, where subjects should actively remember or forget some images, Xie et al. (2018) find no difference in P300 nor N200 amplitudes for subjects with depressive tendencies and healthy controls.

Palmwood et al. (2017) conducted a study in 2017 where the subjects were prompted to stop a given action or not, generating two types of EEG recordings, successful stops (SSt) and unsuccessful stops (USSt) and find that only healthy control evidenced larger difference in P300 amplitudes when comparing SSt to USSt tasks, while participants with more depressive and reflective pondering symptoms show smaller difference, the authors find no difference for N200 amplitudes. Landes et al. (2018) conducted a monetary reward/punishment experiment in 2018, where the individuals had an anticipation delay before the reward (or punishment), they find that depressed show prolonged P300 latencies during anticipation also presented shorter P300 latencies after feedback in reward versus punishment condition, which was not found in controls.

Using LPP Burkhouse et al. (2017) notice that depressed adolescents show an enhanced LPP compared to healthy controls, the study conducted by Xie et al. (2018) next year also finds enhanced LPP in depressed related to negative words, although a study conducted by Grunnewald et al. in the same year (Grunewald et al., 2019) finds attenuated LPP in depressed children and adolescents.

Regarding N1, a study conducted by Ruohonen and Astikainen (2017) find differences in N1 for first-episode depressed versus

recurrent depressed or healthy controls, first-episode depressed show high amplitude in N1. Using P1 in a recent work conducted by Bedwell et al. (2018), the authors find that reduced P1 amplitude was associated with increased delusion severity. Using P200, Xie et al. (2018) find larger P200 amplitudes at frontal region in subjects with depressive tendencies when presented negative words.

Table 5
Summary of findings regarding evoked potential related features.

Article	Feature	Findings
Mumtaz et al. (2016)	P300	Using visual oddball task, find increased latency and decreased amplitude for P300 in depressed.
Liu et al. (2017)	P300	Using a memory task, find increased latency and amplitudes for P300 in depressed.
Xie et al. (2018)	P300, N200	Using memory task, no difference in P300 nor N200 between depressed or healthy controls.
Palmwood et al. (2017)	P300, N200	Using a prompt-to-stop task, healthy controls elicited greater difference in successful stops (SSt) compared to unsuccessful stops (USSt). No difference found regarding N200.
Landes et al. (2018)	P300	Using a monetary reward/punishment experiment, find that depressive had prolonged P300 latencies during anticipation and also presented shorter P300 latencies after feedback.
Burkhouse et al. (2017)	LPP	Enhanced LPP in depressive adolescents.
Xie et al. (2018)	LPP	Enhanced LPP related to negative words for depressive.
Grunewald et al. (2019)	LPP	Attenuated LPP in depressed children and adolescents.
Ruohonen and Astikainen (2017)	N1	High amplitude in N1 for first-episode depression compared to healthy controls and recurrent depressives.
Bedwell et al. (2018)	P100	Reduced P1 amplitude related to delusional severity.
Xie et al. (2018)	P200	Larger P200 amplitudes at frontal region in subjects with depressive tendencies when presented with negative words.

Table 6
Summary of findings regarding other biomarkers.

Article	Feature	Findings
Koo et al. (2018)	EEG vigilance	MDD spent less time in A2 and A3 (relaxed wakefulness) and more time at stages B2 and B3 (drowsiness).
Sander et al. (2018)	EEG vigilance	Higher vigilant states in depressed even after sleep deprivation.
Santangeli et al. (2017)	Slow wave in sleep	Lower slow wave (SW) amplitudes during sleep and slower rising of SW through the first NREM episode in depressed. Also a flatter dissipation of these waves in the frontal area of the brain.
Burkhouse et al. (2017)	Pupillary reaction	Using an emotional face presentation task, the authors find that current depressed adolescents had stronger pupillary reactions to every emotional face.

Evoked potentials seem to be a promising line of study for depression biomarkers, since they are related to event processing in the brain, one barrier to further agreement on these studies is that these potentials may have different interpretations depending on the task. Further investigation on evoked potentials may be necessary to achieve reliable biomarkers.

3.6. Other biomarkers

Researchers also explore more uncommon features, so this subsection discusses other possible biomarkers that could not be categorized in previous subsections, given that only one or two studies apply these features, we describe them alongside with the related works.

While the brain prepares to sleep there is a natural flow of activity, called EEG vigilance, that can be analyzed through alpha wave. It is an indicator of brain arousal and can be used to quantify subjective alertness during the resting state, ranging from high alertness, relaxed wakefulness, to drowsiness and sleep onset (Koo et al., 2018; Sander et al., 2018). Only two recent works present direct studies regarding EEG vigilance, for studies prior to 2014 we recommend (Olbrich and Arns, 2013). Koo et al. (2018) present that MDD spent less time in stages A2 and A3 (relaxed wakefulness) and more time at stages B2 and B3 (drowsiness) but Sander et al. (2018), on the same year, find higher vigilant states in depressed even after sleep deprivation, although they indicate that further study is needed and the results obtained may not be comparable with other studies.

Also regarding sleep, Santangeli et al. (2017) with a small sampled (10 healthy subjects, 9 depressed) sleep study, find that depressed adolescent boys had lower slow wave (theta and delta) amplitude and showed a slower rise of slow wave power in the course of the first Non-Rapid-Eye-Movement (NREM) episode, also presented a flatter dissipation through the night in the frontal area of the brain. The way slow wave amplitude dissipated was associated with severity of depressive symptoms, and the authors conclude that sleep regulation may be impaired in depression.

One work conducted by Burkhouse et al. (2017) using an emotional face presentation task, finds that current depressed adolescents had stronger pupillary reactions to every emotional face.

It is important to keep an open mind over which characteristics may be an indicative of depression, EEG vigilance is somewhat intuitive since depression is often related to sleep disturbances (Thase, 2006), but it is important to notice also selective memory (Xie et al., 2018), pupillary reactions (Burkhouse et al., 2017), self-consciousness (Fingelkurts and Fingelkurts, 2017) and other possible reactions that may help to better understand depression mechanisms.

3.7. Research questions

We hope that the previous sections have enlightened the reader about the many approaches literature present to better understand and obtain depression biomarkers, yet the two research questions that motivated this review need to be addressed:

- **Q1:** Is non-invasive EEG a reliable tool to detect depression?
  Non-invasive EEG is safe for use, since it requires no surgical procedure, it also has a great temporal resolution which has been used to classify depression correctly with great accuracy in many studies, e.g. Mahato and Paul (2019), Acharya et al. (2018), Mohammadi et al. (2015) and Hosseinifard et al. (2013), even using smaller EEG setups as Bachmann et al. (2017) and Shen et al. (2017). Classification will be further improved with the development of new ways to study the EEG signal, e.g. SASI in Hinrikus et al. (2009) and Bachmann et al. (2017), and a better understanding of depression mechanisms in the brain;
- **Q2:** What are the best biomarkers to detect and understand depression using only non-invasive EEG?
  For diagnostic purposes, there is evidence of the importance of gamma band (Fitzgerald and Watson, 2018; Bachmann et al., 2018), theta band seems promising (Hosseinifard et al., 2013; Shen et al.,

Table 7
Accepted articles ordered by year then alphabetically, the *Ref* column contains the reference index it may be marked (*) indicating that the article was manually added to our review. The table also presents the impact factor of the journal in the year of publication, obtained using SCImago (Scimago ranking, 2019).

Ref	Title	Year	Impact Factor
Grin-Yatsenko et al. (2010)*	Independent component approach to the analysis of EEG recordings at early stages of depressive disorders	2010	3.962
Hosseinifard et al. (2013)*	Classifying depression patients and normal subjects using machine learning techniques and nonlinear features from EEG signal	2013	2.510
Nusslock et al. (2015)*	Asymmetrical frontal cortical activity associated with differential risk for mood and anxiety disorder symptoms: An RDoC perspective	2015	3.431
Mohammadi et al. (2015)	Data mining EEG signals in depression for their diagnostic value. Clinical decision-making, knowledge support systems, and theory	2015	2.927
Mumtaz et al. (2015)	Detrended fluctuation analysis for major depressive disorder	2015	Conference
Kalev et al. (2015)	Lempel–Ziv and multiscale Lempel–Ziv complexity in depression	2015	Conference
Li et al. (2016)	An EEG-based study on coherence and brain networks in mild depression cognitive process BT	2016	Conference
Mumtaz et al. (2016)	P300 intensities and latencies for major depressive disorder detection	2016	Conference
Shen et al. (2017)	A novel depression detection method based on pervasive EEG and EEG splitting criterion	2017	Conference
Li et al. (2017)	Beta oscillations in major depression – Signalling a new cortical circuit for central executive function	2017	4.676
Ruohonen and Astikainen (2017)	Brain responses to sound intensity changes dissociate depressed participants and healthy controls	2017	3.237
Liu et al. (2017)	Deficient manipulation of working memory in remitted depressed individuals: Behavioral and electrophysiological evidence	2017	4.061
Palmwood et al. (2017)	Electrophysiological indicators of inhibitory control deficits in depression	2017	3.237
van der Vinne et al. (2017)	Frontal alpha asymmetry as a diagnostic marker in depression: Fact or fiction? A meta-analysis	2017	4.901
Burkhouse et al. (2017)	Increased neural and pupillary reactivity to emotional faces in adolescents with current and remitted major depressive disorder	2017	4.185
Hou et al. (2017)	Long-range temporal correlations of broadband EEG oscillations for depressed subjects following different hemispheric cerebral infarction	2017	2.270
Dolsen et al. (2017)	Neurophysiological correlates of suicidal ideation in major depressive disorder: Hyperarousal during sleep.	2017	4.184
Cai et al. (2017)	Pervasive EEG diagnosis of depression using Deep Belief Network with three-electrodes EEG collector	2017	Conference
Orgo et al. (2017)	Resting EEG functional connectivity and graph theoretical measures for discrimination of depression	2017	Conference
Bruder et al. (2017)	Right brain, left brain in depressive disorders: Clinical and theoretical implications of behavioral, electrophysiological and neuroimaging findings	2017	9.700
Bachmann et al. (2017)	Single channel EEG analysis for detection of depression	2017	3.728
Santangeli et al. (2017)	Sleep and slow-wave activity in depressed adolescent boys: A preliminary study	2017	3.947
Jesulola et al. (2017)	The effects of gender and depression severity on the association between alpha asymmetry and depression across four brain regions	2017	3.253
Fingelkurts and Fingelkurts (2017)	Three-dimensional components of selfhood in treatment-naive patients with major depressive disorder: A resting-state qEEG imaging study	2017	3.244
Shim et al. (2018)	Altered cortical functional network in major depressive disorder: A resting-state electroencephalogram study	2018	4.497
Guo et al. (2018)	Altered electroencephalography functional connectivity in depression during the emotional face-word Stroop task	2018	5.158
Landes et al. (2018)	Altered neural processing of reward and punishment in adolescents with Major Depressive Disorder	2018	4.334
Grunewald et al. (2019)	Attenuated LPP to emotional face stimuli associated with parent- and self-reported depression in children and adolescents	2018	4.008
Acharya et al. (2018)	Automated EEG-based screening of depression using deep convolutional neural network	2018	4.208
Sander et al. (2018)	Changes in brain arousal (EEG-vigilance) after therapeutic sleep deprivation in depressive patients and healthy controls	2018	4.419
Koo et al. (2018)	Combined cognitive, psychomotor and electrophysiological biomarkers in major depressive disorder	2018	3.164
Nusslock et al. (2018)	Comorbid anxiety moderates the relationship between depression history and prefrontal EEG asymmetry	2018	3.585
Nelson et al. (2018)	Depression symptom dimensions and asymmetrical frontal cortical activity while anticipating reward	2018	3.585
Fitzgerald and Watson (2018)	Gamma oscillations as a biomarker for major depression: An emerging topic	2018	5.704
Xie et al. (2018)	Individuals with depressive tendencies experience difficulty in forgetting negative material: Two mechanisms revealed by ERP data in the directed forgetting paradigm	2018	4.419
Smith et al. (2018)	Intracranial source activity (eLORETA) related to scalp-level asymmetry scores and depression status	2018	3.585
Bachmann et al. (2018)	Methods for classifying depression in single channel EEG using linear and nonlinear signal analysis.	2018	4.208
Lee et al. (2018)	Neurophysiological correlates of depressive symptoms in young adults: A quantitative EEG study	2018	1.753
Cerquera et al. (2018)	Nonlinear recurrent dynamics and long-term nonstationarities in EEG alpha cortical activity: Implications for choosing adequate segment length in nonlinear EEG analyses	2018	2.000
Liu et al. (2018)	Randomized EEG functional brain networks in major depressive disorders with greater resilience and lower rich-club coefficient	2018	4.031
Bedwell et al. (2018)	The P1 visual-evoked potential, red light, and transdiagnostic psychiatric symptoms	2018	3.198
Mahato and Paul (2019)	Electroencephalogram (EEG) signal analysis for diagnosis of major depressive disorder (MDD): A review	2019	Book

2017) and signal complexity measured by HFD provided reliable results (Mahato and Paul, 2019; Bachmann et al., 2018; Hosseinifard et al., 2013). In terms of neural structure of the brain, depressed brain appears to have a more random structure (Orgo et al., 2017; Shim et al., 2018; Liu et al., 2018), therefore connectivity measures are advised also. Alpha band seems to be useful for prognostic purposes (van der Vinne et al., 2017), detection of specific symptoms such as suicidal ideation (Dolsen et al., 2017) and to differentiate bipolar from monopolar depression (Nusslock et al., 2015), it is important to notice that anxiety may impact many findings using alpha asymmetry (Nusslock et al., 2018). For a better understanding of brain mechanisms, network features such as FC are useful since they may detect regional influences in brain structure, for instance (Fingelkurts and Fingelkurts, 2017) presents three areas of the brain which are related to rumination and tension.

3.8. Research barriers

Research presents many different features explored as depression biomarkers, some agreement exist, but some inconsistent results were found and need further investigation.

In agreement with Mahato and Paul (2019), we noticed that there are many inconsistencies in setup for the experiments, for instance, there are differences in alpha band choice, as in Cai et al. (2017) the authors consider alpha band as between 8 Hz and 15 Hz instead of the usual 8–12 Hz (Foster et al., 2017), which may lead to inconsistent

results specially in alpha asymmetry and functional connectivity studies. Moreover, studies differ in electrode positioning and reference; in Jesulola et al. (2017) the authors state that the use of Common Average Reference helps to reduce noise improving the quality of the signal, although many use mastoid as reference (Liu et al., 2017; Mohammadi et al., 2015). Yet another difference regards to the sampling rate of EEG acquisition, some studies use 250Hz (Xie et al., 2018; Shen et al., 2017; Grin-Yatsenko et al., 2010) and one which used 128 Hz (Dolsen et al., 2017), even though it seems not to be a problem given the scope of each work, the higher the sampling rate, the higher the resolution and signal features (e.g. dimension correlation) can be better calculated. Regarding band power, unless the authors want to study high frequency waves even a small sampling rate, such as 64 Hz, should be enough, since it can capture waves up to 32 Hz and there is evidence that the majority (98%) of the spectrum is in the range 0.5–30 Hz (Fingelkurts and Fingelkurts, 2015; Hosseinifard et al., 2013; Klimesch, 2012; Fingelkurts et al., 2006).

With respect to participants, studies differ in sample sizes, often with less than 20 subjects (total) (Acharya et al., 2018; Santangeli et al., 2017; Koo et al., 2018), there are many with more than 100 subjects, e.g. (Bedwell et al., 2018; Shen et al., 2017), and few present more than 200 subjects (Smith et al., 2018; van der Vinne et al., 2017; Grin-Yatsenko et al., 2010). Sample size is important to achieve statistical significance, for instance van der Vinne et al. (2017) suggest that at least 300 subjects are needed to have stable and biological plausible effect for frontal alpha asymmetry in depression; with that in mind many articles that we presented in alpha asymmetry could have sampling size too small to achieve statistical meaning.

Furthermore, subject characteristics differ among studies, some are applied to a certain age or gender; this matters because these affect the brain functionality and therefore may impact some biomarkers (Bruder et al., 2017), for instance Jesulola et al. (2017) found increased alpha activity in right hemisphere could only differentiate depressed and healthy female subjects, not males.

Beside the aforementioned, the studies differ when considering drug use (either medication or not) and diagnosis. In studies for treatment resistant depression or treatment prediction is natural to study medicated patients, although medication (and other drugs) affect the functionality of the brain and may affect the biomarkers, also medication may have unknown interactions among themselves changing even more the EEG signal. For diagnostic, different questionnaires are used (Gorka et al., 2017 presents a brief explanation of many questionnaires), each questionnaire focuses on some aspects, being the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association et al., 2013, 2000) the most common, followed by Beck Depression Inventory (BDI) (Beck et al., 1996). DSM even being quite complete, may not be up-to-date to diagnose disorders (Nusslock et al., 2015), the variety of questionnaires used make it difficult to compare the results among studies.

Lastly, there is a lack of explicit public datasets with EEG data from depressed individuals, for articles reviewed in this work only one explicitly said that the data is available for anyone who ask (Sander et al., 2018). Every new study may have to collect their own data, and surpass all difficulties simply to start the actual research.

We suggest that, if aligned to the study, future works should use the Common Average Reference (Jesulola et al., 2017) and one of the international electrode positioning systems, even for pervasive studies; also use the standard band definitions and higher sample rates. For the subjects, include many unmedicated subjects with varying ages, gender and also with little or well defined comorbidity, or conduct specific research to check the impact of these variables. Regarding psychological questionnaires, apply as many as possible in such way to, not only have more information about possible comorbidity and better description of the patient state of mind, but also making it easier to compare with other studies. And lastly, make the dataset available for the community. We understand that in many cases it is not possible to achieve that, specially because of patient's privacy, but we suggest to keep in mind this setup. Similar setups make studies comparable helping to isolate variables in further studies.

4. Conclusion

This work is a report of a systematic mapping regarding EEG depression biomarkers and presented many recent studies, with a brief explanation and comparison for each of them also discussing the state-of-the-art achievements, difficulties and suggesting ways to contour some barriers and further develop this subject research. We categorized potential biomarkers in 6 categories and concluded:

- **Band Power:** gamma and theta band have good diagnostic capabilities (Fitzgerald and Watson, 2018; Liu et al., 2017; Mohammadi et al., 2015), other bands may be useful for diagnostic using classifiers (Acharya et al., 2018; Hosseinifard et al., 2013);
- **Alpha Asymmetry:** has little diagnostic capabilities (van der Vinne et al., 2017) and is susceptible to anxiety (Nusslock et al., 2018), although it seems to predict specific symptoms (Nelson et al., 2018; Nusslock et al., 2015), specially those related to mood swings, since alpha asymmetry is related to the approach-withdraw model (Coan and Allen, 2004; Davidson, 1995);
- **Signal Based Features:** the fractal dimension of EEG signal, measured by Higuchi's fractal dimension, seems to be greater in depressed patients (Bachmann et al., 2018; Mahato and Paul, 2019). The use of correlation dimension provided good accuracy in depression diagnostic, but no direct information about the value of CD was provided (Cai et al., 2017; Hosseinifard et al., 2013);
- **Network Based Features:** depressed brains seem to have a more random networks (Orgo et al., 2017; Shim et al., 2018; Liu et al., 2018), although specific features such as cluster coefficient and path length provide conflicting values for depressed;
- **Evoked Potentials:** usually the specific potential to be analyzed depends on the context, but they appear to be more useful when related to specific symptoms, such as memory alterations (Liu et al., 2017; Xie et al., 2018), emotional processing (Xie et al., 2018; Landes et al., 2018) or delusional thinking (Bedwell et al., 2018);
- **Other Biomarkers:** specially regarding EEG vigilance, studies have found that depressed tend to have sleep disturbances (Santangeli et al., 2017; Koo et al., 2018; Sander et al., 2018). Another work concluded that depressed adolescents had stronger pupillary reaction to emotional faces (Burkhouse et al., 2017);

Some features are subject to noise and provide different values in different similar experiments, since depression present high comorbidity with other neurological disorders, specially anxiety, we found that it is important not only to study depression as a single package, but also each one of its characteristics (Insel, 2014; Insel et al., 2010).

This work has some limitations, the review process was conducted by only one person, impacting on the time to finish and report it, therefore only works up to November 2018 were found, also it impacted on internal validity, as subjective choices may have impacted on the review process, in order to alleviate it, we reduced the scope of the mapping only for the most recent years and carefully took notes using Mendeley (Mendeley, 2019) and Parsifal (Parsifal systematic review tool, 2019). Furthermore, articles that compare only treatment response were rejected by our selection criteria, but may be useful for a better understanding of depression biomarkers and should be studied in further reviews.

Conflict of interest

The authors declare no conflict of interest. The funding agencies had no impact on the methodology or the report of the conducted research.

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