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Biological markers in non-invasive brain stimulation trials in major depressive disorder: a systematic review

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Abstract

Objectives—The therapeutic effects of Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) in patients with major depression have shown promising results; however, there is a lack of mechanistic studies using biological markers (BM) as an outcome. Therefore, our aim was to review non-invasive brain stimulation trials in depression using BM.

Method—The following databases were used for our systematic review: MEDLINE, Web of Science, Cochrane, and SCIELO. We examined articles published before November 2012 that used TMS and tDCS as an intervention for depression and had BM as an outcome measure. The search was limited to human studies written in English.

Results—Of 1234 potential articles, 52 papers were included. Only studies using TMS were found. BM included immune and endocrine serum markers, neuroimaging techniques and electrophysiological outcomes. In 12 articles (21.4%) endpoint BM measurements were not significantly associated with clinical outcomes. All studies reached significant results in the main clinical rating scales. BM outcomes were used as predictors of response, to understand mechanisms of TMS, and as a surrogate of safety.

Conclusions—fMRI, SPECT, PET, MRS, cortical excitability and BDNF consistently showed positive results. BDNF was the best predictor of patients' likeliness to respond. These initial results are promising; however, all studies investigating BM are small, used heterogeneous

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samples, and did not take into account confounders such as age, gender or family history. Based on our findings we recommend further studies to validate BM in non-invasive brain stimulation trials in MDD.

Keywords

transcranial magnetic stimulation; biological markers; neuroimaging; BDNF and EEG

Introduction

Major Depressive Disorder (MDD) is a common condition that is widespread in the population. Community-based surveys conducted in several countries using ICD-10 criteria have shown a lifetime prevalence of MDD ranging from 6–12%, with an annual prevalence of 3–11% [1–4]. MDD is a chronic, recurrent disorder, with nearly 80% of patients relapsing after the treatment of an episode [5]. Finally, about one third of patients have treatment-resistant depression (TRD), which is defined as the failure to achieve adequate response of symptoms after two or more antidepressant treatment trials [6–7]. In fact, the high prevalence of TRD associated with failure to respond to antidepressants is an important concern when managing major depression.

During the last decades the understanding of the pathophysiological mechanisms of different psychiatric disorders has increased dramatically. Consequently, there have been gains in available pharmacological, psychological and physical treatments [8–10]. In this context, non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), have received special attention as potential clinical tools [11–12]. Repetitive TMS (rTMS) is a commonly used type of TMS that consists of using varying magnetic fields to induce cortical electric currents to a specific brain area in order to modulate cortical excitability [12]. On the other hand, tDCS is the application of a weak constant electrical current through the skull and into cortical areas via cranial (and also extracephalic) electrodes [12]. The aim in both types of stimulation is to induce therapeutic neuroplasticity through the application of electrical currents in the brain.

Past studies have revealed encouraging results for the therapeutic use of these techniques in the mental health field; however, results are still mixed despite many positive clinical outcomes [11–12]. One reason for the lack of more robust results is the variety of stimulation parameters being applied since there is still no consensus on the optimal parameters of stimulation. One possible resolution to this issue is the use of biological markers (BM) as a guide to stimulation parameters. In addition to shedding light on the mechanisms of action, BM are useful in psychiatry as they provide an objective marker, therefore providing a more reliable (uniform) evaluation of biological state [13–14].

BM are defined as biochemical, physiological or anatomical traits that are specific to particular conditions. An important aim of BM discovery is the detection of disease correlates that can be used as diagnostic tools. Ideally, BM should have predictive power, should be available during routine assays, and allow the identification of individuals at risk. Furthermore, useful markers should allow the monitoring of progress of not only the disease, but also its treatment. In the field of psychiatry, they are of great interest because they can

aid researchers in understanding the cause of diseases like depression, or schizophrenia and can also serve as surrogate outcomes to measure the efficacy of treatments [15]. Serum levels of several hormones, functional magnetic resonance image (fMRI), single photon emission computed tomography (SPECT), positron emission tomography (PET) and electroencephalography (EEG) are some of the techniques that have been used in psychiatric trials to measure biological markers [13–14].

Due to the importance of BM and surrogate outcomes to provide more information, guide treatment and provide a deeper understanding for neurophysiologic mechanisms of non-invasive brain stimulation techniques, we aimed to review the TMS and tDCS trials in MDD using BM as outcomes. Our main goal was to review the most commonly utilized BM to provide insights for future research.

Methods

We screened all articles that used TMS and tDCS as an intervention for MDD. We searched for all articles published before November 2012 using the following databases: MEDLINE, Web of Science, Cochrane, and SCIELO. We also examined reference lists in systematic reviews and retrieved papers that seemed to fulfill our criteria.

Our search strategy included (*transcranial magnetic stimulation* OR transcranial *direct current stimulation*) AND (*depressive disorder*). The reviewed studies are shown in Table 1.

Search criteria

The following inclusion criteria were adopted: (i) manuscript written in English; (ii) studies using TMS or tDCS as a intervention, including clinical trials and case reports, for major depressive disorder (iii) studies using any biological marker as an outcome (main or secondary outcome); (iv) studies conducted in humans; (v) studies published before November 2012.

Positive vs. negative finding

In our research, we define positive findings when there was a significant clinical improvement. On the other hand, negative findings are the clinical results that were not significant.

Data extraction

Data were extracted independently by the authors (GM, TMF, MEM, MVBS, and NMC) using a structured form. The following variables were extracted: 1) author and year of publication; 2) number of patients studied in the paper; 3) parameters of stimulation (i.e., frequency, intensity, duration and number of sessions); 4) study design; 5) main findings; 6) conclusion. The discrepancies were resolved by consensus, and the corresponding author (FF) was consulted when needed.

Data analysis

We described results qualitatively as there was no quantitative information to perform a meta-analysis.

Results

Overview

We found 1234 references in our preliminary search. We initially selected papers that used TMS or tDCS as an intervention for MDD. Out of those, 1008 papers were excluded in the first analysis and 239 articles were further reviewed. Out of the 235 remaining articles, 52 papers met our inclusion criteria and data was extracted from all of them. All articles were published between 1999 and 2012 and all used rTMS.

The parameters used most frequently were: ten daily sessions of brain stimulation (20 articles – 38.5%) at 100% of the motor evoked potential (MEP) (17 articles – 32.7%) with frequency of 10 Hz (10 articles – 19.2%). Interestingly, most did not use a sham group, which was present in only 17 of the articles (32.7%). Cross over (9 articles – 17.3%), randomized clinical trials (16 articles – 30.1%) and open-label trials (22 articles – 42.3%) were the most common experimental designs used and within these trials, most had small sample sizes (the highest sample size was n=90).

With the exception of three articles, the biological marker was the main outcome studied. In all of the articles, the biological markers were assessed along with other clinical outcomes, such as the Hamilton Depression Rating Scale (HDRS) and the Montgomery-Asberg Depression Rating Scale (MADRS).

In 16 of the reviewed articles (30.8%), there was no significant correlation between BM and clinical outcomes; however, in some of the articles such as the one by Szuba et al. there was a significant difference between the biological markers' assessment before and after brain stimulation. Interestingly, all papers reached positive findings in the main clinical rating scales; however, a placebo effect is possible since many of these studies did not have a control-sham group.

Biological Markers

We grouped the biological markers into the following categories: neuroimaging, electrophysiological and neuroimmunoendocrine studies. Advantages and disadvantages of the selected biological markers are summarized in Table 2 [16–17].

1. Neuroimaging studies—Neuroimaging was the most commonly used biological marker and was used in 27 out of the 52 reviewed articles (51.9%). Functional magnetic resonance imaging (fMRI), Single-photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance spectroscopy (MRS) and near infrared spectroscopy (NIRS) were among the available neuroimaging modalities and are discussed below.

A. fMRI: fMRI is a tool that detects regional blood flow in cerebral areas [18]. It analyzes variations in signal intensity from hemoglobin according to the blood oxygenation level dependence (BOLD effect). Additionally, when combined with TMS, fMRI allows for the mapping of corticocortical and corticosubcortical connectivity in brain. Despite the fact that combining TMS and fMRI can be technically challenging (due to magnetic interference of TMS and fMRI scanner), it is valuable in that fMRI has good time and spatial resolution, and can be repeated without limitation because it does not expose subjects to radioactive tracers, among other advantages [19]. In our review we found 5 fMRI studies [20–24].

fMRI studies have shown activity changes in the site of stimulation as well as in distant areas. In fact, the main use of fMRI data is to detect the neural network associated with TMS effects. For instance, in a study using fMRI as its biological marker, Fitzgerald et al. [24], found that the antidepressant effects of TMS are related to a bilateral reduction in task-related prefrontal cortex activation. In this case, the subject's task was to silently articulate words beginning with a standard letter that were presented to him or her. In this context, the task-related deactivation changes observed in the study may represent an optimization of the executive network for planning and reasoning supported by rTMS applications, assuming a pattern of over-activation when performing cognitive process when compared to baseline. The researchers also found that TMS produces a reduction in bilateral prefrontal cortex activation. Another study by Li et al. found that TMS was associated with an increase in blood flow at the site of stimulation and in connected limbic regions in a sample of 14 depressed patients. Significant deactivation was found in the right ventromedial frontal cortex. However, due to the small sample size, the different medications and different dosage, these results cannot be generalized [21]. Functional MRI and PET have shown how depressive behavior can be correlated with hypermetabolism of the subgenual cingulate cortex and amygdala [94] as well as hypometabolism of the dorsal PFC and striatal regions [93], based on this imaging studies a "depressive circuit" can be drawn having the amygdala as disinhibited structure due to lesion-like effects at the striatum, PFC, and orbital PFC. It might be possible for rTMS to exert its modulatory influence via white matter tracts, thus being able to regulate the fMRI/PET responses at these structural levels.

B. PET and SPECT: PET and SPECT are two emission tomography techniques that allow for real-time viewing of brain functioning through the detection of gamma rays [18, 25]. This information is then used to reconstruct a tridimensional image of active brain areas. Although it maps more limited brain areas, SPECT presents gamma rays with longer half-lives and does not require a cyclotron for image generation as does PET. Thus, it is less expensive and more easily obtained. Moreover, the longer half-lives make it possible for researchers to observe biological processes *in vivo* for several hours or days after the administration of the compound [18, 25]. In our review we found 2 studies that used PET, 6 studies that used SPECT, and 1 study that used both PET and SPECT [26–34].

Similar to fMRI, PET studies also found clinically related changes in cerebral blood flow in the stimulated area or related areas, such as the cingulate cortex. Kito et al. 2008 [26–27] studying 14 treatment resistant patients, found a significant increase in cerebral blood flow in the left dorsolateral prefrontal cortex, according to their SPECT images after TMS stimulation. This increase also correlated to an increase in subgenual cingulated and the

limbic-paralimbic regions. These alterations were clearly correlated with a decrease in HDRS. In a PET study, Baeken et al. [33], found that a higher baseline brain glucose metabolism of the anterior cingulate cortex was a marker of a positive intervention response. In this study, 21 treatment-resistant depressed patients were included. Small sample size and the absence of a sham groups are the two main limitations of these and most of the other PET and SPECT studies included.

Although imaging studies are demonstrating promising evidence for the understanding of MDD, the above mentioned techniques relay in regional changes of cerebral blood flow (CBF) and glucose metabolism. Consequently, we can assume these dynamic alterations are the result of activity-dependent terminal field synaptic transmission. If the network activity is increased, then augmented neurotransmission via afferent pathways originating at the observed structure or distally interconnected circuits will demand an elevation of metabolic consumption and increases in CBF. Imaging studies have demonstrated that this pattern of changes can be modulated by either rTMS or tDCS, nevertheless, studies using fMRI, PET, or SPECT still lacking the effect size needed in order to reach the desired sensitivity or specificity. Temporal and spatial resolution are unique characteristics of functional imaging studies, in order to reliably determine the functional area, a high signal-to-noise ratio is critical to map accurately those foci being imaged for functional assessment. Therefore, it is important to understand how specific those areas really are for MDD involvement. Using traditional BOLD methodology for resolution, increases in neural activity will induce increases in tissue metabolic demand and this will yield to a certain spatial specificity for metabolic changes. However, those changes also will affect and modulate hemodynamic responses, including; CBF, cerebral blood volume (CBV), and venous oxygenation levels, thus, the assessment of these parameters will enhance dramatically the specificity and sensitivity for structure-related pathology. The advancement and refinements of such techniques will permit the development of receptor binding neurotransmitter for PET utilization or high-resolution CBF and discriminatory hemodynamic assessment, which in turn, might allow better imagining resolution in real time and to identify the mechanistic properties of the MDD involved structures, also by getting a better categorization of these changes; fMRI, PET, and SPECT will become specific and sensitive enough to consider them as reliable BM.

C. MRS: Another brain imaging technique, magnetic resonance spectroscopy (MRS) allows a through view of brain chemical activity [35–36]. Using spectroscopic analysis, specific brain metabolites such as GABA and glutamate, can be investigated by examining the area under each peak produced [19, 36]. When MRS is combined with TMS it is also possible to examine the underlying mechanisms of long-term changes in brain excitability and to investigate the metabolic and neurotransmitter effects of rTMS and tDCS, directly and non-invasively [16, 19]. In our review we found 1 MRS study [37].

Because MRS provides levels of neurochemical metabolites, it provides valuable information also on baseline states. In fact, Luborzewski et al. used MRS to assess glutamate concentration on the DLPFC of the patients before and after rTMS. According to their findings, 6 out of 17 patients responded to the treatment and, in those, the baseline

concentrations were lower than non-responder. After treatment, these concentrations were elevated in responders and decreased in non-responders.

However one main limitation of MRS is that the location of stimulation needs to be determined a priori [37].

It is important to notice that in this study the above mentioned changes happened in cases of unipolar depression where most studies have reported decreased glutamate levels, while subjects with bipolar depression have shown elevated glutamate/glutamine levels, thus, the abnormalities reported in unipolar and bipolar seemed to have an opposite hypo/hyper directionality, although there are no MRS studies reporting metabolite changes in bipolar or unipolar depression using tDCS, it would be attractive to evaluate if polarity-dependent tDCS modulation is able to modify neurochemical signaling in MRS as TMS already showed. In the case of MDD, the choline (Cho) peak has been considered a BM for alterations of signal transduction at the membrane metabolic level [98], nevertheless, inconsistent results among studies still being the main obstacle to consider this metabolite as a good neurochemical marker for TMS or tDCS effects in neural tissue. A comprehensive MSR assessment must be performed when estimating BM for MDD and noninvasive brain stimulation, these should include a varied range of neurochemicals, such as; N-Acetyl Aspartate (NAA), Myoinositol, Glutamate and N-methyl-d-aspartate (NMDA), glutamate and glutamine, choline, and GABA.

D. NIRS: NIRS is a neuroimaging technique that allows for the visualization of hemodynamics in the brain. One study by Eschweiler et al. examined such changes within the brain pre and post rTMS. After two 5-day periods of stimulation Eschweiler and his team observed significant decreases (−5.4 average points on the HDRS) in feelings of depression in his patients and an absence of task-related increase in hemoglobin concentration at the immediate site of stimulation, but not in other brain areas [38]. NIRS technology uses the BOLD signal principle to measure changes in deoxyhemoglobin.

A wide variety of both commercial and custom-built NIRS instruments are currently in use. Three distinct types of NIRS implementation have been developed for functional assessment: time-resolved systems, frequency-domain systems, and continuous wave spectroscopy systems, each with its own strengths and limitations. Time-resolved and frequency-domain systems provide information on shifts in both phase and amplitude of the light and are necessary for more precise quantification of functional signals. Continuous wave systems apply either continuous or a slow-pulsed light to tissue and measures the attenuation of amplitude of the incident light (Bunce, 2006). Thus, for better characterization of cortical activity response to TMS or tDCS, a frequency domain system will be preferable due to its specificity for superior parameter assessment and the possibility to reduce physiological noise in response to the stimulation by itself, also, absolute physiological measurements will provide better information than just relative measurements.

Functional Near-Infrared Spectroscopy (fNIRS) relies on this optical technique to detect changes in the hemodynamic response within the cortex when sensory, motor, or cognitive

activation occurs. Following this principle fNIRS may be particularly applicable to some of the unique research problems associated with neuropsychiatric disorders.

2. Electrophysiological studies—Another method to detect brain activity directly is using electrophysiological methods that have an important advantage of measuring electrical activity directly and thus a better temporal resolution; however the spatial resolution is usually more limited than that of neuroimaging methods. A total of 9 articles among the 36 reviewed (25%) used electrophysiological outcomes such as EEG and TMS-indexed cortical excitability, and saccadic eye movements.

A. EEG: Electrophysiological tools such as EEG are also used as biological markers [39]. Electroencephalography is a graphic representation of the difference in voltage between two distinct brain points. Most of the electrical activity measured is generated in the cortex and is captured by volume conduction after overcoming the resistance of the skull and of the scalp [40–42]. Several attempts were made to identify surrogate patterns of EEG to some psychiatric disorders, without success [41]. In addition, the search for a surrogate pattern remains, trying to correlate EEG alterations with fMRI or PET/SPECT findings. In our review we found 4 studies using EEG [43–46].

EEG studies add important information to TMS applications. Due to the detailed information that EEG provides on cortical brain oscillations that is different than fMRI, which only detects a change as compared to a previous time point, EEG has been used also to predict patients who may be responders to TMS treatment. Narushima et al. [45], using a LORETA technique, identified that increased low-theta power in the subgenual anterior cingulated cortex was associated with antidepressant response, suggesting that EEG could be used as a predictor for antidepressant response to rTMS among patients with treatment-resistant vascular depression. Arns et al. also stated a marker of positive response to TMS application by using EEG. The author declared that a high individual alpha peak function acted as a predictor of response. This seems to be a promising application for EEG to be used to identify surrogates of intervention response [43]. Micolaud-Franchi [100] also reported changes in the parieto-temporal alpha power as predictor of TMS response; however, to reliable use EEG parameters as predictors of treatment, a large database is needed to recognized phenotypic EEG features as BM of TMS or tDCS response. On the other hand, Price et al. also explored EEG as a correlate of clinical changes in rTMS treatment of depression and also found no significant difference between patients suffering from depression and normal and clinical control groups. Price et al. suggest that although they did not find a significance in this study, several other findings provide support to continue research on this topic [44].

EEG recordings have been long considered, as the activity generated at thalamic level, thus, the conceptualization of the so called thalamocortical circuits are the foundation for the analysis of healthy and disease EEG patterns, this establishment may not be sensitive enough to accept specific EEG characteristics as BM in MDD, since the neuromodulatory effects promoted by noninvasive stimulation act at a network level that includes extra thalamic and cortical structures, though, new research is focusing in the presence and influence of localized rhythms at cortical, thalamic, and extra thalamic areas, to understand

the role of the intrinsic oscillatory properties that any given network can generate, rather than just the spectral analysis of specific frequencies. This is mainly due to the fact that a certain frequency band may ambiguously reflect various conditions or phenomena originating at different locations of the brain. The understanding of these properties will provide a functional meaning for the oscillatory network activity that can be then used as BM during TMS and tDCS applications, therefore spatial characteristics can be distinguished from just frequency aspects of the EEG recordings. In the particular case of TMS an initial disruption of the ongoing network activity will be seen immediately under the coil area and interconnected systems as well, thus, spatio-temporal changes generated by the evoked TMS stimuli can be detected and measured by EEG network oscillations models, as a result of this, oscillatory network patterns can be described as possible neurophysiological BM, although, specificity may be a problem due to “multi-connectivity” epiphenomena or the so called “noise to signal” dilemma, on the other hand, the development of better modeling methods, including those for source localization and the fact that TMS will generate an immediate measurable electrophysiological response, may be the answer for the use of EEG-based BM approach. As for the case of tDCS, spectral analysis of frequency bands can be a more suitable method for BM development, especially when applying quantitative methodology for full EEG analysis (qEEG) since tDCS effects on the EEG recording are not going to be immediately measurable, mathematical signal characterization coupled with cognitive task could be used for measurements of coherence and synchronization network activity, by taking advantage of the relationship between cognitive processing and network modulation by tDCS, electrographic changes can be measured with a better specificity and sensitivity since network connectivity and oscillations can be either facilitated in the case of anodal or inhibited if cathodal stimulation is being applied.

On the other hand, EEG can also be used as a surrogate for safety. The study by Berman et al. applied rTMS while using EEG at baseline, pre-treatment and post-treatment [46]. The authors found no differences between different EEG measures, which according to the authors suggest that rTMS under the parameters used is a safe technique. Advances in the use of ongoing EEG recording while stimulation and cognitive tasks are applied in real time, can be facilitated by using the methods and technology described by Schestatsky et al, allowing the continuous assessment of raw signal, and frequency spectrogram analysis as well.

B. TMS-indexed cortical excitability: Cortical excitability is an individual measure related to the responsiveness of the brain to a stimulus [47]. This technique uses a TMS approach to measure cortical excitability by assessing the integrity of central motor pathways [11–12]. Those magnetic pulses induce a secondary electric current in the brain that causes cell depolarization. Single pulse TMS is used to measure motor threshold and motor evoked potentials [11–12, 47], whereas the paired-pulse technique assesses intracortical inhibition or facilitation, possibly indexing gabaergic and glutamatergic activity, respectively [48]. In our review we found 4 studies using cortical excitability [48–51].

One important limitation of TMS studies in depression is that it can only measure excitability of motor and visual cortex; therefore the information is somewhat limited.

However, because TMS has good temporal resolution, it may be an important marker especially to assess interhemispheric differences. In fact, Maeda et al. showed that patients with major depression presented interhemispheric differences in motor threshold with lower excitability in the left side [51]. This can be related to a change in the balance of neurotransmitters on left hemisphere of the brain [48, 51]. With the same objective, Bajwa et al. found that patients with major depression have an imbalance in the right and left prefrontal and motor cortex measured with MEP after the use of rTMS (1Hz). These differences are related to slow interhemispheric switching mechanisms. Also this difference was associated with patients with a higher level of disease severity [48]. Other studies have also shown that high frequency rTMS can alter the amplitude of MEP's, which was also related with improvement of depressive symptoms [5, 49–50]. These studies help at some extent for better understanding of the mechanisms related to theses diseases and also forms of treatment used for depression, correlating neurophysiologic and clinical data.

C. Saccadic eye movement: Saccadic eye movements are the rapid movements of both eyes, which are largely controlled by the prefrontal cortex in the brain [52]. Saccades can be measured through the use of visual targets in guided reflexive tasks, prosaccade tasks, and antisaccade tasks. In guided reflexive tasks, subjects are required to look toward peripheral targets that appear randomly in the left and right visual field. Prosaccade tasks present the subject with two targets (one to the right and the other to the left), an arrow that switched direction unpredictably pointed to which target the subject should be looking toward. Finally, antisaccade tasks require the subject to look opposite of the randomly presented target [52–53]. In our review we found 1 study using saccadic eye movements [52].

As aforementioned, saccadic eye movements would provide an indirect measurement of prefrontal activity and therefore another useful neurophysiological index of TMS effects especially when applied to prefrontal cortex as usually done in depression. Crevits et al. used the three saccade measurement techniques described above to examine the before and after effects of rTMS on saccadic eye movement in patients with depression [52]. In this study, it was found that the use of rTMS over the left DLPFC did not significantly influence reflexive or prosaccade movements. On the other hand, the study did show that rTMS had a shortening effect on the latency of antisaccade movement, suggesting that rTMS may affect certain aspects of saccade movement in patients with depression. Because this was only a pilot study using a small sample population of 11 subjects, the results must be interpreted with discretion.

3. Neuroimmunoendocrine studies—In our review, 11 articles measured neuroimmunoendocrine factors, such as serum cortisol, serum thyroid hormones (thyroid-stimulating hormone or thyroxine), BDNF (brain derived neurotrophic factor), homovanillic acid, interleukins and sexual hormones such as luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, progesterone and dehydroepiandrosterone (DHEA).

A. Serum cortisol: Reid et al. measured cortisol level using the dexamethasone suppression test (DST) before and after rTMS [54]. In this setting, the author found out that rTMS was capable of changing DST status from positive to negative, showing a link between serum

cortisol levels and depression. However, since this is a case report, these findings should be interpreted with caution.

In light of the previous study, Zwanzger et al. performed a clinical trial similar to Pridmore 1999, where drug-free patients with treatment resistant depression where evaluated by the combined dexamethasone corticotrophin releasing hormone test (DEX/CRH test) before and after 13 daily sessions of rTMS [6, 55]. There was a significant time vs. group effect for basal cortisol levels, but not for basal ACTH levels, and a significant positive correlation between the reduction of HDRS scores after rTMS and the reduction of post-dexamethasone basal cortisol levels. However, there was no significant difference in stimulation patterns of cortisol and ACTH after CRH challenge between responders and non-responders before and after rTMS treatment. Moreover, the CRH-induced ACTH and cortisol increase did not change significantly after rTMS, even in patients showing a remission of depressive symptoms. These results indicate that the Hypothalamic-pituitary-adrenocortical system remains overactive after rTMS treatment, and thus, there may be a high risk for relapse of depressive symptoms in responders to rTMS [56]. In this context, serum cortisol may identify patients who may respond to rTMS treatment and may also be useful to identify risk of relapse.

B. BDNF: Brain-derived neurotrophic factor (BDNF) is a neurotrophin related to neuronal survival, synaptic signaling and synaptic consolidation [57]. It has been associated with several disorders, such as substance-related disorders, eating disorders, mood disorders, schizophrenia, pain modulation and epilepsy [15, 56, 58] as it may provide a general index of neuroplasticity. Given the effects of rTMS on neuroplasticity, this biomarker has been investigated; however, it has important limitations such as lack of spatial resolution – in other words, if there is a change in BDNF it is not possible to determine where these changes were originated.

BNDF has also been studied as a main marker to identify responders to rTMS treatment. Two studies included BDNF as a BM [59–60]. In article by Zanardini et al. the authors assessed BDNF serum levels with ELISA in 16 patients with treatment resistant depression before and after rTMS. The study revealed a negative correlation between BDNF serum levels and the severity of the disease as assessed by the HDRS. In addition, they also showed that by using TMS they where able to raise BDNF levels, suggesting a normalizing effect of the rTMS antidepressant treatment. These promising results should be considered with caution, since the sample size in this study is small [60]. However, these are important findings that strengthen the link between BDNF and depression. Experimental increases of hippocampal BDNF levels produced antidepressant-like effects in behavioral models of depression [97], while an impairment of BDNF signaling produces certain depression-related behaviors and impairs the action of antidepressants [96], in this context BDNF can be consider an ideal BM for stress related behaviors, cognitive impairments, and promotion of synaptic plasticity within MDD. The increments in the expression of BDNF by rTMS may provide therapeutic neuroprotection against chronic stress in patients with MDD, and facilitate plastic changes aimed to modify the occurrence of “depressive circuitry” Thus, it may be possible for rTMS to induced BDNF expression and possibly reverse some of the neural atrophic changes observed in postmortem studies [92]. Direct current stimulation

(DCS) in the rat model has demonstrated modulatory effects on BDNF by increasing its secretion and promoting dependent synaptic plasticity that can be observed in the primary motor cortex and hippocampus as well, although no studies have reported these findings in the DCS depressed animal model yet, it can be reasonable to speculate that tDCS may have also BDNF modulatory effects when applied in subjects with MDD, though, more experimental research needs to be performed before we can accept this statement.

In another article by Yukimasa et al. BDNF levels where assessed along with catecholamines 3-methoxy-4-hydroxyphenylglycol (MHPG) and homovanillic acid (HVA) in 26 treatment resistant patients. Again, these results suggest that rTMS treatment brings about some improvement in refractory depression, especially for symptoms such as agitation, by influencing MHPG and BDNF. These results are in accordance with previous reports showing that BDNF was increased by various antidepressants treatments. However, this study also has a small sample size, did not use a control group, and the patients where on antidepressants, which are factors that may cloud the effects of TMS [59].

BDNF normalization by rTMS applications may represents itself as optimal electro-chemical treatment, and a marker of clinical improvement for the depressive disorders, it is important to recognize how the electric stimulation generated by a train of magnetic fields is capable to induce changes of endogenous trophic factors. This transition from externally induced physical forces to endogenous modulated biochemical processes, exemplifies the importance of noninvasive stimulation as an adjunctive technique for the management of MDD. To better understand these BDNF findings and to make relevant clinical correlations with the reported rTMS beneficial effects, more research must be done, especially when BDNF physiological variability is considered and rTMS parameters still not completely standardized.

C. Serum thyroid hormones: Serum thyroid hormones may also be a useful biomarker as the hypothalamus-pituitary-thyroid (HPT) system has also been shown to be dysfunctional in major depression and that antidepressant treatment may revert some of this dysfunctional state [61].

Although there is a rationale for using thyroid hormones as biomarkers, results in rTMS trials are mixed. In a clinical trial by Kito et al. 2010, the serum levels of TSH, fT3 and fT4 of treatment-resistant patients where evaluated before and after rTMS. Clinical improvements were observed as assessed by HDRS. The serum levels of fT3, and fT4 showed no significant differences between the responders and non-responders; however, TSH levels in pre-treatment responders were significantly lower compared with TSH levels in non-responders. TSH showed a significant therapeutic efficacy-by-time interaction. Responders and non-responders were analyzed separately and the outcomes showed a significant decrease in TSH levels for responders. In addition, the results revealed that TSH levels of responders rose significantly and that TSH levels of non-responders tended to decrease following TMS treatment sessions [62].

Conversely, Szuba et al. found no significant difference between mood and TSH. While both mood (measured by HDRS) and TSH levels (measured by radioimmunoassay)

increased after active TMS, no cause and effect relationship between the two could be demonstrated. Possible reasons for the lack of correlation are the small sample size, late timing of the blood draw leading to less than peak TSH level achieved, or it may also be that mood and TSH levels are unrelated, as no correlation was found in a similar study in healthy subjects [63–64].

D. Dopamine and Serotonin: Dopamine and Serotonin are two important neurotransmitters that play a role in mood control. Dopamine acts on the mesolimbic and mesocortical circuits in the brain and is responsible for the experience of pleasurable feelings [65–67]. The 5-HT systems of Serotonin extend throughout the brain and are thought to be involved in many functions such as mood, aggression, feeding and sleep. Disturbances in the Serotonin pathways have been linked to impulsivity, depression, and in some cases, suicide [68]. For these reasons, antidepressant medications seek to regulate these two neurotransmitters by inhibiting reuptake to increase their extracellular levels. While antidepressants work for some, treatment resistant depression is common (35–40%), thus the possible role of non-invasive brain stimulation in these patients [66, 69].

Although neurotransmitter levels may be a very useful biomarker, the main limitation is that these neurotransmitters are measured in the plasma, thus correlation with brain levels may be decreased. In fact, a study examining TMS in drug-resistant MDD patients by Miniussi et al. revealed that despite seeing a clinical response after active treatment, no clear relationship could be established between clinical response and biochemical outcomes of dopamine and serotonin. Despite this, the authors suggest that there is still a possibility that the observed improvement is partially attributed to the effects of TMS on the dopaminergic system due to the significant correlation found between pre and post-TMS HVA levels as HVA is dopamine's main metabolite. Some limitations to the study that may have negatively impacted significance between clinical response and biochemical response were the small sample size, a non-TMS control group, and the short duration of treatment, which lasted 5 days [17, 66].

E. Other Neuroimmunoendocrine Markers: Other neuroimmunoendocrine markers such as LH, FSH, estradiol, progesterone and DHEA have been tested. These studies show positive clinical outcomes, but vary in their finding of significant marker differences before and after rTMS. For example, a study by Padberg et al. revealed that patients' depression decreased by about 40% post-rTMS, though they observed no change in progesterone and DHEA levels[70]. In a study by Huang et al. observed a reduction in depression as well an association between rTMS response and LH, FSH and estradiol levels in women [71]. The latter study suggests that sexual hormone changes may be related to mood improvement rather than a direct effect of rTMS on hypophyseal hormones as suggested by electroconvulsive therapy studies [72].

Discussion

Major depressive disorder is still an entity difficult to dissect completely from the pure clinical perspective and the pathology behind it. Elusive functional and structural alterations by imaging studies continue presenting heterogeneous data that cannot be completely

accepted as a landmark source for clinical relevance. Biochemical profiling has the potential as an option to characterized specific *"depressive syndromes"* and genetic/epigenetic assessment will definitely provide a great insight into the nature and evolution of the disease, unfortunately, we are still waiting for the advancement and refinement of such technologies. Until now, surrogate biomarkers when analyzed carefully in the context of clinical evidence, can provide the information that will point towards a better understanding of MDD.

We reviewed all published articles that evaluated TMS as an intervention among patients with major depressive disorder through the use of biological markers. No studies on tDCS were found according to our inclusion criteria. The majority, but not all of the studies reported clinical improvement in patients and positive correlation to BM.

According to our findings, fMRI, SPECT, PET, MRS, cortical excitability and BDNF consistently showed positive results in the papers reviewed. Positive correlations between EEG and TSH were also found, but results were inconsistent as some articles included in the review found no significance between the outcomes measured. On the other hand, saccadic eye movements, dopamine and serotonin were all found to have no significance in the papers we reviewed.

There are a number of similarities between the papers reviewed that could possibly account for the results obtained. First, due to the fact that most of the studies reviewed used a small sample size, the trials may be lacking the power to show a significant difference. This is also the reason that the measures that were found to be consistently positive cannot yet be implemented as surrogate outcomes for MDD as small sample sizes may also lead to type I error. Another reason that could account for these results is the stimulation parameters were inconsistent between trials. One important parameter to note is the length of the study. The majority of the studies lasted for 3 weeks within which subjects underwent 10 sessions of rTMS. This time period may not be long enough to detect a change in the expression of those biomarkers. In fact we only found two large trials in this review [49, 66].

Additionally, many of the reviewed studies used heterogeneous samples and did not take into account confounders such as age, gender or family history. Creating a standardized biochemical evaluation would improve the power of comparison among studies and therefore add more data to the field, as was stated by the Consensus of the 7th expert meeting on Psychiatry and Immunology [73].

The Use of Biomarkers as Surrogate Outcomes

It is important to address the use of BM as surrogate outcomes. Although there are several possible definitions for surrogate outcomes, they are usually understood as measurements that substitute clinically meaningful outcomes and are direct measures of a patient's state of health. Additionally, surrogate outcomes should also be able to predict the outcomes of therapies [5, 74]. The major difference between BM and surrogate outcomes is that BM are the precursors to official surrogate outcomes.

The great advantage in finding BM to act as surrogate outcomes is that surrogate outcomes substitute “hard” clinical outcomes such as death or serious disabilities and reduce the need for long-term, usually very expensive, research. In order for a BM to be implemented as a surrogate outcome, the BM must demonstrate sensitivity, specificity, and a decrease in symptoms (assessed by validated measures) in an adequate number of well-designed clinical trials [74]. In our review, the BMs that showed the greatest potential for becoming surrogate outcomes were BDNF and neuroimaging studies.

When considering the role BDNF plays in neuroplasticity and the proposed neurotrophic hypothesis presented by Pittenger and Duman [95], is reasonable to assume that rTMS therapeutic effects are based in its intrinsic neuromodulatory properties on cortical excitability, the changes in synaptic plasticity as a result of rTMS application could possibly be the effect of BDNF modulation under the site of stimulation and deeper areas as well, the last as a result of cortical-subcortical connections. If local increments of BDNF and production of others growth factors at the hippocampal level have already shown antidepressive-like effects in animal models, it may have a profound impact as a treatment for MDD, however, peripheral administration of BDNF still challenging pharmacokinetic principles, and the potential for deleterious side-effects outweigh the use of BDNF. It is then reasonable to use rTMS as exogenous tool to facilitate BDNF secretion.

BDNF in particular had the greatest support for use as a surrogate outcome. All studies that used BDNF as a correlate for depression post-rTMS treatment showed positive results. In a secondary search, a systematic review examining the role of neuroplasticity on BDNF levels by Brunoni et al. 10 case control studies and 13 clinical trials were analyzed showing a strong correlation between BDNF levels and depression. The main finding was that BDNF levels in the blood increased if depression was treated with rTMS and antidepressants, suggesting that BDNF levels in patients with MDD are associated with changes in neuroplasticity [75], modulation of BDNF levels and downstream of its signaling can be considered a stressor that might lead to impaired adult hippocampal neurogenesis, promoting the development of atrophic changes and deficits in synaptic plasticity, which in turn, it may explain the hippocampal atrophy observed in postmortem studies [95]. One question here though is whether BDNF levels would be a general marker of antidepressant response or be specific for the type of treatment – i.e. pharmacological vs. non-pharmacological. While these results are encouraging, further studies are necessary to elucidate the link between this and other biomarkers and depression in order to identify strong surrogate outcomes.

The significance of genetic variability and its influence in treatment responses is becoming an area to explore in the fields of genetic/epigenetic research. For instance, BDNF polymorphisms has a direct impact in the development of synaptic plasticity, thus biomolecular assessments aimed to recognize such genetic variations may become the foundation for personalized pharmacological and non-pharmacological treatments, including, thus, non-invasive brain stimulation.

It is also important to consider the role of cognitive performance as functional marker in the treatment of MDD. Noninvasive brain stimulation, especially in the case of TMS and tDCS

can be used as therapeutic techniques to improve the cognitive impairments observed in neuropsychiatric disorders [120] and on the other hand, cognitive dysfunction may be also a functional and therapeutic marker for disorders associated with cognitive dysfunction such as MDD [121].

Future Directions

In addition to performing larger, longer and sham-controlled studies on the biomarkers reviewed here in the future, other potential parameters, techniques, and markers should be considered. An interesting finding of our review is that the majority of studies explored the alterations of the DLPFC and the effects of TMS on the activity of that area. In addition to the DLPFC, recent studies in non-invasive brain stimulation and functional imaging have identified the ventromedial prefrontal cortex (VMPFC) as an area involved in the pathophysiology of depression. According to several authors, depression is associated with abnormally high levels of VMPFC activity [76–79] and abnormally low levels of DLPFC activity [76, 80–81]. While a study by Koenings and Grafman found that patients with bilateral VMPFC lesions had significantly lower levels of depression than patients with bilateral lesions of the DLPFC, Li et al. found that performing rTMS on the VLPFC lead to a considerable decrease in activity of that area [21, 82]. Thus, the VLPFC would be an interesting site of stimulation for future studies as it may be able to elicit results that would allow for the identification of BM and implementation of surrogate outcomes.

Another factor that may affect BM results is the type of stimulation used. As was mentioned before, all of the studies reviewed employed TMS techniques; however, it is important to realize the potential of tDCS in this setting as well [57, 73]. Unlike the pulses that cause action potentials in TMS, tDCS is thought to manipulate neuronal signaling by applying a low electric current through electrodes placed on the scalp [83]. Although the perceived mechanism of action may be slightly different, both TMS and tDCS techniques allow for the induction of excitatory or inhibitory effects. Because tDCS is also able to induce these changes, it may be a good choice for patients with depression. tDCS also has the advantage of being more user-friendly during double-blind or sham-controlled trials as well being easier to use when used with other measures and tasks, allowing for further exploration of BM and surrogate outcomes [83].

One important finding by Langguth et al. in 2005 revealed that there might be a link between inflammation and depression [84]. According to several authors, it has been demonstrated that there is in fact an increase in pro-inflammatory cytokines such as interleukin-1 [85–86] and interleukin-6 [85, 87–89] in depressed patients. In turn, inflammation may lead to plastic changes in the nervous system [90]. Because of this relationship, it may be possible in the future to use these cytokines as BM in depression; however, it is not clear from current studies the affect of non-invasive brain stimulation on these cytokines [84, 91]. A case study revealed an improvement in the patient’s depression, but an increase in her rheumatoid arthritis post treatment with rTMS. These results were obtained multiple times in the same patient and the reproducibility suggests a link between rTMS immunomodualtory effects [84]. On the other hand, a study performed in rats by Okada et al. found no significant increase in the up-regulation of pro-inflammatory

cytokines [91]. Thus, additional studies must be performed in order to determine the affect of non-invasive brain stimulation techniques on these potential BM.

Final Remarks

In summary, TMS is a strong choice for the treatment of depression, with several studies trying to explain its clinical effects due to biological changes, or find the best predictors of response as to optimize response to rTMS. Although we are not yet able to use the BM as surrogate outcomes for depression treatment response, there are strong candidates that will hopefully be able to fulfill this role in the near future. In order for these BM and surrogate outcomes to be identified, it is important that more funding be directed not only to neuromodulation studies, but also to neurobiological studies in Psychiatry. This would make the measurements of larger samples and the inclusion of a sham or control group possible. As a result, advances in psychiatric evaluation would be possible, leading to higher quality care of patients and in turn, better clinical outcomes.

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Table 1

Studies Reviewed

	Author	Year	Patient #	Design	Sham (yes/no)	Biomarker	Clinical Outcome (pos/neg)	BM vs. Clinical Correlation (pos/neg)
Neuroimaging	Kito	2008	14	Open-label trial	no	SPECT	pos	pos
	Conca	2002	4	Open-label Trial	no	SPECT	pos	NR
	Baeken	2010	21	Cross Over Trial	no	SPECT	pos	pos
	Furtado	2012	46	Cross Over Trial	no	fMRI	pos	neg
	Kito	2012	26	Open label trial	no	SPECT	pos	pos
	Kito	2011	14	Case report	no	SPECT	pos	pos
	Kozel	2011	14	Randomized Trial	yes	fMRI (dMRI)	pos	pos
	Kuroda	2010	8	Open-label Trial	no	PET	pos	neg
	Li	2010	23	Open-label Trial	yes	PET	pos	pos
	Palliere Martinot	2011	31	Parallel Randomized Trial	yes	PET-MRI	pos	pos
	Peng	2012	30	Parallel Randomized Trial	yes	fMRI	pos	pos
	Richieri	2011	33	Open-label trial	no	SPECT	pos	pos
	Zheng	2010	34	Parallel Randomized Trial	yes	MRSI	pos	pos
	Kito	2008	14	Open-label trial	no	SPECT	pos	pos
	Loo	2003	18	Parallel Randomized Trial	yes	SPECT	pos	pos
	Pogarell	2006	5	Cross-over trial	no	SPECT	pos	pos
	Nadeau	2002	7	Open-label trial	no	SPECT	pos	neg
	Peschina	2001	4	Pilot Study	no	SPECT	pos	NR
	Baeken	2009	21	Cross-over Trial	no	PET	pos	pos
	Herwig	2003	25	Parallel Randomized Trial	yes	PET	pos	neg
	Nahas	2000	32	Parallel Randomized Trial	no	fMRI	pos	neg
	Li	2004	14	Open-label Trial	no	fMRI	pos	pos
	Li	2003	14	Cross-over Trial	no	fMRI	pos	neg
	Herbsman	2009	54	Parallel Randomized Trial	yes	fMRI	pos	pos
	Fitzgerald	2007	26	Parallel Randomized Trial	no	fMRI	pos	pos

	Author	Year	Patient #	Design	Sham (yes/no)	Biomarker	Clinical Outcome (pos/neg)	BM vs. Clinical Correlation (pos/neg)
	Luborzewski	2006	17	Open-label Trial	no	MRS	pos	pos
	Eschweiler	2000	12	Cross-over Trial	yes	NIRS	pos	neg
Electrophysiological	Micolaud-Franchi	2012	13	Open-label trial	no	EEG	pos	pos
	Arns	2010	18	Cross-over Trial	no	EEG	pos	pos
	Croakin	2012	8	Open-label Trial	no	Cortical excitability	pos	neg
	Price	2008	39	Parallel Randomized Trial	not stated	EEG	pos	neg
	Khodayari-Rostamabad	2011	27	Pilot study	yes	EEG	pos	pos
	Narushima	2010	65	Parallel Randomized Trial	yes	EEG	pos	pos
	Berman	2000	20	Parallel Randomized Trial	yes	EEG	pos	neg
	Chistyakov	2005	59	Parallel Randomized Trial	yes	cortical excitability (single/paired pulse TMS)	pos	pos
	Triggs	1999	10	Open-label Trial	no	Cortical excitability (single/paired pulse TMS)	pos	NR
	Maeda	2000	16	Parallel Randomized Trial	yes	Cortical excitability (single/paired pulse TMS)	pos	pos
	Bajwa	2008	13	Parallel Randomized Trial	yes	Cortical excitability (single/paired pulse TMS	pos	pos
	Crevits	2005	11	Open-label Trial	no	Saccades	pos	neg
Neuroimmunoendocrine	Reid	1999	1	Case report	no	Serum cortisol	pos	pos
	Zwanzger	2003	37	Open-label Trial	no	Serum Cortisol	pos	pos
	Malaguti	2011	90	Open-label trial	no	DNA analysis SERTPR, 5-HT1A, and COMT genes	pos	pos (for 5HT 1a) neg (for COMT and SERTPR)
	Trojak	2011	1	Case report	no	TSH (plasma)	NA	pos
	Yukimasa	2006	26	Cross-over Trial	no	Plasma BDNF	pos	pos
	Zanardini	2006	16	Open-label Trial	no	Serum BDNF	pos	pos
	Kuroda	2006	9	Open-label Trial	yes	Dopamine	pos	neg
	Miniussi	2005	71	Cross-over Trial	yes	Dopamine and Serotonin	pos	neg
	Kito	2009	19	Open-label Trial	no	TSH	pos	pos
	Szuba	2001	16	Parallel Randomized Trial	yes	TSH	pos	neg*

	Author	Year	Patient #	Design	Sham (yes/no)	Biomarker	Clinical Outcome (pos/neg)	BM vs. Clinical Correlation (pos/neg)
	Langguth	2005	1	Open-label Trial	no	C reactive protein, soluble IL2-R, IL6, IL10, TNF	pos	neg
	Huang	2008	46	Open-label trial	no	LH, FSH, Progesterone and estradiol	pos	pos
	Padberg	2002	37	Open-label Trial	no	Plasma Neuroactive steroids (i.e, progesterone, DHEA)	pos	neg

Abbreviations: SPECT: Single-photon emission computed tomography; PET: Positron emission tomography; fMRI: Functional magnetic resonance imaging; MRSI: Magnetic Resonance Spectrum Imaging; MRS: Magnetic resonance spectroscopy; NIRS: Near infrared spectroscopy; EEG: Electroencephalography; TSH: Thyroid stimulating hormone; IL: Interleukin; LH: Luteinizing hormone; FSH: Follicle stimulating hormone; DHEA: Dehydroepiandrosterone; SERTPR: Serotonin transporter promoter region, 5-HT1A : Serotonin receptor 1a; COMT: Catechol-O-methyltransferase NR: Not reported

[*] No correlation, but significant group differences

Table 2

Advantages and Disadvantages

Biomarker Type	Biomarker	Advantages	Disadvantages
Neuroimaging	fMRI	- Detects regional blood flow in cerebral areas - Analyzes variations in signal intensity from hemoglobin according to blood oxygen level dependence (BOLD effect) - Signal intensity can be used as indirect measure of excitatory input to neurons - Total scan time can be very short as opposed to PET - No additional scans for neuroanatomical correlative information as in PET - TMS-fMRI has better time and spatial resolution than PET - TMS-fMRI does not expose participants to radioactive tracers - Can be repeated without limitation - TMS-fMRI can map corticocortical and corticosubcortical connectivity in brain	- BOLD responses can only measure hemodynamic changes in blood flow, blood volume etc., but does not provide complete answers to the relationship between cerebral hemodynamic changes and neural activation. - Technically challenging, difficult handling, and imaging artifacts due to interference of magnetic fields of TMS and MR scanner
	PET	- Allows real-time view of brain functioning - Ability to reconstruct 3-D image of active brain areas - Higher image quality due to higher image resolution and sensitivity than SPECT - Usually uses chemical elements that are naturally present in the human body for labeling - PET isotopes can be labeled to almost every organic molecule - PET measurements can be quantified absolutely - TMS-PET allows for the ability to examine and visualize corticocortical and corticosubcortical connectivity in the brain - TMS-PET seems to be a valid tool to examine the connectivity in the brain, based on tracer studies done in monkeys - TMS-PET can be used to compare voluntary and	- Requires cyclotron for image generation - More expensive than SPECT - Shorter half-life of gamma rays does not allow for observation *in vivo*. - Requires more intensive staff training - Limited repetition due to radioactive tracers

Biomarker Type	Biomarker	Advantages	Disadvantages
		external activation of networks in the brain. - TMS-PET has the capability to assess specific neurotransmitter system activity	
	SPECT	- Allows real-time view of brain functioning - Does not require a cyclotron for image generation - Ability to reconstruct 3-D image of active brain areas - Less expensive than PET - Longer half-lives of gamma rays allow for observation of biological processes *in vivo*. - Training of staff is less intensive than PET	- Maps limited brain areas - Lower image quality than PET - Uses tracers that often behave differently and that are designed with certain compromises - Variety of radiopharmaceuticals is limited - Measurements can not be quantified absolutely
	MRS	- Allows thorough view of brain chemical activity - TMS-MRS can be used to examine the underlying mechanisms of long-term changes in brain excitability - Measures the levels of most important inhibitory (GABA) and excitatory neurotransmitter (glutamate) - Direct and non-invasive - May be used to investigate the metabolic and neurotransmitter effects of rTMS and tDCS	- Low sensitivity - Lower spatial and temporal resolution - Offers fewer metabolic BM that can be followed *in vivo*.
Electrophysiological	EEG	- Allows for measurement of TMS effects within the brain with high temporal and spatial resolution regardless of the location of stimulation - EEG electrodes can immediately record the TMS evoked potential (TEP) after TMS pulse, which very likely results from the activation of the stimulated brain area - Can be used to assess effective connectivity of remote, but anatomically connected areas of the brain - In TMS-EEG, the TEP can be considered an evoked brain oscillation - TMS-EEG is able to gather information on cortical	- TMS-EEG is technically challenging - TMS-EEG requires TMS-compatible EEG amplifiers - TMS-EEG highly state dependent, so results may not be generalizable

Biomarker Type	Biomarker	Advantages	Disadvantages
		excitability at the time of the applied TMS pulse - Advance analysis using quantitative assessment and mathematical modeling	
	Cortical Excitability	- Excitability can be related to concentration of neurotransmitters - Assesses integrity of motor pathways - Provides physiological information regarding inhibitory vs. excitatory modulation in brain activity - Can target different circuits depending on intensity of stimulation	- There is a possibility that rTMS may not produce changes in brain activity that are local to the area of stimulation
	Saccadic Eye Movements	- Effect of single pulse TMS is specific to area of brain stimulated and timing of stimulation - rTMS can influence specific eye-movement control - Small intrapersonal variability so results pre and post-TMS are comparable and subjects can act as their own controls - May be used to examine the lateralization of ocular motor control	- Effects of rTMS are not always inhibitory or excitatory and are highly parameter dependent - Mechanism of rTMS effects in saccadic activity are not yet fully understood
Neuroimmunoendocrine	BDNF	- Provides an objective measure of BDNF levels - BDNF is known to play a large role in the hippocampus which is responsible for memory, learning and emotions, which may effect depression - Relatively inexpensive to obtain	- Requires blood draw - Requires time intensive processing to calculate BDNF serum levels
	Serum Cortisol	- Hypothalamic-pituitary-adrenocortical system has been identified in the pathogenesis of depression, making it a good target - Dexamethasone and the DEX/CRH suppression test has reasonable sensitivity and specificity for depression - Provides an objective measure of cortisol levels	- Requires blood draw - Medications can easily influence results, so subjects must be medication free prior to the study - Dexamethasone and DEX/CRH tests require subjects to ingest an oral dose of each during the trial
	Serum thyroid hormones	- TSH follows a natural circadian pattern, making it	- Requires blood draw

Biomarker Type	Biomarker	Advantages	Disadvantages
		easier to see if rTMS can actually counter TSH decline - Provides an objective measure of thyroid hormone levels	- Underlying thyroid disease may be a confounding illness
	Dopamine and Serotonin	- Dopamine and serotonin are highly involved with pleasurable feelings and mood - Since these are the two main targets of antidepressant medications, it is a good point of comparison to determine the effects of TMS	- Neuroendocrine measures can be complex and may be influenced by a number of other physiological processes