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Personalized Medicine: Review and Perspectives of Promising Baseline EEG Biomarkers in Major Depressive Disorder and Attention Deficit Hyperactivity Disorder

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Abstract
Personalized medicine in psychiatry is in need of biomarkers that resemble central nervous system function at the level of neuronal activity. Electroencephalography (EEG) during sleep or resting-state conditions and event-related potentials (ERPs) have not only been used to discriminate patients from healthy subjects, but also for the prediction of treatment outcome in various psychiatric diseases, yielding information about tailored therapy approaches for an individual. This review focuses on baseline EEG markers for two psychiatric conditions, namely major depressive disorder and attention deficit hyperactivity disorder. It covers potential biomarkers from EEG sleep research and vigilance regulation, paroxysmal EEG patterns and epileptiform discharges, quantitative EEG features within the EEG main frequency bands, connectivity markers and ERP components that might help to identify favourable treatment outcome. Further, the various markers are discussed in the context of their potential clinical value and as research domain criteria, before giving an outline for future studies that are needed to pave the way to an electrophysiological biomarker-based personalized medicine.

Introduction – Genetics, Endophenotypes and Biomarkers

In some fields of medicine, individualized and personalized treatment has become state of the art. Especially in oncology, the assessment of individual biological properties of the patient and the cancer cells helped to make treatment more efficient, reduce side effects and improve secondary prevention strategies [1]. The paradigm shift from standard 'one-size-fits-all' treatment plans according to descriptive markers such as stage and locus of the cancer to individual therapy algorithms based on e.g. genetic markers is thought to be of value also for neuropsychiatric disorders and raises new hopes for tailored therapies in psychiatry. However, a mental disorder is completely different from a well-observable and definable solid tumour: there is no clear organic correlate that is responsible for the symptoms; instead, multidimensional

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and possibly very heterogeneous alterations of brain function sum up to the clinical syndrome.

Although psychiatric disorders such as major depressive disorder (MDD) have an assumed high heritability of up to 37% [2], large-scale genome-wide association studies have thus far failed to link genetic variants with MDD [3]. This underpins the suggested polygenetic nature of psychiatric disorders [4] and implies the need for endophenotypes that are seen as an intermediate step between genotype and behaviour. Endophenotypes are more closely related to genotype than behaviour alone and may be a possible way to stratify a population for genome-wide association studies [5]. Although some promising findings using different sets of clinical and neuroimaging endophenotypes in major depression have been reported [6], a recent study on psychophysiological endophenotypes can be seen as a drawback to this approach since the authors were unable to replicate significant associations between endophenotypes and candidate genes [7].

Given that the link between endophenotypes and genetics might not be that strong or simple as suggested, an association between endophenotypes and disorder might still be present and could help to improve treatment and diagnostic decisions. In this context the term 'biomarker' seems relevant, that is according to the National Institutes of Health 'a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention' [8]. The value of a personalized medicine approach is not determined by the association of a marker with genetic variants but by the improvement it yields for the diagnostic process (by making it more objective) and, probably more importantly, by the increased effectiveness of the treatment (i.e. a more prognostic biomarker). As Thomas Insel, director of the National Institute of Mental Health, stated: 'The task is to identify the biomarker that predicts response – whether the treatment is a medication or a psychosocial intervention.' The first step towards this 'precision medicine' development was the introduction of the Research Domain Criteria project which is aimed to transform clinical syndrome-based diagnosis into an individualized framework of psychophysiology to support the diagnostic process of mental disorders [9] and – hopefully – improve treatment. Currently several large-scale studies are ongoing that should be able to shed more light onto this development, such as the international Study to Predict Optimized Treatment Response (iSPOT) in 2,016 patients with MDD and 672 children and adolescents with attention deficit hyperactivity disorder (ADHD; see also Williams et al. [10] for further protocol details) and the EMBARC study (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression; https://clinicaltrials.gov/ct2/show/NCT01407094).

Electroencephalogram and Biomarkers

Sparked by the discovery that the mode of function of the human central nervous system is based on electric activity [11, 12], the invention of electroencephalography (EEG) and its first description in humans [13] provided the possibility to analyse the brain at its core functional level. Taken as a tool for the assessment of biomarkers that, according to the definition, should be assessable objectively and provide information about physiological or pathological processes or responses to treatment interventions [14], EEG also fulfils the criteria of a cost-efficient, nowadays broadly available and already established tool in the diagnostic clinical practice. Further, EEG captures ongoing neuronal activity with a temporal resolution that surpasses any other neuroimaging modality such as functional magnetic resonance imaging or positron emission tomography. Also, the electroencephalogram is not a surrogate marker of neuronal activity (such as the blood deoxygenation level-dependent signal in functional magnetic resonance imaging or the glucose utilization in positron emission tomography; see Logothetis [15]) but is a direct reflection of neuronal activity (postsynaptic potentials) [16]. It is therefore highly plausible that a personalized medicine approach in psychiatry could gain from electrophysiological markers.

Although electrophysiological biomarkers have been studied throughout many psychiatric disorders, the current review is dedicated to only two of them: MDD and the ADHD. The following work describes the current state of the art of baseline EEG parameters by means of their diagnostic and predictive (prognostic) value. Treatment-emergent biomarkers that yield information about changes in the early course of treatment will not be subject of the review, and the interested reader is referred to Olbrich and Arns [17] or Arns and Olbrich [18] for more coverage of those.

Biomarkers

EEG Sleep Research

EEG biomarkers in sleep are robust, and their advantage can be found in the link between clinical symptoms such as sleep initiation problems, early awakening or dis-

rupted sleep in both MDD and ADHD and electrophysiologically assessable parameters. In MDD, the most consistently reported findings include a disturbed sleep architecture, comprising an increased rapid eye movement density [19, 20], decreased rapid eye movement sleep latency [21, 22] and altered slow-wave sleep in MDD [23, 24].

While slow-wave power seems to have a discriminative value between MDD and healthy controls (HCs) [23, 25], a predictive value for recurrence of depressive symptoms was found for decreased slow-wave sleep, decreased sleep efficiency and delayed sleep onset [26–28]. Also the slow-wave activity itself seems to be important for treatment prediction. Luthringer et al. [29] reported increased relative delta power in sleep EEG recordings in responders to antidepressant treatment, although others failed to replicate these findings [30, 31]. Still, Nissen et al. [31] reported decreased slow-wave activity in responders, expressed in a high delta sleep ratio, a finding that again could not be replicated by Argyropoulos et al. [32]. Besides classical sleep EEG parameters, also a decreased coherence within the beta, delta and theta bands in sleep EEG predicted non-response in adolescents and the occurrence of depressive episodes [33].

In ADHD there is a clear lack of studies that examine EEG-derived sleep parameters, although other measures such as actigraphy and salivary melatonin measurements suggest a delayed sleep onset in a majority of children and adults with ADHD, also termed sleep onset insomnia [34–36] characterized by a delayed melatonin onset. This delayed sleep onset results in reduced sleep duration – and thus chronic sleep restriction – in ADHD, which becomes visible as the typical drowsiness patterns that can be observed in the EEG such as impaired vigilance (see EEG Vigilance below) or excess theta waves (see Frequency-Specific Biomarkers: Theta); for a review, see also Arns et al. [36] and Arns and Kenemans [37].

EEG Vigilance

Another possible EEG biomarker that has proven its value for differentiating between patients suffering from MDD and HCs is EEG vigilance regulation. Hegerl et al. [38] and Olbrich et al. [39] reported that MDD is associated with an increased EEG vigilance during rest with fewer and slower declines to lower vigilance stages during a 15-min resting condition. The appeal of this marker reflecting a high tone of CNS arousal can be found in the linkage between clinical symptoms and EEG parameters of wakefulness regulation. A hyperstable vigilance regulation in MDD is interpreted as an electrophysiological correlate of the often reported sleep problems. Increased vigilance might further explain the behavioural withdrawal of patients suffering from MDD to avoid a further increase in arousal [40].

The EEG vigilance framework further suggests that a fast decline of EEG vigilance during rest might result in increased sensation seeking and hyperactive behaviour to stabilize wakefulness regulation. Hegerl and Hensch [40] suppose that not only manic patients [41] reveal unstable EEG vigilance regulation patterns, but also patients suffering from ADHD [37, 42]. In line with this, increased theta power as a marker of drowsiness has frequently been reported in patients with ADHD [43], and as described above the majority of patients with ADHD exhibit sleep onset insomnia [34, 35, 37], further supporting this notion. However, a recent meta-analysis also suggested increasing levels of theta power for healthy children and stable levels for ADHD children across the last 10 years [44], suggesting a possible gene × environment (sleep, circadian clock) interaction for this measure requiring further research.

Paroxysmal Patterns and Epileptic Discharges

Unlike in neurology, there are no distinct 'grapho-elements' in EEG recordings that are pathognomonic for a psychiatric syndrome. However, already in 1939 was it demonstrated that during subclinical epileptiform activity patients had slower reaction times, while others did not respond at all [45], suggesting that paroxysmal activity in 'non-epileptic patients' can have behavioural consequences.

The occurrence of paroxysmal EEG in affective disorders has not been investigated in much detail, but previous analyses suggest a prevalence of 3–5% in depression [46] to 20–40% in affective disorders, mostly mania [47]. The 3–5% in depression are comparable to the 1–6% prevalence of paroxysmal EEG in normal populations [47–50]. On the other hand, the occurrence of paroxysmal patterns in ADHD has been estimated to be between 12 and 15% [51–53] to approximately 30% [54], which is relatively high, compared to normal populations. A more recent study found epileptiform discharges in 25% of children with suspected ADHD [55].

The implications for treatment in psychiatric patients with paroxysmal patterns or epileptiform discharges – but without a history of seizures – remain unclear. It is still remarkable that several studies found that ADHD patients [56–58] do respond to anticonvulsant medication, e.g. to carbamazepine [59]. Furthermore, there is some evidence that antidepressant treatment augmentation

with anti-epileptic drugs is effective in treatment resistant MDD [60, 61], although data about the association of response and epileptiform discharges are lacking. As a further example, previous studies have demonstrated an association between paroxysmal EEG activity and panic attacks [for a review, see 62, 63]. Patients with panic disorder and epileptiform EEG patterns have been found to clinically respond to anticonvulsants [64], thus suggesting that there could be a subgroup of psychiatric patients in whom paroxysmal/epileptiform EEG activity could be associated with their psychiatric complaints and for whom anticonvulsant treatment could be a choice for augmentation of treatment or as stand-alone treatment. However, this requires further controlled research.

Frequency-Specific Biomarkers: Alpha

One of the most prominent features of a resting-state EEG is the EEG alpha activity with heritability estimates of up to 79% [65]. Alpha activity in adults has a mean frequency around 10 Hz with a range between 7 and 13 Hz and has maximum amplitudes at parieto-occipital locations in the eyes-closed condition.

In MDD a consistent finding is an elevated absolute [66–70] or relative alpha power [71, 72] at mainly parietal and frontal [68, 73] or occipital sites [74]. The reason that some studies did not find alpha power differences between patients and HCs [75, 76] or found decreased (relative) alpha activity in comparison to other patient groups [77] might be related to differences of recording periods, where shorter recording periods prevent the differences described above [38, 39] in vigilance regulation to occur (e.g. 6 min in Knott and Lapierre [76] vs. 15 min in Hegerl et al. [38] and Olbrich et al. [39]).

In addition, there is some evidence that EEG alpha power can predict treatment outcome with low parieto-occipital [74, 78, 79] or lowered frontal alpha power [80] associated with non-response to antidepressants, although this could not be replicated in the recent multicentre iSPOT-D (for depression) study in 1,008 MDD patients [81]. However, for treatment with repetitive transcranial magnetic stimulation (rTMS), the opposite was reported [79, 80], maybe related to higher levels of treatment resistance in these rTMS studies.

EEG alpha asymmetry has been investigated as a biomarker for MDD with a decreased alpha power at right frontal sites relative to the left side [82–86], although many studies have failed to replicate these findings [81, 87–91]. Interestingly in ADHD, Keune et al. [92] found the opposite pattern of alpha asymmetry with increased right frontal alpha power.

Two studies by the same group investigated the prognostic value of alpha asymmetry in MDD and found conflicting results [74, 93]; however, in the iSPOT-D study it was found that frontal alpha asymmetry (right frontal alpha dominance) was specifically related to response to the selective serotonin reuptake inhibitors escitalopram and sertraline, but not to the serotonin norepinephrine reuptake inhibitor venlafaxine in females only [81], underscoring the importance of large samples that allow testing for gender- and drug class-specific predictors of treatment outcome.

A slow background rhythm, also called a slow alpha peak frequency, has been consistently found a predictor for non-response to several treatments such as stimulant medication in ADHD [94], rTMS in depression [95, 96] and the antidepressants pirlindol and amitriptyline [79]; for a review, see Arns [97].

Frequency-Specific Biomarkers: Theta

Several studies have reported elevated slow-wave activity in MDD [69, 98–101], with the focus of this elevated theta activity localized to frontal areas and often to the anterior cingulate cortex (ACC) [68, 101, 102], though decreased ACC activity in MDD has also been reported [103] and some studies found no differences between MDD and controls [104, 105].

High frontal theta activity has been associated with non-response to antidepressant treatments [96, 106, 107] while Cook et al. [108] found no differences. Seemingly contrary to this, Spronk et al. [109] reported that low theta activity at the frontal midline was associated with non-response. Note that several authors [96, 106, 107] reported on widespread frontal (not midline) theta activity, most likely a reflection of 'drowsiness' theta power as discussed above (see EEG Vigilance) on vigilance [37], whereas Spronk and colleagues found the opposite pattern for frontal midline theta activity. This suggests these two types of theta activity could have different implications and different origins. In line with Spronk et al. [109], several studies have indeed shown low theta activity localized to the ACC, as estimated by source localization techniques, to respond worse to various antidepressant treatments [110–113]. These findings are in line with positron emission tomography and functional magnetic resonance imaging studies demonstrating low metabolic activity in the ACC is associated with worse treatment outcome; see also Pizzagalli [114] for an excellent review and meta-analysis on the rostral ACC (rACC) and treatment outcome. Contrary to this notion, several groups have reported high perfusion in the subcallosal cingulate (SCC;

in earlier work this area was also referred to as rACC) [115] or rACC for non-responders [116, 117], also reviewed in Arns et al. [101]. In line with this, recent results of the iSPOT-D study reported increased rACC and frontal theta activity to be associated with non-response, albeit with a small effect size [101]. Interestingly, these results tended to be driven mostly by treatment resistance, suggesting that future studies should also investigate the role of treatment resistance for the association of rACC/SCC perfusion and treatment outcome [101]. Conversely, deep-brain stimulation targeting the SCC in treatment-resistant MDD patients has been shown to result in clinical benefits [118], positing this area as a critical node in the depression network. However, the exact direction of these findings (high or low frontal midline theta activity) and exact localization (rACC vs. SCC) remains unclear from these lines of research, and future studies might shift the focus on investigating the connectivity of this specific area with other structures rather than focusing solely on EEG theta power given the above contradictory findings.

In ADHD, excess theta activity compared to controls is an often-reported finding, sometimes also expressed in the theta/beta ratio (TBR) [43], and several reports have termed the TBR a solid biomarker to identify ADHD. These findings resulted in this measure being FDA approved as a 'diagnostic test' for ADHD [for a commentary, see 119]. However, a recent meta-analysis could not confirm that this metric is a reliable 'diagnostic test' for ADHD [41], due to an increased TBR across the last 10 years for controls, suggesting that this marker is a non-specific marker for drowsiness, and insufficient as a diagnostic biomarker for ADHD. Apart from the diagnostic use, this metric does hold potential as a prognostic biomarker being able to predict treatment outcome. A substantial proportion (26–38%) of ADHD subjects did have a high TBR and excess theta activity, and these subgroups have been found to be responders to stimulant medication [80, 94, 120] and neurofeedback [96, 121], making this measure more likely a prognostic than diagnostic measure [119], albeit still requiring further replication.

Frequency-Specific Biomarkers: Beta

In MDD there is some evidence for increased beta EEG activity [99, 122]. The predictive value for treatment outcome has not been investigated systematically so far.

In ADHD there is evidence for a subgroup of ADHD patients who are characterized by excess beta activity or beta spindles that make up 13–20% [123–125]. Several studies demonstrated that this subgroup does respond to stimulant medication [126–128]. A recent study further demonstrated that spindling excessive beta activity is a result of sleep maintenance problems and thus can indeed be considered a 'subvigil' beta state and is specifically associated with impulse control problems, irrespective of diagnosis [129]. This would make the effectiveness of wakefulness-promoting drugs plausible in these patients.

EEG Connectivity Measures

First reports of altered connectivity in MDD in contrast to HCs stem from findings of altered coherence between EEG electrode sites [130, 131]. More recent studies used a huge variety of connectivity measures like partial directed coherence, Granger causality, structural synchrony index and phase synchrony index. Some found decreased EEG connectivity in MDD [122, 132–134] while others report of increased EEG connectivity in MDD, mainly in the alpha band [135–138]. More studies are needed to disentangle the complex relationship between the different connectivity measures and their physiological interpretation and to estimate the value for treatment prediction. In this context, one study [138] found an association between increased phase connectivity in the beta band between the subgenual prefrontal cortex and the right medial frontal cortex and treatment response. As suggested above in relation to theta activity, these approaches, when replicated, could further shed light onto the controversy between increased or decreased metabolism in the rACC/SCC.

Also in ADHD there is increasing evidence that EEG-based measures of connectivity could be used to differentiate between patients and HCs. Interestingly, most studies find increased measures of coherence especially within the beta and theta bands during the resting state [139–141]. Also graph theory network parameters seem to support an increased functional connectivity in ADHD [142]. Regarding a possible predictive value of connectivity measures, Dupuy et al. [143] describe an association between intrahemispheric coherence in the beta band and response to methylphenidate. These findings are promising and possibly pave the way for an improved differential diagnosis and consecutive treatment.

Event-Related Potentials

The event-related potential (ERP) is a waveform of averaged EEG activity, time-locked to a stimulus in a cognitive task. Several components of this ERP have been studied for their predictive value in treatment outcome.

In MDD research, the main focus has been on two measures, namely the P3 [144] and the loudness dependence auditory evoked potential (LDAEP), which is a de-

rivative of the N1/P2 amplitude and its changes with increasing stimulus intensity [145]. So far, research involving the P3 has been ambiguous. Jaworska et al. [146] found that responders to antidepressants have larger P3 amplitudes than non-responders. A similar finding was reported by Bruder et al. [147] for the P3 amplitude at occipital sites. In contrast, responders to treatment with rTMS were found to have lower P3 amplitudes than non-responders, although this effect was limited to Pz and only marginally significant [96]. Regarding P3 latency, the results have been mixed as well, where some found no effect [146], while other studies found slower P3s in non-responders [148–150].

The LDAEP has proven to be a more robust predictor for antidepressant treatment response. A strong LDAEP, i.e. a steeper increase with stimulus intensity, is supposedly indicative of a low level of serotonergic activity [145, 151] and is related to better outcome compared to a selective serotonin reuptake inhibitor [152], whereas the effect is reversed for responders to noradrenergic antidepressants [111, 153, 154]. A recent study, however, failed to replicate this relation between LDAEP and treatment outcome, even though a relation between treatment response and current source densities of the N1 LDAEP was obtained [155]. Related to this measure, Spronk et al. [109] found that a larger (more negative) N1 amplitude was related to a larger reduction of depressive symptoms after treatment with antidepressants.

In ADHD, ERP components have also been investigated as predictors for treatment response to stimulants. Sangal and colleagues found the topography of the P3, specifically the right frontocentral to parietal amplitude ratio, to be predictive of response to various stimulants, i.e. methylphenidate [156], atomoxetine [157] and pemoline [158]. They also reported a study in which poor responders to pemoline were treated with the antidepressant imipramine. Within this subgroup, poor responders to imipramine demonstrated slower P3 latencies [159]. Sunohara et al. [160] could not replicate ERP P3 and N2 latencies as baseline predictors for treatment outcome in ADHD children but found some treatment-emergent effects which are in agreement with Winsberg et al. [161].

Conclusion

Sleep EEG parameters have been found to be of discriminative and predictive value, especially in MDD. A widespread clinical use might be dampened due to the relatively large subject burden, e.g. one night at a sleep laboratory or even two to rule out first-night effects from findings [162]. In ADHD, there is a lack of studies that analyse EEG sleep parameters, although an association of the disorder with the sleep-wake cycle and especially circadian alterations is evident.

EEG vigilance measures seem to provide a less cost- and effort-intensive approach to assessing wakefulness regulation during rest in contrast to polysomnography. Another advantage of EEG vigilance-based markers can be found in its association with clinical features of MDD and ADHD as outlined above. A biomarker that has a direct link to the behavioural level is more likely to be accepted in clinical routine. Still, there is a clear lack of controlled studies that demonstrate the discriminative value of EEG vigilance parameters for response or non-response in MDD and in ADHD.

For patterns of paroxysmal or epileptiform activity, it remains unclear if treatment or augmentation with anti-epileptic drugs such as valproate, or some specific antidepressants, increase response rates in these MDD or ADHD subgroups. Some evidence exists that non-responders to first-line treatment may benefit. Studies that analyse the treatment of MDD or ADHD with anti-epileptic drugs should report on subgroups based on the occurrence of pathological but subclinical EEG patterns in the future.

Several quantitative EEG markers, especially within the alpha and theta range, revealed a discriminative value regarding treatment outcome. However, findings in this field are often contrary to what might be explainable by the variance of studied patient groups (treatment resistant or not) and at last not by the different treatment approaches that have been studied. Further, methodological and interpretation aspects need to be clarified as it is the case with the difference between diffuse frontal theta versus frontal-midline theta activity in MDD. Based on the existing findings, quantitative EEG measures of the alpha activity, alpha asymmetry and theta frequencies deserve to be in the main focus in future studies of treatment prediction.

EEG connectivity analysis has seen a revival within the past few years, and first findings seem to be promising with regard to its value for treatment prediction. However, the used measures differ broadly; there is almost no study that uses the same measures for the assessment of network interaction and connectivity. Therefore, the studies are hardly comparable. Further, many studies on EEG connectivity do not make an a priori hypothesis about alterations of connectivity between brain regions, resulting in a high number of tests that analyse every pos-

sible connectivity pattern, possibly resulting in type I errors. Identification of the most reliable and valid connectivity parameters and application on hypothesis-driven, predefined networks should be among the first goals of future research in this field.

Not only spontaneous EEG activity, but also ERPs hold value for the improvement of treatment. However, as it is the case in many resting-state EEG markers, there are promising markers that sometimes could not be replicated in small-scale studies. Therefore, larger study groups and controlled trials are needed to estimate the full potential of ERPs.

Since the aim of a personalized medicine approach is to improve treatment of the individual, studies are needed that analyse the predictive value of central nervous system arousal in patients for treatment outcome. Currently, data from the iSPOT and EMBARC trials in MDD are being analysed using this approach.

It should be noted that personalized medicine with a focus on treatment prediction is in need of addressing interindividual variance, which is in contrast to the search for biomarkers that reflect homogeneous diagnostic groups. Therefore, the mentioned differences in findings, sometimes even contrary to one another when looking at predictive markers for treatment response, might yield important information about different treatment options: it is possible that a marker predicts response to one treatment while it also could be found in non-responders to another treatment. The goal will be to disentangle these relationships with standardized and controlled trials, including a variety of treatment arms and by embracing heterogeneity.

Perspectives

The Research Domain Criteria provide a good framework to overcome subjective decisions in the treatment of psychiatric disorders and might help to bridge the gap to the advances made in medical treatment in other domains of medicine. In face of the myriads of available EEG-based parameters, it seems obvious that there will not be one single marker that fulfils all criteria to aid in the diagnosis and even predict treatment in different neuropsychiatric disorders. It will require combining a set of neurophysiological but also clinical and other biomarkers to fulfil the promise of a personalized medicine approach. Simulations on existing data sets and probably the usage of non-linear methods such as artificial networks could help in the analysis of large data matrices to extract meaningful combinations for treatment prediction [96]. It should be noted that the goal is not a final threshold or combination of biomarkers for prediction but a matrix of meaningful parameters that should be subject to further refinements. Furthermore, one fundamental problem to be faced is that of defining clinically meaningful treatment end points. Several different primary outcome measures have been used ranging from the Beck Depression Inventory-II (BDI-II) to the Hamilton Depression Inventory, and also using different criteria such as remission or response, whereas the agreement between these scales is far from perfect [163], thus making the 'ground truth' of 'clinical response' a moving target dependent on the instruments and definitions used.

In the first place it is now necessary to initialize biomarker-guided treatment decisions that lead to increased remission rates in comparison to treatment as usual. Furthermore, in MDD one faces the huge variety of treatment options, ranging from psychotherapy with different branches, over psychopharmacological interventions with completely different modes of action to brain stimulation methods such as TMS or electroconvulsive therapy but also sleep deprivation. In face of the high non-response rates, a framework is urgently needed including different biomarkers that allow for an evidence-based choice of the right treatment option at the right time for the right patients. Preferably markers should be taken into account that can be interpreted in the context of their physiological meaning since this will increase the acceptance of a marker by clinicians. Furthermore, as mentioned above concerning alpha asymmetry, large sample sizes are required to also address gender-, age- and drug class-specific predictors. Therefore, large multicentre studies for the identification of those markers and their thresholds to predict treatment outcome have to be carried out, as is the case with the iSPOT-D and EMBARC studies. The next step will then be to initiate prospective randomized controlled trials that compare the biomarker-based treatment versus treatment based on therapist and patient preferences as it is currently good clinical practice. This way, personalized medicine could help to apply the already existing treatment options in a hopefully more effective and efficient way and thereby decrease the individual burden of disease for patients.

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