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The intervention, the patient and the illness – personalizing non-invasive transcranial brain stimulation in psychiatry

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Abstract

Current hypotheses on the therapeutic action of non-invasive transcranial brain stimulation (NTBS) in psychiatric disorders build on the abundant data from neuroimaging studies. This makes NTBS a very promising tool for developing personalized interventions within a precision medicine framework. NTBS methods fundamentally vary in their neurophysiological properties. They comprise repetitive transcranial magnetic stimulation (rTMS) and its variants (e.g. theta burst stimulation – TBS) as well as different types of transcranial electrical stimulation (tES), with the largest body of evidence for transcranial direct current stimulation (tDCS). In the last two decades, significant conceptual progress has been made in terms of NTBS targets, i.e. from single brain regions to neural circuits and to functional connectivity as well as their states, recently leading to brain state modulating closed-loop approaches. Regarding structural and functional brain anatomy, NTBS meets an individually unique constellation, which varies across normal and pathophysiological states. Thus, individual constitutions and signatures of disorders may be indistinguishable at a given time point, but can theoretically be parsed along course- and treatment-related trajectories. We address precision interventions on three levels: 1) the NTBS intervention, 2) the constitutional factors of a single patient, and 3) the phenotypes and pathophysiology of illness. We propose solutions and discuss future perspectives, e.g. individual MRI-based electrical field strength as a proxy for NTBS dosage, and also symptoms, their clusters, or biotypes instead of disorder focused NTBS. In conclusion, we propose interleaved research on these three levels along a general track of reverse and forward translation including both clinically directed research in preclinical model systems, and biomarker guided controlled clinical trials. Besides driving the development of safe and efficacious interventions, this framework could also deepen our understanding of psychiatric disorders at their neurophysiological underpinnings.

Keywords: non-invasive transcranial brain stimulation, NTBS, TMS, affective disorders, major depression, bipolar disorder, schizophrenia

Abbreviations:

PM precision medicine

NTBS non-invasive transcranial brain stimulation

TMS transcranial magnetic stimulation

tES transcranial electric stimulation

mA milliampere

rTMS repetitive transcranial magnetic stimulation

TBS theta-burst stimulation

DBS deep brain stimulation

tDCS transcranial direct current

tACS alternating current stimulation

FUS transcranial focused ultrasound stimulation

tNIRS transcranial near-infrared stimulation

MDDmajor depressive disorder

EEG electroencephalography

ML machine learning

MT motor threshold

MRI magnetic resonance imaging

AMT active motor threshold

RMT resting motor threshold

RCT randomized controlled trial

MEP motor evoked potentials

DLPFC dorso-lateral prefrontal cortex

18FDG-PET 18fluor-deoxy-glucose positron emission tomography

LTP long-term potentiation

HD tDCS high definition transcranial direct current

IAF individual alpha frequency

FEM finite element models

ECT electroconvulsive therapy

MST magnetic seizure therapy

rsFC resting state functional connectivity

ACC anterior cingulate cortex

DMPFC dorso-medial prefrontal cortex

sgACC subgenual anterior cingulate cortex

GABA gamma-Aminobutyric acid

SC structural connectivity

mMRI multimodal magnetic resonance imaging

ELECT-TDCS Escitalopram versus Electrical Current Therapy for Treating Depression

TRT test-retest reliability

ICC intra-class correlation

HAM-D Hamilton Depression Rating Scale

GMD gray matter density

PANSS Positive and Negative Syndrome Scale

BAC balanced accuracy

IML interpretable machine learning

ALE accumulated-local-effect

STAR*D Sequenced Treatment Alternatives to Relieve Depression

CO-MED Combining Medications to Enhance Depression Outcomes

VMPFC ventro-medial prefrontal cortex

1. Introduction

Precision medicine (PM) represents a concept driven by the aim to individualize treatment and prevention by taking individual genetic, environmental, and lifestyle factors into account. Although these ideas are not completely new (one of many examples is the search for breast cancer genes since the 1980's), the founding of the "Precision Medicine Initiative" in the United States in 2015 (Collins and Varmus, 2015) has led to increased focus on the combination of individual factors to improve treatment in various medical domains. Examples of a successful application of PM are manifold in somatic medicine (e.g. in precision oncology) in which discovery of oncogenic driver mutations and therapies targeted to these mutations have led to impressive progress in the development of treatments for advanced lung cancer. However, precision medicine in oncology also faces its challenges (Panagiotou et al. 2020). For example, biomarker-drug pairing still strongly varies in predicting treatment response and there are instances where computational predictive systems have been used prematurely and image-based treatment monitoring is still in its development.

PM in psychiatry or "precision psychiatry" (a term that, interestingly, first shows up on pubmed.gov in 2015 and gives only 95 results so far – without taking into accounts synonyms such as personalized therapy or individualized treatment) has been conceptualized in parallel to PM in other medical disciplines. Precision psychiatry may represent a paradigm shift in mental health concepts that moves towards individual endophenotypes rather than the broad diagnostic boundaries available to date, technical advances, and predictors of response, or "biomarkers" (Fernandes et al., 2017). For decades, diagnostic categories in psychiatry have been conceptualized in manuals (most recently DSM-5 and ICD-11) based on the best of expert opinions and available data. However, these categories have been in question not to represent true nosological entities (Insel and Cuthbert 2015; Bdzok and Meyer-Lindenberg 2018). One very prominent example is the categorization of depressive disorders that comprises various conditions differing in their phenotypes, neurobiological underpinnings and treatment outcomes. In the past five years, several groups identified depression subtypes

based on biomarkers (e.g. resting state MRI connectivity patterns), which are still under debate (Drysdale et al. 2017; Dinga et al. 2019). For instance, for the categorization of psychosis (Chand et al. 2020; Dwyer et al. 2020), many projects are underway (Brückl et al. 2020). In this scenario psychiatric treatments capable of specifically targeting anatomical structures in the brain come into play such as non-invasive transcranial brain stimulation (NTBS).

NTBS comprises several techniques. Two main representatives are transcranial magnetic stimulation (TMS), where a stimulation coil generating a rapidly changing magnetic field (up to 3 Tesla) induces electric fields at cortical levels, and transcranial electric stimulation (tES), where weak direct or alternating currents (in the magnitude of mA) are applied via electrodes placed on the scalp. Adaptations of these techniques have led to the development of specific treatment protocols used in neuropsychiatric disorders, such as repetitive TMS (rTMS), theta-burst stimulation (TBS), transcranial direct current (tDCS) or alternating current stimulation (tACS). From time to time, novel application forms emerge, such as the recently developed transcranial focused ultrasound stimulation (FUS) or transcranial near-infrared stimulation (tNIRS).

Today's method of applying TMS and TES dates back to the mid 1980's and late 1990's, respectively (Barker et al., 1985; Nitsche and Paulus, 2000). Here, we address how NTBS has developed in terms of its clinical relevance and the current efforts to integrate NTBS into a precision psychiatry framework.

2. The starting point

Precision medicine, individualized or personalized medicine are terms often used interchangeably. In psychiatry, NTBS development began in therapy-resistant major depressive disorder (MDD). First reports on the efficacy of rTMS for depression date back to 1993 (Belmaker and Fleischmann, 1995; Höflich et al., 1993); while only two patients were examined, the result was similar to what we know today - response rates among pharmacotherapy-resistant depressed patients lie around 50% (Blumberger et al., 2018).

Specifically, TMS had no effect in one patient and a slight effect in the other. First studies including more participants found similar effect sizes (4 out of 6 patients improved (George et al., 1995) or 11 out of 17 (Pascual-Leone et al., 1996)). Until today, rates of response to a given intervention obtained by rigorously designed randomized, placebo-controlled trials, have been the therapeutic benchmark for research in MDD, irrespectively of whether pharmacological treatments, psychotherapy or brain stimulation were applied or which psychiatric disorder was studied. Although this is still considered the gold-standard approach to prove the efficacy of an intervention, this heuristically implies a dichotomy where there is a rather large variety of individual trajectories of response, both for active interventions as well as for placebo treatments.

In fact, the application of rTMS at prefrontal stimulations sites for MDD followed a precision-psychiatry rationale based on early neuroimaging findings (Baxter et al. 1998; George et al. 1995; Pascual-Leone et al. 1996) to overcome the depression-based dysfunction in prefrontal cortex activity (George et al., 1994; George et al., 1995) - and argued that rTMS effects might be induced by modulating the activity of whole brain regions and through effects on hormone levels (George et al., 1995; George et al., 1996). The rationale for tDCS in depression followed the same principles (Boggio et al., 2008; Fregni et al., 2006), with an earlier focus on whole-brain activity and brain oscillations (Keeser et al., 2011a; Keeser et al., 2011b), possibly due to the non-focal character of the stimulation and great compatibility with electroencephalography (EEG). Remarkably, even early studies underlined the importance of adjusting technical stimulation parameters (Padberg et al., 1999; 2002). Individual titration of stimulation intensity in relation to the motor threshold (MT) and identification of 100% to 120% MT intensity as effective were an early achievement in personalizing rTMS treatment, and have been applied until now (Blumberger et al. 2018; Sackeim et al. 2020). Early studies also paid attention to but also of individual factors on the patient level such as medication intake and characteristics of the depressive episode (George et al., 1995; Pascual-Leone et al., 1996).

Today, these factors are discussed in relation to the heterogeneity of individual response patterns. While heterogeneity of response trajectories was traditionally discussed as a limitation, the PM focus has reframed heterogeneity, as advanced statistical methods from machine learning (ML) to Bayesian statistics allow parsing of patient-individual components and response dynamics and could reveal pathophysiological underpinnings and mechanistic principles. Heterogeneity in NTBS response can already be demonstrated in standard excitability measures at the primary motor cortex (Wiethoff et al., 2014; Strube et al., 2015; Latorre et al., 2019). Such variability may be attributed to all three interacting entities, namely the intervention, the individual person and the illness, i.e. an individual state: a) Intervention: e.g. standardized protocols either based on individual motor threshold (MT) measures for adjustment of TMS intensity or fixed stimulation intensities as in tDCS may produce inter individually varying electric field densities at the cortex level; b) constitutional factors comprising anatomical and neurophysiological characteristics may for example create magnetic resonance imaging (MRI) based functional connectome patterns as individual as a fingerprint (Finn et al.; 2014); c) a disorder interacts with the individual´s constitution and may finally change it, e.g. in a chronic course of disease. In MDD, biotypes or endophenotypes may be identified which could be differentially responsive to NTBS treatments (Drysdale et al. 2017; Dinga et al. 2019).

3. The intervention:

3.1 Parameters and the issue of dosage

There are a multitude of stimulation parameters for each NTBS intervention and there is no single parameter for defining NTBS “dosage”. Some parameters, e.g. stimulation intensity or number of stimuli, were particularly focused as clinically relevant parameters in order to increase effect sizes of the respective method. For other parameters, minor differences may lead to divergent effects. Examples are intermittent and continuous theta burst protocols (iTBS

and cTBS) as variants of traditional rTMS protocols (Huang et al. 2005). Both iTBS and cTBS only differ in terms of stimulation free intervals, but neither in bursts, frequencies and stimuli numbers. The tendency towards selecting putatively more effective protocols is also valid for iTBS. While Huang et al. (2005) applied 80% active motor threshold (AMT) intensity , 80% resting MT (RMT) intensity was used for antidepressant iTBS instead (Holzer and Padberg 2010), and most recently iTBS intensity was increased up to 120% RMT stimulation intensity in the large THREE-D randomized controlled trial (RCT), where iTBS was found to be non-inferior to 10 Hz rTMS in terms of antidepressant efficacy (Blumberger et al. 2018; Chu et al. 2020).

3.2 From scalp measurements to functional targets

Development of NTBS targeting has evolved in parallel to our understanding of brain function and connectivity. In MDD, the target for rTMS in early studies (George et al. 1995; Pascual-Leone et al. 1996) followed a topographical idea of prefrontal dysfunction (Baxter et al. 1989). Motor evoked potentials (MEPs) served as a precise method for directing TMS to the M1 region, thus many rTMS protocols in non-motor regions chose M1 as a reference. This resulted in the development of algorithms like the so-called “5 cm rule” for targeting the left DLPFC. Accuracy of these approaches was low (Herwig et al. 2000). In a next step, Herwig et al. (2003) tried to functionally target relevant DLPFC locations based on identifying hypometabolic regions in individual 18fluor-deoxy-glucose positron emission tomography (18FDG-PET), however, could not observe a superior antidepressant effect compared to without hypometabolic targets. Later, anatomical targets were chosen based on structural anatomic landmarks, and the superiority of such approaches over the standard 5 cm position in terms of their antidepressant effects has been shown (Fitzgerald et al. 2009). Most recently, functional connectivity measures represent the most promising track for individual targeting, e.g. Fox and colleagues have demonstrated along an impressive line of research that individual connectivity between DLPFC targets and the subgenual cingulate gyrus is a very promising target for rTMS

treatment in depressive disorders (Fox et al. 2012; Weigand et al. 2018, Cash et al. 2020). However, optimal targets may differ for subtypes/biotypes of MDD and different rTMS protocols (Drysdale et al. 2017). Connectivity targets were based on a large connectome database (N=1000; Weigand et al. 2018), and findings in the discovery sample (N=30) were reproduced in the active (N=87) compared to a sham replication sample (N=87).

Other approaches toward functional targeting rely on neurophysiological (e.g. MEP parameters) or physiological (e.g. heart rate) readouts. A most promising research line using MEP measures for state-dependent NTBS is represented by so-called closed-loop approaches (Bergmann 2018, where e.g. TMS directed to EEG negative vs. positive peak of the sensorimotor μ-rhythm led to long-term potentiation (LTP)-like vs. no change in corticospinal excitability (Zrenner et al. 2018). An example of prefrontal functional TMS targeting guided by physiological read-out is the neuro-cardio-guided TMS approach, where heart rate modulation was observed after 10 Hz or 1 Hz rTMS in terms of deceleration or acceleration, respectively (Iseger et al. 2017; Kaur et al. 2020). The findings support the notion of an existing fronto-vagal-network that may provide a functional readout for developing therapeutic NTBS methods in MDD and other psychiatric disorders (Iseger et al. 2020).

Regarding the precision of NTBS methods themselves, accuracy may depend on the focality and for rTMS turning a figure-of-8-coil around its center may lead to the recruitment of different resting state networks (default mode or frontoparietal, Opitz et al. 2016). Even for a very non-focal NTBS approach, i.e. transcranial electrical stimulation (tES), precise positioning of electrodes may matter to an extend we are not aware of: Combining direct intracranial measurement of electric fields (efields) generated by tES in epilepsy patients and computational efield modeling, Opitz et al. (2018) recommended electrode placement accuracy to be < 1 cm for a reliable application of tES across sessions.

In sum, accuracy in targeting NTBS and precision in target selection are separate topics. Using online neuronavigation targeting for rTMS and more focal tES modalities, e.g. high definition tDCS (HD tDCS), accuracy easily reaches a millimeter range. Target selection, however, is

related to state dependent functional brain connectivity in MDD and its interaction with structural or more stable characteristics.

3.3 Extending the parameter space

From early days of rTMS, the parameter space has been extended in various attempts to increase treatment efficacy (Brunoni et al. 2017). Examples of this evolution are protocols with higher numbers of daily stimuli in comparison to earlier studies (O´Reardon et al. 2007; Padberg et al. 2001) up to accelerated rTMS protocols where a four-week treatment is collapsed into a few days with multiple treatment sessions per day, or increasing stimulation intensity from subthreshold dosage below the individual AMTor RMT to 120% RMT in two large rTMS RCTs in MDD (O`Reardon et al. 2007; Levkovitz et al. 2015).

In the frequency parameter space, patterned rTMS and individualized rTMS frequencies have been developed. For example, individual alpha frequency (IAF) guided rTMS has been applied with conflicting results across disorders: Controlled trials of rTMS for negative symptoms in schizophrenia showed that IAF guided rTMS was superior to sham, 3 Hz, or 20 Hz stimulation (Jin et al. 2006), or to sham alone (Jin et al. 2012), but this was not found to the same extend for MDD (Arns et al. 2010). Results of more recent trials again suggest an intriguing relationship between a putatively effective rTMS frequency and the IAF (Corlier et al. 2019; Roelofs et al. 2020). In contrast to IAF guided rTMS, patterned rTMS protocols were not further individualized in terms of individual EEG guidance, i.e. original TBS protocols (Huang et al. 2015) have been applied in early clinical case series or studies in MDD and schizophrenia with the exception, that RMT instead of AMT was used for individual adjustment of prefrontal rTMS intensity (Grossheinrich et al. 2009; Holzer and Padberg 2010; Plewnia et al. 2014 a; b). Blumberger et al. (2018), however, investigated iTBS at much higher dosage of 120% RMT in a large RCT where 10 Hz and iTBS were compared in a non-inferiority design as compared to prior studies. The rationale behind these strategies appears to be related to basic observations for primary motor areas where MEPs increase in amplitude in relation to the intensity

expressed as maximum stimulator output, i.e. the so-called sigmoid input-output I/O curve. However, the issue of intensity may be much more complex as dose response relationships may not be linear, and different intensities may lead to recruitment of different neuronal populations in cortical layers.

Finally, there is a trade-off between stimulation intensity and focality: Higher intensities may exert stimulation effects in a larger grey matter volume, but could also alter the topography of stimulation. Consequently, effects may be localized at different cortical targets when the optimal does not equal the maximum dosage. In this respect, high intensity protocols may point in a similar direction as the application of less focal rTMS coils, e.g. so called H-coils (Levkovitz et al. 2015).

Another approach for increasing the efficacy of iTBS is represented by accelerated iTBS protocols (Duprat et al. 2016; Cole et al. 2020). For example, 20 to 50 sessions of iTBS may be condensed to four days at five sessions per day (i.e. a total of 32.400 pulses/day; Duprat et al. 2016) or even to five days at ten sessions per day (i.e. a total of 90.000 pulses/day; Cole et al. 2020). Effects of these protocols have been observed on MDD psychopathology, on suicidality as well as on structural MRI measures (Duprat et al. 2016; Cole et al. 2020; Desmyter et al. 2016; Baeken et al. 2020).

3.4 Introducing efield modeling

Up to date, however, rTMS protocols have mainly been individualized in terms of rTMS intensity, but not beyond adjustments using AMT or RMT related criteria, and tES protocols have not even been individualized according to intensity criteria.

Computational finite element models (FEM) of efields have been developed for modeling NTBS induced efields in order to establish dose effect relationships based on cortical electric field density as a proxy of dosage (Thielscher et al. 2011). Translational approaches have systematically developed our understanding of efield modelling and additionally validated these models based on in vivo measurements in animals and humans (Opitz et al. 2016,

Alekseichuk et al. 2019). In a subsequent translational step, pilot studies provide first data in humans suggesting that efield strength is indeed related to behavioral or physiological effects (Antonenko et al. 2019, Mezger et al. 2020). Nevertheless, the jury is still out on this topic and larger controlled experimental or clinical studies are needed to confirm the relevance of efield models for behavioral or therapeutic effects of NTBS.

Inter-individual variability, however, also plays a major role in efield parameters. Antonenko et al. (2020) investigated efield strength and focality for different tES montages in younger and older adults. Strength but not focality of efields was highly correlated across montages. The average spatial distributions were similar in both age groups with a higher variability in the younger group. Moreover, there was a robust inverse relationship between general field strength and head volume as well as relative skull, skin, and CSF volumes. Beyond the level of average efield strength, there is a large inter-individual variation between subjects, which is not yet fully explored (Figure 1). Thus, future studies should investigate these variations in more or less homogeneous groups and between samples (i.e. comparing patients with MDD or and schizophrenia and healthy subjects) and extend this approach also from NTBS to convulsive methods (i.e. electroconvulsive therapy [ECT] and magnetic seizure therapy [MST] (Lee et al. 2017; Kallioniemi et al. 2019). First protocols are now proposed for introducing MRI based efield guided tDCS and TMS in experimental or clinical applications (Kennedy et al. 2018; Balderston et al. 2020).

4. The patient

To adjust NTBS to individual patients´ needs, constitutional characteristics and functional changes due to a psychiatric disorder interact in a highly complex and interleaved manner. The earlier the disease onset in life occurs (e.g. early onset during adolescence) and the longer a disorder persists (e.g. in persistent depressive disorder) the more difficult it becomes to

disentangle state and constitution. Structural and functional connectomes are personal characteristic features as unique as individual fingerprints (Hill et al. 2010; Finn et al. 2015). Nevertheless, MRI derived resting state functional connectivity (rsFC) shows a considerable variability in single subjects (Laumann et al. 2015; Gordon et al. 2017) though rsFC is determined by common organizational principles and stable individual characteristics, whereas task-state and day-to-day variability depending on investigated brain regions and networks exhibit rather modest contributions (Gratton et al. 2018). Moreover, individual rsFC variability was highest in heteromodal association cortices (i.e. PFC regions) and minimal in unimodal cortices (i.e. unimodal sensory and motor cortices) (Mueller et al. 2013). For therapeutic NTBS applications in psychiatric disorders, this is particularly relevant, as PFC subregions are main target areas.

Based on rsFC networks, novel targets, representing hub regions interconnecting networks associated with different functions, such as cognitive control, rumination, and motivation generation, emerged. These include more frontal/ medial as well as later regions of the PFC, such as the dorsomedial, ventromedial, or ventrolateral PFC, or the frontopolar cortex (Downar and Daskalakis, 2013).

A further advance was the report of a specific interconnection, i.e. the anticorrelation between the PFC target region and the limbic subgenual anterior cingulate cortex (ACC), to be associated with the efficacy of rTMS (Fox et al., 2012).

Overall, a large body of evidence from the last 10 years suggested FC of several regions, very often involving a combination of prefrontal regions - DLPFC, DMPFC, or ventromedial PFC - and subcortical regions - predominantly cingulate cortex, but also hippocampus, amygdala, striatum – as predictors of rTMS response in depression (Wu et al., 2020a) (Salomons et al., 2014) (Furtado et al., 2013) (Boes et al., 2018) (Avissar et al., 2017; Lan et al., 2016; Liston et al., 2014). These regions are of importance not only as single units, but mainly in their role as parts of larger resting-state networks involved in specific emotional processes, the most prominent example being the default mode network involved in in-ward

thoughts processes, such as rumination (Downar et al., 2014; Philip et al., 2018b; Siddiqi et al., 2020). For tDCS, regional functional activation has been associated with response outcomes, by showing that baseline activation of the left DLPFC can differentiate between tDCS responders and non-responders with a high accuracy (Nord et al., 2019).

A recent meta-analysis showed that rsFC of the default mode network predicted response to several antidepressant treatments, such as pharmacotherapy, psychotherapy, electroconvulsive therapy, vagus nerve stimulation, and, finally, with the largest effect size also rTMS – for the latter, specifically the perigenual ACC – VMPFC connectivity predicted improvement after rTMS (Long et al., 2020).

Other than functional activation of brain regions, the metabolic activity of the subgenual anterior cingulate cortex (sgACC) (Baeken et al., 2015; Cash et al.) or DMPFC and limbic structures (Li et al., 2010) could be associated with rTMS response in depression as well, but did not prove as an effective targeting method (Paillere Martinot et al., 2010). Magnetic resonance spectroscopy – a technique that measures concentration of brain metabolites, mainly glutamate and gamma-Aminobutyric acid (GABA) – led to detection of promising predictive factors as well. Baseline concentrations of glutamate in the DLPFC have been shown to be characteristic for rTMS responders (Luborzewski et al., 2007) and GABA increase in the MPFC was described in all patients treated with rTMS, showing a stronger increase in responders (Dubin et al., 2016).

Finally, recent resting EEG studies propose markers for future response prediction and further development towards a personalized NTBS. For antidepressant pharmacotherapy for example, latent-space machine-learning algorithms tailored for resting-state EEG allowed identifying sertraline-specific signatures (Wu et al. 2020). Corlier et al. (2019) reported that both IAF and the absolute difference between IAF and 10 Hz rTMS frequency (IAF-10Hz) are related to treatment outcome after unilateral 10Hz rTMS of the left DLPFC, but not after unilateral 5 Hz rTMS or sequential bilateral rTMS, which has been replicated for 10 Hz rTMS by Roelofs et al. (2020). More general EEG markers, e.g. increased theta connectivity in

responders at baseline (Bailey et al. 2018), were not replicated (Bailey et al. 2020), underlining the importance of independent, external validation.

In comparison to markers mentioned so far, representing rather fast-changing markers of brain states, brain structure is believed to undergo changes rather slowly and is often considered a trait marker. A promising approach is to correlate these state and trait markers, i.e. compare the FC and structural connectivity (SC) derived from diffusion-weighted images. As such, frontocingulate SC has been shown to predict antidepressant response after rTMS, interestingly identifying the same key regions known from FC analyses (Klooster et al., 2020).

In tDCS studies, metabolites, in particular the glutamate-GABA ratio, an “index of neurochemical excitability” proved useful in modulating behavior after stimulation in healthy subjects (Filmer et al., 2019). Although the transition to the psychiatric clinical population is still lacking, GABA has been identified as a promising factor enabling recovery from motor stroke (Blicher et al., 2015).

For tES methods, it is more difficult to focally target cortex regions. However, high definition (HD) approaches have been established (Bikson et al. 2019), and more precise focusing may be achieved by functionally involving brain regions through additional tasks or interventions that could activate a distinct cortex region within a wider regional field of effective neuromodulation (Bajbouj and Padberg 2014; Philip et al. 2017) Recently, our group has analyzed prefrontal grey matter volumes and rsFC based on the parcellation by Sallet et al.. (2013) in a multimodal MRI (mMRI) data set from the ELECT-TDCS study by Brunoni et al. (2017). The Escitalopram versus Electrical Current Therapy for Treating Depression Clinical Study (ELECT-TDCS) is the largest RCT on tDCS in MDD to date and compared tDCS (plus placebo medication), escitalopram (plus shamtDCS), and a double placebo condition (i.e. placebo medication and shamtDCS) within a three-arm non-inferiority design including 245 subjects. This study could not show non-inferiority of the tDCS condition to the escitalopram condition, however, the tDCS arm had a better outcome than the double placebo condition (Brunoni et al. 2017). In a subsample of ELECT-TDCS patients with mMRI data at baseline,

our group did not observe a significant association between baseline rsFC for PFC regions and patients' antidepressant response (Bulubas et al. 2020). Most interestingly, however, the individual antidepressant response was associated with grey matter volumes of PFC subregions in the tDCS group only, however, this association was not observed for escitalopram and placebo groups (Bulubas et al. 2019). In addition, Suen et al. (2020) observed that the individual clinical outcome was related to the individual efield strength in the left ACC. Thus, also for tDCS a therapeutic outcome may be related to individual factors of cortex morphology. Continuing this line of tDCS research, Wörsching et al. (2018) investigated the test-retest reliability (TRT) of neuromodulatory effects by DLPFC tDCS (2mA, 20 min, anode over F3 and cathode over F4) on rsFC in healthy subjects. Interestingly, the distribution of voxel-wise intra-class correlation (ICC) coefficients was shifted towards lower TRT reliability after active, but not after sham tDCS across three sessions. Thus, we hypothesize that prefrontal tDCS may even increase intra-individual variability in rsFC, in addition to inter-individual variability already observed for the primary motor cortex (Wiethoff et al. 2014; Chew et al. 2015). Such intra- and inter-individual variability may reflect different aspects of state-dependent as well as constitutional factors which are closely linked to each other.

5. The illness

The third space of parameters allowing personalization of NTBS methods be, is represented by the disorder and its subtypes, endophenotypes or biotypes. Due to the limitations of current and future classifications systems (DSM-IV to DSM-5; ICD-10 to ICD-11), limited progress has been made in the development and validation of diagnostic categories for the major psychiatric disorders (i.e. MDD, schizophrenia, bipolar disorder, and others). Thus, cross-sectional data may provide only very limited information in this respect, but can theoretically be enriched by biomarkers derived from MRI based information (e.g. rsFC MRI parameters) or biological factors, (e.g. neurotrophic factors, interleukins and their receptors; Drysdale et al. 2017; Brunoni et al. 2018). However, the level of the disorder extends the space of parameters in the

dimension of time, i.e. longitudinal trajectories can be identified for average scores of psychopathology rating, symptom clusters, biological markers, and response characteristics. Thus, such trajectories are informative regarding the dynamics of psychopathology and pathophysiology as they allow an in-depth analysis of the capacity for the system for change. In this respect, cross-sectional data at baseline may predict changes on these different levels, as well as early change in distinct domains may predict a later change during the long-term course. In a first step, such data may be extracted from large RCTs, e.g. the ELECT-TDCS trial. However, these trials have been powered for clinical outcomes, but not for prediction, and biomarker-enhanced RCTs as well as real-world mega cohorts (e.g. the Global ECT-MRI research collaboration [GEMRIC] consortium in the field of ECT) will provide superior solutions for addressing this issue.

In early predictor studies, disease-related factors were proposed based on regression analysis derived models in limited data sets from open and controlled trials (Holtzheimer et al. 2004; Fregni et al. 2006; Brakemeier et al. 2007; 2008). Several factors were replicated, i.e. (pharmaco) therapy resistance and episode duration (Holtzheimer et al. 2004; Fregni et al. 2006; Brakemeier et al. 2007; 2008), similar to findings for medication or ECT (Rush et al. 2006; Prudic et al. 1996). However, numerous other factors, e.g. baseline sleep disturbances or single items of depression were not consistently detected (Brakemeier et al. 2007; 2008). More recent studies confirmed single earlier findings, e.g. univariate predictor analysis based on the sample of the large RCT on rTMS in MDD by O´Reardon et al. 2007 confirmed that a lower degree of pharmacotherapy resistance predicts better antidepressant response to rTMS, treatment resistance was also capped by protocol to less than five adequate treatment failures in the current episode (Lisanby et al. 2009). Trevizol et al (2020) investigated prediction of remission based on the data of the most recent large rTMS RCT in MDD (Blumberger et al. 2018). Baseline severity of depressive and anxiety symptoms, employment status, failure of more than two antidepressant trials, and age exerted effects on the odds of achieving remission after rTMS defined by an 17-item Hamilton Depression Rating Scale (HAM-D)

Score. Again some of these findings converge with previous reports, e.g. from meta-analyses or analyses of pooled data (Kedzior et al. 141; Fitzgerald et al. 2016), though these findings are so far not of major clinical relevance, e.g. for stratified treatment.

The advances in analytical methods including machine learning algorithms, Bayesian statistics and others currently leverage a rapid development in analyzing clinical data in conjunction with multiple levels of observations, e.g. multimodal imaging data, serum marker, and genetic/epigenetic information (Koutsouleris et al. 2018). Based on a large RCT on rTMS for negative symptoms in schizophrenia (Wobrock et al. 2015) 92 individual structural MRI data sets at baseline were analyzed from the multisite RESIS trial, and the MRI-based pattern (i.e. reduced gray matter density [GMD] in prefrontal, insular, medio-temporal, and cerebellar cortices, and increased GMD in parietal and thalamic structures) predicted the endpoint (i.e. nonresponse vs response defined by a ≥20% pre-post Positive and Negative Syndrome Scale (PANSS) negative score reduction) with a cross-validated balanced accuracy (BAC) of 85% for active rTMS, and only 51% (48%/55%) for sham rTMS. As said above, however, it cannot be differentiated whether this pattern rather comprises constitutional or disease related factors.

In a comprehensive attempt, we recently analyzed clinical data on tDCS in MDD from the ELECT-TDCS trial (Brunoni et al. 2017). In the first study, a machine learning approach was used for the single subject prediction of the clinical response to tDCS, escitalopram and placebo. The feature data set included baseline data for sociodemographic, clinical, somatic, treatment-related and depression-related domains (Kambeitz et al. 2019). Using a XGBoost tree boosting algorithm, response to tDCS was predicted with 67% (95%CI 62-71%), to escitalopram with 56% (50-61%) and to placebo with 45% (39-52%) balanced accuracy.

Though promising, these findings are lacking external validation in independent samples as well as interpretability. Both limitations may be overcome, the first within an Open Science framework which could provide independent samples from other RCTs, the latter by approximations to the directionality of effects in feature importance using interpretable machine learning (IML) tools such as accumulated-local-effect (ALE) approaches (Figure 3).
Thus, we propose to apply such approaches across large data sets from different RCTs on therapeutic NTBS, even comparing rTMS and tDCS studies.

Understanding the variability of individual trajectories according to subgroups and investigating their specific response predictors is another strategy for identifying the best responders in advance, but also patients who are very unlikely to benefit from rTMS at all (Figure 4). Using data from a large THREE-D study on rTMS (Blumberger et al. 2018), Kaster et al. (2019) identified four rTMS response trajectory groups and associated baseline features. However, Kaster et al. (2019) did not compare rTMS findings with pharmacotherapy or placebo responses, which leaves the question of specificity of these findings unanswered. Also based on the ELECT-TDCS trial, we analyzed response trajectories for tDCS, escitalopram and placebo (Goerigk et al. accepted) and observed distinct within-treatment trajectories: They were identified as “no/minimal”, “slow” and “rapid” trajectories, and some were already detected after week one of treatment. Comparison between groups revealed that there were numerically more rapid improvers in tDCS vs. placebo, and less no/minimal improvers in escitalopram. Our data also confirmed that factors, such as benzodiazepine use, treatment resistance, and depression severity were negatively associated with the primary outcome for tDCS.

In addition, the analysis of change in symptom clusters as well as biotypes and their prediction completes the array of strategies rather based on individual subjects than on groups (Figure 4). Chekroud et al. (2017) described a three symptom cluster solution (i.e. core emotional, atypical and sleep symptoms) for the response to pharmacotherapies in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial and applied machine

learning to predict outcomes specific to each symptom cluster in a second large sample from the Combining Medications to Enhance Depression Outcomes (CO-MED) trial. The concept of symptom clusters can be easily extended to phenotypes and biotypes.

In their seminal work identifying four biotypes of depression based on clinical (anhedonia vs. anxiety-related traits) and functional connectivity (frontostriatal vs. limbic connectivity traits) characteristics (Drysdale et al., 2017), Drysdale et al. have also shown that two of these biotypes were associated with a significantly stronger response to DMPFC rTMS. If replicable (Dinga et al., 2019), this precision medicine-based approach might lay ground for a more precise diagnostic classification of depressive disorders. The relevance of a combination of rsFC and clinical symptoms was further supported by Downar et al. (2014) by showing that non-responders to DMPFC rTMS are characterized by higher levels of anhedonia symptoms and aberrant connectivity to the left ventro-medial prefrontal cortex (VMPFC), from several regions, for example reduced connectivity from DLPFC and DMPFC to VMPFC (Downar et al., 2014).

In a very recent study, Siddiqi et al. (2020) reported that targets may differ for discrete clusters of depressive symptoms, i.e. dysphoric symptoms (e.g. sadness and anhedonia) and anxiety and somatic symptoms responded best to different circuit targets. If replicated, these findings are encouraging for the development of personalized NTBS approaches guided by clinical information about the disease.

6. Conclusions and Perspectives

Personalization of NTBS needs to address the variability of people and disorders. Inter- and intra-individual variability were traditionally regarded as a limitation for the development of standardized procedures and treatment. Also translational research from bench to bed had usually encountered this problem, i.e. what works in controlled experiments in animal models does not work in the colourful variety of human conditions. Due to rapid development of applied statistics during the last decade, an armamentarium of new methods is now available which offer solutions for complex questions of variability. This parallels the rapid development in

multimodal neuroimaging which also leads to an increase of the explanatory power in neuroimaging informed clinical trials.

On the intervention site, variation of parameters is ubiquitous, and accuracy precision may be differentiated, i.e. accuracy could mean an accurate TMS coil or tDCS electrode position in relation to a structural cortical target, whereas precision may refer to directing the intervention to pathophysiologically relevant targets. The latter is particularly based on our current understanding of brain networks, representing not only topographically linked nodes, but rather dynamic arrays defined by oscillatory brain activities.

Development of personalized treatment also means to address constitutional characteristics and disorder related factors in their interdependence, and the course over time (i.e. single patient trajectories) may allow to disentangle these interactions. Large RCTs on NTBS may provide data sets for multilevel analyses (e.g. combining machine learning for prediction from baseline, detection of symptom clusters and their dynamics during and after NTBS, and identifying response trajectories as well as characteristics of trajectory membership). In a next step, however, multimodal, biomarker-informed RCTs as well as Mega-Cohorts will reveal new pathways for research on individual factors.

Though unknown, whether precision psychiatry will ultimately succeed in individualized tools, it will add a very valuable line of research which assesses the interaction between the system and an intervention (or generally speaking the patient and the therapist), which will provide many new fundamental insights into the origin and the dynamic of mental disorders. In another complex system (“the weather”), meteorology has led to deep insights into climate and its changes, though the forecast beyond a week is still limited.

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