Chapter 12: Translation to the clinic and other modalities


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The translation of neurofeedback (NF) into legitimate, tangible, clinical applications requires focusing on three elements in the procedure (see Figure 1): 1. **Improved precision** of neural targeting through activity decoders, network functional-connectivity, and/or feedback context. For example, data-driven NF, where the targeted neural signal is selected using AI/machine learning algorithms, has already demonstrated promising implications for “precision” in neuromodulation (see Chapter 10 for clinical applications). By using such an approach, the specific neural circuit related to a psychiatric disorder or the specific pattern of neural activity an individual has to symptom-provoking stimuli can be determined and targeted. 2. **Increased scaling** of application through EEG informed by fMRI and the use of mobile devices. For example, using AI to develop common EEG “electrical fingerprints” to predict fMRI BOLD activity in the target region of interest (Meir-Hasson, Kinreich, Podlipsky, Hendler, & Intrator. 2014; Meir-Hasson et al., 2016). NF targets selected by this approach have been successfully used for selfregulation (see Chapter 8 for clinical applications). The advantage of this technique is that, relative to fMRI-NF, EEG-NF is cheaper and more accessible, thus allowing for the potential application of NF to a much greater range of patients. In the future, EEG-NF is likely to become even less costly, potentially to the point where it may be run through mobile interfaces such as cellphones. 3. **Enhanced personalization** of the training procedure. This can be achieved by employing mobile technology to cue training based on state indices, by improving individual targeting through disorder-specific content in the feedback, and by using adaptive feedback based on on-line predicted success or monitored state. For example, using trauma-related individual content as feedback was proven more effective for NF in Post-Traumatic Stress Disorder (PTSD) than using neutral content (see Chapter 8). Likewise, pictures of individual phobia objects (e.g. snake or mice) have been successfully used to decode personal brain targets (see Chapter 10). In this chapter we will discuss the aforementioned developments, with the aim to best guide the way forward for the adaption of NF into real-life usage.
1. Precision of the neuromodulation target

Recent NF techniques have begun to borrow from AI approaches when selecting neural signals to be targeted. In comparison to experimental designs that aim to manipulate hypothesized neural signals (hypothesis-driven), these recent techniques allow for experimental designs that aim to manipulate neural signals that are inherent in the data itself (data-driven). When NF is applied based on neural signals that were selected in a data-driven manner, the concerns that these signals were selected due to human bias or bias in the literature can be ruled out. In terms of clinical applications, the targeting of “dysfunctional” neural signals that were selected in a data-driven manner should allow NF to directly influence the specific neural circuits related to a specific disorder. This is an advantage over more traditional symptom-based treatments for psychiatric disorders, which are blunter and less specific; for example, SSRIs, which are given to patients who are diagnosed with a range of disorders from depression to anorexia, inhibit serotonin reuptake receptors across the whole brain and even in other parts of the body such as the dietary tract. Because data-driven NF aims to manipulate neural activity in more localized regions of interest (ROIs), the side-effects are expected to be greatly reduced when compared to traditional treatments such as medication. Depending on the exact technique selected, the related NF can be individualized with a high degree of precision and/or it can be used to train individual patients to induce healthier network-level brain activity. Two such data-driven NF techniques—Decoded Neurofeedback and Functional Connectivity Neurofeedback—will be described below in terms of current status and future promise. In addition, the use of immersive virtual reality technology and the use of context appropriate interfaces to more precisely induce the neural activity of interest will be discussed.

a. Decoded NeuroFeedback (DecNeF). Conventional fMRI NF paradigms are usually employed with the goal of training participants to either up- or down-regulate average fMRI signals from specific brain ROIs in a univariate way. Instead of being trained to regulate average fMRI BOLD signals, participants in a DecNeF paradigm are trained to implicitly regulate multi-voxel patterns (MVP) of BOLD signals (see Chapter 2 for details). Recent advancements in decoding techniques have allowed for the MVP decoding of individual subjects’ neural patterns of activity to specific stimuli. This means that disease-relevant stimuli, for example stimuli that elicit phobic responses, can be decoded and this can be used as a target for NF. As a consequence, DecNeF has recently grown rapidly as a novel neurofeedback procedure with many potential basic science, as well as clinical, applications (Watanabe et al., 2018; Shibata et al., 2019; Chapters 4, 10, 13, and 14).

Importantly, DecNeF does not require trainees to understand what mental state or neural representation is associated with brain activation manipulation success (Chapters 4, 10 and 13). This is especially beneficial for clinical purposes, as it can bypass the distress induced by conventional therapies, such as exposure therapy. Not only does DecNeF appear to hold much promise in clinical settings, but additionally it may prove helpful in the clarification of the causative effects of the induction of different neural activity patterns within predetermined ROIs on whole-brain neural activity, symptoms, and/or behavior.
There are two possible approaches to designing DecNef experiments in a clinical setting. First, one can design a DecNef experiment where the “to-be-induced” brain activity is similar to that which is induced during more conventional treatments. For example, by the implicit DecNef induction of brain activity patterns corresponding to feared stimuli, it has been shown that objective fear to these stimuli can be reduced (Koizumi et al., 2016; Taschereau-Dumouchel et al., 2018) This is comparable to exposure therapy without conscious awareness (Figure 2). DecNef might also be used to reproduce the effects of treatments that involve Transcranial magnetic stimulation (TMS) or Transcranial direct-current stimulation (tDCS). TMS and tDCS can be used to activate or deactivate neural activity in a ROI by an electromagnet or a low electric current. There are cases in which the mechanism behind the disease might not reside in the TMS stimulated ROI itself. Instead the therapeutic effects may occur as a result of the TMS stimulated ROI modulating neural activity in other “disease-related” regions of the brain (e.g. see Fonzo et al., 2017). Using MVPA, the “disease-related” patterns of neural activity could be directly decoded from these “disease-related” regions and then directly targeted with DecNef. DecNef targeting of these “disease-related patterns” in the “disease-related” regions should be less invasive than TMS, and since it would be more direct it might also prove more effective. Second, one can design DecNef experiments to “normalize” disease-specific abnormal brain activity patterns. By comparing brain activity patterns between patients and healthy controls, or by comparing those between pre- and post-effective treatment, we can define “normal” brain activity patterns. Subsequently, by the use of DecNef procedures in which “normal” patterns of brain activity are induced, patients (including potentially those who are resistant to standard therapies) may find a reduction in symptomatology.

DecNef comes with its own list of considerations required for clinical application. First, target patterns of neural activity must be decoded in advance. The procedure itself can sometimes induce distress (e.g. the decoding of a fearful object may require repeated presentation of this object to the patient). Solving this problem requires originality and ingenuity. Several lines of research have attempted to solve this, for example via the unconscious stimuli presentation method (Chiba et al. 2019) and the hyperalignment technique (Taschereau-Dumouchel et al. 2018; Haxby et al. 2011) (see Chapter 10). In addition to the considerations that arise from clinical demand, technical matters must be taken into consideration. The design of decoder construction experiments must be well thought out so that the decoder will correctly decode the categories of interest, rather than other irrelevant information. For example, if one wished to construct a decoder that classified between angry and happy faces, then one would need to ensure that the stimuli being presented to participants only differed in this feature of interest (face emotionality). Otherwise one might accidentally construct a decoder that classified features of no interest (e.g. backgrounds, genders of the faces, luminance, etc). Second, decoding MVP for specific stimuli requires a large number of data points, which isn't always possible due to time/financial constraints. To decode useful information from a ROI, which may contain hundreds to thousands of voxels, a large number of data points are required. This problem might be solved by the use of hyperalignment (Taschereau-Dumouchel et al. 2018; Haxby et al. 2011), which allows for the concatenation of data from multiple different individuals. Third, the target pattern of neural activity and ROI must be carefully considered with regard to the target psychiatric disease. For example, in DecNef targeting Obsessive-
Compulsive Disorder (OCD), one may predict that repeated induction of brain activity for symptom-provocative images may reduce OCD symptoms, because participants in the DecNef procedure are rewarded for correct induction and so this neural pattern of activity may become associated with reward. Alternatively, however, one may predict that the exact same paradigm could lead to increased OCD symptoms, because the participants learn to induce the symptom-provocative brain activity more often. Therefore, the potential effects of the “to-be-induced” brain activity must be considered very carefully. Because of these considerations, a deep understanding of both psychiatry and machine learning is required for effective DecNef design. Basic researchers and clinical experts should design DecNef experiments together.

Overall, DecNef is a promising method for dealing with various disease-based processes, as shown by previous findings. In addition, DecNef may help in the elucidation of mechanisms driving disease. However, so far, mainly due to its reliance on fMRI, DecNef has not yet been formally established in a clinical setting.

b. Functional Connectivity NeuroFeedback (FCNef). During FCNef training, a participant’s real-time BOLD activity is measured using fMRI and used to calculate measures of the functional connectivity (FC) between predetermined neural ROIs. The connectivity level is then converted to a form of feedback that is presented to the participant so that they may attempt to subsequently increase or decrease the desired connectivity pattern. Depending on the task design, participants may be instructed to perform a specific task to increase feedback scores or they may be given no explicit instruction except that their goal is to increase the feedback scores “somehow”. The goal is usually to directly change the participants’ connectivity between these ROIs and thereby induce related changes in resting-state connectivity, behavior, cognitive performance and/or clinical symptomatology. A fundamental study showed that, via FCNef training, one group of participants learned to upregulate and another group of participants learned to downregulate the FC between their primary motor and lateral parietal cortices (Yamashita et al., 2017). This indicates that (at least with the right ROIs) people can successfully learn to regulate their own FC. In this study, cognitive performance was also found to change depending on the direction of FC regulation, which indicates that changes in FC engendered by FCNef training can have real-life consequences.

FCNef is beginning to be applied to various diseases with the aim of ameliorating their clinical symptoms. Preliminary evidence suggests that FCNef may be an effective way to treat various psychiatric symptoms such as state (Koush et al., 2017) and trait (Zhao et al., 2019) anxiety, nicotine cravings (Kim et al., 2015), ASD symptoms (Ramot et al., 2017), and depressive symptoms (Yamada et al., 2017). Recent studies have begun to identify generalizable FC neural “biomarkers” for different psychiatric diseases. Using whole-brain resting-state fMRI data and machine learning algorithms, these biomarkers are created in a data-driven manner to identify FCs that can be used to discriminate between patient groups and healthy controls. For example, FC biomarkers have been made for autism spectrum disorder (Yahata et al., 2016), schizophrenia spectrum disorder (Yoshihara et al., 2020), major depressive disorder (Yamashita et al., submitted), and OCD (Takagi et al., 2017).
Because they are data-driven, FC biomarkers can further be used to identify and target disease subtypes. For example, Drysdale et al (2017) demonstrated that patients with therapy-resistant depression can be subdivided into four neurophysiological subtypes defined by distinct patterns of dysfunctional connectivity in limbic and frontostriatal networks. Another study identified three subtypes of depression that can be characterized using a biomarker which incorporates FC between the right angular gyrus and other default mode ROIs, as well as scores from the Child Abuse Trauma Scale (Tokuda et al., 2018). The advantage of this is that it may allow for more precision than traditional symptom-based diagnoses, which are often very heterogeneous in terms of symptoms and treatment response.

After a FC biomarker has been identified (whether for a disease in general, or for a disease subtype), it may then be targeted in FCNef to try to alleviate the clinical symptoms of patients. For example, the FCNef study by Yamada et al (2017) targeted a FC that was identified as a melancholic depression biomarker by Ichikawa et al (2020). In Yamada et al.’s study, subclinically and clinically depressed participants whose FC became more similar to that of healthy controls after FCNef training displayed a reduction in their depressive symptoms. This result indicates that FC biomarkers might provide relevant targets for the clinical applications of FCNef training.

When compared to traditional activation-based NF, or even to DecNef, another big advantage of FCNef is that it may affect more global-network patterns of neural activity. NF, in general, is not expected to affect the brain in the same blunt global way as, for example, an SSRI does. It is expected to affect more than just the small ROIs being targeted because the brain works in intrinsic functional networks. FCNef might be particularly effective at changing global-network function because activity in multiple ROIs, that are known to be functionally connected, is targeted for feedback. The study by Megumi et al (2015) showed that the upregulation of FC between the primary motor and lateral parietal cortices during FCNef training led not only to a greater FC between these two ROIs, but also to a subsequent greater FC between the two intrinsic networks to which these ROIs belonged (the motor/visuospatial network and the default mode network, respectively). This indicates that FCNef training may be used to induce broad network-level changes in neural plasticity.

One potential limitation of biomarker targeted FCNef is that biomarkers need to be constructed for each disease or collection of symptoms which will be targeted with FCNef. Given the number of participants required using current methodology to build these biomarkers, this is highly expensive in terms of time and cost. Nonetheless, this work has already begun and so a range of biomarkers have already been discovered (e.g. Yahata et al., 2016; Ichikawa et al., 2020; Yoshihara et al., 2020; Yamashita et al., 2019; 2020; Takagi et al., 2017; Drysdale et al., 2017; Tokuda et al., 2018).

Compared to DecNef, one potential disadvantage of FCNef is that FCNef does not utilize individual-specific multi-voxel patterns of neural activity within ROIs. Therefore, the feedback that is provided in FCNef training is less tailored to the individual participant or patient than that which would be provided via DecNef training. Attempts can be made, however, to make
FCNef training as individually-tailored as possible. Some ways in which this may be achieved are discussed in the section about “Personalizing the neuromodulation effect” below.

While initial studies using FCNef have proven promising, there still remains a lot to be determined. What different parameters may influence NF “success” and how can these parameters be optimized? For example, is it better to give a continuous or intermittent form of feedback? How long should each participant spend on each FCNef trial trying to manipulate their own neural activity? How many sessions of FCNef are required for optimal long-term effects? Furthermore, it needs to yet be determined whether the optimal parameters differ dramatically for each type of FCNef paradigm (e.g. FCNef to reduce depressive symptoms versus FCNef to reduce nicotine craving), or if there is some acceptable “one-fits-all” set of parameters. Preliminary studies addressing some of these questions have been conducted (e.g. Oblak et al., 2017), however, much is still unknown and the parameters used in most FCNef studies to date have been arbitrarily set and thus are potentially not optimal. Future research to address these questions is imperative for the evolution of optimal FCNef.

It remains undetermined whether, but seems unlikely that, FC between all pairs of ROIs in the brain can be equally and volitionally self-regulated. As is the case with all sciences, null results are not often published in the NF domain, and so as publications increase we are likely to learn more about which ROIs can have their FC self-regulated, but not about which ROIs cannot. As the literature showing which ROIs can have their FC self-regulated increases, different outcomes- behavioral, psychological, and neural- are likely to be found to be related to these FCs, which should open the way for newer treatments. However, it is important that studies showing which ROIs cannot have their FC self-regulated are also published, so that future researchers do not waste time and money testing something that has already been shown not to work. Even if a functional connection is selected by a data-driven biomarker as relevant, FCNef targeting this functional connection will be of no use if it cannot be self-regulated by the patients.

Whether or not the use of FCNef will be of advantage to practitioners and researchers depends on the goals of their intervention and/or experiment. This has to be determined on an individual basis. However, overall, if the goal is to train participants to induce a specific pattern of activity to a given stimulus within a specific ROI, then a more individual-specific multi-voxel pattern targeted NF approach, such as DecNef, will more likely be of use than a FCNef approach. On the other hand, if the goal is to induce long-term changes in global neural-network level function, then a FCNef approach will more likely be of use than an activity-based NF or DecNef approach.

Given that DecNef and FCNef both have their own advantages, the next logical step might be to design a NF paradigm which combines these. Rather than measuring connectivity as the simple correlation between the averaged activity of two ROIs, the weights for how much each voxel from each ROI contributes to the overall connectivity could be determined using MVPA. Then the MVPA weighted connectivity could be used as a target for NF. Like DecNef, the use of MVPA would mean that this paradigm could be tailored to be specific to the individual
participant or patient. However, because this paradigm would target the connectivity (weighted by MVPA) between ROIs, rather than just the activity within one ROI, like FCNef this paradigm should be able to affect long-term changes in neural-network plasticity in a more targeted manner. In the future, this type of new NF paradigm may provide a more precise, individualized, form of NF that could target network-level changes in plasticity.

c. **Process specific feedback context.** The majority of NF studies, to date, have used an abstract meter as a feedback interface. This type of feedback does nothing to specifically provoke the neuro-mental processes targeted during NF training. There are however, two promising ways in which process precision during NF might be improved (see Lubianiker et al., 2019, for a detailed account). One is via the use of immersive environments and the other is through contextual interfaces. The use of immersive virtual reality (VR) technologies that simulate highly naturalistic environments can facilitate improved learning, generalizability, and process-specificity. A study comparing abstract versus animated feedback showed that animated feedback resulted in more engagement and longer sustainability of the learning (Cohen et al., 2016). Contextual interfaces, likewise, may aid participants in inducing the neural process of interest, especially if these are disease-related. A revealing example for this is the NF study by Paret et al. (2016), where aversive images were presented on-screen alongside a meter which individuals were trying to regulate with their neural activity. This approach assumes that exposing trainees to the emotional stimuli while they were attempting to self-regulate activity in their amygdala, would aid them in inducing the targeted emotion-related neural activation. A different approach was applied by Young et al. (2017) in a randomized controlled trial in depression. Trainees (patients with depression) were asked to recall positive memories while trying to up-regulate their amygdala activity. They showed increases in positive mood after training. Future research, using different types of context induction, should try to determine the conditions under which activation of neural hubs (that are involved in multiple processes) can be provoked. Furthermore, other feedback interface factors may also be harnessed for process induction. These include the utilization of different feedback protocols for process targeting, as well as NF task instructions (i.e., providing participants with suggestions for specific process-related imageries).

2. **Scaling up the neuromodulation procedure**

fMRI NF has proven promising for modulating well-defined brain functionality for basic research and clinical use. Yet, its high cost and immobility stand in its way to broadly being applied for clinical purposes in psychiatry and neurology. In addition, being dependent on hospital technology, such as MR scanners, precludes the hope of integrating NF into daily life. To better scale fMRI NF, different brain recording methods as well as the use of mobile interfaces must be considered. These will be described in this section.

a. **Electrical Finger Print NF (EFP-NF).** EEG is an accessible and widely used neural monitoring device, both for NF and for other uses. Yet, its spatial resolution is much inferior to that of fMRI, making it less useful for the guiding of precise NF. Computational advancements in AI and machine learning could assist in overcoming this issue by injecting spatial information into the EEG recordings. This could be done, for example, by using low-
resolution electromagnetic tomography (LORETA; Grech et al., 2008) or its variants (Congedo, Lubar, & Joffe, 2004). However, these computationally estimated solutions necessitate the use of a dense grid of electrodes. This limits mobility and accessibility, and at the same time makes recording highly sensitive to noise, particularly when from deep subcortical areas (Yao & Dewald, 2005). Other approaches have used fMRI to improve EEG inverse localization models (Sato et al., 2004; Valdes-Sosa et al., 2009; Aihara et al., 2012), while relying on critical a-priori assumptions regarding the biophysical origins of the EEG and fMRI signals. Yet, this type of approach again requires high density recording sites and thus hampers scalability. To overcome this, data-driven statistical approaches have been applied to associate EEG and fMRI signals (Laufs, Daunizeau, Carmichael, & Kleinschmidt, 2008), using either simple correlations between EEG frequency bands and localized BOLD activity (Emmert et al., 2017; Ben-Simon, Podlipsky, Arieli, Zhdanov, & Hendler, 2008; de Munck et al., 2007) or machine learning tools to predict BOLD activity from EEG frequency bands (Mantini, Perrucci, Del Gratta, Romani, & Corbetta, 2007). The latter approach, termed Electrical Finger-Print (EFP), has repeatedly been used to successfully predict fMRI BOLD activations in the amygdala and medial prefrontal cortex from EEG data, even from a single EEG channel (Meir-Hasson, Kinreich, Podlipsky, Hendler, & Intrator, 2014; Meir-Hasson et al., 2016). Of importance to this chapter, the amygdala EFP model has been successfully used as a modulation target in NF, yielding evidence that EEG-NF training can be successfully used for precise modulation of a deeply located limbic region (Cavazza et al., 2014; Keynan et al., 2016; Cohen et al., 2016).

Results from validation experiments have demonstrated that participants who were trained outside the fMRI scanner to downregulate their amygdala-EFP model not only successfully decreased amygdala BOLD activity during fMRI-NF in a following session, but also showed reduced amygdala reactivity to threatening visual stimuli and improved performance in an emotion regulation task (Keynan et al., 2016). The efficacy of the amygdala-EFP method was further demonstrated in several NF studies in both healthy and patient cohorts (e.g. stress resilience in combat soldiers (Keynan et al., 2019), and emotion regulation in chronic pain patients with fibromyalgia (Goldway et al., 2018). EFP-NF combines the strengths of EEG and fMRI, providing both high accessibility and more precise spatial localization of the neuromodulation. From a clinical perspective, it paves the way for the development of additional ‘fingerprints’ for various target regions (for example, see Klovatch-Podlipsky, Or-Borichev, Sar-El, Lubianiker & Hendler (2016), which presents the development of a right inferior frontal gyrus EFP model), for network-level metrics, for multivoxel-based patterns (like the ones utilized in DecNef) and/or for FC networks (like in FCNef). Furthermore, since it relies on EEG only, neuromodulation can be performed in relatively naturalistic and/or virtual/augmented environments, allowing for more process-specific targeting (see review Lubinaker et al., 2019).

The EFP approach contains some limitations. First, it does not uniquely monitor a specific brain region, but rather a set of regions that are co-activated along with the target region. Indeed, when examining the BOLD correlates of the amygdala EFP in an EEG–fMRI experiment on a new group, it was found that the EFP was associated not only with the signal fluctuations within the amygdala but also with additional functionally related regions such as the insula and higher-
order visual areas (Keynan et al., 2016). Second, even though EFP models were developed and validated for BOLD activations in single regions, fingerprinting more complex neural indices (i.e. MVPA, network connectivity, etc.) might prove to be more challenging in terms of susceptibility to movement and/or physiological artifacts and/or other factors influencing signal to noise ratios. Future empirical work is required in order to demonstrate whether reliable fingerprint models for such complex network indices are feasible. Third, it is assumed that an EFP index is a general correlate of BOLD activations in a specific target region. However, it remains to be determined whether an EFP model that is created in one MRI acquisition context can generalize to other contexts (for example, NF task, clinical outcome tasks, resting-state scans, etc.). Future studies should provide evidence for the generalizability of models across various datasets and contexts. Lastly, the EFP was developed as a common model (Meir-Hasson et al., 2016), yet its application to clinical populations might require further optimization and possibly more personal calibration due to the large inter-individual variability among patients. One way to deal with this issue, without requiring an fMRI scan for each trainee (thus impairing scalability), is by establishing a library of EFP sub-classes, each depicting different parts of the whole model variance (Jacobs, Jordan, Nowlan, & Hinton, 1991). Previous work has shown that, while the common amygdala-EFP model has reasonable predictive power across individuals ($r$ Pearson = 0.4), predictive power is highest ($r= 0.5-0.8$) when an individual’s own amygdala-EFP model is used to predict their amygdala activity (Meir-Hasson, Kinreich, Keynan, Nimrod & Hendler, T (in prep). Mixture of fMRI-inspired EEG experts to sense the amygdala activity). This calls for a computational approach that allows some level of individualization, without having to conduct an fMRI scan for each individual. Close examination of the common amygdala-EFP model performance suggests that this performance is affected by other individual characteristics such as EEG frequency bands distribution and the correlation of the common amygdala-EFP model with alpha and theta power. Thus, creating subtypes of the common amygdala-EFP model may improve the model performance. Consistently, preliminary testing conducted on previous data (Meir-Hasson et al., 2016) has revealed that assigning different models to different individuals according to the characteristics mentioned above may improve the model performance by up to 20% percent (Meir-Hasson, 2016).

In addition to the approach described above, it is possible to test the performance of other datadriven approaches when trying to associate EEG and fMRI data. From a machine learning perspective, the above is a problem of learning a mapping between two continuous signals. In the nomenclature of deep learning, this is known as sequence to sequence modeling (Sutskever, Vinyals, & Le, 2014). The spatiotemporal nature of these signals, and their high dimensionality, make the problem challenging, but state of the art methods like LSTM (Graves & Jaitly, 2014) have the potential for achieving satisfactory accuracy on this task. Additionally, the mappings will need to take into account the intrinsic statistics of both the fMRI and EEG signals (namely, irrespective of their correlations). This is handled within the framework of structured-prediction, which can be used to elegantly represent statistical properties in prediction (Meshi et al., 2010).
b. Harness mobile technology towards increasing NF accessibility. Recent years have seen consumer electronics gain many abilities and become widely accessible. These include cheap and easy-to-use devices for physiological measurements, such as EEG headsets (Ratti, Waninger, Berka, Ruffini & Verma, 2017), heart-rate monitors (Wang et al., 2017), and sleep monitors (Kang et al., 2017). Fortuitously, the reported data quality for many of these is of acceptable levels. At the same time, virtual and augmented reality glasses, as well as internet-connected mobile phones, have become virtually ubiquitous. The clearest utility of this progress for NF is the accessibility of affordable, consumer-oriented EEG headsets, which could allow patients to practice NF anywhere. This change can be thought of as bringing the clinic into the patient’s natural environment. This is in line with prevalent psychotherapy protocols, such as Cognitive Behavioral Therapy and Dialectical Behavioral Therapy (Hofmann & Smits, 2008; Dimeff & Koerner, 2007), which augment in-clinic treatment with teaching patients skills and techniques that they can use in their day to day lives. Bridging the gap between the clinic and patient environment is likely to improve both treatment efficacy and accessibility. Patients’ ability to practice NF in their own homes should help disseminate the treatment, as well as allow for exploration of protocols that are more frequent than clinic conditions usually allow for. It would be worthwhile to consider mobile phones as a feedback instrument. If mobile phones can be used to deliver feedback, then, coupled with a mobile EEG headset, this would mean that patients are not limited to practicing NF at home or in a clinic, but that they could do it practically anywhere. As this aim is realized, however, it is also important to bear in mind the potential that widely disseminated NF has for social influence and to guard against abuse (for example, by those marketing NF systems). Please see Chapter 14 for further discussion of ethical considerations.

3. Personalizing the neuromodulation effect

The need for personalization in the diagnosis and treatment of psychiatric disorders has been largely acknowledged in the last decade. This has led to large scale neurocognitive studies looking for potential biomarkers that can assign patients to clinical subtypes or objectively defined biotypes (Buckholtz & Meyer-Lindenberg, 2012; Lubianker et al., 2019). The personalization of NF training should focus on the training target (when and what to train) and on improving training protocols (how to train). Both aspects require further technological developments along the following considerations.

a. Timing of training. While current NF protocols involve training in a clinic or a lab, moving NF to the home (as described above) could allow for training to be completed at the time-points which are most clinically efficient and needed. This could be done by timing NF practice according to environmental aspects or physiological aspects. Behavioral factors that are associated with psychiatric disease, such as sustained attention, working memory, and attentional bias, can fluctuate dynamically even within a single behavioral experiment that lasts 5-10 minutes (Naim, Kivity, Bar-Haim & Huppert, 2018; DeBettencourt, Keene, Awh & Vogel, 2019). Recent research has shown that, when BOLD signal is used to determine trial onset, resulting behavioral outcomes can differ to some extent (Chew et al., 2019). Therefore, the efficacy of NF (and conventional) treatments might likewise dynamically fluctuate and it is worth examining if such fluctuations could be decoded using MVPA and/or physiological
measurements. If so, then decoder outputs (that estimate whether or not the effect is likely to be maximum) and/or physiological indices could be used to inform the timing of feedback. For example, patients suffering from alcohol abuse could induce the relevant neural activity in a NF training procedure to reduce their desire for alcohol when the neural and/or physiological indices indicate the desire is the largest. Real-time decoding methods might also be useful for modifying feedback threshold. Since the NF success in each regulation block fluctuates dynamically, it may not be reasonable to use the same feedback threshold throughout the session. On-line prediction of the next regulation block’s success may allow continuous modification of the feedback threshold accordingly, and increase the effectiveness of NF protocol overall.

Many psychological treatment protocols attempt to give patients tools that can be used in situations that patients find difficult to handle, commonly referred to as guided self-help (GSH; Bennett et al., 2019). GSH has been shown effective in disorders such as eating disorders (Wilson & Zandberg, 2012), anxiety, and depression (van’t Hof, Cuijpers & Stein, 2009; Haug, Nordgreen, Öst & Havik, 2012), and PTSD (Lewis et al., 2017). These difficult to handle situations are often highly context-dependent. In explicit NF, patients normally practice the induction of a mental strategy to be used in difficult situations and then have to try and apply their strategy in real-life in the absence of external feedback. Using a mobile setup, where NF is monitored using an affordable EEG headset and feedback is delivered by a mobile phone application (mobile-NF) would allow patients to receive feedback in real-life challenging situations. Potential use-cases could include social anxiety (e.g. practicing NF prior to giving a public speech, or attending an important meeting), Attention deficit hyperactivity disorder (ADHD; e.g. practicing inside a classroom, or while trying to concentrate at home), and specific phobias (e.g. practicing when encountering the phobic object). Another alternative is to time NF practice according to the patient’s state. NF could utilize the high recent accessibility of wearable physiological monitors (including heart rate and skin conductance) to time NF sessions according to a patient’s physiological state (heart rate, skin conductance, pupil dilation). This could be highly relevant in disorders that are characterized by high physiological arousal states (Chalmers, Quintana, Abbott & Kemp, 2014; Imeraj et al., 2011), such as general anxiety, PTSD, or even ADHD. Furthermore, this could also be beneficial in major psychiatric disorders such as depression and schizophrenia, where stress can exacerbate core symptoms. Decreased heart-rate variability is an established marker of high arousal modulation (Thayer et al., 2012), and could serve as the relevant physiological marker for stress. Data from a heart-rate monitor could be used to alert a patient that their arousal levels are rising, and suggest that it might be time to practice NF. Such practice could also be highly valuable to healthy individuals under especially demanding situations (e.g. pilots) for improvement of their performance.

b. Individually-tailored disorder-specific interface content. In some psychopathologies, symptoms are often triggered by a specific external stimulus. These include disorders such as: specific phobias (e.g. fear of spiders or heights), social anxiety disorder (social criticism), substance abuse (smoking, drugs), PTSD (traumatic content and its reminders), and OCD (washing, checking). Indeed, prevalent cognitive-behavioral therapy protocols have long
demonstrated that using a controlled exposure to the patient’s specific stressors could be beneficial for treatment (Foa, Hembree & Rothbaum, 2007; Choy, Fyer & Lipsitz, 2007). This concept has recently been demonstrated in PTSD patients (Fruchtman et al., 2019, see Chapter 8 clinical application ER disorder) by combining amygdala EFP-NF and trauma-related content as feedback in a gradual manner. It has likewise been demonstrated for OCD and phobia, where the MVP for disorder-related stimuli were targeted using DecNef (see Chapter 10). The next step may be combining NF with immersive technologies (e.g. Virtual/Augmented Reality; VR/AR) to allow personal specificity of the scenario’s content used for feedback. This could be based on work already performed using VR based exposure therapy in anxiety disorders (Carl et al., 2019).

While existing 2D computerized applications allow high controllability, they provide low ecological validity and thus hamper generalizability to daily life experience and/or to dynamics in the mental state of an individual. In this regard, immersive 3D technologies such as VR/AR can provide a middle ground with both high controllability and strong contextuality (Bohil, Alicea & Biocca, 2011; Sanchez-Vives & Slater, 2005). Since the experience induced via these technologies is entirely programmable, different types of feedback cues can communicate continuously with behavioral (e.g. eye-tracking and movement) and biological (e.g. skin conductance, ECG, EEG, respiration, heat maps) signals. Importantly for psychiatric interventions, the VR/AR experience is predominantly mediated by highly engaging sensory-perceptual processes, which may circumvent resistance to treatment and increase adherence. The fundamental idea is that in each disorder, particular situations induce maladaptive behaviors (Schmitz & Grillon, 2012; Sjoerds et al., 2013; Domsalla et al., 2014). Therefore, the VR scenario can be designed to reward each participant for acting appropriately in the specific situations that best simulate their real-life difficulties (e.g. lowering the height of an elevator or decreasing traumatic story intensity). Continued eye-tracking, behavioral monitoring and physiological measures will constitute domain-specific readouts for better characterizing the experience in association to neuromodulation.

Averaged activity in predefined ROIs can capture crucial ingredients of a disorder and in some cases thereby work as effective targets for NF. For example, NF targeting average activity in a left amygdala ROI has been shown to influence emotional processing in patients with major depressive disorder (Young et al., 2014). However, in other cases it might be of benefit to more precisely define the target ROI for the individual patient. This may particularly be the case for patients whose symptoms are provoked by specific stimuli, such as those suffering from addiction, OCD, and PTSD. In patients with these disorders, neural representations for these symptom-provoking stimuli are thought to be abnormally wired within their reward and/or fear circuitry. This means that pre-defined ROIs might not capture the relevant circuitry well for these patients. Functional localizers are often used in such cases, so that the neural regions active in response to symptom-provoking stimuli can be determined for each individual patient and targeted in NF (e.g. see Gerin et al., 2016; Hampson et al., 2012; Rance et al., 2018; Scheinost et al., 2014; Subramanian et al. 2011). Taking this one step further, the exact multivoxel patterns of activity a patient displays to symptom-provoking stimuli can be used to define ROIs, which thereby capture even more fine-grained representations. These are the type...
of ROIs that are targeted in DecNef (see Chapter 2). For example, the pattern of activity a phobic person has to the specific stimulus that they are scared of can be determined (either straight from their own neural activity or by inferences based on the neural patterns of activity of surrogates, see Taschereau-Dumouchel et al., 2018). Then on each trial of DecNef, the likelihood that the current multivariate pattern of activation is related to the phobic-specific stimulus can be determined and feedback given accordingly (see Figure 2). DecNef using this design (where for each participant, induction of the multivariate pattern of activation related to their phobic-specific stimulus was counter-conditioned with reward), has been shown to reduce participants' fear of phobia-specific stimuli (Taschereau-Dumouchel et al., 2018). DecNef and other approaches involving functional localization of target regions or patterns can thus be utilized for personalized treatment by targeting (in the case of DecNef individual patterns of) brain activity of an individual patient to a specific stimulus.

FCNef, particularly when the target is determined by a biomarker, is less personalized than DecNef. However, some attempts have been made to personalize FCNef as much as possible. FC is often calculated as the coefficient for the correlation between the ongoing BOLD activity in two ROIs. In FCNef, feedback is often given depending on the sign and absolute value of this correlation coefficient. Rather than using absolute correlation coefficients to determine feedback, the correlation coefficient representing FC on each trial of FCNef can be compared to that of an individually determined baseline to calculate feedback. For example, in the study by Yamada et al (2017), each participant’s baseline correlation coefficient was determined during a SHAM session. During the SHAM session each participant completed the exact same task as that which they would complete on FCNef sessions, but with random feedback. Then during subsequent FCNef sessions, each participant’s feedback was calculated based on how much more positive or negative the correlation coefficient calculated for the current trial was relative to that measured during that participant’s SHAM session. This allowed each participant to try to improve on their own specific FC, rather than try to attain some predetermined “ideal level” of FC. Another way in which FCNef can be somewhat tailored to the individual is by determining the ROIs in a functional localizer task, rather than by simple anatomical parcellation. This method of ROI selection may not be pertinent, however, if the FC of interest was determined from a biomarker that was created using anatomical parcellation. Nonetheless, biomarker targeted FCNef, itself, has the potential to become very personalized. If researchers continue to make new FC biomarkers then one day we could reach the stage that a patient comes into the clinic and is diagnosed based on their resting-state brain activity, rather than on self-reported symptoms. Based on this data-driven approach, the likelihood of factors such as which FCs in this individual patient differ the most from healthy controls, how likely this individual patient is to respond well to FCNef, and whether FCNef, medication, or a combination of these is most likely to be of benefit for this individual patient, could be easily and quickly determined. Once we reach this stage, then FCNef based on such diagnoses could be considered well personalized. This individualized type of AI-driven “precision” could help reduce the number of “misdiagnoses” and non-effective treatments that currently arise due to the subjective manner in which clinicians are forced to work.

Conclusion
In this chapter we have highlighted several strategies we believe could be beneficial for the dissemination of NF as an effective treatment for varied psychopathologies. These strategies include translation of state of the art imaging and computational approaches into neuroscientifically precise treatments (Dec-NF, FCNeF), as well as strategies for integrating imaging techniques with computational and consumer-electronics advances to enhance scalability and personalization of treatment (EFP, mobile- and VR-NF). Regarding precision, we presented evidence for the utility of advanced image analysis tools to depict distributed activation or functional connectivity, as well as interfaces tailored for relevant processes. The need for scalability was discussed with respect to accessible signal probing and mobility of application through EEG rather than fMRI. Lastly, personalization was highlighted with regard to timing of treatment and individually tailored indications for brain probes and feedback interface. Table 1 summarizes how well a number of currently popular NF approaches implement these three strategies.

Achievement of the ideas put forth in this chapter can be achieved through collaboration between clinical and basic/methodological scientists, as well as by trying to improve the accessibility of tools which are currently only available to highly technically oriented research groups. This challenge could be overcome by publishing toolboxes, which could make these technical processes accessible to clinical scientists, for example, by producing EFPs, performing hyperalignment, or by creating a cloud computing interface for EEG-NF through mobile phones. Unlike pharmacological treatments, if these steps are taken, NF has the potential to become a highly "open source" treatment protocol - highly accessible and modifiable for specific individuals, disorders or sub-disorders. Ethical considerations and perils of ease-of-access should not be neglected (see Chapter 14 for an in-depth consideration), but, in our view, improving accessibility for patients and clinicians could highly advance the field.

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