



Predictors of neurofeedback training outcome: A systematic review

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ABSTRACT

Neurofeedback (NF), a training tool aimed at enhancing neural self-regulation, has been suggested as a complementary treatment option for neuropsychiatric disorders. Despite its potential as a neurobiological intervention directly targeting neural alterations underlying clinical symptoms, the efficacy of NF for the treatment of mental disorders has been questioned recently by negative findings obtained in randomized controlled trials (e.g., Cortese et al., 2016). A possible reason for insufficient group effects of NF trainings vs. placebo could be related to the high rate of participants who fail to self-regulate brain activity by NF (“non-learners”). Another reason could be the application of standardized NF protocols not adjusted to individual differences in pathophysiology. Against this background, we have summarized information on factors determining training and treatment success to provide a basis for the development of individualized training protocols and/or clinical indications.

The present systematic review included 25 reports investigating predictors for the outcome of NF trainings in healthy individuals as well as patients affected by mental disorders or epilepsy. We selected these studies based on searches in EBSCOhost using combinations of the keywords “neurofeedback” and “predictor/predictors”. As “NF training” we defined all NF applications with at least two sessions.

The best available evidence exists for neurophysiological baseline parameters. Among them, the target parameters of the respective training seem to be of particular importance. However, particularities of the different experimental designs and outcome criteria restrict the interpretability of some of the information we extracted. Therefore, further research is needed to gain more profound knowledge about predictors of NF outcome.

1. Introduction

Neurofeedback (NF) is a special kind of biofeedback during which participants learn to deliberately regulate their brain activity and thereby gain control over processes usually not available for conscious regulation (Holtmann et al., 2014). By changing brain activity, cognitive function, symptoms or behavior are supposed to be improved. This is possible via online feedback of changes recorded by different technologies, mainly, electroencephalography (EEG) or – as a more recent development – hemodynamic methods such as functional magnetic resonance imaging (fMRI) or functional near-infrared spectroscopy (fNIRS) combined with the paradigm of operant conditioning. In this way, participants/patients can observe their changes in brain activity acoustically, tactilely or visually (on a computer screen), in real-time, e.g., via an auditory tone, via a screen showing a thermometer type display, a moving ball or a plane moving across the screen. The task for participants is to regulate their brain activity (e.g., representing a

moving ball) upwards or downwards, depending on specific instructions before each trial. After each feedback trial, participants get positive/negative feedback (e.g., verbal feedback by the trainer, tactile feedback by a vibrating pad or visual feedback by a positive/negative visual symbol on a screen) as reinforcement for changes in activity in the correct direction; for a complete illustration, see Strehl (2013).

Besides applications in healthy subjects aimed to improve cognitive performance (Gruzelier, 2014a,b; Yamashita et al., 2017), clinicians employ this self-regulation of brain activity to achieve symptom reductions in patients suffering from neuropsychiatric disorders including attention-deficit/hyperactivity disorder (ADHD; Gevensleben et al., 2009; Gevensleben et al., 2014), obsessive-compulsive disorder (OCD; Kopřivová et al., 2013) or epilepsy (Sterman and Egner, 2006). Specific advantages of NF training over other treatment options (e.g., medication) may be the longevity of clinical effects that are evidentially stable up to two years following the end of the training period (e.g., Basta et al., 2017; Choobforoushzadeh et al., 2015; Gani et al., 2008;

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Gevensleben et al., 2010; Meisel et al., 2014; Steiner et al., 2014; Strehl et al., 2006). Beyond that, NF represents an alternative treatment option for patients who cannot profit from medication. For example, it can help to reduce seizures in epilepsy patients, where drugs proved to be ineffective (e.g., Daum et al., 1993; Rockstroh et al., 1993; Strehl et al., 2005). Regarding the neurophysiological parameters targeted by such a training, a common finding in patients with ADHD is a reduced beta activity and higher theta activity compared to healthy subjects in quantitative EEG analyses (Monastra et al., 1999). Therefore, a frequently used training protocol for ADHD aims to reduce theta activity and increase beta activity to reach an attentive and relaxed state (Heinrich and Gevensleben, 2013). Although the frequency alterations cannot necessarily be corrected through such a training (Serman, 2000), many studies could show substantial symptom reductions (for an overview see Marzbani et al., 2016). The implementation of blinded and randomized controlled trials, however, has opened a controversial debate about the efficacy of NF trainings as some of these studies failed to demonstrate a statistically significant superiority of NF over the respective control group (Cortese et al., 2016; Sonuga-Barke et al., 2013). Unfortunately, a rigorous examination of the method is further complicated by the fact that a relatively large proportion of participants fail to acquire regulation capability of their brain activity (e.g., Enriquez-Geppert et al., 2013; Gevensleben et al., 2009; Kotchoubey et al., 1999; Weber et al., 2011). In these cases, the essential purpose of the NF method could not be achieved. Consequently, a positive effect can not be expected. The rate of non-responders (i.e., “non-learners” who do not achieve stable self-regulation of the target parameter over the course of the training) range approximately between 16% and 57% (Alkoby et al., 2018). But there may be differences depending on the training protocol as some training protocols may be more difficult to learn than others. Furthermore, assessment of the number of non-responders is further complicated by the fact that guidelines for a uniform classification as (non-)responder are missing. Above all, the difference between learning success and training outcome in terms of symptom reduction or the improvement of cognitive performance must be taken into account. Because learning outcome (i.e., the ability to learn self-regulation) is not necessarily linked to treatment success (i.e., clinical/functional outcome) and vice versa, treatment success could be due to unspecific effects.

One of the factors potentially contributing to above mentioned problems may be the application of standardized NF protocols that are usually not tailored to individual pathophysiological alterations.

Mental and neurological disorders are, however, very heterogeneous regarding their neurophysiological correlates (e.g., Albrecht et al., 2015), which is why the application of individualized training protocols based on specific pathophysiological deviations is likely to be more effective (Hammond, 2010). As one such example, a recent study could demonstrate that ADHD patients who received theta/beta NF based on individual differences in alpha activity were more successful and showed stronger symptom improvements than those who received standard, non-individualized NF (Bazanov et al., 2018). However, while individualized NF trainings are becoming more common (e.g., Karch et al., 2019), they are far from the norm. In order to further develop such an individualized approach, it is therefore critical to identify factors that can reliably predict who will be generally able to profit from NF trainings and what kind of protocol is indicated.

Recently, Alkoby et al. (2018) published a review in which they highlight the inefficiency problem and summarize predictors of NF training success. As an important first step, thereby, the authors focused on studies which investigated psychological and neurophysiological predictor variables. We now build on this initial publication on the topic by providing a systematic review of interventional studies investigating predictors of NF training outcome. We, however, address the topic from a psychiatric/therapeutic point of view, where NF is used to support learning of the regulation of deviant cortical activity in terms of overarousal, underarousal or disinhibition associated with a certain mental state or symptom (in contrast to broader brain-computer interface/BCI applications that focus on using brain signals for communication, device control or motor optimizing purposes).

In this review, we differentiate between predictors for the ability to learn regulation of brain activity and predictors for the improvement of symptoms or abilities, in order to address two major questions: Who will be able to learn in the context of a NF training and who is most likely to profit from it in a meaningful clinical/functional way?

2. Method

The first author performed the literature search in June 2016 for the first time with EBSCOhost (Business Source Premier/EconLit; update: 2019, December 31), an online research service with 375 full-text databases including leading ones such as PubMed. The review protocol was not pre-registered. The PRISMA flowchart in Fig. 1 describes the literature search of this review. The search key was developed by the study team and has been a combination of the words “neurofeedback“

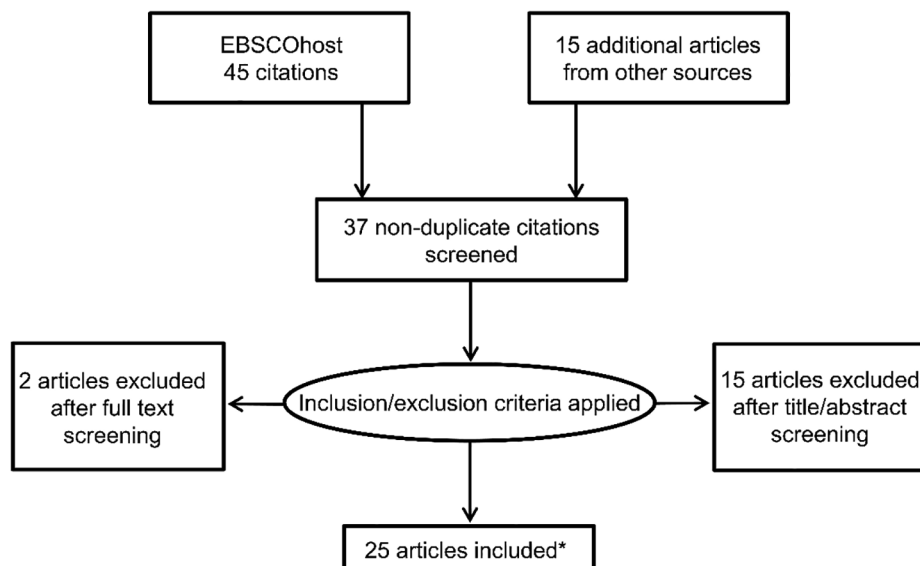


Fig. 1. Study selection process *Two additional studies (Diaz Hernandez et al., 2018; Karch et al., 2019) were added to the database after our first literature search. Finally, we included a total of $n = 24$ studies (25 reports).

and "predictor/predictors" without date restrictions. This combination of keywords resulted in $n = 45$ articles. After elimination of duplicates, a total of $n = 26$ articles remained. The inclusion criteria (see below) were again developed by the study team with the intention to receive a range of practice-oriented NF training studies that are focused on the investigation of predictors. Thereby, we wanted to make sure to be able to draw conclusions that are representative for frequently used NF trainings aimed at improving mental health and cognitive performance. Besides studies focusing on healthy controls (as model population or for prevention in subclinical clients or risk groups to strengthen cognitive resources) and different psychiatric disorders, NF studies in patients with epilepsy were included as well, as the training protocols applied for the treatment are comparable to some of those used for psychiatric disorders and are based on a similar neurobiological background. In contrast, BCI studies were generally excluded. Similar to NF, the BCI method involves a direct communication between the brain and an external device. However, in contrast to NF, studies investigating this method usually use it as a tool for communication/control of devices or to deal with motor behavior, whereas NF (as a specific form of BCI; see Wood et al. (2014)) typically aims at improving cortical self-regulation. As the findings of BCI studies are normally hardly comparable to the application of NF as a complementary neuropsychiatric treatment tool, we decided not to include such studies.

All abstracts were screened for eligibility by the first, co- and senior author. After removal of ineligible studies, remaining studies underwent full text review by the first and the last author. To be included, each study had to be a study using NF as a medium for self-regulation of brain activity. Therefore, we discarded three BCI studies that did not pursue this objective. In addition, we discarded seven references after title and abstract screening, because the described predictors did not refer to the effectiveness of NF, or NF was solely mentioned as a potential method of neuromodulation (without being the primary topic of the manuscript). For the purpose of this review, we defined "NF training" as all NF applications/trainings with at least two sessions. Against the background of our topic "NF learning and long-term symptom improvement/improvement of cognitive functions", we justify these restrictions as follows: 1) we are interested in lasting learning or treatment effects, which we cannot expect after only one session; 2) we have doubts regarding the data quality of the first session, because individual participants and especially certain patient groups first have to accustom themselves that they are not allowed to move during NF or they react with sweating or muscle tension to the new demands; 3) we expect that the time and possibly the sleep in between sessions is important for the consolidation of acquired skills (Moyano et al., 2019); 4) previous studies have shown that successful regulation efforts can (spontaneously) occur within the first feedback session(s) that are unrelated to actual training effects (Drechler et al., 2007). We only included original and peer-reviewed articles to ensure a high-quality standard; based on this criterion, we discarded two more publications. For the same reason, we decided not to report analyses computed with less than five participants (see Button et al., 2013). We identified eleven publications from other sources, i.e., reviews or original research articles studied during the primary literature search and afterwards we detected three additional studies (Koush et al., 2017; Scharnowski et al., 2012; Scharnowski et al., 2015). Since our literature search in June 2016, we have been constantly monitoring the database regarding new publications. From that time on, the database has added two more relevant publications (Diaz Hernandez et al., 2018; Karch et al., 2019), which we decided to additionally include. Therefore, we considered 24 studies (reported in 25 papers) in the final analyses. All of these articles were published in English. After the selection process, the first author created a table extracting data from each article to evaluate the selected references. The following variables were assessed: predictors, statistical values, outcome, treatment duration, number of participants, age and state of health of participants (clinical group/healthy participants), training protocol (incl. the procedure in the control group) and factors

without an effect on training outcome. A meta-analysis could not be performed, as the studies being evaluated lacked sufficient similarity regarding the population, training protocol, experimental design and outcome measures.

3. Results

The present systematic review aims to investigate predictors of NF training success and treatment outcome. The 24 studies (25 papers) we included in this review are listed with all relevant information in Table 1. 13 of the studies investigated predictors for the ability to learn regulation of brain activity (i.e., learning outcome) and twelve investigated predictors for the improvement of symptoms or abilities (i.e., clinical/functional outcome).

3.1. Neuroanatomical and electrophysiological predictors (pre-training measures)

3.1.1. Predictors for learning ability

Structural imaging studies have revealed several predictors of learning ability in NF trainings, which might be considered the neuroanatomical basis of the ability to learn self-regulation of one's own brain activity. For example, in healthy adults, the ability to increase frontal-midline (fm) theta was associated with larger gray matter volumes of the right midcingulate cortex and higher white matter concentration of the right cingulate bundle and larger volumes of the left cingulate bundle (Enriquez-Geppert et al., 2013). Results of a sensorimotor rhythm (SMR)-training with participants not affected by major medical illnesses, psychiatric or neurological disorders have shown positive associations between gray matter volumes of the left anterior insula, left thalamus, right frontal operculum, right middle frontal gyrus and white matter near right putamen, right insula and right lingual gyrus and learning outcome (Ninaus et al., 2015). In contrast, negative associations occurred with the gray matter volume in the left inferior temporal gyrus and white matter volume close to the right postcentral gyrus. Moreover, gray matter volume within the supplementary motor area and the left middle frontal gyrus predicted the outcomes of gamma training. The results also show evidence for partially overlapping neuroanatomical correlates of SMR and gamma NF and therefore support the assumption of a more general (frontally focused) NF network in the brain, which is responsible for focusing attention to inner states and adjusting it with external feedback (Ninaus et al., 2013). Hence, the structure and functioning of this network could be important for the learning ability of NF, possibly irrespective of the specific training protocol.

Scharnowski et al. (2012) conducted an fMRI-based NF training study that aimed to improve visual perception in healthy participants. As part of the evaluation, they calculated a correlation between the proportion of the voxels V1; V2; V3 (before beginning) that constitute the visual target region of interest and training success, however, without a significant finding. In addition, electrophysiological parameters related to the training measure seem to be useful predictors of the response to NF. The data analyses of a sample of healthy adults, who completed a training of instrumental SMR conditioning, showed the possibility to predict later SMR performance by means of eyes-open resting state (rs)-SMR power before training (Reichert et al., 2015). Rs-SMR power was generally higher in responders than in non-responders, and a discrimination analysis revealed that responders could be differentiated from non-responders on the basis of rs-SMR power within a left central region of interest (classification accuracy 82%). This information suggests that a certain level of rs-SMR power should be available before the start of the training. The analyses of the control group (gamma- or sham-EEG) did not provide any opportunity to predict later SMR performance, but 9 of 10 participants from the gamma group also showed an increase in SMR power during training and improvements seem to be comparable to those of the SMR power training

Table 1
Overview about population, design and relevant results of studies investigating predictors for the success of neurofeedback trainings ($n = 25$).

Study	Predictors	Method & significance	Outcome	Treatment duration	Participants	Age (M)	Training protocol	No effect
Learning ability Diaz Hernandez et al. (2016)	Motivational incongruence	Pearson correlation with outcome TF condition $r = -0.6; p < .05$ FB condition $r = -0.65; p < .05$	Microstate class D performance	10 double sessions + 1 follow-up single session	20 healthy adults	24.8 y	Microstate class D contribution	Life satisfaction, Personality, Body Awareness, Anxiety trait
Enriquez-Geppert et al. (2013)	Vol. r. MCC Conc. r. cingulate bundle Vol. l. cingulate bundle	Regression analysis $\beta = 0.63; p < .05$ $\beta = 0.68; p < .05$ $\beta = 0.68; p < .05$ Pearson product-moment correlation $r = 0.61; p < .05$	Training success	8 sessions	19 healthy adults	24 y	Fm-theta	Inferior, superior, middle frontal cortices
Kober et al. (2013)	Initial training phase SMR group <i>Strategy group</i> No strategy ($n = 4$) Specific strategy ($n = 6$) Strategy * time Between subjects <i>Last training session</i> No strategy vs. specific strategy <i>Within subjects</i> <i>Specific strategy</i> Last vs. first session No strategy Last vs. first session	ANOVA & post hoc <i>t</i> -test $F(1,8) = 7.69; p < .05$ $M = 1.12$ $M = -0.58$ $F(1,8) = 7.41; p < .05$ $t(8) = -3.15; p < .05$ $t(5) = -0.38; ns.$	SMR & (Gamma) power	10 sessions	20 healthy adults	46.4 y	SMR ($n = 10$) Gamma ($n = 10$)	
Koush et al. (2017)	State anxiety	$t(3) = -2.46; p < .10$ Pearson correlation $p = -0.94; p < .05$	Training success	3 sessions	15 healthy adults	26.2 y	fMRI connectivity based Emotion regulation network NF ($n = 9$) Sham FB ($n = 6$) Alpha ($n = 16$) Control group without any training ($n = 16$) Beta/theta	
Nan et al. (2012)	Mental strategy (positive thinking)	Qualitative analysis	Training success; short term memory improvement	20 sessions	32 healthy adults	23.28 y		
Nan et al. (2015)	Low beta resting baseline: Leamer vs. non-leamer Eyes open Eyes closed Initial performance: beta 1 ($n = 17$) SMR group + Gray matter volumes AI bilaterally r. MFG l. thalamus r. FO + White matter volumes r. insula r. putamen r. lingual gyrus - Gray matter volumes l. inferior temporal gyrus - White matter volume	Linear discriminant analysis & <i>t</i> -test $t(16) = 2.53; p < .05$ $t(16) = 2.49; p < .05$ $t(15) = 3.10; p < .05$ Two sample <i>t</i> -tests $t(5) = 20.97; p < .05$ $t(5) = 10.88; p < .05$ $t(5) = 14.16; p < .05$ $t(5) = 17.66; p < .05$ $t(5) = 10.79; p < .05$ $t(5) = 12.56; p < .05$ $t(5) = 12.14; p < .05$	Learning ability	5 sessions	18 healthy adults	24.33 y		
Ninaus et al. (2015)			Learning ability	10 sessions	19 healthy adults	46.4 y	SMR ($n = 9$) Gamma ($n = 10$)	

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Table 1 (continued)

Study	Predictors	Method & significance	Outcome	Treatment duration	Participants	Age (M)	Training protocol	No effect
	r. postcentral gyrus Gamma group + Gray matter volumes SMA bilaterally I. MFG	$t(5) = 13.29; p < .05$ $t(5) = 9.19; p < .05$						
Reichert et al. (2015)	+ Resting SMR power (eyes open)	$t(5) = 12.25; p < .05$ $t(5) = 10.38; p < .05$ Linear discriminant analysis $F(1,26) = 10.87; p < .05$	Learning ability	10 sessions	47 healthy adults	SMR group 24.6 y (young) 57.3 y (middle-aged) Control group Sham EEG-IC: 25.0 y Gamma EEG-IC: 46.0 y	SMR (n = 28) Gamma (n = 10) or sham EEG-IC control group (n = 9)	Age
Schamowski et al. (2012)	-	Pearson's correlation voxel area: V1: $r(14) = 0.04; ns$ V2: $r(14) = -0.16; ns$ V3: $r(14) = 0.02; ns$	Learning ability	~3 sessions	16 healthy adults	18-37 y	Real-time fMRI experimental group retinotopic visual cortex NF (n = 11) Control group ventral striatum NF (n = 5) Real-time fMRISMA-PHC	V1; V2; V3 voxels, mental strategy, attention, physiological measures
Schamowski et al. (2015)	-	all $ps > 0.05$	Learning ability	~5 sessions	7 adults	23-26 y	Alpha	spatial orientation, creative imagination, mood
Wan et al. (2014)	Resting alpha activity: + Eyes open	Regression analysis L1: $R^2 = 0.208; p < .05$ L2: $R^2 = 0.186; p < .05$ L3: $R^2 = 0.291; p < .05$ L1: $R^2 = 0.221; p < .05$ L2: $R^2 = 0.299; p < .05$ L3: $R^2 = 0.398; p < .05$	Learning ability	20 sessions	25 healthy adults	23.12 y		Initial training phase
Weber et al. (2011)	+ Eyes closed Initial performance (as of end of 11th session)	Spearman correlation (amplitude increase of each TP with amplitude increase for TP 25) & Mann-Whitney U test (difference amplitudes performers/non-performers) $ps < 0.05$	Learning ability	25 sessions (exp 1) 30 sessions (exp 2)	13 healthy adults (exp 1) 14 healthy adults (exp 2)	Exp. 1 30.17 y Exp. 2 27.89 y	SMR	
Witke et al. (2013)	Control beliefs Learning within sessions: Low KUT (n = 5) vs. High KUT (n = 5)	t-test $t = 3.37; p < .05$	SMR power	10 sessions	20 healthy adults	24.4 y	SMR (n = 10) Sham NF (n = 10)	
Treatment success Daum et al. (1993)	+ Block-tapping span: FB TF + Verbal learning: FB + Digit spans: FB TF - Random errors WCST: TF Verbal memory:	t-tests $t = 2.38; p < .05$ $t = 3.69; p < .05$ $t = 2.54; p < .05$ $t = 2.76; p < .05$ $t = 4.06; p < .05$ $t = 2.24; p < .05$	Training success Seizure reduction (n = 13)	28 sessions	14 epilepsy patients	29.9 y	SCP	IQ ($p < .08$), Visuospatial memory, Frontal tests, Visuospatial functioning

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Table 1 (continued)

Study	Predictors	Method & significance	Outcome	Treatment duration	Participants	Age (M)	Training protocol	No effect
Drechsler et al. (2007)	FB + Block-tapping span: -	$t = 2.15; p = .052$ $t = 3.29; p < .05$ Mann Whitney U test (difference between good and poor performers) All $ps > .05$	ADHD symptom reduction	15 double sessions	30 ADHD patients	NF training 10.5 y Group therapy 11.2 y	SCP (n = 17) Group therapy (n = 13)	Sex, Medication, Diagnosis, IQ, Age, Initial symptoms, Parental support Age, HAWIK-III
Gevensleben et al. (2009)	Theta/Beta-training block Resting theta activity Change of theta activity SCP-training Resting alpha activity	Regression analysis $R = 0.465; p < .05$ $\beta = -0.28; p = .1$ $\beta = -0.33; p = .05$ $R = 0.339; p < .05$ $\beta = -0.34; p < .05$ Correlational analysis $r = 0.6; p = .06$ $r = 0.61; p = .06$ Wilcoxon test $p < .05$ t-tests	ADHD symptom reduction	9 double sessions Theta/beta training & 9 double sessions SCP training	72 ADHD patients (children)	NF training 9.9 y AST group 9.4 y	Theta/beta SCP (n = 46) AST group (n = 26)	
Gevensleben et al. (2014)	Negativity 5th session 9th session	$r = 0.6; p = .06$	Inattention	13 double sessions	10 ADHD patients (children)	11.4 y	SCP	
Karch et al. (2019)	Anger (inward)	Wilcoxon test $p < .05$ t-tests	Tobacco use	3 sessions	36 tobacco use disorder patients	43.8 y	Real-time fMRI Individualized region of interest for craving [ACC, insula or DLPFC] Sham NF (n = 14) NF (n = 22)	Verbal intelligence, Personality, Consumption of cigarettes, Anxiety, Impulsivity, Aggression
Cue exposure task (neuronal responses)								
	<i>Relapse > abstinent</i>							
	Fusiform gyrus	$p < .05; t = 5.76$						
	First session							
	<i>Relapse > abstinent</i>							
	l. cingulate gyrus/MFG	$p < .05; t = 5.63$						
	r. cingulate gyrus/medial frontal gyrus	$p < .05; t = 5.96$						
	r. MFG							
	r. ACC/medial frontal gyrus							
	l. MFG/SFG	$p < .05; t = 5.88$						
	r. extra-nuclear/lentiform nucleus/caudate	$p < .05; t = 5.59$						
	l. lentiformnucleus/extra-nuclear/claustrum							
	l. STG	$p < .05; t = 6.30$						
	<i>Relapse < abstinent</i>							
	l. lingual gyrus/fusiform gyrus/inferior occipital gyrus/declive	$p < .05; t = 5.90$						
	r. lingual gyrus/inferior occipital gyrus/fusiform gyrus	$p < .05; t = 5.69$						
		$p < .05; t = 6.39$						
Kopřivová et al. (2013)	Pre-treatment Delta low alpha oscillations high beta	$p < .05; t = 6.44$ sLORETA correlations $r \geq 0.660; p < .05$ $r \geq -.74; p < .05$ $r \geq 0.653; p < .05$ Chi ² -test $\chi^2(2) = 8.77; p < .05$	OCD symptom severity Symptom change Seizure reduction	25 sessions	18 OCD patients	26.5 y	ICA NF (n = 8) Sham NF (n = 10)	
Kotchoubey et al. (1999)	SCPs (negative) first phase	Correct attribution of responders (24/27) Multiple regression analysis & t-tests $R = 0.82; p < .05$ $t = 3.2; p < .05$	Seizure reduction	35 sessions	27 epilepsy patients	32.4 y	SCP	Age, Sex, Seizure, history Medication, Localization of focus Diagnosis, Baseline Seizure Frequency
Rockstroh et al. (1993)	Age SCP differentiation:	$t = 4.0; p < .05$ $t = 2.7; p < .05$	Seizure reduction	28 sessions	25 epilepsy patients	30.1 y	SCP	

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Table 1 (continued)

Study	Predictors	Method & significance	Outcome	Treatment duration	Participants	Age (M)	Training protocol	No effect
Scheimost et al. (2014)	FB TF	Whole brain connectivity analysis $p < .05$	contamination anxiety	2 fMRI sessions	10 subclinical participants & (5 OCD patients) ¹	OCD patients 46 y	Real-time fMRI-based target region OFC/BA 10, APC	
	Resting state brain connectivity in OFC/BA 10							
Strehl et al. (2005)	SCP initial training phase	Regression analysis $F(6.25) = 10.99; p < .05$	Seizure reduction	35 sessions (+ booster session at six months follow up)	34 epilepsy patients	34.2 y	SCP	Sex, Age, Education, Seizure history, Seizure rate, Medication, EEG parameters other than SCP
	Epileptic focus	$\beta = -1.02; p < .05$	Outcome class (improvement, indefinite, failure)					
	Life satisfaction	$\beta = 0.46; p < .05$						
	SCP control at end	$\beta = -0.25; p < .05$	Complex partial					
	Negative emotionality	$\beta = 0.26; p < .05$	Overall					
	Avoidance	$\beta = 0.35; p < .05$						
Strehl et al. (2006)	Satisfaction with therapy	$F(3/20) = 10.90; p < .05$						
	Visual memory	$\beta = -0.37; p < .05$						
	SCP amplitudes (negative transfer trials) successful vs. unsuccessful self-regulation	$\beta = -0.43; p < .05$						
Wangler et al. (2011)	Complete NF training	$F(3/28) = 7.75; p < .05$	ADHD symptom reduction	30 sessions + 3 follow-up sessions	23 ADHD patients (children)	9.3 y	SCP	
	Theta/beta CNV & alpha baseline	$\beta = -0.37; p < .05^2$						
	Alpha	t-test & Pearson χ^2 -test						
	CNV baseline	$t(12) = -6.58; p < .05$						
Wangler et al. (2011)	Complete NF training	$\chi^2 = 5.24; p < .05$	ADHD symptom reduction	9 double sessions Theta/beta training & 9 double sessions SCP training	84 ADHD patients (children)	NF group 9.8 y AST 9.3 y	Theta/beta SCP NF (n = 56) AST (n = 28)	Age, IQ
	Theta/beta CNV & alpha baseline	Regression analysis $R^2 = 0.214; \beta = 0.46; p < .05$						
	Alpha	$R^2 = 0.085; \beta = 0.29; p < .05$ n. sR = 0.286 $\beta = 0.41; p < .05$ $\beta = 0.26; p < .1$						

Abbreviations: transfer (TF); feedback (FB); volume (Vol.); right (r.); midcingulate cortex (MCC); concentration (Conc.); left (l.); frontal midline (Fm); sensorimotor rhythms (SMR); functional magnetic resonance imaging (fMRI); neurofeedback (NF); positive/negative association (+/-); anterior insula (AI); middle frontal gyrus (MFG); frontal operculum (FO); supplementary motor area (SMA); electroencephalography (EEG); instrumental conditioning (IC); parahippocampal cortex (PHC); Learning index (L); changes between periods (L1); within day-change (L2); learning speed across the whole training time (L3); time period (TP); experiment (exp); Kontrollueberzeugung im Umgang mit Technik (KUT); Wisconsin Card Sorting Test (WCST); slow cortical potentials (SCP); intelligence quotient (IQ); Attention Deficit Hyperactivity Disorder (ADHD); attention skills training (AST); Hamburg-Wechsler-Intelligenztests für Kinder (HAWIK III); anterior cingulate cortex (ACC); dorsolateral prefrontal cortex (DLPFC); superior frontal gyrus (SFG); superior temporal gyrus (STG); standardized low resolution brain electromagnetic tomography (SLORETA); Obsessive Compulsive Disorder (OCD); independent component analysis (ICA); orbitofrontal cortex (OFC); Brodmann Area (BA); anterior prefrontal cortex (APC); contingent negative variation (CNV)

¹ consistently, analyses of $n < 5$ were not reported (see method section).

² After partialling out the focus variable the correlation changed its sign.

group (see Fig. 3b) in Reichert et al. (2015)). This result suggests that at least gamma NF training also affects other nontarget frequencies.

Similarly, Wan et al. (2014) identified higher resting alpha activity at the beginning of the training as a significant predictor for better learning indices for alpha NF in healthy participants. A control group was not implemented. The authors differentiated between three learning indices: the training parameter changes between two periods (session 1 & 20; L1), mean within day-change across all training days (L2) and the learning speed across the whole training time (L3). Within linear regression analyses, eyes-open and eyes-closed resting alpha amplitudes turned out to be significant predictors amounting to 20.8%/22.1% ($p < .05$) of the variance in L1, 18.6%/29.9% ($p < .05$) in L2 and 29.1%/39.8% ($p < .05$) in L3.

Finally, a NF training study of beta/theta ratio with 18 healthy participants found higher rs-low beta amplitudes in responders than in non-responders (Nan et al., 2015). In order to determine learning ability, the authors utilized two indices: the learning ability within sessions (L1) and the linear regression slope of beta/theta ratio over five sessions (L2). However, they found only significant differences between responders and non-responders for the index L2 associated with eyes-open ($p < .05$) and eyes-closed ($p < .05$) resting low beta. Finally, based on a leave-one-out cross-validation, they could classify 88.2% of participants ($n = 17$, due to an outlier) correctly as responders or non-responders.

Taken together, current research results suggest that differences in NF learning ability can be traced back to neuroanatomical and electrophysiological baseline characteristics. Regarding structural predictors, there are only investigations with participants not affected by a major disease or a certain mental disorder, therefore it is unclear how these predictors can be transferred to patient groups. Both studies (Enriquez-Geppert et al., 2013; Ninaus et al., 2015) found an association between the structure of brain areas that are involved in the generation of the trained frequency band and training outcome. Findings reported by Ninaus et al. (2013) also indicate the existence of a more general NF-network in the brain. As long as brain areas involved in these networks and structures are not impaired by a disorder or illness, the findings we reported in this section should be largely transferable to patients. However, since research in this area is still in its infancy, the most important thing now should be to try to replicate these findings and start new investigations with other training protocols. While to date only a few studies identified structural predictors for NF learning ability, more evidence is already available for electrophysiological predictors, particularly for those baseline parameters that are targeted within the following training sessions.

3.1.2. Predictors for treatment success

Beyond the learning of self-regulation itself, a few studies reported predictors of farther-reaching functional consequences (e.g., symptom improvements) on OCD and ADHD. Within a group of OCD patients, Kopřivová et al. (2013) investigated the effectiveness of the independent component NF method, which allows for customized trainings as it is based on an individual diagnosis of pathological EEG sources. For this purpose, 18 patients were randomly assigned to either real ($n = 8$) or sham NF ($n = 10$). The data analyses with standardized low-resolution brain electromagnetic tomography revealed that a high amount of delta and a low amount of alpha oscillations as well as a low amount of high beta activity before treatment were associated with poor treatment outcome (in terms of OCD symptoms). Analyses indicated that patients in the NF group had a superior reduction in the compulsion score (56% vs. 21%) as compared with patients in the sham feedback group. However, investigations of differences in both symptoms together (obsessions and compulsions) indicated comparable improvements after NF and sham feedback. It is difficult to say under these circumstances whether the study indeed identified patients that are not able to profit from this NF training method or whether they identified patients that are generally more resistant to changes in symptoms.

Scheinost et al. (2014) utilized fMRI-based NF in a pilot study for the treatment of contamination anxiety. The final sample consisted of three OCD patients and ten subclinical participants with contamination

anxiety that learned to modulate a target region of the orbitofrontal cortex and anterior prefrontal cortex, Brodmann area 10. In both groups, higher connectivity of the orbitofrontal cortex/Brodmann area 10 prior to the training (based on a whole-brain connectivity analysis) predicted behavioral improvements following fMRI-based NF. However, due to the very small sample size in the OCD group ($n = 3$), results must be interpreted with caution.

Gevensleben et al. (2009) identified predictors of clinical change in a group of 46 children with ADHD passing through a combined theta/beta (18 sessions) as well as an SCP (slow cortical potentials; 18 sessions) NF training. Besides, as a control group, 26 ADHD patients took part in an attention skills training. Linear regression analyses revealed no significant predictor variables for the results of the complete NF training (theta/beta + SCP). However, for the theta/beta training block, the authors found an association of higher pre-training theta activity and a larger decrease of theta activity over the course of the training with more pronounced behavioral improvements. Moreover, for the SCP training block, lower pre-training alpha activity and a stronger increase of alpha activity over the course of the training predicted stronger symptom reduction. The results of the attention skills training showed an association between the increase of beta activity in the course of the training and the decrease of hyperactivity and impulsivity. Overall, as expected, the NF group benefited more from the intervention. Finally, the authors conclude that children with different EEG patterns may benefit from different NF protocols.

In a second subgroup analysis of the same sample, Wangler et al. (2011) also found significant associations between baseline EEG measures and NF-related clinical improvements in $n = 59$ children with ADHD, this time focusing on the contingent negative variation (CNV) elicited by the Attention Network Test in a baseline assessment. In more detail, their results show a relation of a higher pre-training CNV during spatial cue trials ($n = 44$) with larger symptom improvements (parental behavior ratings) following the SCP block as well as the complete (i.e., combined SCP-theta/beta) training. For theta/beta training outcome (as well as the effects of an attention training control group), the authors were not able to identify significant predictors. The authors conclude that transfer to everyday life may be facilitated when patients can recruit more resources right from the start, suggesting to regard baseline CNV amplitude as an indicator for the number of SCP training sessions necessary in individual patients. Furthermore, they reported that combining the predictor of pre-training alpha activity as reported by Gevensleben et al. (2009; see above) with pre-training CNV amplitude in a regression model on the clinical outcome of SCP training explained nearly 30% of the variance. Based on these findings, they suggest optimizing NF trainings by tailoring them to individual neurophysiological profiles.

3.2. Predictors based on the initial training phase

3.2.1. Predictors for learning ability

Instead of using baseline parameters before the first training session as potential predictors of NF outcome, an alternative approach is to perform initial trainings and evaluate early responses to predict future training success. In this respect, Weber et al. (2011) developed a procedure to predict SMR NF success for healthy subjects. Based on data from a first experiment they achieved an almost perfect classification into performers and non-performers for the second experiment. Consequently, a prediction of training outcome was possible from the eleventh out of 25 sessions. Of course, this is a late time point for a prediction, because a lot of time and effort has already been invested. Nevertheless, for the therapists it could be a valuable information, because at some point the question will arise whether one should keep on motivating the patient/participant or whether it would be better to stop the training and instead look for other treatment options. As long as no other factors are available that reliably predict training success, it would also be helpful to know if training at an advanced stage should be continued.

Moreover, [Enriquez-Geppert et al. \(2013\)](#) could predict the increase of fm-theta-activity at the end of the training based on the theta increment obtained during the second session of fm-theta NF. Similarly, initial beta-1 amplitudes in the first block of the first session were higher in responders of theta/beta NF than in non-responders ([Nan et al., 2015](#)). In contrast, the alpha amplitude change obtained during the first sessions does not seem to be a useful predictor for later performance during alpha NF training ([Wan et al., 2014](#)).

3.2.2. Predictors for treatment success

[Strehl et al. \(2005\)](#) examined predictors for SCP trainings in epilepsy patients. The basic idea behind this training for epilepsy patients is that repression of cortical negativity leads to a state where epileptic discharge is restricted. The acquisition of self-regulation skills through the training of cortical activation (SCP training; alternation between positivation and negativation) should enable patients to prevent seizures. [Strehl et al. \(2005\)](#) found a negative effect of large negative SCPs at the beginning of the training on subsequent symptom improvements. EEG parameters other than SCPs were unrelated to training outcome. The authors assume that achievement of long-lasting changes may be difficult for a specific subgroup of epilepsy patients, who generally react with a pronounced increase of cortical excitability in demanding situations. Similarly, [Kotchoubey et al. \(1999\)](#) found no evidence for seizure reduction if patients produced larger negative SCPs in the initial training phase. In this study, they predicted treatment success on the basis of negative SCPs after the first 20 sessions (out of 35) in 24 out of 27 cases.

Regarding SCP differentiation (i.e., the amplitude difference between negative and positive regulation tasks), [Strehl et al. \(2005\)](#) found an increased association with clinical outcome only towards the end of the training, that is, performance (in terms of SCP differentiation) in the last session correlated more with post-training seizure reduction than the scores of the first and second training phase. Unfortunately, the authors did not report about a change score of SCP differentiation across the whole training and they also did not report if they took the SCP differentiation of each participant at the beginning into account. The correlation of SCP differentiation with seizure rate at the end suggests that this is due to the better regulation that would be expected at the end of the training. From the reported results, however, it cannot be clearly determined whether a permanent improvement in self-regulation has actually led to the reduction in seizure rate. If so, it would underpin the value of training success for treatment success.

As part of the evaluation of an SCP training consisting of 13 double-lesson sessions with 4 blocks in total (36–48 trails), the authors also looked for early predictors ([Gevensleben et al., 2014](#)). However, it was not possible to predict treatment success from a certain time point in the sample of ten boys affected by ADHD. There was only a positive correlation between negativity in the fifth double-lesson session (and 9th session) and improvements of inattention symptoms at post assessment. However, this correlation only approached significance ($p = .06$) and, remarkably, the authors could not find a corresponding correlation for the negativity of the last training session. Regarding the overall training outcome, negative mean amplitudes in negativity trials were achieved, but not positive mean amplitudes in positivity trials. It should be mentioned that these analyses occurred in an exploratory mode and, therefore, should be interpreted cautiously, especially because of the calculation of various tests without correction for multiple statistical testing, increasing the likelihood of type I errors.

A recent fMRI-based NF study that applied individualized feedback investigated neuronal responses during the first training session of a combined NF training/psychotherapy program for patients affected by tobacco use disorder ([Karch et al., 2019](#)). For comparison, a sham feedback group from tobacco-dependent participants was formed. The authors found differences in the neuronal response between responders and non-responders of the experimental group. Participants who relapsed after three months showed increased neuronal responses in dorsolateral prefrontal areas, the anterior cingulate cortex and the

supplementary motor area during the first training session. The authors suggest that participants from the relapse group had more difficulties to downregulate craving related responses in brain areas associated with emotional or cognitive processes. This information about differences in craving related neuronal responses could be useful for predicting short-term treatment success in tobacco use disorder. A limitation of the study concerns the rate of abstinence, which is comparable to the sham group, so there might also be other factors influencing treatment outcome that need to be figured out.

3.3. Sociodemographic predictors

To date, a few studies investigated sociodemographic factors that may be associated with NF training or treatment outcome. Only [Rockstroh et al. \(1993\)](#) found a correlation of age (range 15–49 y) and the ability to acquire SCP-control in epilepsy patients, with none of the patients over 35 showing successful regulation. Younger patients were better able to learn SCP-control and to transfer this ability to other situations. Accordingly, they also showed an advantage in the reduction of seizure frequency. Other SCP training studies for epilepsy patients ([Kotchoubey et al., 1999](#); [Strehl et al., 2005](#)) did not reveal a relation with age (17–50 y) just as a SMR training study that investigated learning performance in healthy participants from a wide age range from 22 to 84 years ([Reichert et al., 2015](#)). The difference between the results may be related to differences in medication status and/or disease specific factors.

In contrast, [Wangler et al. \(2011\)](#) found indications for a disadvantage of younger age in their sample of 8–12 years old children affected by ADHD. Dropouts due to insufficient learning or insufficient signal quality were characterized by younger age. However, age was not a significant predictor variable for ADHD symptom outcome. Likewise, the results reported by [Drechsler et al. \(2007\)](#) do not suggest a linear influence of age on clinical outcome in ADHD (SCP training) on the basis of samples with a similarly small age range (9–12 y). The presence of non-linear effects has not been explicitly investigated so far but is considered possible by [Gevensleben et al. \(2009\)](#). Furthermore, the results of [Gevensleben et al.](#) suggest that age differences can cause different starting conditions for NF trainings at least in children. Data of a pre-training EEG measure show a decrease of activity in slower frequency bands and a reduction of the theta/beta ratio with increasing age.

An association of sex or education with seizure reduction was not observed ([Kotchoubey et al., 1999](#); [Strehl et al., 2005](#)). Similarly, there was no difference between girls and boys regarding NF learning performance in a sample of ADHD patients ([Drechsler et al., 2007](#)).

3.4. Psychological & neuropsychological predictors

3.4.1. Predictors for learning ability

[Diaz Hernandez et al. \(2018\)](#) reported a negative correlation between motive satisfaction in terms of satisfactory realization of individual goals as assessed by a life-satisfaction questionnaire and NF training performance in a paradigm of EEG-based microstates. Thus, low levels of motivational satisfaction may be related to an ineffective interaction with the environment that may also complicate successful NF training. This predictor explained about 36% of the variance for the mean increase of the target microstate across sessions during the transfer condition. Furthermore, the predictor explained 42% of the variance for the mean within-session increase during the training condition. The influence of other variables of life satisfaction as well as personality, body awareness or anxiety on learning ability did not reach statistical significance. [Koush et al. \(2017\)](#) designed a fMRI-based connectivity study to investigate the regulation of functional brain networks in 15 healthy participants; 6 of them were assigned to a control group and received sham feedback. Participants trained to control the emotion regulation network while positive social images were presented with the aim to upregulate positive emotions and strengthen top-down connectivity. Thereby, the authors noticed an unfavorable influence of state anxiety, measured by the State-

Trait Anxiety Inventory, on learning success. State anxiety seemingly suppressed a successful regulation, as in the experimental condition the increase in dorsomedial prefrontal cortex activity was less pronounced with higher state anxiety scores at the beginning. Another real-time fMRI-based study assessed mood, spatial orientation and creative imagination, but these variables could not be associated with training success in terms of regulating brain activity in the supplementary motor area and the parahippocampal cortex (Scharnowski et al., 2015). Scharnowski et al. (2012) also did not find a difference in attention between learners and non-learners for fMRI-based NF in healthy participants.

3.4.2. Predictors for treatment success

Since learning is an important part of NF training, general learning skills and cognitive abilities might impact the regulation of brain activity. However, both older and more recent studies did not reveal any evidence in this regard. As an early example for the relevance of cognitive abilities for NF success, we briefly want to mention the findings of Holzapfel et al. (1998) reporting about an epileptic person with an IQ of 64 who reached successful SCP-control and also achieved a considerable reduction of the seizure rate (the inclusion criteria for this review were not met). Accordingly, the authors conclude that successful SCP-regulation can also be achieved in patients with decreased cognitive abilities. Similarly, the results of Strehl et al. (2005) also show that in their sample patients with poor cognitive test results had no particular difficulties reaching self-control during SCP training. Overall, the majority of studies could not find a significant relation between intelligence and the ability of self-regulation of brain activity or NF treatment success (Daum et al., 1993; Drechsler et al., 2007; Gevensleben et al., 2009; Karch et al., 2019; Wangler et al., 2011). Karch et al. (2019) found an effect of inward anger on treatment outcome after real-time fMRI NF for the treatment of tobacco use disorder. Participants who became abstinent had a higher score in inward anger. Anxiety, impulsivity and personality had no discernable effect on treatment outcome.

Daum et al. (1993) associated attention measures, such as digit span or block-tapping span, with performance during SCP training which is in line with its attentional demands. Thereby, they noticed that predictors of SCP training performance were not identical with those for seizure reduction. Those patients who scored better in a verbal learning test and had longer digit spans improved their performance more over the course of the training. Patients with larger differentiation scores had longer block-tapping spans and those with longer block-tapping spans reached a more pronounced seizure reduction. So, while seizure reduction was associated only with block-tapping spans, learning SCP-control was associated with general attention (block-tapping or digit-spans). No consistent relations existed between visuospatial or frontal lobe function (as assessed by the Wisconsin Card Sorting Test) and NF success, with the exception of fewer random errors for patients with larger improvements across sessions.

Though interesting, the results of this investigation should be interpreted with caution, especially because many tests were calculated without correction for multiple statistical testing, increasing the likelihood of type I errors. Additionally, the authors could not replicate their results in a subsequent study.

3.5. Strategies

There is still little knowledge of what patients should do to learn fast and easy to regulate their brain activity by themselves. Only very few studies have addressed this topic. Among them, Witte et al. (2013) explored the effect of control beliefs regarding technology on regulation of SMR power within healthy participants. They reported a negative correlation between control beliefs and SMR power, i.e., those participants who felt less control while dealing with technology were more successful. The authors also found a trend for this association in the control group (sham-NF). The authors conclude that participants who have strong control beliefs over technical devices invest more effort to be successful and thus spend additional resources. This activation of resources could interrupt

brain states of relaxation, which are reflected through SMR power, thus interfering with SMR-synchronization. The authors therefore suggest instructing participants not to push themselves and instead try to relax. Likewise, Kober et al. (2013) confirmed that relaxation may be the most appropriate procedure for regulating SMR power. Those participants who stated after the last NF session that they had not used any strategy showed a trend toward a linear improvement of performance between the first and the last training session. This was not the case for participants who reported using a strategy, possibly due to an excessive mental/cognitive effort. However, this observation may only be valid for SMR power. For training of gamma power, Kober and colleagues could not evaluate such effects as only one participant of this training group decided not to use any strategy. A limitation of the study is that the participants changed their strategy and also their decision not to use a strategy across the training sessions. Scharnowski et al. (2015), on the other hand, reported that their participants only learned the regulation of supplementary motor area and parahippocampal cortex by fMRI-based NF after a strategy was proposed to them that was related to motor imagery and spatial navigation, in accordance with the functional role of these brain areas.

Regarding alpha-band training, Nan et al. (2012) have shown that positive strategies were most effective in their study. Participants who thought about friends or family were more successful. Scharnowski et al. (2012) did not find any difference between learners and non-learners that could be attributed to the strategy. Here, healthy participants imagined different things such as pictures, moving things or situations with other people, to improve visual perception which was the aim of this fMRI-based NF training. In summary, the available literature suggests that effective strategies may strongly depend on the specifics of the NF protocol and target parameters.

3.6. Disease-specific predictors for treatment success

With regard to the treatment of neuropsychiatric disorders by NF, it is important to know if there are any disease-specific characteristics which reduce or enhance the chance to profit from such a treatment. Unfortunately, there is only limited evidence available which is restricted to epilepsy. Strehl et al. (2005) suggest that there may be a subtype of left temporal lesions with an impaired ability to acquire self-regulation through NF training. Drugs, seizure history, seizure rate and diagnosis seemingly had no influence on seizure reduction after SCP training for epilepsy patients (Rockstroh et al., 1993; Strehl et al., 2005). Moreover, predictors for seizure reduction differed depending on the kind of seizures as a better ability of SCP differentiation at the end of the training, a coping style of avoidance and lower early therapy satisfaction predicted only a reduction for complex partial and secondary generalized seizures, but not for simple partial seizures (Strehl et al., 2005). However, the samples of epilepsy subtypes assessed by Strehl et al. (2005) were too small (between nine and 15 patients each) to make strong inference on which group of patients will profit most from an SCP training.

3.7. Learning success as a predictor for treatment success

Until now, learning success and treatment success were considered as two outcome levels/variables of NF trainings. However, the process of successfully learning self-regulation of the NF target parameter may also be a predictor for subsequent functional outcome (i.e., treatment success). Some studies investigating samples of ADHD patients during an SCP training found an association of the ability to generate negative SCP shifts as well as the ability to differentiate between positivity and negativity (transfer trials) with resulting symptom reduction (Drechsler et al., 2007; Gevensleben et al., 2014; Strehl et al., 2006). For epilepsy patients, seizure frequency seems to be similarly related to the achievement of SCP-control (Rockstroh et al., 1993; Strehl et al., 2005). Rockstroh et al. (1993) found an important difference between patients who achieved seizure reduction compared to patients who did not: for successful patients, transfer (trials without feedback) performance was

five to 20 times higher. The results of [Strehl et al. \(2005\)](#) showed that in the group of participants who did not adequately respond to the training (<50% seizure reduction), more patients showed low changes in SCP-control at the end of the training compared to the other two outcome groups: “improvement” (significant seizure reduction) and “indefinite” (non-significant seizure reduction). However, the authors concluded that attaining a certain level of SCP differentiation does not always lead to a satisfying symptom reduction. There is even evidence that patients who were able to learn to regulate their SCPs ultimately did not achieve any seizure reduction ([Kotchoubey et al., 1999](#); [Rockstroh et al., 1993](#)). As a possible explanation, [Strehl et al. \(2005\)](#) stated that the skill of self-regulation of brain activity must be successfully transferred into daily life and should maybe also be combined with other self-regulation methods. Clearly, the research results mentioned above indicate a substantial association between training success and treatment success in terms of symptom reductions. Consequently, learning ability may be also an important predictor for training success (e.g., clinical outcome).

4. Discussion

According to current research results, about 30% of NF participants are not able to learn self-regulation of brain activity successfully ([Enriquez-Geppert et al., 2013](#); [Gevensleben et al., 2014](#); [Reichert et al., 2015](#); [Zoefel et al., 2011](#)). In order to improve this rate, variables need to be identified which determine success for NF trainings and allow for a selection of patients or participants who are most likely to benefit from NF. For this reason, we provide a review of predictors for NF training outcome, with the aim of improving the effectiveness and efficiency of future NF trainings in both research and practice.

In this review, we have identified predictors of NF learning as well as predictors of NF treatment success for different NF protocols, which can be classified into seven categories: neuroanatomical and electrophysiological predictors, predictors derived from initial training performance, sociodemographic predictors, psychological and neuropsychological predictors, strategies, and disease-specific predictors. Furthermore, NF learning success can be considered as a predictor for NF treatment success (i.e., clinical/functional outcome). Below, we summarize and discuss the main findings from each of these categories.

With respect to the neuroanatomical and neurophysiological basis for learning self-regulation of brain activity, to our knowledge, only three studies investigated *structural predictors* of NF success in multi-session training protocols. Besides some specific findings on gray and white matter volumes within different brain areas, [Ninaus et al. \(2015\)](#) provided a summary of findings regarding overlapping neuroanatomical correlates for different NF protocols and highlight the possibility of a more general “NF network” in the brain. Regarding underlying functional processes, previous fMRI data suggest that some activation during both sham- and real-NF reflects self-referential processes and general self-control mechanisms ([Ninaus et al., 2013](#)) substantiating the idea of overarching networks involved in various training protocols. Regarding more specific functional correlates, both studies on structural predictors that investigated participants without major disorders also found an association between training success and volume in brain areas, which are known to be involved in the generation of the trained frequency bands ([Enriquez-Geppert et al., 2013](#); [Ninaus et al., 2015](#)). This finding could facilitate the selection of regions of interest in future studies. However, [Enriquez-Geppert et al. \(2013\)](#) pointed out that – according to their results – these areas were not useful to predict lasting training effects. For the maintenance of training effects, the authors assumed that other brain regions, maybe those involved in learning and memory, could be more important.

Besides structural parameters, *electrophysiological baseline measures* have also been considered as potential predictors of EEG-NF training outcome. A higher degree of baseline activity (i.e., activation before the beginning of the training) seems to be beneficial for subsequent training outcome in healthy participants as well as ADHD patients ([Nan et al., 2015](#); [Reichert et al., 2015](#); [Wan et al., 2014](#); [Wangler et al., 2011](#)). In

these cases, baseline measures were simultaneously the parameters targeted by the training. But an important question for future studies is whether or not the search for predictors should be restricted to the specific training parameters. More precisely, it is unclear at this point whether predictors for EEG-based frequency trainings should generally be derived from the frequency band targeted by the training or if other frequency bands also carry relevant information. Under the studies investigated in the context of this review, only [Gevensleben et al. \(2009\)](#) reported a substantial influence of baseline alpha activity for the outcome of an SCP training with ADHD patients. All in all, these results initially appear somewhat contradictory, because one would assume that in participants with more pronounced deficits there would be more room for improvement and stronger effects of an intervention specifically targeting these deficits (for an example of such a finding in a drug trial, see [Ehlis et al., 2012](#)). However, this seems to be different with NF. In contrast to the treatment with drugs, which is a rather passive treatment and usually does not place any special requirements on the patients previous condition, NF is an active treatment method and therefore probably requires a certain basic level of self-regulation skills right from the start. A higher baseline activity could indicate a better overall self-regulation capacity making it easier for these participants to further improve their self-regulation ability by NF. Maybe, these participants already know “how it should feel” so that they can use NF better for themselves, perhaps because they have more control over such processes by nature (or previous training/experience). If future research could enable to pre-select participants based on structural or electrophysiological parameters, this would be very beneficial for participants given the amount of time and effort involved in NF trainings. Additionally, future research should investigate ways to predict the best training protocol for each individual patient/participant on the basis of electrophysiological baseline parameters.

Based on EEG studies with healthy participants, ADHD and epilepsy patients as well as an fMRI study with tobacco-dependent patients which investigated *initial training success* as a potential predictor variable, we cannot draw any reliable conclusions because of inconsistent findings and a lack of comparability (see also below). The time point from which it was possible to predict training success ranged between session 1 out of 3 and 20 out of 35. Similarly, individual learning curves of a real-time fMRI study showed different courses. Some participants were consistently good, right from the start, some of them initially performed good but then worsened, some of them ended up improving again, and then there were also some “last-minute learners” ([Auer et al., 2015](#)).

With respect to *sociodemographic variables*, according to current evidence, age and sex do not seem to play an important role for learning self-regulation of brain activity or achieving symptom reductions through NF training, neither in healthy participants nor in ADHD or epilepsy patients. Similarly, *general cognitive abilities* or measures of higher cognitive functions including IQ do not seem to significantly impact the ability to learn self-regulation of brain activity in patients with ADHD, epilepsy patients, or tobacco-dependence. *Personality traits* were also investigated as possible predictors, but also seem to be of limited relevance for NF training success, at least in healthy participants and tobacco-dependent patients ([Diaz Hernandez et al., 2018](#); [Karch et al., 2019](#)). Overall, psychological predictors seem to depend strongly on the purpose of the training and the disorder/disease.

To date, we are not aware of any training *strategies* which we can reliably recommend for the acquisition of self-regulation of brain activity, although such information would be very helpful for therapists. The results of the two SMR NF studies which examined this issue in a group of healthy participants suggest that it could be beneficial not to invest too much cognitive effort ([Witte et al., 2013](#)), or not to use any strategy at all and instead relax ([Kober et al., 2013](#)). However, it may be that participants who reported not to have used any strategy in fact implicitly learned a strategy, which they used automatically ([Kober et al., 2013](#)). Moreover, an appropriate strategy could also depend on the trained frequency band or specific target parameter. Regarding alpha-band training, for example, positive thinking was shown to be

most effective in healthy participants (Nan et al., 2012). A NIRS-based NF study with healthy participants, conducted by Barth et al. (2016), uncovered diverse strategies which were well suited to induce activation of the prefrontal cortex (e.g., mental to-do lists or word fluency tasks). All in all, most strategies applied in this NF training seemed to be effective to achieve prefrontal self-regulation. Currently, evidence on *disease-specific predictors* is restricted to epilepsy. According to one study (Strehl et al., 2005), left temporal lesions could be related to the inability to learn or apply self-regulation of brain activity to reduce seizure rate. Drugs, seizure history, initial seizure rate and diagnosis seemingly had no influence on the success of NF training in epilepsy (Rockstroh et al., 1993; Strehl et al., 2005). Beyond that, the influence of brain damage on frequency bands is not sufficiently known for patients suffering from epilepsy, which makes the comparability of such patients difficult, because alterations could affect metabolic, neuroanatomical, functional and cognitive aspects of the central nervous system (Reichert et al., 2015). Since these disease-specific predictors are restricted to epilepsy, generalizability is not given.

Finally, the *ability to self-regulate brain activity* has been identified as a predictor of clinical outcome, at least for the treatment of ADHD (Strehl et al., 2006) and epilepsy (Rockstroh et al., 1993; Strehl et al., 2005). Drechsler et al. (2007) compared an SCP training with group therapy to evaluate the specificity of NF. Thereby, they also tried to find out how to facilitate learning in children affected by ADHD by investigating parental support in form of an additional training using transfer cards at home. However, children receiving more pronounced parental support were not more successful during the NF training. Unfortunately, further research results on how to facilitate NF training success could not be found. But, in order to understand the mechanisms of NF trainings, it is important to know to which extent learning success is indeed a necessary precondition for treatment success.

5. Limitations

A limitation of this review is the circumstance concerning the comparability of the studies available given the differences in sample characteristics (including the target disorder) and methodology, including the training protocol, training frequency, number of trials as well as differing definitions of success. In addition, we may not have identified studies that did not explicitly investigate predictors and therefore did not use the term predictors. Due to our focus on the psychiatric/therapeutic area, which is also reflected in the limited search terms, the generalizability of our conclusions to a broader population could be limited.

6 Conclusion

Many studies indicate beneficial effects of NF. However, relatively high non-responder rates limit the efficiency of this treatment method. Thus, it will be important to predict on an individual basis whether a participant will be likely to profit from the training. Moreover, a further development regarding the individualization of NF protocols in terms of interventions tailored to specific pathophysiological backgrounds should become a main focus of future research.

According to our findings, currently, the most promising predictor seems to be the (neurophysiological) baseline activity, derived from the parameter targeted by the training. With five studies (six papers) reporting largely consistent results, a relatively good evidence base is available compared to the other potential predictor variables. In summary, these findings suggest that a higher baseline level of the training parameter seems to be advantageous for training success, at least when an increase of activity is sought.

From the evidence available at this point, we can derive only one practical recommendation regarding general changes or instructions for future designs of NF protocols. The results suggest that for the training of SMR power it could be helpful to instruct participants before the training not to be dogged and instead try to be relaxed. But, as already noted by Alkoby et al. (2018), whether or not this recommendation

holds for all NF protocols remains an open question.

In summary, we could extract some valuable hints from the existing literature, but further systematic studies regarding the potential predictor variables discussed in this review are needed. In our view, it would be particularly important for future research to find out more about the usefulness of different training strategies for different training protocols. Besides, investigations of motivation and discipline could be important, as NF trainings normally require a lot of frustration tolerance and power of endurance. In general, for better comparability, a more uniform procedure regarding outcome criteria and other modalities such as the number of sessions, the duration and frequency of NF trainings should be established. This could be implemented by creating guidelines from an expert committee. All in all, more profound knowledge about predictors of NF outcome may be the most promising future avenue to further improve the efficacy of such interventions.

CRedit authorship contribution statement

Lydia Anna Weber: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing, Project administration. **Thomas Ethofer:** Conceptualization, Writing - review & editing, Supervision. **Ann-Christine Ehlis:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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