Brain Topogr
DOI 10.1007/s10548-015-0460-4

ORIGINAL PAPER

Towards Using Microstate-Neurofeedback for the Treatment of Psychotic Symptoms in Schizophrenia. A Feasibility Study in Healthy Participants

Laura Diaz Hernandez[1] · Kathryn Rieger[1,2] · Anja Baenninger[1] · Daniel Brandeis[3,4,5,6] · Thomas Koenig[1,2]

Received: 2 July 2015 / Accepted: 28 October 2015

Abstract Spontaneous EEG signal can be parsed into sub-second periods of stable functional states (microstates) that assumingly correspond to brief large scale synchronization events. In schizophrenia, a specific class of microstate (class "D") has been found to be shorter than in healthy controls and to be correlated with positive symptoms. To explore potential new treatment options in schizophrenia, we tested in healthy controls if neurofeedback training to self-regulate microstate D presence is feasible and what learning patterns are observed. Twenty subjects underwent EEG-neurofeedback training to up-regulate microstate D presence. The protocol included 20 training sessions, consisting of baseline trials (resting state), regulation trials with auditory feedback contingent on microstate D presence, and a transfer trial. Response to neurofeedback was assessed with mixed effects modelling. All participants increased the percentage of time spent producing microstate D in at least one of the three conditions ($p < 0.05$). Significant between-subjects across-sessions results showed an increase of 0.42 % of time spent producing microstate D in baseline (reflecting a sustained change in the resting state), 1.93 % of increase during regulation and 1.83 % during transfer. Within-session analysis (performed in baseline and regulation trials only) showed a significant 1.65 % increase in baseline and 0.53 % increase in regulation. These values are in a range that is expected to have an impact upon psychotic experiences. Additionally, we found a negative correlation between alpha power and microstate D contribution during neurofeedback training. Given that microstate D has been related to attentional processes, this result provides further evidence that the training was to some degree specific for the attentional network. We conclude that microstate-neurofeedback training proved feasible in healthy subjects. The implementation of the same protocol in schizophrenia patients may promote skills useful to reduce positive symptoms by means of EEG-neurofeedback.

Keywords EEG · Neurofeedback · Resting state · Microstates · Modelling · Schizophrenia

✉ Laura Diaz Hernandez
laura.diaz@puk.unibe.ch

[1] Translational Research Center, University Hospital of Psychiatry, University of Bern, Bolligenstrasse 111, 3000 Bern 60, Switzerland

[2] Center for Cognition, Learning and Memory, University of Bern, Fabrikstrasse 8, 3012 Bern, Switzerland

[3] Department of Child and Adolescent Psychiatry, University of Zürich, Neumünsterallee 9/Fach, 8032 Zurich, Switzerland

[4] Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, J5, 68159 Mannheim, Germany

[5] Zurich Center for Integrative Human Physiology, University of Zürich, Zurich, Switzerland

[6] Neuroscience Center Zurich, University and ETH Zürich, Zurich, Switzerland

Introduction

Despite major progress, treatment options for patients suffering from schizophrenia are still suboptimal. The default treatment strategy is anti-psychotic medication. However, those patients who respond to treatment, besides having residual symptoms, can also suffer important and disturbing side effects (involuntary movements such as tremor and rigidity, drug-induced Parkinson's disease, tardive dyskinesia, hyper-salivation, increased heart rate,

Published online: 19 November 2015

metabolic syndrome, and weight gain) that often require an additional medication. These side effects are frequently the reason for treatment discontinuation and consequent relapse. Furthermore, approximately 30 % of patients do not respond sufficiently to anti-psychotic medication (Ritsner 2010; Shergill et al. 1998). Consequently, current pharmacological options are insufficient and it is necessary to develop new treatment options.

Among treatment alternatives, neurofeedback has generated wide interest in the clinical domain. This method allows learning voluntary control of momentary brain states that otherwise would be inaccessible, making the self-regulation of pathological states possible (Gruzelier 2013). Neurofeedback has been repeatedly shown to be effective for recovering functions and for optimizing performance. Examples of clinical applications are epilepsy (Sterman and Egner 2006), attention deficit hyperactivity disorders (Arns et al. 2014; Gevensleben et al. 2014; Liechti et al. 2012) addiction (Schneider et al. 1992a) and tinnitus (Hartmann et al. 2014), among others. Importantly, evidence has demonstrated that neurofeedback is feasible in schizophrenia patients (Bolea 2010; Gruzelier et al. 1999; Ruiz et al. 2011; Schneider et al. 1992a, b; Surmeli et al. 2012), who could learn, for example, volitional regulation of brain activity that leads to changes in the perception of emotions and modulates brain network connectivity (Ruiz et al. 2011).

We can envisage several neurofeedback-target-states based on the replicable functional differences of patients compared to healthy controls. Amidst them we can include the abnormal evoked brain activity to auditory stimuli like the longer latencies in mismatch negativity and P300 (Shutara et al. 1996) and the diminished N100 in schizophrenia patients (Saletu et al. 1971), activity circumscribed to brain areas known to be part of a dysfunctional network, like the anterior insula, or the aberrant electrophysiological activity at rest that is reflected in EEG (Boutros et al. 2008).

Schizophrenia has often been discussed as a disconnection syndrome (Andreasen et al. 1998), in which deficits in access, engagement and disengagement of large-scale networks play a prominent role (Menon 2011). Functional magnetic resonance imaging (fMRI) studies in patients have shown that functional resting-state networks show less connectivity in the executive control and dorsal attention networks, suggesting that functional specialization is altered (Woodward et al. 2011). Also, the default mode and central executive networks have spatially shifted connectivity and abnormal signal amplitudes (Littow et al. 2015). Interestingly, research on EEG signatures of subsecond transient network activity has consistently shown as well that particular subtypes of networks appear to be less stable in schizophrenia. These transient networks are observed as so called microstates, i.e. sub-second time epochs in the EEG, in which the electrical field topography is quasi-stable (Lehmann 1987). Each microstate is assumed to reflect a different transiently stable distributed neuronal network corresponding to different brain functions (Koenig et al. 1998, 1999; Lehmann et al. 1998). Britz and colleagues, in a combined EEG-fMRI study, showed that the fMRI correlates of EEG microstates coincide with some of the well-known large-scale functional networks identified with fMRI (Britz et al. 2010).

In several independent samples of patients with schizophrenia, a microstate class labelled "D" was found to be consistently shortened compared to healthy controls (Kikuchi et al. 2007; Koenig et al. 1999; Lehmann et al. 2005; Strelets et al. 2003) and this shortening was correlated with the presence of positive psychotic symptoms (Koenig et al. 1999). A later study by Kindler et al. (2011) showed that the shortening of microstate D was linked to the acute presence of auditory verbal hallucinations. Furthermore, in a study with neuroleptic-naïve schizophrenia patients, it was shown that the patients who responded to medication increased the duration of microstate D after it (Kikuchi et al. 2007) and the decrease in psychotic symptoms after treatment correlated with the increase of duration of microstate D. Additionally, adolescents with the 22q11.2 deletion syndrome, a strong risk factor for schizophrenia, showed the same abnormality, namely a reduction of microstate D among other differences compared with controls (Tomescu et al. 2014). It is therefore reasonable to assume that an intervention affecting microstate D will also affect psychopathology (Tomescu et al. 2014).

The aim of the present feasibility study was to test whether it is possible to influence microstate D by means of EEG neurofeedback. To our knowledge, this is the first study that attempts to modify microstates. Therefore, we decided to test this possibility in a healthy population before undertaking the same protocol in a population of individuals suffering from schizophrenia. With this objective, we developed a neurofeedback protocol in which the presence of microstate D was fed back moment-to-moment to the participants who were instructed to increase the percentage of time spent producing it (microstate D contribution). Given the exploratory nature of this study, we also aimed at evaluating all types of learning derived from the neurofeedback training protocol (hence the evaluation of 'success'). This includes learning effects within and across-sessions and between and within-subjects. Furthermore, we wanted to elucidate the unspecific and specific effects of neurofeedback training as well as the impact of each training condition by means of mixed-effects modelling statistics.

Materials and Methods

Participants

A total of 20 healthy subjects participated in the study (ten males and ten females, mean age = 24.8 ± 3.61 years). They were recruited through advertisements (billboards within the University of Bern) or directly via the researchers involved in the experiment. They received monetary compensation for participation (425 CHF at the end of the study, plus an additional reward was given to the participant who showed the highest learning during the neurofeedback training, of a value of 500 CHF). Participants completed a health-related questionnaire in order to screen out subjects with a history of psychiatric or neurological disorders, misuse of drugs or alcohol, psychoactive medication or ongoing pregnancy. No volunteers were excluded. Based on the assessment with the Handedness questionnaire (Oldfield 1971), 15 participants were right-handed, 3 were left-handed and 2 were ambidextrous. All participants gave written informed consent, and all procedures were in accordance with the declaration of Helsinki and approved by the local ethics committee.

Design and Experimental Procedure

The design of the study is shown in Fig. 1a. It included a (1) pre-session, (2) ten double neurofeedback training sessions and a (3) follow-up neurofeedback training session. In the pre-session (1), subjects received all the information regarding study participation and signed the informed consent. Then, they chose among two options of sound (one was a simple piano melody, and the other was a simple forest sound with birds, both with similar amplitude and volume) which one they preferred as a neurofeedback signal followed by the completion of questionnaires (see "Questionnaires" section below). Finally, two technical EEGs were recorded, first a resting-state EEG with eyes closed (4 min) and open (4 min) and second an EEG with voluntary eye movements. The neurofeedback training (2) was performed in the following ten visits to the lab. Each visit included two consecutive training sessions. After completing the questionnaires relevant to assess the participant's momentary physiological and psychological state (see "Questionnaires" section below), the first session lasting about 30 min took place. Before starting the second session, participants had a brief pause and completed questionnaires again. The double training sessions took place on two non-consecutive days per week, at approximately the same time during the day. At the beginning of each visit, participants received a graphical description about their performance in the previous training sessions. The follow-up (3) was scheduled 6 months after the last training session and consisted of a single neurofeedback training session preceded by the usual questionnaires at approximately the same time during the day than the previous training sessions.

EEG Recording and Feature Extraction

During the experiment, participants sat in an electrically shielded and sound-attenuated Faraday cage. EEG signals were recorded from 32 active electrodes (layout based on the extended 10–10 system) using the ActiCAP system (Brain Products GmbH, Germany). Reference and ground electrodes were placed at FCz and AFz, respectively.

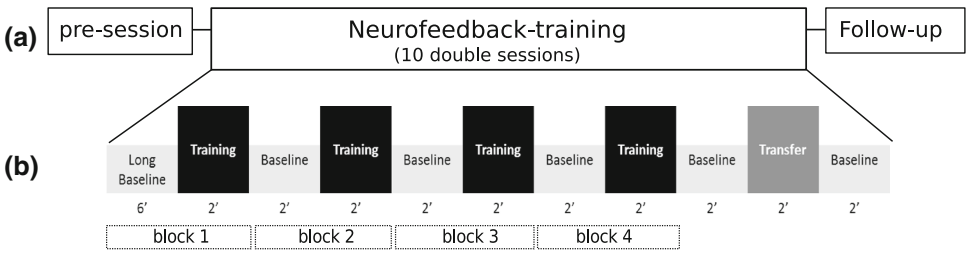


Fig. 1 Experimental design and neurofeeback protocol. **a** Experimental design of the study, executed in 12 different visits to the laboratory. The pre-session was composed of a resting state EEG with 2 min eyes closed, 2 min eyes open, 2 min eyes closed and 2 min eyes open. Additionally voluntary eye movements were recorded. The neurofeedback training took place in lab-visits 2–11. Each day two consecutive neurofeedback trainings were performed. The follow-up took place 6 months after the last training session and included one neurofeedback training session. **b** Neurofeedback training protocol. Each session began with a long baseline trial (three min in silence and three min with the feedback sound) in which subjects were required to stay quiet with their eyes closed. They were instructed to let their thoughts flow and passively and effortless pay attention to the sound. This trial was used to calculate the contribution of microstate D and set the individual threshold for delivering feedback. During the training trials, the feedback sound was contingent upon microstate D contribution exceeding the individual threshold. And, if this percentage was lower than in the baseline, a white noise sound was played. Subjects were given the following instruction: 'your task is to make the sound appear and when you hear it you have to keep it and increase its volume'. During the transfer trials subjects were instructed: 'now make the sound'. They were required to perform as during the training trials, although no feedback sound was delivered. Eyes were closed during the whole training

Impedances were kept below 25 kΩ. Signal recordings were amplified by a BrainAmp 32-Channel amplifier (BrainAmp, Brain Products GmbH, Munich) at a sampling rate of 250 Hz, band pass-filtered between 0.3 and 70 Hz. The feature extraction during the neurofeedback sessions was based on individual microstate topographies and on individual spatial filters designed to minimize the effect of eye-movements, both extracted from the pre-session EEG, as follows: for each subject four microstate topographies were identified in the eyes closed EEG of the pre-session, following the procedure of Koenig et al. (2002). To identify the individual microstate D topography, a Matlab (R2012a the MathWorks) permutation algorithm assigned these four microstate maps to the four microstate classes A, B, C and D shown in the literature (Koenig et al. 2002). To obtain a spatial filter to suppress eventual eye-movement artifacts, the EEG with voluntary eye-movements was submitted to an ICA, and the components showing the spatial distributions and temporal dynamics typical for eye-movements were used to construct the individual filter to suppress these artifacts (Delorme et al. 2007).

The online computation of microstate D contribution was implemented using the build-in and in-house developed plug-ins for RecView (Brain Products GmbH, Munich). The raw EEG data was online filtered from 2 to 20 Hz (24 db/oct) and notch filtered (50 Hz). Eventual eye movements where corrected by means of the individual spatial filter and the EEG was recomputed to average reference. In the next step, each moment of the EEG was assigned to one of the four individual microstate classes (Koenig et al. 2002) and the contribution (percent time spent in) of the individual microstate D topography was computed. See Fig. 2 for details.

Neurofeedback Training Protocol

The neurofeedback training protocol of each session is shown in Fig. 1b. Each training session was composed of (1) baseline, (2) training and (3) transfer trials. Each session began with (1) a long baseline trial (3 min in silence and 3 min with the feedback sound chosen by the participant) in which subjects were required to stay quiet with their eyes closed. They were instructed to let their thoughts flow and passively and effortless pay attention to the sound. This whole trial (6 min) was used to calculate the contribution of microstate D, namely the percentage of time in which microstate D was present. Then, the individual threshold for delivering feedback was set as the percentage of time producing microstate D necessary in order to receive feedback during 50 % of the trial duration. During (2) the training trials, the feedback sound was contingent upon microstate D contribution exceeding the individual threshold. Also, if this percentage was lower than in the baseline, a white noise sound was played. Subjects were given the following instruction: '*Your task is to produce the sound and when it appears, try to increase its volume*'. Auditory feedback was computed based on the contribution of microstate D in the recent past (half-time of the influence on feedback was 1 s, see Fig. 2). The minimal increase from baseline necessary to start the feedback sound was 2 %, and with a 20 % increase the feedback sound had had reached its maximal volume. The volume of the feedback sound was updated each 20 ms. During (3) the transfer trials, subjects were instructed: '*Now, produce the sound*'. They were required to perform as during the training trials, although no feedback sound was delivered. Eyes were closed during the whole training. As depicted in Fig. 1b, we classified each training session in four blocks. Each block was the combination of the consecutive trial conditions. Block 1: long baseline and training 1, Block 2: baseline 2 and training 2, Block 3: baseline 3, training 3, Block 4: baseline 4 and training 4. For each trial, microstate D contribution was retained for later analysis.

Questionnaires

Participants filled out several questionnaires before the first neurofeedback training session: a Handedness questionnaire (Oldfield 1971), the body awareness questionnaire (Shields et al. 1989), the five-factor personality inventory (Borkenau and Ostendorf 1993), the Life Satisfaction Questionnaire (Fahrenberg et al. 2000), the Brief Symptom inventory (Derogatis and Melisaratos 1983), the Incongruence Questionnaire (Holtforth and Grawe 2003), the Multiple Choice vocabulary test MWT-B (Lehrl et al. 1995) and the State Trait Anxiety Inventory; trait version (Spielberger 2010). Additionally, every time they came to the lab they completed a questionnaire about their physiological state (sleep, tiredness, coffee and alcohol consumption), the State Trait Anxiety Inventory; state version and the Positive and Negative Affective Scale (PANAS, Watson et al. 1988). This last questionnaire was given at the beginning of each training session. Most of these data were collected for analyses outside the scope of this study and are thus not further reported here with the exception of the effect of PANAS on the first baseline of each session, which is reported in "Effect of Affective State on Microstate D Neurofeedback Training and Side Effects" in the results section). Finally, they were given a neurofeedback safety register (developed in the lab) to report any side effects that they might have related to the neurofeedback training (see the "Effect of Affective State on Microstate D Neurofeedback Training and Side Effects" results section).

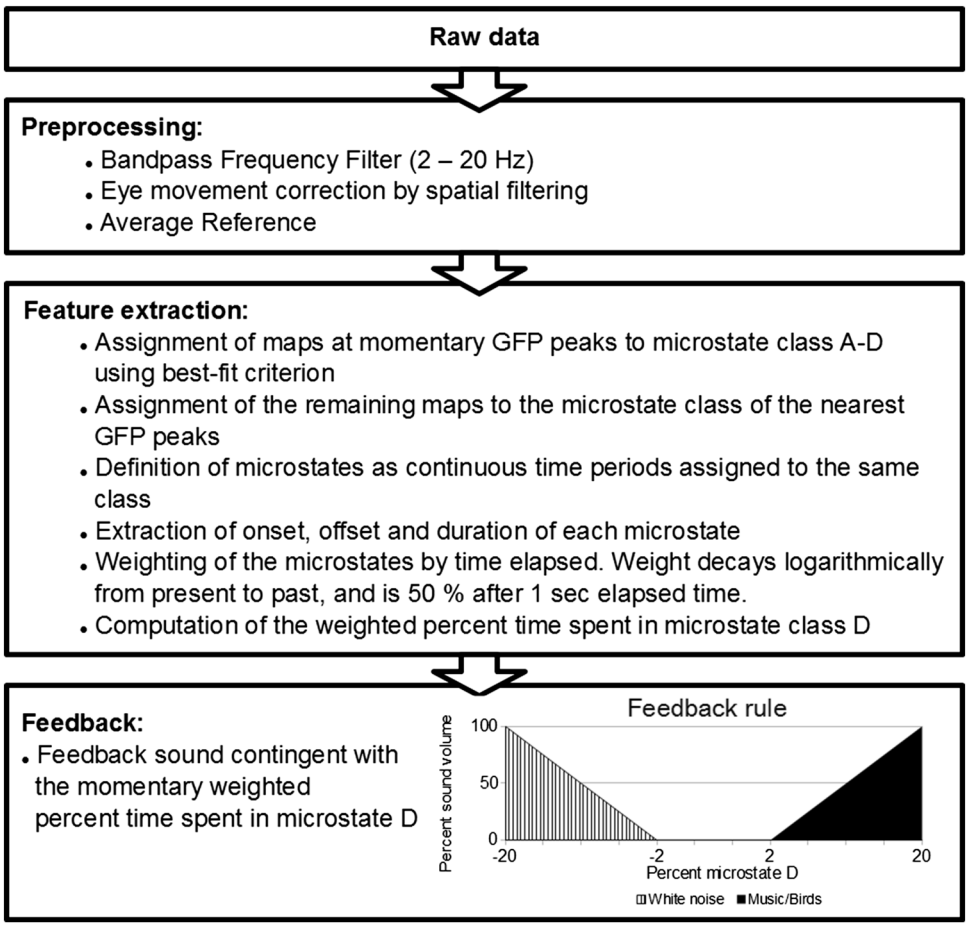


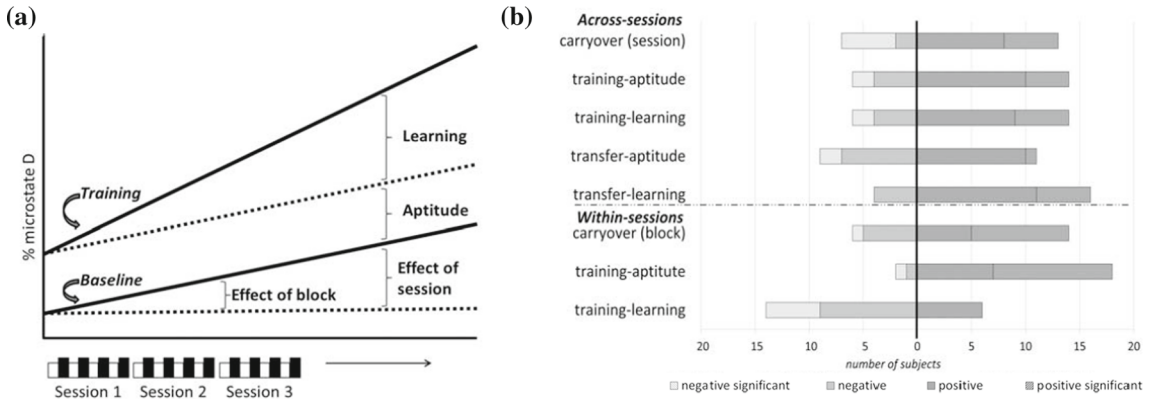
Fig. 2 Online analysis processing steps

Statistical Analysis of Response to Neurofeedback Training Across- and Within-Sessions

The statistical analysis quantified the responses to microstate-neurofeedback training across-sessions and within-sessions, and on a group level (between-subjects) as well as on the individual subjects (within-subjects). For across and within-sessions response to neurofeedback we assessed (1) unspecific effects of training, namely the contribution of microstate D during baseline within and across-sessions, and (2) the specific effects of the active conditions (training and transfer) in microstate D contribution. We further subdivided specific effects into two categories: *aptitude* and *learning*. *Aptitude* was defined as the constant difference of microstate D contribution between an active condition (training and transfer) and baseline; therefore we had *training-aptitude* (constant difference between training and baseline, independent of time) and *transfer-aptitude* (constant difference between transfer and baseline, independent of time). Learning was defined as the interaction between condition (training and transfer vs. baseline) and session in microstate D contribution (i.e. increasing the percentage of time spent producing microstate D in training trials across several sessions in relation to baseline). This classification yielded the categories *learning-training* and *learning-transfer*. See Fig. 3a and the glossary for a description.

To statistically evaluate these indices of response to neurofeedback, we employed regression models. For the analyses, microstate D contribution was thus accounted for by a constant, by a time factor (i.e. session or block), by condition (baseline, training and transfer) and by the interaction of these two factors. For the between-subjects analyses, some of these factors where considered as random variables (mixed effects modelling). The covariance structure used in the model was unconstrained and allowed the random intercepts and slopes to be correlated. For the single subject analyses, the same models were used, but assuming all factors to be constant (fixed effects modelling). To verify the consistency of our results, we also performed a median-split on the second vs the first half of the sessions (as in Ros et al. 2009 for neurofeeback studies) and repeated measures ANOVA for the within-sessions analysis.

Previous research has shown that neuroplastic changes may produce carryover effects from the training of one session to the baseline of the following session (Cho et al. 2008). This hypothesis was tested using a mixed model with a random intercept per subject that quantified the amount of baseline microstate class D contribution



Glossary

Across-session models yielded five neurofeedback success indices:

1) ***Effect of session or session-carryover***: Reflects the increase or decrease, by session, of microstate D contribution independently of condition.

2) ***Training-learning***: Interaction between session and condition training. Reflects the increase or decrease, by session, of microstate D contribution during training as compared to baseline.

3) ***Transfer-learning***: Interaction between session and condition transfer. It reflects the increase or decrease, by session, of microstate D contribution during transfer as compared to baseline.

4) ***Training-aptitude***: Main effect of the condition training. Reflects a constant difference (across-sessions) between training and baseline in microstate D contribution.

5) ***Transfer-aptitude***: Main effect of the condition transfer which reflects a constant difference (across-sessions) between transfer and baseline in microstate D contribution.

Within-session models yielded three neurofeedback success indices (as there is only one transfer trial per neurofeedback training session, this analysis only includes baseline and training trials).

1) ***Effect of block or block-carryover***: Reflects the increase or decrease, by block, of microstate D contribution independently of condition.

2) ***Training-learning***: Interaction between session and condition training. Reflects the increase or decrease, by block, of microstate D contribution during training as compared to baseline.

3) ***Training-aptitude***: Main effect of the condition training. Reflects a constant difference (across-blocks) between training and baseline in microstate D contribution.

Fig. 3 **a** Response patterns. Explanation of the indices in which response to neurofeedback was evaluated. In the example only training and baseline curves are depicted. Effect of session, reflects the unspecific effect of time across-sessions, namely increasing the session number. Learning, reflects the increase (or decrease) of microstate D contribution in training trials in relation to baseline, across time (session or block). Aptitude, reflects the constant difference between training and baseline independent of time. Effect of block, reflects the unspecific effect of time within-session, namely increasing blocks. **b** Distribution of participants in each of the response patterns evaluated. Different color bars represent the direction and significance of the results

explained by the level obtained in the last training block of the preceding session.

Statistical analyses were performed in R (R Core Team 2014) with the package lme4 for mixed effects models (Bates et al. 2014).

Follow-up Evaluation

To evaluate to which degree subjects had retained the acquired skills, we identified the training session that was most similar to (i.e. had the smallest difference from) the follow-up session per subject. We computed the linear regressors corresponding to the training trials of each session (1–20) and also the regressor corresponding to the training trials of the follow-up session. Similarity of a training session with the follow-up session was defined by the smallest difference between the slope of the follow-up and the slope of each session.

Effect of Affective State on Microstate D Neurofeedback Training

We evaluated if the affective state of the participant right before each neurofeedback training session (measured with PANAS) had any influence on the microstate D contribution at the beginning of the session (long baseline measurement). We modelled the effect of positive and negative affective state on microstate D in the first baseline (long baseline) of each session by means of linear mixed effects modelling.

Effect of Sound in Neurofeedback Training Response

To disambiguate between sensory-induced (extrinsic) changes in the EEG, namely the effect that the sound used as feedback signal might have had in microstate D

contribution, and intrinsic (volitional) changes (due to training) we performed an extra analysis.

The rationale we followed was that if the sound was the cause of the increase in microstate D contribution during training trials, this effect should be independent of time and therefore could be equated to aptitude. To assess if this hypothesis was correct, first, we evaluated the effect of sound on microstate D contribution for each participant in the first session's long baseline (6 min). In this trial participants had no experience with the feedback training; therefore this was a neutral trial appropriate to conduct this analysis. We used two minutes of silent baseline (from 0.5 to 2.5 min) and 2 min with sound baseline (from 3.5 to 5.5 min) and computed microstate D contribution for each of these two segments per subject. If the above mentioned hypothesis was true, then the difference of contribution during silence and sound baseline should be correlated to the aptitude value for each subject. We thus subtracted microstate D contribution during silence to the contribution during sound and correlated this difference with the aptitude for each subject.

Alpha Power and Microstate D Training Correlation

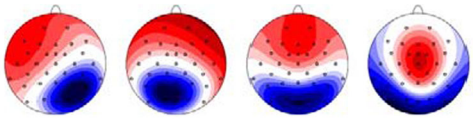
It has been previously shown that the attentional network found in fMRI, localized in fronto-parietal cortical areas (Laufs et al. 2003a, b), was inversely correlated with alpha power activity in the EEG.

As microstate D is it suggested to be an electrophysiological correlate of the attentional network (Britz et al. 2010) we investigated whether a modulation in microstate D contribution had a correspondence in alpha power activity. To this end we calculated an FFT for each of the training trials for each subject and session, and pooled power (8–12 Hz) from O1 and O2. Then we correlated these values with the corresponding microstate D contribution over trials, for each subject separately (due to technical reasons this analysis was performed in 19 out of the 20 participants).

Results

Microstate Topographies and Parameters

The mean maps are shown in Fig. 4. Microstate classes A and B had diagonal axis orientations of the mapped field, microstate class C had an anterior–posterior orientation and microstate class D had a fronto-central extreme location. These configurations matched the literature on the topography of resting-state microstates. The four microstate classes accounted for a mean of 71.5 % of the data variance in our sample (based on squared correlation coefficients across all electrodes and comparing all EEG topographies with its best-fitting microstate map). Figure 4 shows the contribution (percentage of time occupied by each microstate class), the occurrence (mean number of times that each microstate occurred per second) and the mean duration per occurrence of each microstate class.



Microstate	A	B	C	D	A-D
Contribution	0.25	0.24	0.26	0.26	
Occurrence	3.58	3.64	3.53	3.86	14.61
Duration	67.33	67.06	74.01	67.72	69.03

Fig. 4 Microstate topographies validation. Mean topographies of the extracted microstate templates across the studied sample of participants. Microstate classes A and B had diagonal axis orientations of the mapped field, microstate class C had an anterior–posterior orientation and microstate class D had a fronto-central extreme location. *Contribution* percentage of time occupied by each microstate class. *Occurrence* mean number of times that each microstate occurred per second. *Duration* mean duration in milliseconds per occurrence of each microstate class. All information was according to the microstate characteristics found in the literature

Response to Neurofeedback Training; Between-Subjects Analysis

The most complete linear mixed effect model that yielded stable estimates contained, apart from the pre-defined fixed effects, random effects of subject for the constant, and for the time factor (i.e. session or block).

As shown in Table 1a, across-sessions analysis showed highly significant effects for training-learning ($\beta = 0.07$, $p < 0.001$), training-aptitude ($\beta = 0.54$, $p < 0.05$) and transfer-learning ($\beta = 0.11$, $p < 0.001$). The mean percentage of increased time spent producing microstate D across all training sessions was 0.42 % during baseline trials, 1.93 % during training trials and 1.83 % during transfer trials (see Table 2a). Given that the mixed effect model gives an intercept (the constant) for microstate D of 27.06 %, and having the absolute increase in microstate D per condition, we also computed the relative increase per condition. In baseline the relative increase was 1.55 %, in training 7.13 % and in transfer 6.77 %. Figure 5a depicts the evolution of each of the training conditions (baseline, training and transfer) averaged across subjects. Participants performed better in the second part of the training (sessions 11–20) than in the first part (sessions 1–10). These results were corroborated by the median-split analysis on the second vs the first half of the sessions for the following

Table 1 Response to microstate neurofeedback training. (a) Between-subject results assessed with linear mixed effect modelling. (b) Within-subject results assessed with linear fixed effect modelling

(a) Response to microstate neurofeedback training between-subjects

	Across-session effects					Within-session effects		
	Baseline	Training		Transfer		Baseline	Training	
	Carryover	Aptitude	Learning	Aptitude	Learning	Carryover	Aptitude	Learning
Estimate	0.02 (SE = 0.05)	**0.54** (SE = 0.24)	**0.07** (SE = 0.02)	−0.27 (SE = 0.38)	**0.11** (SE = 0.03)	**0.41** (SE = 0.15)	**2.51** (SE = 0.29)	**−0.49** (SE = 0.11)
t value	0.46	2.25	3.44	−0.71	3.3	2.68	8.43	−4.55
p value	0.65	**0.02****	**<0.001****	0.48	**<0.001****	**0.01****	**<0.001****	**<0.001****

(b) Response to microstate neurofeedback training within-subjects

	Across-session effects					Within-session effects		
	Baseline	Training		Transfer		Baseline	Training	
Subj	Carryover	Aptitude	Learning	Aptitude	Learning	Carryover	Aptitude	Learning
1	−0.293****	−6.045****	0.37****	−5.003***	0.279*	1.021***	1.663	−1.527***
2	−0.15****	1.759**	0.031	0.119	<−0.001	0.187	3.437****	−0.54
3	−0.12*	−1.065	0.163*	−3.582**	0.327**	0.734**	1.99*	−0.539
4	−0.465****	−0.038	0.288**	2.01	0.129	0.002	3.436*	−0.179
5	−0.26***	1.372	0.253*	−3.203	0.355*	−0.593	2.338	0.677
6	0.311****	1.4	−0.008	1.298	0.057	1.077*	2.837	−0.61
7	0.602****	−0.929	0.101	1.771	0.082	3.439****	6.181*	−2.421*
8	0.098	1.625	0.161	2.247	0.152	0.714*	3.406*	−0.037
9	0.137**	1.185	−0.172**	0.048	−0.06	0.691**	2.186*	−1.122***
10	0.034	0.636	0.026	−0.758	0.087	−0.224	0.287	0.247
11	−0.055	−1.727	0.089	0.148	−0.189	−0.289	1.096	−0.756
12	−0.035	0.235	0.06	0.164	−0.021	−0.289	−0.15	0.406
13	0.042	0.285	−0.049	−0.312	0.009	0.405*	0.613	−0.336
14	0.102	2.632**	−0.074	0.896	0.019	0.392	3.262**	−0.564
15	0.139*	2.027	0.043	−1.37	0.067	0.035	5.552****	−1.228*
16	0.089	4.568****	−0.098	2.993*	0.035	0.649**	5.142****	−0.642
17	0.073	−1.851*	0.015	0.384	0.026	0.453	−2.03*	0.134
18	0.055	3.926****	−0.274***	−0.875	0.051	−0.871***	0.533	0.206
19	0.006	0.447	0.15	−2.325	0.407**	0.943**	5.077****	−1.22**
20	0.111*	0.403	0.314****	−0.066	0.294**	−0.244	3.253**	0.178

Signif. codes: **** <0.0001, *** 0.001, ** 0.01, * 0.05

conditions: long baseline, training and transfer. We computed t-tests between the halves of each condition. There was no significant difference regarding the long baseline ($t = 1.09$, $p = 0.28$), but a significant increase in the second half for training ($t = 4.17$, $p = 3.20e\text{-}5$) and transfer ($t = 2.55$, $p = 0.01$).

The mixed effect model testing for the carryover effect from the last training of one session to the long baseline period of the next session yielded a significant positive relation ($\beta = 0.19$, $p < 0.001$). Across subjects, the mean correlation coefficient between these values was 0.147.

Within-sessions analysis effects were significant: baseline carryover ($\beta = 0.41$, $p = 0.01$), training-learning ($\beta = -0.49$, $p < 0.001$) and training-aptitude ($\beta = 2.51$, $p < 0.001$) (Table 1a). The mean percentage of increased time spent producing microstate D across blocks was 0.53 % in training trials and 1.65 % in baseline trials (Table 2a). Given an intercept of 26.23 % and the aforementioned percentage increases in microstate D contribution, we computed the relative increase in these two conditions: 6.29 % in baseline and 2.02 % in training. Figure 5b depicts the mean evolution of microstate D contribution within session.

Table 2 Percentage of time increased at the end of microstate neurofeedback training. (a) Between-subjects results. (b) Within-subjects result

(a) Percentage of time increased spent producing microstate D between–subjects

	Across-sessions			Within-session	
	Baseline	Training	Transfer	Baseline	Training
(n = 20)	0.42 %	1.93 %	1.83 %	1.65 %	0.53 %

b) Percentage of time increased spent producing microstate D within-subjects

	Across-sessions			Within-session	
Subj	Baseline	Training	Transfer	Baseline	Training
1	−5.86	1.36	0.57	4.08	−4.45
2	−3.01	2.39	0.11	0.75	1.28
3	−2.40	2.19	2.97	2.93	−0.17
4	−9.31	5.72	4.59	0.01	2.72
5	−5.19	6.44	3.89	−2.37	5.05
6	6.22	1.23	2.45	4.31	0.40
7	12.05	1.09	3.41	13.76	−3.50
8	1.95	4.84	5.28	2.86	3.26
9	2.74	−2.25	−1.15	2.77	−2.30
10	0.69	1.15	0.97	−0.90	1.28
11	−1.10	0.05	−3.64	−1.16	−1.93
12	−0.71	1.44	−0.26	−1.16	1.47
13	0.84	−0.69	−0.13	1.62	−0.73
14	2.03	1.15	1.29	1.57	1.01
15	2.79	2.90	−0.02	0.14	0.64
16	1.79	2.60	3.69	2.60	2.57
17	1.47	−1.55	0.91	1.81	−1.50
18	1.10	−1.56	0.15	−3.48	1.36
19	0.13	3.46	5.81	3.77	0.20
20	2.22	6.68	5.82	−0.98	3.97

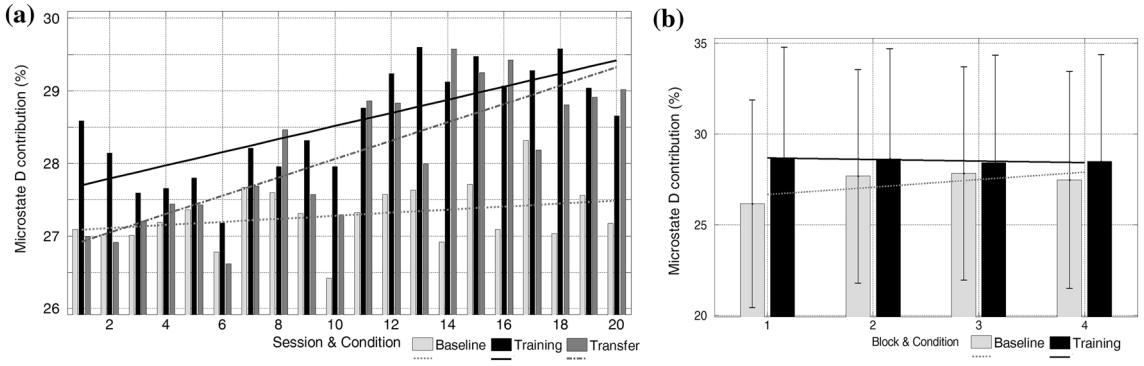


Fig. 5 Between-subjects average response to neurofeedback training. **a** Across-sessions analysis. Displays microstate D contribution averaged per session and condition. **b** Within-sessions analysis. Depicts microstate D contribution per block and condition

Figure 5b suggests that, within-sessions, the values during training changed only little, whereas there was a entraining of the baseline values, which became higher after each training block. Thus, the data suggests that only the first baseline before the training was a reliable reference for within session learning. This is on one side accounted for by significant effect of the the training-aptitude effect of the model, which is in reference to the estimated baseline

before training. To further corrobate this, we subtracted the long, pre-training baseline from all training values, and computed a linear mixed model. This model yielded, as expected, a significant offset of the training-long baseline values from zero ($\beta = 2.60$, $p = 2.32e\text{-}05$), but no effect of training block ($p > 0.5$).

Response to Neurofeedback Training; Within-Subject Analysis

Results of the statistical models for across and within-sessions effects, for each participant, are shown in Table 1b. Figure 3b illustrates how many subjects had significant (and non-significant) results for each of the indices evaluated. The majority of participants had significant effects in at least one of the indices modelled.

Follow-up

For five subjects the closest session to the follow-up session was training session 5, for one session 6, for two session 7, for another two session 9, for one session 10, for two session 16, for one session 18 and for six subjects it was session 20. A χ^2 test confirmed that this distribution was significantly different from the null-hypothesis ($\chi^2 = 56$, $df = 19$, $p < 0.001$).

Effect of Affective State on Microstate D Neurofeedback Training and Side Effects

The model used to assess the effect of affective state on microstate D included an intercept, a fixed effect for positive affect, a fixed effect for negative affect and a random intercept for subject and a random slope for the interaction between session and subject. We modelled the increase or decrease in microstate D in the first baseline of the session with positive and negative affect. No effect was significant (positive affect $\beta = -0.05$, $std = 0.04$, $t = -1.40$, $p = 0.16$, negative affect: $\beta = -0.11$, $std = 0.07$, $t = -1.65$, $p = 0.09$). The neurofeedback safety register reported no side effects for all subjects and all sessions.

Effect of Sound in Neurofeedback Training Response

For the first long baseline of each subject we subtracted microstate D contribution during silence to the contribution during sound and correlated the value with the aptitude for each subject. The result was not significant ($r = -0.05$, $p = 0.88$). We thus argue that the effect that sound might have had on microstate D contribution is unlikely to explain the training effects.

Table 3 Correlation between alpha power (8–12 Hz, O1–O2) and microstate D contribution per each subject

subject	rho	p value
1	0.23	0.08
2	−0.68	<0.01
3	0.19	0.15
4	−0.13	0.32
5	−0.85	<0.01
6	−0.85	< 0.01
7	0.59	<0.01
8	−0.68	<0.01
9	−0.10	0.47
10	−0.73	<0.01
11	0.37	<0.01
12	−0.17	0.19
13	−0.77	<0.01
14	0.50	<0.01
15	−0.61	<0.01
16	−0.56	<0.01
17	−0.29	0.03
18	−0.52	<0.01
19	−0.59	<0.01

Alpha Power and Microstate D Training Correlation

Table 3 shows the correlations between alpha power and microstate D contribution per each subject across all training sessions and conditions. For the majority of the participants there was a strong and significant negative correlation between alpha power and microstate D contribution.

Discussion

We developed an EEG-neurofeedback protocol to train, for the first time, EEG resting state microstates. We demonstrated that healthy participants were able to increase the percentage of time spent producing microstate D (contribution) by means of auditory feedback. Britz et al. (2010) showed that microstate D is an electrophysiological correlate of the central executive resting state network, which has been shown to be involved in reflexive aspects of attention (i.e. detect behaviorally relevant stimuli), its reorientation (Corbetta and Shulman 2002) as well as in decision making and working-memory. The stability of the central executive network is assumingly reflected in the stability of microstate D. Therefore, by influencing the presence of this microstate we are directly targeting the stability of the executive network. In patients with schizophrenia, there is converging evidence that microstate D, and functions assumingly associated with it, are

reduced. Consequently, the possibility of effectively influencing microstate D may constitute a treatment option with a potential positive effect on schizophrenia.

Different Types of "Success" in Neurofeedback

Whereas the majority of neurofeedback studies classically differentiate between responders and non-responders to training, we modelled the response to neurofeedback by means of a series of indices for specific and unspecific effects of training, within and between-subjects. This method gave evidence that response to our training can and should be differentiated into several categories of individual response patterns. The majority of participants showed significant effects of training in at least one of the learning indices modelled (Fig. 3b). For the across-sessions analysis these indices were: unspecific effects of session (or carryover across-sessions), training-aptitude (i.e. constant difference between training and baseline independent of time), training-learning (i.e. increase of percentage of time spent producing microstate D in training trials in relation to baseline, across time) transfer-aptitude (i.e. constant difference between transfer and baseline) and transfer-learning (i.e. increase of percentage of time spent producing microstate D in transfer trials in relation to baseline, across time). For within-sessions effects these indices were: unspecific effects of block (or carryover within-session), training-aptitude (i.e. constant difference between training and baseline independent of block) and training-learning (i.e. increase of percentage of time spent producing microstate D in training trials in relation to baseline, across blocks).

Results indicated that aptitude and learning during training trials was positive and significant across the sampled participants, whereas for transfer, only learning was significant while aptitude was negative and non-significant. This difference between training and transfer trials could be due to the fact that transfer trials occurred in a situation that was more similar to baseline (with no feedback, when subjects are required to be at rest) than to training and that transfer occurred only once and at the end of the neurofeedback session. Perhaps some subjects drifted away in these trials from the task and were more in a resting state than in a task state. Indeed, at the end of each session, participants were asked about their strategies during training and transfer and some said that it was sometimes difficult to focus on the transfer trial for two min. Another possible explanation for this lack of focus could be that because transfer occurred towards the end of the session, subjects were already tired by then. On the other hand, we could also adventure that more sessions of neurofeedback are needed before subjects can perform equally well in transfer and training trials. Training-learning and transfer-learning were significant between-subjects, showing that besides the fact that subjects could influence microstate D thanks to aptitude, they also benefited from the repeated neurofeedback sessions (they performed better as the training advanced).

Within-sessions, we observed two interesting effects. (1) There was a carryover effect to the following baseline trial and (2) training-aptitude was positive and significant while training-learning was negative and significant. (1) The carryover effect raises the question whether the baselines interspersed with the training trials were a valid measure of baseline or, what seems more plausible; these baselines include a post-effect of the preceding trial produced by a mechanism of Hebbian plasticity (Knoblauch et al. 2012). As we found this effect in the majority of subjects, we reason that two minutes of baseline following two min of training are too short to stop the processes (consciously or unconsciously) employed during training and go back to a real baseline state. Two possible consequences emerge here. First, it may be that only longer baselines allow participants to go back to an original resting state. This would imply that the measures of baseline taking place immediately after a training trial are not a valid measure of baseline and should not be considered as such. Second, given that the goal of neurofeedback training in many situations is to modify the tonic EEG in the direction of training, we may consider this within-session carryover together with the across-session carryover as a desired effect of training and hence as success. (2) We also point to the fact that training-aptitude and training-learning were both significant albeit in opposite directions. This showed that it was not possible to increase microstate D contribution while the session progressed, and as consequence, the difference between microstate D levels at baseline and training trials became smaller with time. Nevertheless, as training-aptitude was positive there was a constant difference between the two conditions (baseline and training). We would think then, that more blocks would maybe represent no extra-benefit for the training, as the biggest increase from baseline to training takes place in the first block. On the other side, it is also possible that all this extra-training across blocks was the cause of the carryover across-sessions, affecting the tonic EEG and therefore accomplishing one of the goals of the neurofeedback training, namely increase percentage of time spent producing microstate D.

Overall, within-session results indicate that there does not seem to be possible to increase microstate D contribution beyond a certain level during the training session. Nevertheless across-session results show that neurofeedback training produced a carryover effect to the next session. This pattern of response to neurofeedback, in which the target feature does not increase (decrease) dramatically

within-sessions but increases (decreases) across-sessions, has already been found for other EEG features like alpha power. The studies from Cho et al. (2008) and Ros et al. (2013) targeted (differently) alpha neurofeedback and found that amplitude at the end of a neurofeedback session positively correlated with the following session's resting state (Cho et al. 2008) and immediate post-session resting state (Ros et al. 2013). This response pattern has been attributed to a basic mechanism of Hebbian plasticity very elegantly illustrated in a recent publication by Ros et al. (2014). The fact that our study, targeting a complete different EEG feature, parallels the same pattern of response to training adds more evidence to Hebbian plasticity as the explanatory mechanism. This same mechanism would be responsible of the carryover effects observed within sessions.

Understanding Response to Neurofeedback Training

To understand how subjects respond to neurofeedback training, we consider important to report all the indices in which this response can be modelled as described in this manuscript. Future studies would benefit from this information, for example, in the design phase of the study (e.g. by adding more or less trials). It would also be advantageous for the use of neurofeedback as a patient's treatment because it could allow tailoring the treatment to each patient based on the pattern of response (e.g. in the case of a patient showing a small training-aptitude but a positive progressive training-learning, it would be convenient to add large amount of sessions).

We modelled the response to the follow-up and assessed which was the training session in which the response to each type of trial was more similar. Overall we could divide our subjects in two groups regarding this measure; one group that responded to the follow-up as in the first part of the training (sessions 5–10) and another group that responded as in the last part of the training (sessions 11–20). None of the subjects displayed a pattern as in the very first session, indicating that all of them learned across-sessions and the learning remained more or less the same 6 months after the last training session. Also, subjects who responded best to neurofeedback during training sessions had also follow-up sessions closer to the last training sessions.

Patients with schizophrenia show less percentage of time covered by microstate D compared to healthy individuals. The differences range from: 4 % less time (Strelets et al. 2003) to 8.7 % in patients (Koenig et al. 1999). Microstate neurofeedback training produced on average an increase of 1.93 % more time spent producing microstate D during training trials. Even though this increase of time spent producing microstate D seems small, within-subject analysis showed that some of the participants were able to increase up to 6.68 % during training trials. Considering that the trained participants were healthy individuals and that their levels of microstate D were normal, it may not have been possible to produce larger changes in percentage of time covered by microstate D due to a potential ceiling effect. It is reasonable to speculate that patients suffering from schizophrenia would be able to increase microstate D more because their natural levels are lower than the ones of the healthy participants of the present study. Alternatively, however, the shortening of microstate D may reflect a core impairment of these patients, so up-regulating may be a particularly challenging task for them, and possibly require extended training.

It remains to be seen if patients undergoing this microstate neurofeedback training will increase the percentage of time covered by microstate D and if positive psychotic symptoms will be reduced accordingly. We think that there are good reasons to assume this, as there is already evidence that when subjects respond to pharmacological treatment their microstate D duration becomes longer (Kikuchi et al. 2007).

To our knowledge, this is the first neurofeedback study that attempted to target resting state microstates. There are some differences between this EEG feature (microstates) and the spectral features classically trained. First, microstates and spectral power are measured at different time scales. Resting state microstates last <100 ms, while spectral power is measured over seconds. Second, microstates represent the coordination of activity across regions; therefore the training of microstates reflects the training of neuronal networks. This approach represents a type of connectivity training (Mottaz et al. 2014). As schizophrenia is considered a disconnection syndrome, it is reasonable to assume that a training that targets the synchronous activity among areas might be helpful in the treatment of this condition. This study showed that this type of connectivity training is feasible with EEG, being cost-efficient and relatively easy to use as compared to other techniques like fMRI. These advantages would make this protocol a widely available treatment.

Alpha Power and Microstate D Neurofeedback Training

The strong negative correlation between alpha power and microstate D contribution suggests that a modulation of alpha power goes along with microstate D contribution training. This result seems in opposition to a previous paper indicating only weak correlations between alpha power and microstates (Koenig et al. 2002). However, in this study, the statistics were conducted across subjects and not within-subjects. If there were substantial individual

baseline differences in alpha power that were unrelated to the attentional network, between subject designs may not be sensitive to the effect shown in our study. But also in a more recent paper, Britz et al. (2010) showed correlations between EEG power and microstates to be low also in a within-subject analysis. Contrary to our study, their subjects were only at rest, whereas our study is likely to have actively challenged the attentional system. In addition, by directly using the spatial correlation of the microstate topographies with the momentary EEG maps, their methodology used to quantify microstates was less elaborated than the procedure employed here.

On the other side, Laufs et al. (2003a, b) found the attentional network to be inversely correlated to alpha power. Given that we were aiming at enhancing a microstate assumingly related to attentional processes, the observed correlation between microstate D and alpha power is thus confirmatory evidence that our neurofeedback training was to some degree specific for that network. On the other side, this might explain why we did not find a significant effect of aptitude in the transfer trials, where no stimulus could be attended.

Limitations

There are several limitations related to our study. First, the sample size of 20 subjects might not have been large enough to elucidate patterns of response to neurofeedback more clearly (considering all the possible combinations that are possible when assessing response to neurofeedback with the explained indices). Second, as this was a feasibility study we did not run any control group. Each subject was its own control comparing pre and post measures, although we could not control for unspecific effects of neurofeedback. We suggest that other studies could use a control group with for example a protocol targeting another microstate or placebo. Nevertheless, there are several opinions regarding the topic of control conditions in neurofeedback studies and maybe a placebo group would not be the best option as discussed in Gruzelier (2014).

Conclusion

We trained healthy subjects to increase the percentage of time spent producing resting state microstate D by means of EEG neurofeedback. The results show that this training was feasible and therefore, it would be reasonable to implement the same protocol in a population of subjects suffering from schizophrenia. The ultimate aim of this training would be to empower patients to reduce positive symptoms with neurofeedback as treatment tool. Benefits of neurofeedback as treatment are that it can target connectivity directly and bypasses the traditional treatment approaches as medication (of which 1/3 of patients cannot benefit) and cognitive treatment (neurofeedback does not require any awareness of the targeted state to be able to influence it).

These results are encouraging to apply the same protocol in a patient population to test whether they can also increase the percentage of microstate D and if this has as a consequence the voluntary control of positive symptoms.

Acknowledgments This study was supported by the Swiss National Science Foundation (Sinergia Grant #136249) and by the Center for Cognition, Learning and Memory, University of Bern, Bern, Switzerland. We want to give special thanks to Béatrice Zumkehr, Christine Krebs and Leandra Schmid for helping with the data acquisition as well as to all the participants in the study.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Andreasen NC, Paradiso S, O'Leary DS (1998) Cognitive dysmetria as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? Schizophr Bull 24:203–218

Arns M, Heinrich H, Strehl U (2014) Evaluation of neurofeedback in ADHD: the long and winding road. Biol Psychol 95:108–115

Bates D, Maechler M, Bolker B and Walker S (2014) lme4: Linear mixed-effects models using Eigen and S4. R package version 1.1–7. http://CRAN.R-project.org/package=lme4

Bolea AS (2010) Neurofeedback treatment of chronic inpatient schizophrenia. J Neurother 14(1):47–54

Borkenau P, Ostendorf F (1993) NEO-Fünf-Faktoren Inventar (NEO-FFI) nach Costa und McCrae [NEO Five-Factor Personality Inventory (NEO-FFI) according Costa and McCrae]. Hogrefe, Göttingen

Boutros NN, Arfken C, Galderisi S, Warrick J, Pratt G, Iacono W (2008) The status of spectral EEG abnormality as a diagnostic test for schizophrenia. Schizophr Res 99:225–237

Britz J, Van De Ville D, Michel CM (2010) BOLD correlates of EEG topography reveal rapid resting-state network dynamics. NeuroImage 52:1162–1170

Cho MK, Jang HS, Jeong S-H, Jang I-S, Choi B-J, Lee M-GT (2008) Alpha neurofeedback improves the maintaining ability of alpha activity. NeuroReport 19:315–317

Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201–215

Delorme A, Sejnowski T, Makeig S (2007) Enhanced detection of artifacts in EEG data using higher-order statistics and independent component analysis. Neuroimage 34:1443–1449

Derogatis LR, Melisaratos N (1983) The Brief Symptom Inventory: an introductory report. Psychol Med 13:595–605

Fahrenberg J, Myrtek M, Schumacher J, Brähler E (2000) Fragebogen zür Lebenszufriedenheit (FLZ). Handanweisung, Germany

Gevensleben H, Kleemeyer M, Rothenberger LG, Studer P, Flaig-Rohr A et al (2014) Neurofeedback in ADHD: further pieces of the puzzle. Brain Topogr 27:20–32

Gruzelier J (2013). EEG-neurofeedback for optimising performance I: A review of cognitive and affective outcome in healthy participants. Neurosci Biobehav Rev

Gruzelier J (2014) EEG-neurofeedback for optimising performance III: A review of methodological and theoretical considerations. Neurosci Biobehav Rev 1–24

Gruzelier J, Hardman E, Wild J, Zaman R (1999) Learned control of slow potential interhemispheric asymmetry in schizophrenia. Int J Psychophysiol 34:341–348

Hartmann T, Lorenz I, Muller N, Langguth B, Weisz N (2014) The effects of neurofeedback on oscillatory processes related to tinnitus. Brain Topogr 27:149–157

Holtforth MG, Grawe K. 2003. The incongruence questionnaire (ink). An instrument for the analysis of motivational incongruence. Zeitschrift fur Klinische Psychologie und Psychotherapie Forschung und Praxis

Kikuchi M, Koenig T, Wada Y, Higashima M, Koshino Y et al (2007) Native EEG and treatment effects in neuroleptic-naïve schizophrenic patients: time and frequency domain approaches. Schizophr Res 97:163–172

Kindler J, Hubl D, Strik WK, Dierks T, Koenig T (2011) Resting-state EEG in schizophrenia: auditory verbal hallucinations are related to shortening of specific microstates. Clin Neurophysiol 122:1179–1182

Knoblauch A, Hauser F, Gewaltig MO, Korner E, Palm G (2012) Does spike-timing-dependent synaptic plasticity couple or decouple neurons firing in synchrony? Front Comput Neurosci 6:55

Koenig T, Kochi K, Lehmann D (1998) Event-related electric microstates of the brain differ between words with visual and abstract meaning. Electroencephalogr Clin Neurophysiol 106:535–546

Koenig T, Lehmann D, Merlo MC, Kochi K, Hell D, Koukkou M (1999) A deviant EEG brain microstate in acute, neuroleptic-naive schizophrenics at rest. Eur Arch Psychiatry Clin Neurosci 249:205–211

Koenig T, Prichep L, Lehmann D, Sosa PV, Braeker E et al (2002) Millisecond by millisecond, year by year: normative EEG microstates and developmental stages. NeuroImage 16:41–48

Laufs H, Kleinschmidt A, Beyerle A, Eger E, Salek-Haddadi A et al (2003a) EEG-correlated fMRI of human alpha activity. Neuroimage 19:1463–1476

Laufs H, Krakow K, Sterzer P, Eger E, Beyerle A et al (2003b) Electroencephalographic signatures of attentional and cognitive default modes in spontaneous brain activity fluctuations at rest. Proc Natl Acad Sci USA 100:11053–11058

Lehmann D (1987) In: Gevins AS, Remond A (eds) Principles of spatial analysis, Elsevier, Amsterdam, pp 309–54

Lehmann D, Strik WK, Henggeler B, Koenig T, Koukkou M (1998) Brain electric microstates and momentary conscious mind states as building blocks of spontaneous thinking: I. Visual imagery and abstract thoughts. Int J Psychophysiol 29:1–11

Lehmann D, Faber PL, Galderisi S, Herrmann WM, Kinoshita T et al (2005) EEG microstate duration and syntax in acute, medication-naive, first-episode schizophrenia: a multi-center study. Psychiatry Res 138:141–156

Lehrl S, Triebig G, Fischer B (1995) Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. Acta Neurol Scand 91:335–345

Liechti MD, Maurizio S, Heinrich H, Jäncke L, Meier L et al (2012) First clinical trial of tomographic neurofeedback in attention-deficit/hyperactivity disorder: evaluation of voluntary cortical control. Clinical Neurophysiology 123(10):1989–2005

Littow H, Huossa V, Karjalainen S, Jaaskelainen E, Haapea M et al (2015) Aberrant functional connectivity in the default mode and central executive networks in subjects with schizophrenia - a whole-brain Resting-state ICA study. Front Psychiatry 6:26

Menon V (2011) Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci 15:483–506

Mottaz A, Solcà M, Magnin C, Corbet T, Schnider A, Guggisberg AG (2014) Clinical Neurophysiology Neurofeedback training of alpha-band coherence enhances motor performance. Clin Neurophysiol

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113

R Core Team (2014) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/

Ritsner MS (2010) Pregnenolone, dehydroepiandrosterone, and schizophrenia: alterations and clinical trials. CNS Neurosci Ther 16:32–44

Ros T, Moseley MJ, Pa Bloom, Benjamin L, La Parkinson, Gruzelier JH (2009) Optimizing microsurgical skills with EEG neurofeedback. BMC Neurosci 10:87

Ros T, Théberge J, Pa Frewen, Kluetsch R, Densmore M et al (2013) Mind over chatter: plastic up-regulation of the fMRI salience network directly after EEG neurofeedback. NeuroImage 65:324–335

Ros T, Bernard JB, Lanius RA, Vuilleumier P (2014) Tuning pathological brain oscillations with neurofeedback: a systems neuroscience framework. Front Hum Neurosci 8:1008

Ruiz S, Lee S, Soekadar SR, Caria A, Veit R et al (2011) Acquired self-control of insula cortex modulates emotion recognition and brain network connectivity in schizophrenia. Hum Brain Mapp 34:200–212

Saletu B, Itil TM, Saletu M (1971) Auditory evoked response, EEG, and thought process in schizophrenics. Am J Psychiatry 128:336–344

Schneider F, Elbert T, Heimann H, Welker A, Stetter F et al (1992a) Self-regulation of slow cortical potentials in psychiatric patients: alcohol dependency. Biofeedback self Regul 18:23–32

Schneider F, Rockstroh B, Heimann H, Lutzenberger W, Mattes R et al (1992b) Self-regulation of slow cortical potentials in psychiatric patients: schizophrenia. Biofeedback self Regul 17:277–292

Shergill SS, Murray RM, McGuire PK (1998) Auditory hallucinations: a review of psychological treatments. Schizophr Res 32:137–150

Shields SA, Mallory ME, Simon A (1989) The body awareness questionnaire: Reliability and validity. J Personal Assess 53(4):802–815

Shutara Y, Koga Y, Fujita K, Takeuchi H, Mochida M, Takemasa K (1996) An event-related potential study on the impairment of automatic processing of auditory input in schizophrenia. Brain Topogr 8:285–289

Spielberger CD (2010) State-Trait Anxiety Inventory. The Corsini Encyclopedia of Psychology. Wiley, Hoboken

Sterman MB, Egner T (2006) Foundation and practice of neurofeedback for the treatment of epilepsy. Appl Psychophysiol Biofeedback 31:21–35

Strelets V, Faber PL, Golikova J, Novototsky-Vlasov V, Koenig T et al (2003) Chronic schizophrenics with positive symptomatology have shortened EEG microstate durations. Clin Neurophysiol 114:2043–2051

Surmeli T, Ertem A, Eralp E, Kos IH (2012) Schizophrenia and the efficacy of qEEG-guided neurofeedback treatment: a clinical case series. Clin EEG Neurosci 43:133–144

Tomescu MI, Ta Rihs, Becker R, Britz J, Custo A et al (2014) Deviant dynamics of EEG resting state pattern in 22q11.2 deletion syndrome adolescents: a vulnerability marker of schizophrenia? Schizophr Res 157:175–181

Watson D, Clark LA, Tellegen A (1988) Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 54:1063–1070

Woodward ND, Rogers B, Heckers S (2011) Functional resting-state networks are differentially affected in schizophrenia. Schizophr Res 130:86–93