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Targeted training modifies oscillatory brain activity in schizophrenia patients

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ABSTRACT

Effects of both domain-specific and broader cognitive remediation protocols have been reported for neural activity and overt performance in schizophrenia (SZ). Progress is limited by insufficient knowledge of relevant neural mechanisms. Addressing neuronal signal resolution in the auditory system as a mechanism contributing to cognitive function and dysfunction in schizophrenia, the present study compared effects of two neuroplasticity-based training protocols targeting auditory–verbal or facial affect discrimination accuracy and a standard rehabilitation protocol on magnetoencephalographic (MEG) oscillatory brain activity in an auditory paired-click task. SZ were randomly assigned to either 20 daily 1-hour sessions over 4 weeks of auditory–verbal training ($N = 19$), similarly intense facial affect discrimination training ($N = 19$), or 4 weeks of treatment as usual (TAU, $N = 19$). Pre-training, the 57 SZ showed smaller click-induced posterior alpha power modulation than did 28 healthy comparison participants, replicating Popov et al. (2011b). Abnormally small alpha decrease 300–800 ms around S2 improved more after targeted auditory–verbal training than after facial affect training or TAU. The improvement in oscillatory brain dynamics with training correlated with improvement on a measure of verbal learning. Results replicate previously reported effects of neuroplasticity-based psychological training on oscillatory correlates of auditory stimulus differentiation, encoding, and updating and indicate specificity of cortical training effects.

1. Introduction

The striking prominence of cognitive impairment and its impact on functional outcome in schizophrenia (Nuechterlein et al., 2011; Fioravanti et al., 2012; Heinrichs et al., 2013) has fueled the search for effective treatment and prevention and for clarification of neural contribution to cognitive deficits (see Thorsen et al., 2014, for review). Despite promising effects of cognitive remediation treatment (CRT), overall effects have been found to be only mild to moderate (Grynszpan et al., 2011; Wykes et al., 2011; Thorsen et al., 2014), emphasizing the need to consider neural mechanisms of cognitive (dys)function (Silverstein and Wilkniss, 2004; Merzenich et al., 2014) when designing function-specific training. For example, hemodynamic neuroimaging studies using domain-specific tasks (e.g., n-back for working memory) have shown CRT effects on frontocortical activity, supporting the hypothesis of impaired fronto-cortical capacity, potentially related to progressive structural abnormalities (Thorsen et al., 2014).

One model influencing the development of function-specific training advocates that cognitive dysfunction in schizophrenia results from fundamental weaknesses in perceptual and cognitive processing, which in turn are associated with poor neuronal signal resolution, slowed processing speed, impaired generation of sustained activity, or "noisy brain system processing" (Winterer et al., 2000; Harrison and Weinberger, 2005; see also Minzenberg et al., 2009; Merzenich et al., 2014). If neuronal signal resolution fosters higher-order cognitive processes (Merzenich et al., 2014), CRT methods should target fundamental aspects of input representation and discrimination. Evidence of training-driven neuroplasticity and neuroplasticity-based structural and functional changes suggests that efficient training protocols should (a) be targeted, i.e., address specific deficits potentially related to fundamental illness features such as signal discrimination, and (b) consider necessary and optimal conditions for neuroplasticity (Elbert and Rockstroh, 2004; Merzenich, 2013; Merzenich et al., 2014). Protocols implementing this concept to foster neuroplasticity by training auditory–verbal discrimination accuracy and verbal working memory (e.g., Brain Fitness Program, BFP, Posit Science, SF, USA; referred to as

Abbreviations: HC, healthy comparison participants; MEG, magnetoencephalography; CRT, cognitive remediation treatment; BFP, Brain Fitness Program; FAT, facial affect training; SZ, schizophrenia patients.

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Cognitive Exercises, CE, in Popov et al., 2011a,b, and Popova et al., 2014) improved cognitive performance and prompted changes in electromagnetic measures of auditory signal processing (P50/M50, N100/M100, and P300 components of the event-related potential or field) that are often reported abnormal in schizophrenia patients (SZ; reviews by Dale et al., 2010; Fisher et al., 2013, 2015, 2014; Merzenich et al., 2014; see also Popov et al., 2011a; Subramanian et al., 2012). Thorsen et al. (2014) argued that insufficient understanding of CRT mechanisms contributing to neural and cognitive changes limits treatment development.

The present study examined neural oscillatory activity as a mechanism of neuronal activity involved in stimulus encoding and differentiation, which play a critical role in perceptual and cognitive dysfunction. Adding to evidence of dysfunctional regulation of oscillatory dynamics in SZ (e.g., Popov et al., 2011b, 2012, 2014; Popova et al., 2014; Uhlhaas et al., 2008; Uhlhaas and Singer, 2010), trial-by-trial evoked and induced oscillatory activity provides further information about the dynamics of stimulus processing and discrimination (Buzsaki, 2010; Jensen and Mazaheri, 2010; Hanslmayr et al., 2012). In the present approach time-locked activity, often termed evoked, reflects brain activity consistently associated in latency and phase with stimulus onset, typically apparent after averaging across trials. Non-time-locked activity, often termed induced, is measured in single trials and reflects brain activity changes prompted by a stimulus but variable in latency, thus lost in averages. Distinguishing time-locked and non-time-locked oscillatory activity may reveal mechanisms involved in normal perceptual and cognitive performance and disrupted in SZ. For example, in a previous study using a paired-click task, evoked and induced modulation of oscillatory activity in the alpha frequency (8–16 Hz) range[1] distinguished SZ and healthy controls, in that SZ showed less evoked 8–12 Hz power increase (relative to pre-stimulus baseline) to the first click and less induced 10–15 Hz decrease midway between clicks and before S2-onset (Popov et al., 2011b).

With an emphasis on induced alpha power modulation, oscillatory activity was measured in a paired-click task as a means to study mechanisms of auditory signal differentiation. Although the reduced evoked response to the second of two brief, identical clicks in rapid succession is commonly described as gating, interpreted as inhibition of redundant information (e.g., Bramon et al., 2004) or suppressed response during the refractory period following S1 (Mathiak et al., 2011), the task prompts S1 encoding and differentiation of S2 as identical stimuli, thus redundant. Therefore, and as the ratio of click-evoked event-related brain potentials or fields P50/M50 ratio reliably distinguishes SZ and HC (e.g., Adler et al., 1982; Bramon et al., 2004; Hanlon et al., 2005; Smith et al., 2010; Yee et al., 2010; Popov et al., 2011a; Carolus et al., 2014), effects of training were evaluated in the paired-click design in the previous (Popov et al., 2012) and the present study.

In Popov et al. (2012), targeted training (BFP, see above) normalized induced 8–10 Hz decrease in contrast to broad-spectrum cognitive remediation. Whereas, pre-training, small induced alpha power decrease varied with abnormally large M50 ratio, post-training, larger alpha power decrease in SZ varied with smaller M50 ratio, in line with an assumption of improved paired-click processing and differentiation. In the conceptual framework of alpha power decrease as a sign of increased readiness for information sampling and facilitated neuronal network processing (Klimesch, 1999; Jensen and Mazaheri, 2010; Hanslmayr et al., 2012) training-augmented alpha power decrease was interpreted as a sign of facilitated S2 differentiation vis-à-vis S1-encoding. Intense, targeted auditory training normalized both, S1-evoked and induced alpha-power responses in SZ (Popov et al., 2012). This result supported the hypotheses that oscillatory dynamics mediate stimulus differentiation, encoding, and updating and that this neural correlate of cognitive dysfunction (Merzenich et al., 2014; Thorsen et al., 2014) can be modified by targeted psychological training.

The present study replicated the protocol of Popov et al. (2012) in a new sample of chronic SZ and evaluated its specificity by comparing SZ undergoing the BFP protocol and SZ undergoing a newly developed intervention that targeted facial affect discrimination in a similarly intense, neuroplasticity-based learning context[2]. Facial affect discrimination was chosen as a comparison target of training, since social–cognitive impairment is among the domains which most reliably distinguish between SZ and HC (Heinrichs, 2004; Mesholam-Gateley et al., 2009) and since impaired facial affect recognition, discrimination, and expression have been established as prominent elements of impaired social cognition in SZ, which are targets of cognitive remediation and more focused training protocols (Sachs et al., 2012; Wölwer et al., 2012). Therefore, a training protocol matching BFP except for a focus on facial affect discrimination instead of auditory–verbal discrimination accuracy was developed in order to compare training-specific effects on domain-specific brain correlates. Regarding facial affect recognition, Popov et al. (2013) observed a pattern of alpha power decrease over posterior (secondary-visual) regions and an increase in sensorimotor regions during the time window of correct identification of affect in pictures reflecting different degrees of happy or fearful expression. This pattern was smaller in SZ (Popov et al., 2014). Targeted facial affect training increased induced sensorimotor alpha power increase relative to auditory–verbal training and TAU, and alpha power increase after FAT correlated with improvement of performance on the affect discrimination task over the 20 training sessions (Popova et al., 2014).

The primary hypotheses were, first, that previously reported effects of auditory–verbal discrimination training on oscillatory measures (Popov et al., 2012) would be replicated in an independent sample and, second, that effects on oscillatory dynamics in the auditory paired-click task would be specific to the targeted function — auditory information processing. Thus, oscillatory activity in the auditory paired-click task should change after auditory–verbal training but not after visual facial-affect training. Third, given the premise that modification of cortical signal discrimination is fundamental to higher cognitive function (Merzenich, 2013), training-specific improvement in auditory oscillatory dynamics should vary with improvement in verbal learning and memory performance in neuropsychological testing (compared to performance on visual learning and social cognition domains, which were expected to improve more after targeted facial affect training, the active control procedure in the present study, than after auditory–verbal training).

2. Methods and materials

2.1. Participants

Inpatients were recruited from the university inpatient unit of the regional Center for Psychiatry and diagnosed by experienced senior psychiatrists or psychologists using the ICD-10 criteria. The inclusion criteria were normal intellectual function and no history of neurological condition or disorder, including epilepsy or head trauma with loss of consciousness. Prior to the first assessment, patients were randomly assigned to one of three treatment groups: BFP or facial affect recognition training (FAT; see Popova et al., 2014) protocols or the standard treatment-as-usual (TAU) regimen in the unit (see Fig. 1 for the recruitment process). Across the recruitment period, random assignment was continued until 20 patients per training protocol had accomplished pre-

[1] Current views of the "alpha" frequency range involve a larger range of frequencies than the traditional 8–12 Hz range. More recent results refer to alpha frequency windows 14–16 Hz (Mazaheri et al., 2014), 8–14 Hz (Haegens et al., 2014), 7–14 Hz (Spaak et al., 2012), 6–15 Hz (Weisz et al., 2014), or 8–16 Hz (Frey et al., 2014).

[2] Comparing the effects of two specific training protocols benefits from testing effects using tasks that measure the specifically targeted versus non-targeted function. Such a group × task design was employed in the overall project. The present report evaluates intervention effects in the paired-stimulus task, whereas intervention effects on facial affect discrimination in overlapping patient samples and an overlapping healthy comparison sample are reported separately (Popova et al., 2014).

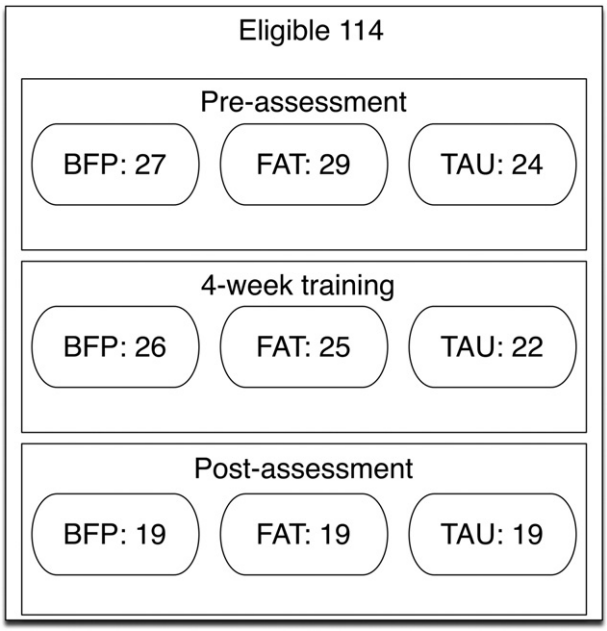

Fig. 1. Schizophrenia patients (SZ) recruitment across the study protocol. Numbers in each box represent the number of SZ per study phase. Eligible: SZ meeting the inclusion criteria. Pre-assessment: SZ consecutively assigned randomly to one of the training protocols before the pre-training assessment of symptoms (PANSS), cognitive performance (MCCB), and MEG. Training protocols: BFP: Brain Fitness Program, FAT: facial affect training and TAU: treatment as usual. Recruitment and assignment were continued until at least 20 SZ per training group were enrolled in the training. 4-week training: number of SZ per training group starting the 4-week training. Post-assessment: number of SZ per training group completing the 4-week training and available for post-training assessment of symptoms, MCCB, and MEG. Considering the complete data sets and MEG data quality, pre–post data analyses are based on $n = 19$ SZ per group.

training assessment, training protocol, and post-training assessment. Due to dropouts, incomplete data sets at the different stages of the study phases, and insufficient MEG data quality, complete data for 57 SZ were available for final analyses. Of these, 44 SZ were diagnosed with paranoid–hallucinatory schizophrenia (ICD-code F20.0), 6 with schizoaffective disorder (ICD-code F25.1), and 7 with other F20.x diagnoses. Table 1 summarizes the sample characteristics. Training groups did not differ in age, gender distribution, IQ (assessed by a standard German test for premorbid intelligence, MWT-B; Lehrl, 2005), years of education, clinical status (Positive and Negative Syndrome Scale — PANSS; Kay et al., 1987), or chlorpromazine equivalent.

Neuromagnetic oscillatory activity and cognitive function before training were assessed by comparison of the SZ with a sample of 28 healthy comparison participants (HC). HC were screened with the Mini International Neuropsychiatric Interview (Ackenheil et al., 1999) to exclude psychiatric or neurological disorder. Patients were older than HC (see Table 1), while groups did not differ in gender distribution or years of education.

2.2. Design and procedure

The study was approved by the ethics committee of the University of Konstanz and registered as a Clinical Trial (ClinicalTrials.gov Registration NCT01781000). The participants provided written informed consent prior to the study and received 30 € upon completion of each session. For SZ the MEG assessment was done pre- and post-training, each session consisting of the assessment of neuromagnetic activity during the paired-click task and cognitive performance on the MATRICS Consortium Cognitive Battery (MCCB) (Nuechterlein et al., 2008).

The two targeted training protocols were identical with respect to computer-based exposure, intensity, shaping, and reinforcement algorithm fostering neuroplasticity (Elbert and Rockstroh, 2004; Merzenich et al., 2014): 20 daily 1-hour sessions were scheduled on consecutive workdays across four consecutive weeks. A computer algorithm provided individual adjustment of task difficulty as a function of performance, and motivating feedback was provided per task and session. BFP focused on auditory–verbal discrimination and memory, and FAT focused on facial affect recognition. BFP consists of 6 computerized exercises: judging gradually more difficult distinctions between frequency-modulation sweeps of auditory stimuli, distinguishing phonemes with synthesized speech, identifying arrays of open and closed syllables in spatial and temporal context, discriminating tone frequencies, and remembering details of short narratives. FAT[3] consists of four tasks, two emphasizing facial affect discrimination and two emphasizing facial affect recollection: deciding whether two different posers are displaying the same or different emotion, or which emotion is displayed by a face blended from two emotions from a single poser, recalling a sequence of emotion faces from a single poser, and recalling the location of identical pairs of poser/emotion combinations among an array of hidden faces (for details see Popova et al., 2014).

2.3. Data collection

Prior to MEG measurement, individual hearing levels were determined for each ear separately via an adapted method of limits (Gescheider, 1997). The paired-click procedure comprised 100 trials, each trial a pair of 3 ms square-wave clicks (S1 and S2) presented with a 500 ms onset-to-onset interstimulus interval within trial, with intervals between S2 and the subsequent S1 varying between 7 and 9 s. Clicks were presented 60 dB above individual hearing level and delivered via 5 m nonferromagnetic tubes. No performance task was involved, except that participants were asked to keep their eyes focused on a small fixation point throughout the procedure.

MEG was recorded while subjects were in a supine position, using a 148-channel magnetometer (MAGNES 2500 WH, 4D Neuroimaging, San Diego, USA). Data were continuously recorded with a sampling rate of 678.17 Hz and a bandpass filter of 0.1–200 Hz. Trials containing movement artifact or SQUID jumps were rejected based on visual inspection. Global noise was removed offline by subtracting external, non-biological noise recorded by an additional 11 MEG reference

[3] FAT includes a series of visual exercises involving human face expression, two emphasizing facial affect discrimination and two emphasizing working memory. FAT was designed to be comparable to BFP in neuroplasticity-based learning, differing in the content of tasks. The same/different task trained the ability to discriminate whether two different posers express the same or different emotions, replacing the discrimination of two syllables/phonemes in the BFP protocol. The blended emotion task addressed the identification of a target emotion in morphed faces, which Popov et al. (2014) found to be impaired in SZ: in order to train this type of affect discrimination, each face combined two 50/50 morphed facial expressions. The participant was asked to indicate which two emotions in an array of seven standard Ekman emotional expressions were combined in the presented face by clicking on the respective expression in the array of facial pictures. The emotion sequence task trained the recognition of the sequence of a series of facial affect expressions from a single poser per trial, corresponding to the BFP task of reproducing the sequence of a series of syllables/phonemes per trial. In the emotion location task, patients learned to recall the location of identical pairs of poser/emotion combinations among an array of hidden faces corresponding to the BFP task of recalling the location of identical pairs of syllables/phonemes that were acoustically presented upon touching the respective cards in an array. Emotional faces were obtained from the KDEF databank (http://www.emotionlab.se/resources/kdef) and included male and female Caucasian faces expressing one of seven emotions (sad, happy, disgusted, fear, surprised, angry, neutral). Within each task, level of difficulty was adjusted to individual performance by increasing difficulty after 6 correct (non-consecutive) responses or decreasing difficulty after 3 consecutive errors. This algorithm ensured increasing difficulty with improving performance. Performance feedback was provided within a session after 6 correct responses per level (the transition to the next level of difficulty) and at the end of each task. Performance on the four tasks was evaluated as the proportion of correct responses per level of difficulty for each task and each session. Performance change following FAT was evaluated by comparing scores for the first and last sessions. The meaning of performance scores varied qualitatively for the different tasks. Therefore, change in performance scores was evaluated separately for each task, using dependent sample *t*-tests and effect size (Hedges' g).

Table 1
Demographic and clinical information.

	Schizophrenia patients	Healthy controls	Stat. diff.	
Age (M ± SD)	37.05 ± 9.06	29.32 ± 9.50	$F1,83 = 13.26$ p < .01	
Gender (f/m)	19/38	14/14	$Chi^2(1) = 2.17$ ns	
Years of education	15.00 ± 2.54	14.55 ± 3.44	$F < 1$	
	Training groups			Stat. diff.
	BFP	FAT	TAU	
Age (M ± SD)	36.95 ± 8.44	39.21 ± 7.91	35.00 ± 10.59	$F2.54 = 1.03$ ns
Gender (f/m)	6/13	9/10	4/15	$Chi^2(2) = 3.02$ ns
Years of education	14.56 ± 3.29	14.68 ± 4.19	14.42 ± 2.99	$F < 1$
IQ	101.47 ± 13.46	109.79 ± 16.13	108.21 ± 17.89	$F = 1.46$ ns
GAF	44.68 ± 13.60	42.32 ± 12.32	42.73 ± 14.32	$F < 1$
PANSS-P	15.42 ± 5.18	16.42 ± 5.27	14.26 ± 5.08	$F < 1$
PANSS-N	18.21 ± 6.55	18.58 ± 6.60	18.84 ± 6.29	$F < 1$
PANSS-G	35.63 ± 5.39	36.68 ± 8.50	34.11 ± 8.98	$F < 1$
CPZ	544 ± 490	671 ± 343	617 ± 403	$F < 1$

Note: GAF: Global Assessment of Functioning (DSM-IV axis 5), PANSS: Positive and Negative Syndrome Scale, scales P (positive symptoms), N (negative symptoms), and G (general symptoms) and CPZ: chlorpromazine equivalents

channels. Offline treatment of the MEG signals was accomplished primarily with the MATLAB-based open-source signal processing toolbox FieldTrip (Oostenveld et al., 2011). Epochs of 1000 ms before and 2000 ms after the first click (S1) of each trial were extracted from continuous recordings. BFP (M ± SD 95 ± 5), FAT (M ± SD 95 ± 3), TAU (M ± SD 95 ± 6) and HC (M ± SD 92 ± 6) did not differ in number of artifact-free trials ($F(3,81) = 1.88$, $p = 0.14$).

2.4. Data analysis

Single-trial time–frequency representation of power (TFR) was estimated using a sliding 500 ms window multiplied by a Hanning taper. Single-trial power estimates were then averaged across trials and expressed as a decibel change from a 200 ms pre-stimulus baseline. In a first step, identification of time–frequency windows of differences between SZ ($n = 57$) during the first assessment (prior to training) and HC ($n = 28$) served to replicate deficient induced alpha power decrease around S2 as described for an earlier, independent SZ sample (Popov et al., 2011b). Relevant time–frequency windows were defined using a cluster-based, independent-sample *t*-test with Monte Carlo randomization (Maris and Oostenveld, 2007) for identification of sensor clusters of significant Time × Frequency × Group interaction. Hypothesis-relevant activity was expected in the 8–16 Hz alpha frequency range during 300–800 ms post-S1 onset, thus including S2, which was presented at 500 ms. A one-way, four-level ANOVA on alpha power change from pre-S1 baseline evaluated responses to the clicks for the three SZ groups prior to training and the HC group.

In the next step, a Group (BFP, FAT, TAU) × Time (pre-, post-training) ANOVA on alpha power change from pre-S1 baseline assessed training effects for the three SZ groups, again using Monte Carlo randomization to define time × frequency × sensor clusters with a significant Group × Time interaction. Where appropriate, significant ANOVA effects were followed up with *t*-tests to aid in interpretation.

Cognitive performance in the SZ samples was assessed with the MATRICS Consortium Cognitive Battery (MCCB; Nuechterlein et al., 2008; German Translation Regents of the University of California, 2006; see Harvey et al., 2010). The MCCB covers seven domains of cognitive function that have been shown to be impaired in schizophrenia: processing speed, attentional vigilance, working memory, verbal learning, visual learning, reasoning, and social cognition. Raw scores were converted to *T*-scores based on a representative U.S.A. community sample of healthy subjects (Nuechterlein et al., 2008; German norms have not been developed). Normal distributions were verified with the Kolmogorov–Smirnov test. A Group (BFP, FAT, TAU) × Domain × Time (pre-, post-training) ANOVA assessed treatment effects. (The present report concentrates on the relationship between changes in performance per domain before and after targeted training or TAU and changes in induced alpha oscillations in the paired-click task. Detailed analyses of the MCCB profile in the SZ sample, including pre-training, post-training, and a 3-month follow-up measurement, are reported in Carolus et al., 2015, and relationships between test performance and facial affect training effects are reported in Popova et al., 2014).

Relationships between changes in cognitive test performance and changes in MEG oscillatory measures were tested by correlations of the change scores. The primary interest was in scores on the verbal learning test, to evaluate the specificity of the three types of intervention according to the third hypothesis.

3. Results

Fig. 2 shows that evoked alpha power increased after S1 and that induced alpha power declined substantially around the onset of S2 in the HC group. Prior to training, SZ showed less evoked alpha power increase and less induced decrease around S2. Group differences in the evoked alpha power increase 50–300 ms after S1 likely reflect the S1-evoked M100 or M200, which is known to be smaller in SZ than in HC.

Within the 8–16 Hz frequency (see Footnote 1) and 300–800 ms time range, the Monte Carlo randomization identified significant group differences for 8–12 Hz between 400–700 ms (around S2 onset). Submitting the scores used in the Monte Carlo randomization test to a conventional one-way ANOVA verified a Group effect, $F(3,81) = 7.50$, $p = .002$. Post-hoc comparisons correcting for multiple comparisons did not show significant pre-training differences between any pair of SZ groups ($p = .2$). Fig. 3 illustrates the impact of training on induced alpha-power response to the click pair. Within the 8–16 Hz frequency range and the 300–800 ms time range, the Monte Carlo randomization identified a significant Group × Time interaction for 12–16 Hz between 300–800 ms (around S2 onset). The Group × Time interaction, $F(2,54) = 4.53$, $p = .015$, and post-hoc *t*-tests confirmed that BFP (effect size d = −.84) fostered more decrease in alpha-power response (thus, partial normalization), with no significant change for FAT (d = −.12) or TAU (d = .52). There was no effect of training on S1-evoked alpha power.

Given that induced (and evoked) alpha power modulations could be driven by differences in prestimulus baseline activity, the power spectra were analyzed for the 1500 ms prestimulus interval. As evident in Fig. 2, groups did not differ in power spectrum during the baseline.

Cognitive test performance improved from pre-training to post-training assessment (Time, $F(1,54) = 24.94$, $p < .001$; Domain × Time, $F(6,324) = 4.40$, $p < .001$, Huynh–Feldt $\varepsilon = .92$), but there was no significant behavioral effect related to training group. Improvement over

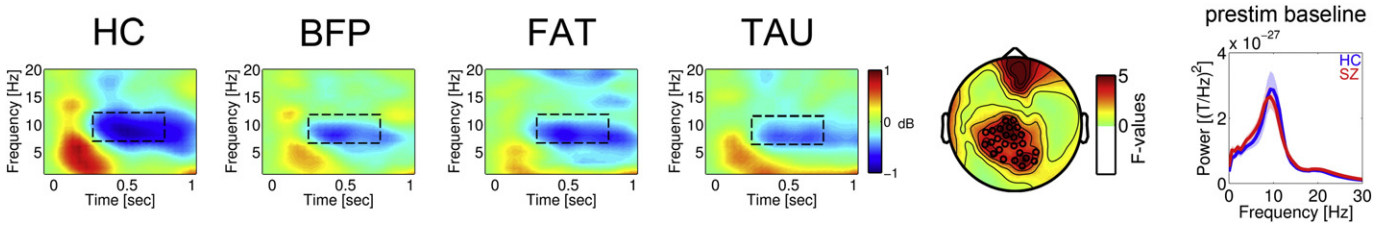

Fig. 2. Schizophrenia (SZ) groups prior to training compared to healthy comparison participants (HC). Four panels to the left: for the HC and for the three SZ later assigned to the Brain Fitness Program (BFP), facial affect training (FAT), or treatment as usual (TAU), time–frequency representations of 0–20 Hz power (dB change from pre-S1 baseline) in response to S1 (0 ms) and S2 (500 ms) are illustrated for the sensor cluster in the topographical representation in the fifth panel. Dashed rectangles indicate the time window (300–800 ms) of significant change in alpha (8–12 Hz) power from baseline, with cool colors (thin color bar) indicating power decrease. Fifth panel: topographical map of statistical tests of group differences. Thick color bar reflects *F*-values (4-group ANOVA), with warm colors indicating larger alpha power decrease in HC than in SZ. Black circles identify the MEG sensors in the analyzed cluster. The power spectrum in the right panel illustrates similar pre-stimulus alpha power in HC (blue) and SZ (red). Shading indicates 1.0 SEM and shows group overlaps.

time occurred specifically for processing speed, attention, and visual learning (each simple main effect of Time $p < .001$). The main effect of Domain ($F(6,324) = 12.19$, $p < .001$, Huynh–Feldt $\varepsilon = .92$) was not of interest. The only effect involving Group was a marginal Group × Domain × Time effect, $F(12,324) = 1.70$, $p < .08$, $\varepsilon = .88$, providing limited evidence of specificity judged not worth interpreting.

Correlations evaluated the impact of training on each MCCB domain, following the third hypothesis that modification of cortical signal differentiation is fundamental to higher cognitive function. In line with this premise, Fig. 4 illustrates a group-specific contribution to the relationship between the training effect on decrease in alpha power around S2 and the change on verbal learning performance. Greater induced alpha power decrease around S2 predicted greater improvement in verbal learning after training in the BFP group (Spearman's $r = -0.7$, $p < 0.01$) but not in the FAT group ($r = -0.1$, $p < 0.5$) or TAU group ($r = 0.03$, $p < 0.5$). The negative BFP correlation differed significantly from the positive TAU correlation. The intermediate FAT correlation did not differ reliably from either. Correlations of training effects with other MCCB tests were non-significant.

4. Discussion

Impairment in neuronal signal resolution, processing speed, and neuroplasticity has been proposed as fundamental to SZ pathology, substantially contributing to characteristic features such as cognitive deficits and functional decline (e.g., Buzsaki and Watson, 2012; Merzenich et al., 2014; Uhlhaas et al., 2008). The present results of less induced alpha power decrease in the processing interval between pair-wise presented identical stimuli in SZ replicate Popov et al. (2011b). The present results showing that training can ameliorate this deficit replicate Popov et al. (2012). Comparison with an active control training provides evidence of the specificity of an intervention mainly affecting a neural mechanism involved in processing of auditory signal differentiation.

Induced alpha power decrease before or around stimulus presentation is believed to reflect the readiness of relevant neuronal assemblies for information intake (Jensen and Mazaheri, 2010) and to facilitate differentiation and matching of temporally adjacent stimuli. This suppression of activity in the alpha frequency range before and around stimulus processing is smaller in SZ than in HC (Popov et al., 2011b, 2012; Carolus et al., 2014). The present results show that this deficit can be at least somewhat normalized by targeted auditory-signal discrimination training, replicating results for a previous sample reported in Popov et al. (2012). Both studies showed larger induced power decrease within the alpha frequency range, though differing slightly in the frequency window of significant group and training effects. Given that individual alpha power characteristics and effects of intervention or experimental manipulation vary between individuals within the range of frequencies assigned to 'alpha' (see references in Footnote 1), slight differences in statistically significant effects between studies do not undermine the similarity of effects.

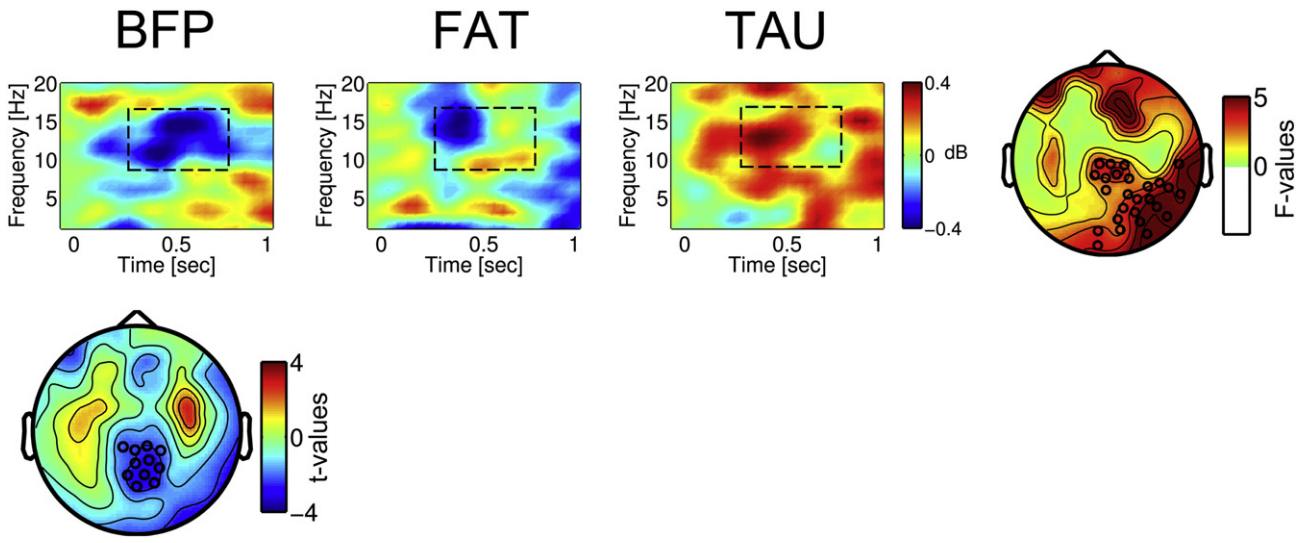

Fig. 3. Schizophrenia-group training effects (calculated as post- minus pre-training) on MEG quantified as time–frequency representations of 0–20 Hz power changes (dB change from pre-S1 baseline) in response to S1 (0 ms) and S2 (500 ms) illustrated for the significant sensor cluster in the topographical map in the right panel. Dashed rectangles indicate the time window (300–800 ms) of significant change in alpha (8–14 Hz) power from baseline, with cool colors (thin color bar) indicating alpha power decrease.

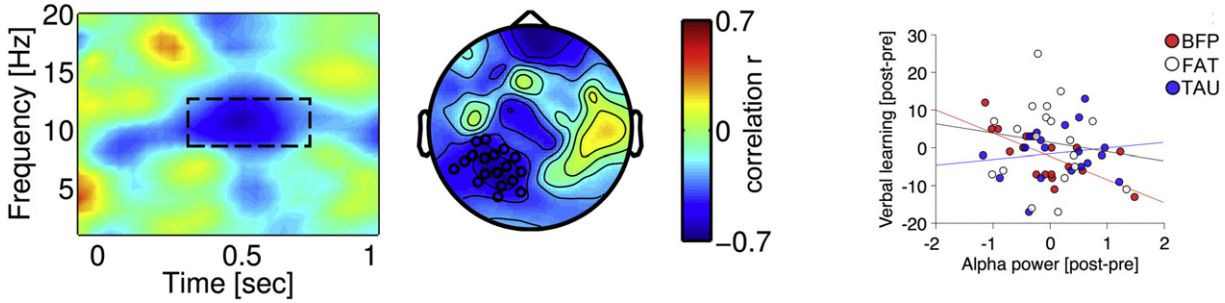

Fig. 4. Scatterplot (right panel) of training effects (BFP = Brain Fitness Program, FAT = facial affect training, TAU = treatment as usual) on change in alpha power suppression (8–12 Hz) from pre-S1 baseline during 300–800 ms after S1 onset (left panel) for a left posterior sensor cluster (middle panel) vs. training effect on performance on the MCCB verbal learning test. Cool colors for the correlation values in the color bar indicate association of larger (more normal) post-S1 decrease post-training than pre-training with higher verbal learning score post-training than pre-training. BFP and TAU slopes differed (homogeneity of regression $F = 6.4$, $p < 0.02$). Other pairs of slopes did not differ.

The present results provide evidence of specificity of targeted training addressing a supposedly dysfunctional system. Fig. 3 illustrates more improvement in oscillatory dynamics during the auditory paired-click task after auditory-verbal training than after facial affect training or treatment as usual. Fig. 4 illustrates a group-specific contribution to the relationship between the training effect on decrease in alpha power around S2 and the change on verbal learning performance, even though performance on verbal learning tests (MCCB) did not improve specifically for the SZ sample overall.

Given the proposal (Merzenich, 2013; Merzenich et al., 2014) that problems in low-level processing underlie problems in higher-level processing, one would hope that a training protocol that targets low-level processing might have benefits extending beyond cognitive tests closest to the target function. Such a pattern was not observed in the present data set, in line with findings for a similar training protocol by Fisher et al. (2015). Merzenich (2013) and Merzenich et al. (2014) proposed neuronal signal resolution as constituting a fundamental neuronal dysfunction in schizophrenia, thereby influencing many basic processes involved in perception, information discrimination, learning, and memory. All these processing elements may be supposed to contribute to cognitive dysfunction at a higher level. Yet it may be too far-reaching to assume that this influence of basic effects on higher-order cognitive functions is reflected in a strong correlation between brain measures of fundamental neuronal signal resolution deficit and test performance. A lack of correlation between such distant levels may result from various influences. For example, cognitive tests may not be sensitive to the specific neuronal process that was modified by training, and many intermediate steps between neural signal resolution and test performance are not measured (Miller and Rockstroh, 2013). Additional behavioral measures reflecting neuronal mechanisms of stimulus perception and differentiation could be added in future studies in order to verify the proposed link between dysfunction at a neuronal level and higher order cognitive function.

Cognitive performance on a test battery specifically designed to capture cognitive deficits in schizophrenia improved over the 4-week period, during which targeted training or the standard treatment regimen (TAU) took place. This was a period of symptom improvement. The present finding of a null effect of cognitive training suggests that the impact of targeted cognitive training was not strong enough to visibly add to the general impact of symptom remission on cognitive improvement. Possible shortcomings of the training protocol (brief duration) or the assessment of cognitive functions (appropriateness of MCCB to capture key training elements) could be explored before concluding whether the present targeted, neuroplasticity-based training protocols affect cognitive performance. For example, the present procedures included 20 1-hour training sessions and evaluated training effects after the end of 4 weeks of training, whereas studies employing a similar training protocol reported stronger effects after 40–50 or more training sessions and a 6-month follow-up. The present restriction to 20 sessions and immediate post-training assessment reflect the inpatient status of the present sample and the administrative priority placed on reducing inpatient treatment duration. The extent to which the present effect sizes were influenced by sample characteristics (more severely impaired inpatient), brevity of training, or brevity of follow-up cannot be evaluated in the present data set and warrants study.

The domain-specific pattern of results was not as strong or consistent as has been reported in some other studies (e.g., Fisher et al., 2015). Across training groups, overall improvement was observed for processing speed, attention, and visual learning domains but not for domains presumably closer to the auditory–verbal focus of BFP, verbal learning and perhaps working memory. Both BFP and FAT involved visual and auditory stimulation (BFP using auditory stimuli for discrimination training and visual stimuli for task instruction and reinforcement, FAT using visual stimuli for affect discrimination training and task instruction with auditory reinforcement), and both included an emphasis on working memory training. These shared features may have obscured specific effects, but it is unclear as to why these domains did not benefit specifically from training. On the other hand, BFP alone fostered a relationship between alpha normalization and verbal learning improvement, providing some evidence of specificity. Moreover, improvement in test performance in the MCCB working memory and verbal learning domains was found in an overlapping sample at a follow-up 3 months after training (Carolus et al., 2015). This evidence, though suggestive, may not be sufficient to conclude that training effects on particularly impaired functions (like working memory or verbal learning) unfold slowly. Third, limited training effects may be a function of the tests used to probe their impact. In an independent sample Popov et al. (2012) used verbal learning and working memory tests from the German version of the California Verbal Learning Test (VLMT, Helmstädter and Lux, 2001) rather than from the MCCB. Without systematic, direct comparison of the respective tests, this possible factor cannot be evaluated.

Further limitations of the present study should be considered. The impact of medication on test performance and training effects must always be considered. It has been suggested that antipsychotic medication can generally dampen effects on cognitive test performance (Kane, 2011; Moritz et al., 2013). However, a recent meta-analysis found no difference in cognitive test performance in medicated and drug-naïve SZ (Fatouros-Bergman et al., 2014). It has also been suggested that antidopaminergic effects of neuroleptics impair learning and neuroplastic capacity (Pessiglione et al., 2006). However, given the general treatment intention to achieve low maintenance dosage, and given the fact that medication (CPZ) did not differ significantly between pre- and post-assessment ($t(53) = 1.29$, $p = .2$) and did not vary with changes in alpha power decrease or cognitive test performance, a substantial influence of medication on the present results seems unlikely.

Moreover, the patient sample accomplishing BFP was older on average than the healthy control sample. Given that the primary goal of the study was the evaluation of training effects within patients – and, for the

entire project, between patient groups accomplishing two different types of targeted training – the HC group served merely to verify the typical pretreatment patient abnormalities reported in the literature. Thus, the HC group was smaller than the overall patient sample, matching the entire sample of $n = 57$ patients included in the project in average age and gender distribution. By chance, matching for the patient sample assigned to BFP did not occur for age, whereas a better match was achieved for the FAT group, which did not differ in age from HC (Popova et al., 2014). Though the lack of one-to-one matching of an HC group of the same size as the entire SZ sample is a limitation of the present project, it should be noted that HC matching here was not intended to control for training effects but only to verify well established pre-training abnormalities, which was successful.

5. Conclusion

In summary, the present results replicate evidence for disruption of a neural oscillatory mechanism in schizophrenia and for the potential of targeted training to improve neural and cognitive function. The present results also indicate specificity of targeted training addressing a dysfunctional system.

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