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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

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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-

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[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).