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The effect of cognitive training on evoked potentials in schizophrenia

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ABSTRACT

Electrophysiological indices are sensitive to cognitive dysfunction in schizophrenia but have rarely been used to assess benefits of cognitive remediation. Our aim was to evaluate the effect of specific cognitive training approaches on event-related potentials.

Forty-six patients with schizophrenia underwent either auditory (AUD) or visuo-spatial (VIS) cognitive training or treatment-as-usual (TAU). Cognitive training was computer-assisted and administered for 10 sessions within two weeks. Event-related potentials during an active odd-ball paradigm together with clinical and neuropsychological variables were assessed before and after training and again at a two-month follow-up.

Compared to the TAU group both the AUD and VIS training groups showed decreased P2 latency following training. At follow-up, the P2-latency reduction was stable in the VIS group but the AUD group experienced a relapse. Training resulted in improved digit-span backward among neuropsychological variables. Increased P2 amplitude was related to more positive symptoms and lower social-occupational functioning and longer P2 latency was associated with greater severity of stereotyped thinking.

The more general visuo-spatial training appears to have a longer-lasting effect on P2 latency than the specific auditory training. Alternatively, there may be specific auditory discrimination deficits in schizophrenia requiring more extensive training for a stable change.

1. Introduction

Cognitive remediation (CR) programs have found entry into the adjunctive treatment of schizophrenia although meta-analytic studies have so far rendered only moderate effect sizes on cognition and functioning (Grynszpan et al., 2011; McGurk et al., 2007; Wykes et al., 2011). It is also still debatable whether cognitive remediation merely provides environmental enrichment thereby having a non-specific enhancing effect on cognition and functioning or whether the training improves specifically targeted domains (Kurtz & Sartory, 2010) indicative of neural plasticity. The latter implies changes in the organization of the respective cortical areas (Pantev et al., 2003; Trainor et al., 2003) which are more likely to occur after drill-and-practice rather than strategy-based approaches. Recently, greater specificity of training and measurement domains was introduced to shed light on the question of neural plasticity.

Electrophysiological measures provide an important research tool when investigating early cognitive processes. In the active odd-ball paradigm participants have to react to rare deviant target stimuli embedded among frequent standard stimuli. The most prominent event-related-potential (ERP) component of this paradigm, the P300, has been linked to the amount of attentional resources allocated to the task (Donchin & Coles, 1988). P300 amplitude was found to be diminished in schizophrenia (Ford et al., 1992; Salisbury et al., 1996) and can show further deterioration over the course of the illness (Mathalon et al., 2000; van der Stelt et al., 2004).

An earlier evoked potential of the active oddball paradigm, the P2, is considered an independent component among vertex potentials (Crowley & Colrain, 2004). P2 appears to index working memory (Lefebvre et al., 2005; Wolach & Pratt, 2001), particularly encoding (Chapman et al., 1978; Dunn et al., 1998) and is modulated by stimulus complexity. In schizophrenia research, ERPs have been mainly studied during presentation of simple stimuli. A meta-analysis by Ferreira-Santos et al. (2012) of 20 studies showed that target stimuli elicited a larger P2 amplitude and longer latency in schizophrenia patients than in controls.

Experience-dependent changes in auditory cortical processing have been studied for some time in healthy individuals (Dahmen & King, 2007). For instance, comparing cognitive with physical training in healthy aging participants, Gajewski and Falkenstein (2012) reported a higher P300-amplitude following the former. There is, however, a dearth of studies of the effect of cognitive training on electrophysiological measures in schizophrenia so far. Popov et al. (2011) compared auditory and memory training with a general remediation program and found the former to lead to a normalization of M50, the magnetoencephalographic version of the gating response (P50) which measures sensory filtering and is deficient in schizophrenia (Potter et al., 2006).

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There was no follow-up assessment ascertaining the stability of the change. Rass et al. (2012) found no effects with regard to P300 following computer-assisted auditory and visual remediation exercises neither post treatment nor at follow-up assessment. In both studies, CR was directed toward a number of cognitive domains which may have obfuscated the relationship between a particular training target and change of a related electrophysiological index.

We aimed to investigate whether specific training of auditory discrimination compared to visual–spatial training and a treatment-as-usual condition would have an ameliorating effect on evoked potentials in schizophrenia patients. Assessments were carried out before and after training and again at a 2-month follow-up.

2. Methods

2.1. Participants

A total of 46 patients diagnosed with schizophrenia or schizoaffective disorder took part in the study. Inclusion criteria were the absence of other major mental or neurological disorders as well as of hearing impairment, an age between 18 and 54 years and an IQ > 70. Only patients on stable medication were included and participants using benzodiazepines were excluded. According to DSM-IV-TR (APA, 2000) 24 of the patients had a diagnosis of schizophrenia of the paranoid type, 6 of the disorganized, 5 of the residual and 2 of the undifferentiated type. Nine patients had a diagnosis of schizoaffective disorder. Mean onset of illness was at 24.0 (SD = 8.1) years with a range of 14 to 47. Thirty patients took atypical antipsychotics, two took typical ones, nine took both and two took depot medication. Twenty-two patients took mood stabilizers/antidepressants. The study was approved by the Ethics Committee of the University of Duisburg-Essen. All participants gave their written informed consent before entering the study and received remuneration. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.2. Design

Patients were randomly allocated to one of three treatment groups: (1) Auditory training (AUD) (11 men, 5 women), (2) visual spatial training (VIS) (10 men, 5 women), and (3) a treatment-as-usual condition (TAU) (9 men, 6 women). Training took place daily during 10 sessions over 2 weeks. Diagnostic assessments, ERP recordings and neuropsychological tests were carried out before and after training and again at a 2-month follow-up by assessors who were blind to the treatment condition.

2.3. Cognitive training

Computer-assisted training was carried out. All tasks were adaptive to performance level. Correct answers were rewarded with the display of a smiling face. Each patient had an 'account' of his/her performance in each task which was carried over across sessions. Both types of training consisted of 4 kinds of tasks (a, b, c, d) each of which was administered in each session.

(1) Auditory training (AUD): Two subprograms from the computer program *Audiolog* (www.phoenixsoftware.de/rehabilitation/produkte-/audiolog-4.0.html) were used namely, 'Same or different' and 'Sequences'. The former consists of tasks in which participants have to decide whether two acoustically presented simple tones are of the same or different (a) pitch or (b) intensity. In the latter, sequences of tones differing in (c) pitch or (d) intensity are acoustically presented and participants have to attribute them to one of three graphic displays.

(2) Visual training (VIS): A number of tasks with abstract stimuli and patterns were presented. (a) 'Comparisons' from the remediation program *Cogpack* (www.cogpack,de/D/frames.htm): Two abstract pictures with minor or no differences are shown and participants have to decide whether or not they are the same. (b) 'Postcards' from *Petra Rigling Rehaservice* (www.rigling.de/): Two patterned rectangles are presented side by side and participants have to decide whether or not they are identical. Finally two tasks from the program *LernReha-Software* (www.phoenixsoftware.de/rehabilitation/produkte/-lernreha-programme.html) were presented namely, (c) 'Comparisons' a matching-to-sample taskwith four patterns to chose the correct one from, and (d) 'Forgery' which consists of a series of two patterned rectangles subdivided into fields. Participants have to indicate which field differs between the two.

Training took place in groups of up to three patients with an advisor who assisted with operating the programs whenever necessary.

2.4. Evoked potentials

An active odd-ball paradigm was administered (1198 auditory stimuli: standard tones (1000 Hz) and target tones (1300 Hz, 9.91 %) both 80 ms, 80 dBA). Stimulus-Onset-Asynchrony was 1000 ms. Participants pressed a button in response to the target stimuli. During the procedure, patients were asked to keep looking at a fixation cross placed 1.5 m in front of them, to avoid movement, and to respond to the target tone as quickly as possible. Stimuli were presented with the program *Presentation* (Version 14.2; Neurobehavioral Systems) and data were recorded with *BrainVision Recorder* (Brain Products GmbH).

2.4.1. EEG recording

Participants were fitted with a 28 Ag/AgCl electrode cap (Easycap). Linked earlobes were used as reference and the forehead AFz placement as ground. EOG was recorded medially from below and above the right eye and the outer canthi of the eyes. Electrode impedance was kept below 5 kΩ at all sites. DC-coupled amplifiers (Brain Amp DC, Brain Products Ltd., Munich, Germany) were used with a band pass filter of DC = 0 to 250 Hz and a digitization rate of 500 Hz. Data reduction was performed offline.

2.4.2. Data reduction

Electrode sites Fz, FCz and Cz were processed in regard to N1, P2 and N2 and Fz, Cz and Pz in regard to P300. Following the removal of grossly artifactual trials by visual inspection, data were passed through an IIR Butterworth Zero phase filter (0.038 (24 dB/oct) to 30 (48 dB/oct) Hz) with a time constant of 5.0 s and a 50-Hz notch filter. Artifacts due to ocular movement were corrected by independent component analysis (Makeig et al., 1997). The pre-stimulus baseline was 100 ms and trial epochs extended to 800 ms after stimulus onset. Target trials were baseline corrected and averaged. ERP amplitude and peak latency of components were determined within the following segments: N1: 80–200 ms; P2: 150–250 ms; N2: 150–400 ms; P3: 280–700 ms.

2.5. Clinical interviews and neuropsychological tests

Participants were interviewed with the *Structured Clinical Interview (SCID) for DMS-IV* (Wittchen et al., 1997) and the *Positive and Negative Syndrome Scale (PANSS)* (Kay et al., 1987). Additionally, the *Global Assessment of Functioning Scale* (APA, 2000) and the *Social and Occupational Functioning Assessment Scale (SOFAS)* (APA, 2000) were used.

Neuropsychological tests included the *Multiple Word Recognition Test* (Lehrl, 1989), a verbal intelligence test, the *Word Fluency Test* (Benton et al., 1976) and part A and B of the *Trail Making Test* (Spreen, 1998). Furthermore, the *Digit Symbol Test* and the *Digit Span Test* (Von Aster et al., 2006) were employed as well as both immediate and