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The effect of auditory and visual training on the mismatch negativity in schizophrenia

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ABSTRACT

Background: The mismatch negativity (MMN) is an electrophysiological index of early auditory attention and has repeatedly been suggested to be associated with cognitive functioning. Despite the frequently reported finding of reduced MMN amplitude in schizophrenia, up to now, studies assessing the impact of perceptual discrimination training aiming to improve MMN measures in schizophrenia patients are scarce.
Method: In the present study, the effect of auditory training (AUD, $n = 14$) on the MMN was compared to that of visual-spatial training (VIS, $n = 14$) and a treatment-as-usual (TAU, $n = 14$) condition in schizophrenia patients. Training consisted of ten 50-min sessions over two weeks. Assessments took place before and after training and at a two-month follow-up. They comprised clinical measures and MMN recordings to frequency and duration deviant stimuli.
Results: There was a significant main effect for type of stimulus deviance with a more negative MMN to frequency than duration deviants. In contrast to our hypotheses, we did not find training specific effects on MMN amplitude or latency.
Conclusion: The visual, as well as the auditory training program failed to result in treatment related MMN changes in schizophrenia patients when compared to treatment-as-usual as a control condition. In contrast to reports in healthy subjects, the induction of training related MMN changes in schizophrenia patients may constitute a specific challenge and require more extensive training protocols.

1. Introduction

1.1. MMN in schizophrenia

The mismatch negativity (MMN), a neurophysiological index of early auditory stimulus processing (Näätänen et al., 1978), has repeatedly been shown to be diminished in schizophrenia (Kärgel et al., 2014; Shelley et al., 1991; Umbricht and Krljes, 2005). MMN is considered an automatic response to auditory stimulus deviance occurring in a context of frequent standard tones. The MMN occurs 100–250 ms after stimulus onset and is obtained by subtracting the response to standard from deviant tones. Although MMN is considered to be independent of attention resources (Näätänen et al., 2007) it may be modulated by attention processes (Müller et al., 2002a; Rissling et al., 2013). In healthy participants, Todd et al. (2008) reported an age-related MMN decline to duration and intensity deviants and more recently related this to deficient prediction error processing (Todd et al., 2012). Type of stimulus deviance was also found to have an effect in schizophrenia. In a meta-analysis, Umbricht and Krljes (2005)) reported more substantial MMN deficits with duration than frequency deviance with deficits of the latter being related to duration of illness. In turn, MMN deficits to duration deviants were recently related to illness onset (Näätänen et al., 2015). While recent evidence indicates that the core of deviance detection itself may be basically intact in schizophrenia (Horacek et al., 2016; Todd et al., 2014) and additional processes may be of relevance (Damaso et al., 2015), there is agreement that the MMN is impaired in schizophrenia (Light et al., 2015; Umbricht and Krljes, 2005). Within this context, training of auditory processing in schizophrenia has evolved as a target in the development of adjunctive interventions in addition to pharmacological treatments of positive and negative symptoms in schizophrenia patients (Dale et al., 2016; Popov et al., 2011; Tarasenko et al., 2016).

1.2. Effects of auditory training on MMN in healthy subjects and schizophrenia patients

Existing evidence suggests that in healthy subjects, auditory training very rapidly induces lasting neuronal reorganization which has been

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assessed by means of evoked potentials, among them the N1 (Melara et al., 2012; Reinke et al., 2003) and P2 components (Orduna et al., 2012; Tong et al., 2009; Tremblay et al., 2010), and the mismatch negativity (Atienza et al., 2002; Kraus et al., 1995; Näätänen et al., 1993; Spierer et al., 2007).

In schizophrenia patients, auditory training interventions have been evaluated in a number of studies. Rass et al. (2012) investigated the effect of auditory and of visual training on the auditory steady state response and the P3 component, comparing cognitive training with watching films and a treatment-as-usual (TAU) condition but found no training-related effects. Our group previously reported an effect of auditory training on P2 latencies but not on the P3 amplitudes (Kariofillis et al., 2014). Another study by Popov et al. (2011) provided patients with either sound discrimination and verbal memory training or general cognitive training. The former training led to a normalization of the magneto-encephalographic analogue of the P50 component which is a measure of sensory gating and has been shown to be dysfunctional in schizophrenia (Bramon et al., 2004). More recently, Dale et al. (2016) reported improvements of the magneto-encephalographic equivalent of the N100 component with auditory training which furthermore was associated with increased executive function but not memory performance. So far, the results of training-induced changes on indices of neurophysiological parameters are inconsistent. Although MMN was identified as a central measure of perceptual/cognitive dysfunction in schizophrenia (Butler et al., 2012) and is considered as an endophenotype marker of the disease (Light et al., 2015) there are as yet no studies on the effect of auditory training on the MMN in these patients.

1.3. Aims and hypotheses

Following the idea that a basic perception and discrimination training might be able to modify underlying neurobiological correlates, here we evaluated the effect of a 10 session lasting discrimination training of auditory or visual perception on electrophysiological parameters of early information processing. We aimed to compare the impact of auditory training (AUD) on MMN to that of visual-spatial training (VIS) or treatment-as-usual (TAU) in schizophrenia patients. Patients in the TAU condition received no specific intervention but continued to take part in their individual standard care program. The latter was based on psychopharmacological intervention, social-psychiatric support and/or outpatient care. None of the study participants were subject to additional cognitive or behavioral interventions. Assessments were carried out before and after training and at a 2-month follow-up (FU) and included MMN to frequency and duration deviants together with clinical assessments. Based on previous results in healthy subjects, we expected auditory training to result in an increased MMN amplitude compared to visual-spatial training and TAU. As the auditory training was primarily directed at pitch discrimination, we expected it to have mainly an effect on MMN to frequency rather than duration deviants.

2. Methods

2.1. Participants (Table 1)

Initially, fifty-one schizophrenia in- and out-patients recruited from psychiatric and psychosocial institutions in and around Essen and Wuppertal signed the informed consent form. Five patients declined participation during pre-assessments leaving forty-six patients to be randomized to the visual-spatial attention training (VIS, $n = 15$), the auditory discrimination training (AUD, $n = 16$) and the treatment-as-usual group (TAU, $n = 15$). None of the randomized patients left training prematurely and all completed the post-assessment. Due to equipment malfunction data from 4 patients (VIS = 1, AUD = 2, TAU = 1) could not be analyzed leaving 42 patients for the pre-post analysis. Three patients were lost to the 2-month follow-up assessment leaving 14 patients in the VIS, 13 in the AUD and 12 in the TAU group for the post-FU analysis. All patients met DSM-IV (Saß et al., 2003) criteria of chronic schizophrenia or schizoaffective disorder as assessed by the treating psychiatrist and confirmed by an experienced research associate using the *Structured Clinical Interview* (*SCID*) *for DSM-IV* (Wittchen et al., 1997). Subject characteristics are given in Table 1.

Onset of illness was at a mean age of 23.8 years (SD = 8.0) ranging between 14 and 47 years. Inclusion criteria of patients were the absence of other major mental or neurological disorders and hearing impairment, an age between 18 and 54 years and verbal IQ estimate [MWT-B (Lehrl, 1989)] not less than 70. Schizophrenia subtype diagnoses and medication are shown in Table 2. Only patients with stable doses of antipsychotic medication were included. Exclusion criteria were alcohol or drug abuse or dependence or past dependencies less than 1 year ago, acute neurological or DSM-IV axis-I disorders other than schizophrenia or schizoaffective disorder and current benzodiazepine medication. The study was approved by the Ethics Committee of the University of Duisburg-Essen. All participants (and their legal representative if applicable) gave their written informed consent before being included and received a small remuneration for their participation.

2.2. Perceptual discrimination training

AUD and VIS training were computer-assisted with each session lasting 50 min. If a session was missed it was subsequently administered ensuring a total of 10 training sessions for each patient. Training tasks were adaptive in terms of their level of difficulty, i.e. when a rate of 80% accuracy was achieved the subsequent task was at the next higher level of difficulty. Performance level was carried over across sessions. Patients were trained in small groups of three participants and sat in front of their training laptop wearing headphones during the sessions.

Table 1
Subject characteristics: group means and SDs of demographic data and clinical ratings at pre-assessment.

Measures	AUD $n = 14$ (M (SD))	VIS $n = 14$ (M (SD))	TAU $n = 14$ (M(SD))	Statistic (*p*-value)
Gender, N (m/w)	9/5	9/5	8/6	$X^2_{2,\,42} = 0.20$ (0.904)
Smokers	10	9	10	$X^2_{2,\,42} = 0.22$ (0.904)
Age, years	38.71 (11.75)	35.64 (10.26)	39.14 (10.05)	$F_{2,39} = 0.44$ (0.644)
Duration of illness, years	12.29 (8.97)	13.21 (6.41)	16.15 (11.62)	$F_{2,39} = 0.65$ (0.530)
Education, years	12.96 (3.02)	14.57 (5.00)	11.71 (3.38)	$F_{2,39} = 1.89$ (0.165)
Inpatient treatments, N	8.86 (9.74)	6.93 (6.17)	6.54 (4.05)	$F_{2,39} = 0.42$ (0.662)
SOFAS	49.71 (9.81)	48.64 (11.71)	42.79 (6.6)	$F_{2,39} = 2.11$ (0.135)
GAF	48.00 (8.93)	47.07 (12.33)	42.14 (6.02)	$F_{2,39} = 1.55$ (0.224)
PANSS positive	10.86 (3.48)	11.21 (3.77)	13.07 (3.65)	$F_{2,39} = 1.50$ (0.236)
PANSS negative	13.29 (6.34)	11.57 (6.32)	15.21 (5.87)	$F_{2,39} = 1.22$ (0.307)
PANSS global	25.71 (7.94)	25.29 (12.83)	32.93 (11.32)	$F_{2,39} = 2.18$ (0.127)
MWT-B IQ	97.00 (10.76)	99.00 (8.58)	98.57 (6.19)	$F_{2,39} = 0.21$ (0.816)

Note. AUD = auditory training, VIS = visual-spatial training, TAU = treatment-as-usual, SOFAS = social and occupational functioning assessment scale, GAF = global assessment of functioning scale, PANSS = positive and negative syndrome scale, MWT-B = Mehrfachwahl Wortschatz Intelligenz-Test (version B), M = mean, SD = standard deviation.