

## 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.

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### 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](http://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](http://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/](http://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](http://www.phoenixsoftware.de/rehabilitation/produkte-/lernreha-programme.html)) were presented namely, (c) 'Comparisons' a matching-to-sample task with four patterns to choose 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 k $\Omega$  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

delayed retrieval of the *Wechsler Logical Memory (Prose Recall) Test* (Beckers et al., 1991; Wechsler, 1987).

## 2.6. Statistical analyses

Groups were compared with regard to clinical, neuropsychological and ERP variables pre-training. As one patient in the AUD group and another two in the TAU group were no longer available at the follow-up assessment, separate analyses were carried out comparing pre with post training and post training with follow-up. Neuropsychological data and amplitude and latency of ERP components were submitted to ANOVAs. In cases of violations of the assumption of sphericity, Greenhouse–Geisser corrected p-values of the F-statistics are reported. Finally, ERP indices were correlated with clinical ratings and neuropsychological scores at pre-training.

## 3. Results

All participants completed 10 training sessions. Groups did not differ significantly with regard to demographic data, illness duration, verbal intelligence or clinical ratings as shown in Table 1.

### 3.1. Clinical ratings

Submitting the clinical ratings to group  $\times$  measurement occasion ANOVAs yielded a significant pre to post-training effect indicative of improvement with regard to all measures (PANSSpos:  $F(1,43) = 9.84$ ,  $p < .01$ ,  $\eta^2 = .19$ ; PANSSneg:  $F(1,43) = 8.50$ ,  $p < .01$ ,  $\eta^2 = .16$ ; PANSSglob:  $F(1,43) = 11.56$ ,  $p < .01$ ,  $\eta^2 = .21$ ; GAF:  $F(1,43) = 8.47$ ,  $p < .01$ ,  $\eta^2 = .16$ ; SOFAS:  $F(1,43) = 8.86$ ,  $p < .01$ ,  $\eta^2 = .17$ ). There were no significant group differences. The comparison of post-training with follow-up yielded no significant effects.

### 3.2. ERP

Grand averages of ERPs at the three measurement occasions are shown in Fig. 1.

There were no significant group differences with regard to number of correct responses and reaction time pre-training (Table 1) nor were there any significant effects comparing pre with post-training and the latter with follow-up.

There were no significant group differences with regard to amplitude or latency of any of the ERP components at pre-training.

N1 latency showed a significant decrease from pre to post training (Prepost:  $F(1,43) = 1.63$ ,  $p < .01$ ,  $\eta^2 = .20$ ) with no other effects or interactions being significant. Comparing post-training with follow-up yielded a significant Group  $\times$  Electrode effect ( $F(2.8, 80) = 2.77$ ,  $p < .03$ ,  $\eta^2 = .122$ ) and a significant PostFU  $\times$  Electrode effect ( $F(1.7, 39) = 3.18$ ,  $p < .05$ ,  $\eta^2 = .07$ ). The former indicated that the AUD group showed a decreasing N1 latency from Fz to the vertex placement not evident in the other two groups. From post-training to follow-up N1 latency increased at the frontal placement not, however, at Cz.

Comparing pre with post-training, P2 latency yielded a significant Group  $\times$  Prepost  $\times$  Electrode effect ( $F(4, 86) = 3.96$ ,  $p < .01$ ,  $\eta^2 = .16$ ) (Fig. 2). Pair-wise post-hoc tests indicated a significant decrease in latency in the VIS group from pre to post-training with regard to electrodes Fz ( $p < .02$ ) and FCz ( $p < .03$ ) and in the AUD group at electrodes FCz ( $p < .02$ ) and Cz ( $p < .01$ ). As shown in Fig. 2, unlike in the TAU group, P2 latency decreased in the two training groups and more so at posterior positions in the AUD ( $p < .01$ ) and in frontal positions in the VIS group. The effect was partially reversed from post-training to follow-up (Group  $\times$  PostFU  $\times$  Electrode:  $F(3.3, 80) = 2.94$ ,  $p < .04$ ,  $\eta^2 = .13$ ). Pair-wise comparisons showed that the P2 latency of the AUD group increased significantly from post-training to FU with regard to electrodes FCz ( $p < .01$ ) and Cz ( $p < .01$ ) unlike in the VIS group which remained stable.

N2 amplitude showed a significant increase from pre to post-training (Measurement occasion:  $F(1,43) = 5.20$ ,  $p < .03$ ,  $\eta^2 = .11$ ) and again from post-training to follow-up ( $F(1,40) = 6.04$ ,  $p < .02$ ,  $\eta^2 = .13$ ).

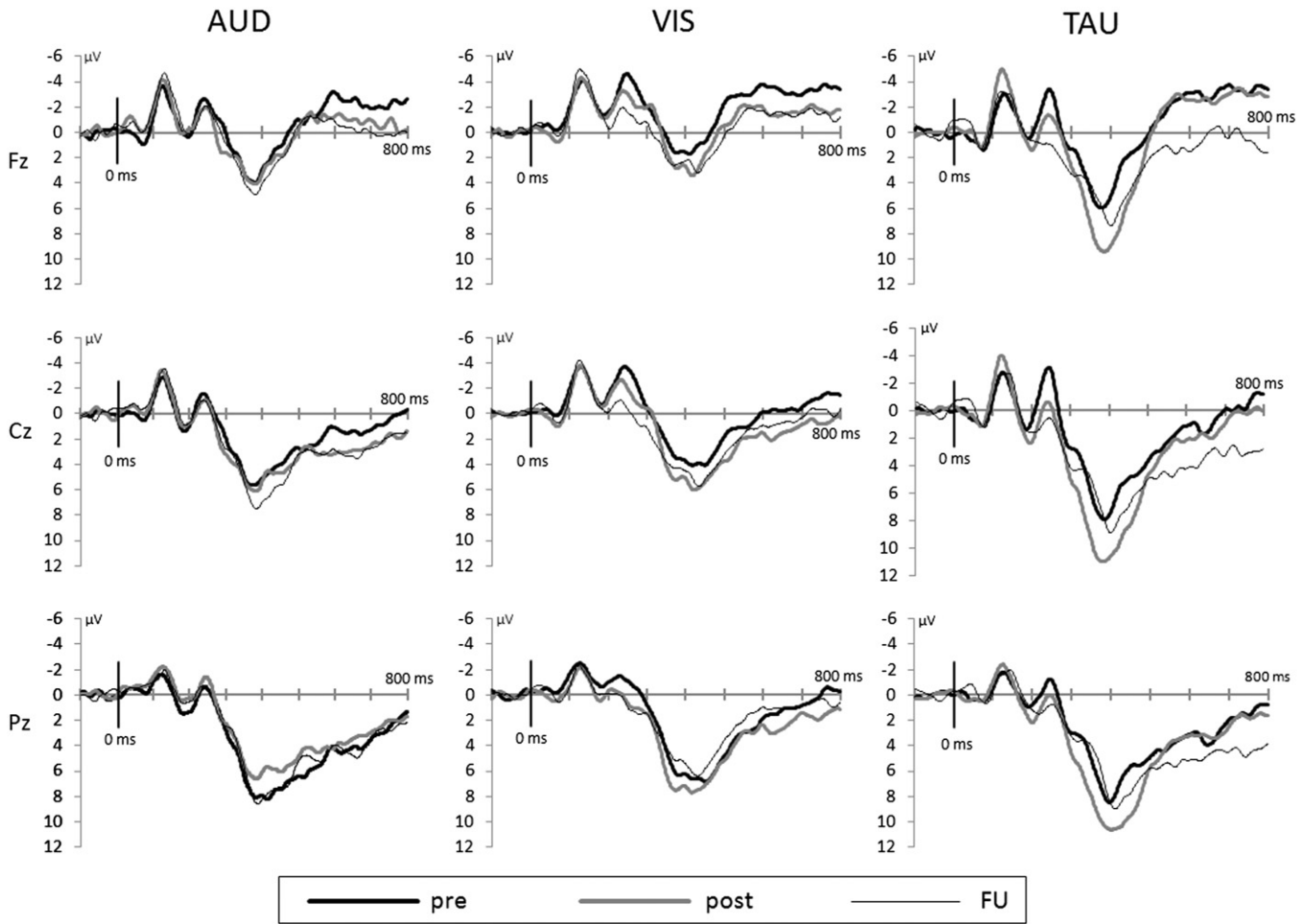
There were no significant effects with regard to P300.

### 3.3. Neuropsychological variables

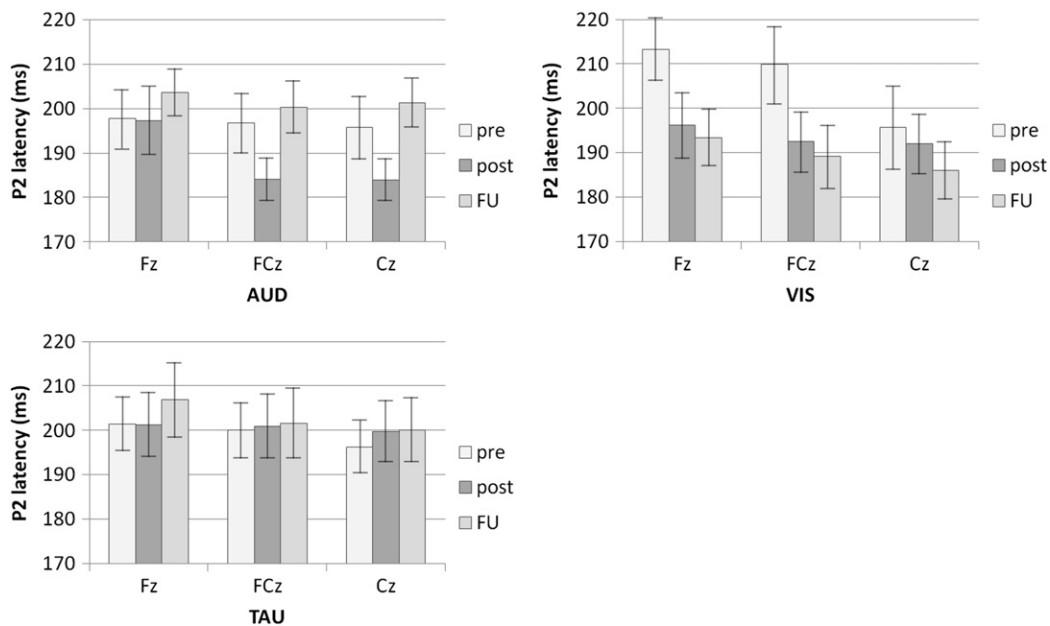
Table 1 shows the group means and SDs of neuropsychological variables at pre-training. There were no significant group differences. There was a significant Group  $\times$  Prepost interaction effect with regard to digit span backwards ( $F(2,43) = 4.85$ ,  $p < .01$ ,  $\eta^2 = .18$ ) showing improvement in the two training groups not evident in the TAU group (post: AUD: 6.1 (2.2), VIS: 6.0 (2.4), TAU: 5.1 (2.0)). There were no significant effects from post-training to FU. Other measures showed improvement from before to after treatment (Prepost: Trails A:  $F(1,43) = 13.47$ ,  $p < .01$ ,  $\eta^2 = .24$ ; Trails B:  $F(1,43) = 5.25$ ,  $p < .03$ ,  $\eta^2 = .11$ ; Digit-symbol test:  $F(1,42) = 24.15$ ,  $p < .01$ ,  $\eta^2 = .36$ ; Prose recall immediate:  $F(1,43) = 24.85$ ,  $p < .01$ ,  $\eta^2 = .37$ ; Prose recall delayed:  $F(1,43) = 32.10$ ,  $p < .01$ ,  $\eta^2 = .43$ ). None of the other effects were significant.

**Table 1**  
Demographic, clinical and neuropsychological group means and SDs pre-training.

| Variable          | Auditory training (AUD) (N = 16) | Visual training (VIS) (N = 15) | TAU (N = 15)     | F(2,43) | p < |
|-------------------|----------------------------------|--------------------------------|------------------|---------|-----|
| Age               | 38.1 (12.1)                      | 35.5 (10.3)                    | 40.9 (.7)        | .94     | .40 |
| Education (years) | 13.0 (2.9)                       | 14.7 (5.4)                     | 12.3 (3.4)       | 1.11    | .34 |
| Illness duration  | 12.6 (9.7)                       | 13.2 (6.4)                     | 16.6 (11.1)      | .60     | .57 |
| PANSS pos.        | 11.1 (4.0)                       | 11.1 (3.7)                     | 13.1 (3.5)       | 1.5     | .23 |
| PANSS neg.        | 13.0 (6.1)                       | 12.2 (6.6)                     | 13.9 (5.9)       | .27     | .76 |
| PANSS glob.       | 25.7 (8.2)                       | 26.8 (13.1)                    | 30.9 (11.1)      | .95     | .39 |
| GAF               | 49.1 (9.5)                       | 47.1 (11.4)                    | 42.9 (5.9)       | 1.8     | .17 |
| SOFAS             | 50.4 (9.9)                       | 47.9 (11.6)                    | 43.5 (6.5)       | 2.0     | .14 |
| Verbal Intell./IQ | 24.9 (5.6)/95.0                  | 25.8 (4.4)/96.8                | 27.1 (3.8)/100.1 | .87     | .43 |
| N corr. reactions | 92.5 (19.1)                      | 98.3 (8.6)                     | 98.5 (18.7)      | .68     | .51 |
| Reaction time     | 428.9 (75.4)                     | 391.3 (58.0)                   | 390.0 (57.0)     | 1.8     | .17 |
| Trails A, s       | 44.9 (26.0)                      | 38.0 (22.2)                    | 43.5 (19.0)      | .39     | .67 |
| Trails B, s       | 105.6 (48.9)                     | 105.8 (54.1)                   | 110.0 (41.6)     | .04     | .96 |
| Digit-symbol test | 40.6 (12.7)                      | 42.4 (12.7)                    | 39.4 (12.0)      | .20     | .81 |
| Letter-digit test | 12.7 (3.5)                       | 13.5 (3.4)                     | 11.3 (3.5)       | 1.48    | .24 |
| Digit span forw.  | 7.1 (1.9)                        | 6.9 (2.4)                      | 7.2 (1.8)        | .11     | .90 |
| Digit span back.  | 5.2 (2.4)                        | 5.3 (2.0)                      | 5.6 (1.5)        | .17     | .84 |
| Word fluency      | 29.1 (10.9)                      | 31.3 (9.9)                     | 30.6 (7.9)       | .21     | .81 |
| Prose recall im.  | 16.1 (7.3)                       | 15.7 (8.1)                     | 15.3 (7.5)       | .04     | .96 |
| - delayed         | 9.8 (4.8)                        | 11.2 (9.1)                     | 10.4 (6.2)       | .16     | .85 |



**Fig. 1.** Grand averages of the evoked potential of the target stimulus of the three treatment groups – auditory (AUD) and visuo-spatial training and treatment-as-usual (TAU) – pre and post training and at the 2-month follow-up (FU).



**Fig. 2.** Group means and standard errors of P2 latency of the three treatment groups – auditory (AUD) and visuo-spatial training (VIS) and treatment-as-usual (TAU) – pre and post treatment and at the 2-month follow-up (FU). Both training groups showed a decreased P2 latency from pre to post training with the AUD group evincing a relapse at FU.

### 3.4. Relations between variables

Owing to the large number of variables, none of the numerous correlations between them survived the Bonferroni correction. Therefore, exploratory correlations were confined to P2 in order to shed light on its functional role. Only significant correlations that extended over at least two adjacent electrode sites are listed. P2 amplitude was significantly positively correlated with PANSSpos (Fz:  $r(46) = .40$ ,  $p < .01$  (Fig. 3); FCz:  $r(46) = .37$ ; Cz:  $r(46) = .32$ ; both  $p < .05$ ) and PANSSglobal (Fz:  $r(46) = .32$ , FCz:  $r(46) = .32$ , both  $p < .05$ ) and significantly negatively with SOFAS (Fz:  $r(46) = -.32$  (Fig. 4); FCz:  $r(46) = -.32$ ; Cz:  $r(46) = -.29$ , all  $p < .05$ ). Higher P2 amplitude was associated with greater severity of symptoms and lower social and occupational functioning. P2 latency was correlated with PANSSneg 7 (stereotyped thinking) (Fz:  $r(46) = .29$ ; FCz:  $r(46) = .29$ ; Cz:  $r(46) = .33$ ; all  $p < .05$ ). Longer latency was related to greater severity of stereotyped thinking.

## 4. Discussion

Results showed a decrease in P2 latency to the target tones from before to after cognitive training in the two training groups. Over the follow-up period, the auditory training group 'relapsed' by showing a renewed increase of P2 latency whereas the reduction of the visual training group remained stable. The significant P2 latency changes were evident at FCz and Cz in the auditory training group and more frontally at Fz and FCz in the visual training group. Among neuropsychological tests only Digit Span Backwards showed improvement due to training in both groups alike. Increased P2 amplitude was related to greater severity of positive symptoms and more deficits in social and occupational functioning whereas longer P2 latency was associated with greater severity of stereotyped thinking.

P2 is thought to index working memory (Lefebvre et al., 2005; Taylor et al., 1990; Wolach & Pratt, 2001), particularly encoding (Chapman et al., 1978; Dunn et al., 1998). The component is diminished in elderly individuals (Finnigan et al., 2011). Shortened P2 latency has been found to be related to elevated alpha synchronization in resting state EEG (Lee et al., 2011) which, in turn, has been associated with speed of information processing (Klimesch et al., 1996). Conversely, P2 latency increase has been attributed to inefficient cortical processing as it may occur with partial hearing loss and increasing age (Campbell & Sharma, 2013; Ross et al., 2007). Accordingly, the two treatment groups may have processed target stimuli more rapidly after training although this did not extend to their reaction time.

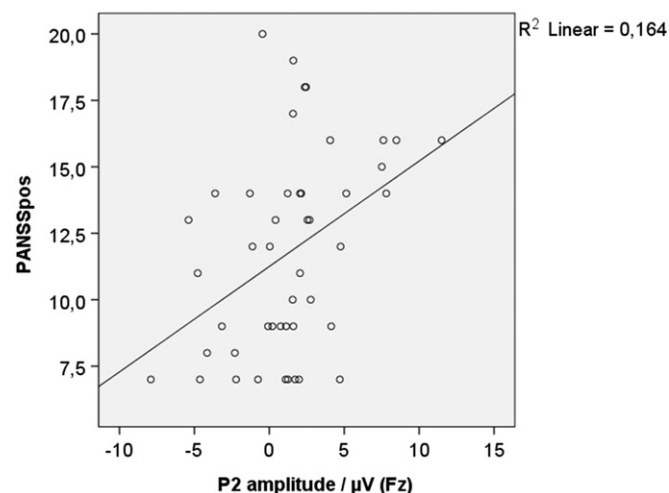


Fig. 3. Scatterplot of P2 amplitude at Fz against PANSS positive symptoms pre-treatment ( $r(46) = .40$ ). The severity of positive symptoms increases with P2 amplitude.

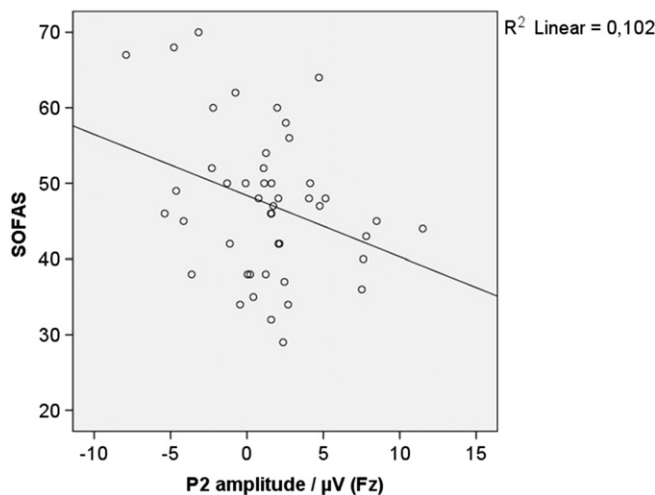


Fig. 4. Scatterplot of P2 amplitude at Fz against the Social and Occupational Functioning Assessment Scale (SOFAS) ( $r(46) = -.32$ ). The higher the P2 amplitude the more impaired daily functioning.

Contrary to our expectation, auditory training failed to show greater improvement than the visual-spatial one. Moreover, the former group also 'relapsed' over the follow-up period. A number of reasons could account for this result. First, the visual training, targeting spatial as well as visual discriminatory function, could be more general than the auditory training. It has been repeatedly pointed out that a more 'broad-spectrum' training led to greater and longer lasting improvement than a more specific training (Fisher et al., 2010; McGurk et al., 2007). If further substantiated, such findings would not be in line with claims of specific neural plasticity. Second, schizophrenia may be less amenable to auditory than to visual-spatial training. The volume of the primary and secondary hearing areas was found to be diminished in schizophrenia (Hirayasu et al., 2000; Kasai et al., 2003; McCarley et al., 1993) which may have contributed to the instability of the improvement. It is noteworthy that, with one exception, the study by Fisher et al. (2009), virtually all successful computerized cognitive remediation programs consist of visual materials, i.e., either of graphic or numerical/verbal displays (e.g. Bowie et al., 2012; McGurk et al., 2005; Sartory et al., 2005). It seems likely that schizophrenia patients respond better to training in the visual rather than the auditory sensory domain. Furthermore, the present training was comparatively short and it is likely that a more extensive training may have led to longer-lasting changes. Finally, it is also noteworthy that the visual-spatial training induced changes in more frontal positions than the auditory training. It is conceivable that targeting indices located in frontal areas induces longer-lasting changes than posterior ones.

There are also other studies of neurobiological indices showing significant effects following cognitive training, for instance, an increase in serum BDNF, which is known to have a role in neuronal development (Vinogradov et al., 2009). But there are also increasingly more neuroimaging studies showing increased activation in prefrontal areas with behavioral improvement (Bor et al., 2011; Haut et al., 2010; Wykes et al., 2002) and greater preservation of gray matter in early schizophrenia patients receiving cognitive enhancement therapy (Eack et al., 2010).

Apart from the improvement of Digit Span Backward in both training groups, type of treatment had no significant effect on neuropsychological variables. This is in contrast to previous studies showing improvement following computer-assisted training (Grynszpan et al., 2011; Sartory et al., 2005). Again, it is likely that a more extensive training may have induced greater training-related changes. Fisher et al. (2009) administered 50 training sessions of sound discrimination extending to the presentation of narratives and found large effects with regard to verbal learning and memory although some of the effect sizes may have been due to the slight deterioration of the control group in

these domains. In the present study, there was a general improvement from the first to the second assessment which was likely to be due to the patients' greater familiarity with the tests. Another reason for the lack of significant results may be the selection of high-functioning patients to enable them to carry out the training tasks. It is noteworthy that Bell et al. (2003) also reported improvement in Digit Span Backward following neurocognitive enhancement therapy independently of severity of cognitive dysfunction.

P2 amplitude was increased with severity of symptoms, particularly positive symptoms, in the present study. A higher P2 amplitude in patients than controls was reported in a meta-analysis of the auditory P2 to target tones in schizophrenia (Ferreira-Santos et al., 2012) and P2 amplitude was further increased in case of a family history of psychosis (Tabarés-Seisdedos et al., 2001). P2 amplitude was also increased with psychosocial dysfunction in patients in the present study. A similar result was previously reported for mismatch negativity (Light & Braff, 2005), another early component of the evoked potentials. The results suggest that early information processing and working memory make an important contribution to social and occupational functioning. It is also noteworthy that CR has a sizeable effect on social cognition (Grynszpan et al., 2011). However, the assessment instruments used in the present study have previously been found to be of only minor validity in terms of real-world-outcomes (Mausbach et al., 2009). Other measures may have been more informative in terms of the relationship between early information processing and functional skills (e.g. Bowie et al., 2006, 2012, 2014; Keefe et al., 2006).

There is no final agreement as to the effect of antipsychotic medication on P2. While Karoumi et al. (2000) found no relationship, other authors reported P2 alterations due to drug treatment (e.g. Winterer et al., 2001). Patients of the present study were, in any case, randomly allocated to groups which did not differ with regard to medication.

Among the limitations of the present study is the small sample size of the groups. A larger sample may have led to the detection of more significant group differences. Additionally, the number of training sessions is among the lowest reported so far (Medalia et al., 2000, 2001) and may be the reason for the lack of a significant training effect on cognitive function other than working memory.

## 5. Conclusions

The more stable reduction of P2 latency following visual-spatial compared to auditory training may be due to the former targeting a broader spectrum of domains than the latter. Alternatively, the result may be due to specific auditory discrimination deficits in schizophrenia rendering this function less amenable to stable change.

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## Contributors

GS and BWM conceived and designed the study. CK and DK recruited participants, collected data and carried out the data analysis. All authors contributed to manuscript writing.

## Conflict of Interest

All authors declare that they have no conflicts of interest.

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