DO NEUROPSYCHOLOGICAL AND SOCIAL COGNITION ABILITIES IN SCHIZOPHRENIA CHANGE AFTER INTENSIVE COGNITIVE TRAINING? A PILOT STUDY

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Abstract

Objective: Schizophrenia is characterized by significant cognitive deficits on attention, memory, executive function, language and/or sensory motor skills. In addition, patients' profile is frequently characterized by marked deficits in the domain of social cognition. Cognitive rehabilitation has recently become an essential component of the rehabilitation process in schizophrenia. However, to date is not clear whether cognitive rehabilitation impacts positively only on the cognitive deficits specifically trained, or whether the positive effects of rehabilitation training may extend also to other domains such as social cognition abilities. Thus, in the present pilot study, we wanted to see whether an intensive cognitive training, in addition to improving neuropsychological abilities, would also have had an impact on social cognition skills.

Method: Ten patients affected by schizophrenia were randomly assigned to two groups: a treatment group (n = 5) undergoing an intensive computerized cognitive training, and a control group (n = 5) undergoing an unstructured computerized control intervention. A detailed neuropsychological, clinical, functional and social cognition assessment was performed before and after the intervention for all the patients.

Results: A significant longitudinal effect in the treatment group was found for the BACS verbal memory (p = 0.016), and for the comic strip task – non-social (p = 0.032). A trend towards a significant effect was found for the FAB (p = 0.056). Single-case analysis via modified t-test was conducted too.

Conclusions: Our preliminary results showed a significant improvement in the cognitive domain after a structured cognitive training. In addition, an improvement in some social cognition abilities was observed too, even if the impact of the cognitive intervention on these abilities was less evident. Implications for further research were discussed.

Key words: cognitive deficits, rehabilitation, schizophrenia, social cognition

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Introduction

Schizophrenia is a severe psychiatric condition characterized by a significant impairment in patients' social and functional domains (American Psychiatric Association 2000). It is now well-established that schizophrenia is characterized by neurobiological underpinnings (Harrison and Weinberger 2005, Keshavan et al. 2008), and typically presents with significant cognitive deficits on attention, memory, executive function, language and/or sensory motor skills (Heinrichs and Zakzanis 1998, Green et al. 2004, Fioravanti et al. 2005, Dickinson et al. 2007). In addition, patients' profile is frequently characterized by marked deficits in the domain of 'social cognition', which include impairments in emotion recognition, theory of mind, and interpreting social cues in order to behave appropriately in the social world (Couture et al. 2006, Walter et al. 2009).

Cognitive deficits appear to be a prominent feature of schizophrenia at the very beginning of the disease already, and it has been demonstrated that these deficits tend to be relatively stable during the course of the disease (Bonner-Jackson et al. 2010). Cognitive impairment has important negative consequences for patients' social functioning, and it has been proposed that it contributes significantly to the marked psychosocial problems that patients with schizophrenia

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typically present (Green et al. 2004, Horan et al. 2011).

Cognitive rehabilitation aims at enabling patients with cognitive deficits to try and achieve a higher level of cognitive functioning, and it has recently become an essential component of the rehabilitation process targeting patients with schizophrenia. In fact, the results of several studies of cognitive rehabilitation in this clinical domain generally support the positive effects of trainings on patients' cognitive abilities (Wykes et al. 2011). However, to date is not clear whether cognitive rehabilitation impacts positively only on the cognitive deficits specifically trained ('focal' effect), or whether the positive effects of rehabilitation training may extend also to other domains, such as the social cognition abilities ('wide' effect). Thus, in the present pilot study, we preliminarily investigated the effects of an intensive computerized cognitive rehabilitation training on neuropsychological and social cognition abilities in a small group of chronic schizophrenic outpatients. We wanted to see whether an intensive cognitive training, in addition to improving neuropsychological abilities, would also have had an impact on social cognition skills.

Methods

Participants

Participants were recruited from the Psychiatric Day Center of Collegno (Turin, Italy), affiliated to the Department of Mental Health (ASL TO3, Turin, Italy). Ten outpatients (seven males and three females) meeting the DSM-IV (American Psychiatric Association, 2000) criteria for schizophrenia (n = 6) or schizoaffective disorder (n = 4), as determined by the Structured Clinical Interview for DSM-IV (Spitzer et al. 1997), agreed to participate. Inclusion criteria were as follows: age between 18 and 56; being under stable drug treatment (at least three months); being in a stable phase of the psychiatric condition (at least 6 months). Exclusion criteria included: significant auditory and/or visual impairment; presence of moderate/severe mental retardation; positive history for any psychiatric and/or neurologic illnesses (other than schizophrenia/schizoaffective disorder); comorbidity of axis II disorders; physical disabilities that precluded the use of the computer; substance abuse or dependence.

The study was granted approval by the local Research Ethics Committee. Informed consent was obtained from all participants.

Procedures

The ten patients recruited for the present study were assigned to one of the two groups (treatment group, and control group). Assignment was performed using a computer-generated randomization list. Detailed neuropsychological, clinical, functional and social cognition assessments were performed twice: at the beginning of the study, and at the end of the three-month intervention. The health professionals responsible for the neuropsychological, clinical, functional and social cognition assessments were blind to the group (treatment versus control group) the patients belonged to.

Neuropsychological assessment. All participants underwent a detailed neuropsychological assessment performed by two experienced neuropsychologists (AS and EB), in order to obtain detailed information about their performance across a wide range of cognitive domains. Firstly, the Brief Intelligence Test (TIB, Colombo et al. 2002), functionally equivalent to the National Adult Reading Test (Nelson 1982), was administered to get an estimation of the pre-morbid Intelligent Quotient. Then, a neuropsychological battery specifically designed to investigate cognitive deficits in schizophrenia (Brief Assessment of Cognition in Schizophrenia, BACS, Keefe et al. 2004, Anselmetti et al. 2008) was administered. The BACS assesses the aspects of cognition found to be significantly impaired and strongly correlated with outcome in patients with schizophrenia (Kurtz 2011; Schaefer et al. 2013). More precisely, it consists of six tests tapping different cognitive functions: verbal memory (list learning task); working memory (digit sequencing task); motor speed (token motor task); verbal fluency (category instances); attention and speed of information processing (symbol coding test); and executive functions (Tower of London test). Lastly, the Frontal Assessment Battery (Dubois et al. 2000) was administered, in order to investigate the possible presence of executive dysfunction by means of more ecologically oriented items.

The neuropsychological assessment was performed twice: at the beginning of the study, and at the end of the three-month intervention.

Clinical assessment. All patients underwent a detailed psychiatric assessment performed by two experienced psychiatrists with more than 10 years of clinical experience. The assessment encompassed the following tools: the Structured Clinical Interview for DSM-IV (SCID, Spitzer et al. 1997), the most widely used diagnostic tool used to determine DSM-IV Axis I and II disorders; and the Positive and Negative Syndrome Scale (PANSS, Kay et al. 1987), a scale used for detecting and measuring symptom severity in schizophrenia.

Functional assessment. All participants were administered the following two tools: the Global Assessment of Functioning (GAF, DSM-IV), used to rate subjectively the social, occupational, and psychological functioning of adults, with the aim of getting a gross indicator of the level of achievement of some important aspects of life; and the Personal and Social Performance scale (PSP, Morosini et al. 2000), developed as a screening measure of personal and social functioning of psychiatric patients in rehabilitation settings.

Social cognition assessment. Two social cognition tasks were used in the present study. The Reading the Mind in the Eyes task (RME, Baron-Cohen et al. 2001) consists of the presentation of 36 black and white photographs of the eye region of both male and female human faces. Participants were required to choose which of four words (printed below the pictures), best describes what the person in the photograph is thinking or feeling. A control task (Baron-Cohen et al. 1997), designed to investigate participants' ability to correctly identify human physical attributes such as gender, was undertaken subsequently.

The second social cognition task is a version of a story completion task used by our research group in previous studies (Walter et al. 2004; Ciaramidaro et al. 2007; Bara et al. 2011; Cavallo et al. 2011a, 2011b; Enrici et al. 2011). It consists of 36 comic strip stories belonging to two theoretical dimensions: *Social Contexts (social)*, and *Non-Social Contexts (non-social)*. The social dimension includes 18 stories depicting both actions with a social goal performed by a single character where a social interaction is foreseen but has not actually taken place (e.g. a single person preparing a romantic dinner), and actions with a social goal performed by two characters in a communicative interaction (e.g. a person obtaining a glass of water by asking another person to get it for her). The non-social dimension includes stories in which no social interactions are shown. The stories belonging to the social dimension require the attribution of social intentions as they concern a social interaction that occurs at the present time or in the future, whereas the stories belonging to the non-social dimension do not require the attribution of social intentions as they do not concern a social interactions between characters. Details of the computerized administration of the task have been published elsewhere (please refer to Cavallo et al. 2011a). Examples of the stories can be found at the following web address:

www.psych.unito.it/csc/pers/adenzato/pdf/neurodegdis.pdf

Cognitive training. Half of the patients (n = 5) were in the treatment group. Each of them received an intensive computerized cognitive training (three 30-minute sessions per week, for 12 consecutive weeks). Each session was performed by the patient together with a psychiatric rehabilitation therapist, as we wanted to conduct the training in an interpersonal context instead of delegating completely the training to the patient in isolation. The intense frequency of sessions had been chosen as previous research demonstrated that the intensity and frequency of training are the crucial issues in planning effective rehabilitation programs: in fact, frequent 30-45 minute sessions appear to be necessary to efficiently drive neuroplastic changes (Jensen et al. 2005). The cognitive intervention used the rehabilitative software Brainer (https://www.brainer.it), that allows the person to go through exercises tapping different cognitive functions and of increasing difficulty as long as the person's performance improves. The software Brainer was designed with the goal of developing a training program and a complex intellectual stimulation systems targeting patients in need of cognitive rehabilitation. Before the beginning of the computerized training, an individual session with each patient was planned, in order to show them the software and to teach them how to use it. Brainer is composed by a set of 72 exercises covering several cognitive functions: visual perception; auditory perception; attention; language; reading and writing; calculations; logic and deduction; memory; sensory motor skills. Before the beginning of the study, exercises tapping the cognitive functions typically impaired in schizophrenia (i.e. attention, memory, executive function, language and/or sensory motor skills) were selected, and three parallel versions of the training (versions 1, 2 and 3) were created. Patients started the training with version 1; after a week, a different version of the training was proposed to the patient, in order to avoid the repetition of the same pattern of exercises throughout the training.

The five patients in the control group followed the same frequency of sessions (three 30-minute session per week, for 12 weeks) together with a psychiatric rehabilitation therapist. During the sessions, a computer connected to the Internet was used and the patient was free to choose to read electronic newspapers, to play games and solve puzzles, and/or reach sites and contents of interest for him/her. The idea was to maintain the same setting as for the treatment condition (using a computer in the presence of a rehabilitation therapist), but without proposing a structured cognitive training designed having rehabilitation purposes in mind.

In addition to the treatment and control interventions planned for the present study, all the patients received standard psychiatric management, including individual case management and occupational laboratories and activities on a weekly basis.

Statistical analyses

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 18.0. Given the limited sample size involved, and as the graphical exploration of data did not allow us to rule out violations of the normality assumption, non-parametric tests were used. Firstly, group comparisons between the two groups of patients (treatment versus control group) on the demographic, clinical, functional, neuropsychological and social cognition variables of interest were performed using Mann-Whitney U tests. Secondly, in order to investigate the possible longitudinal effect of the rehabilitation training, the difference between final and initial performances on neuropsychological and social cognition measures, i.e. $(T_1 - T_0) / T_0$, in the treatment group was compared with the corresponding difference in the control group. Lastly, comparisons of individual patients' score in the treatment group versus controls' scores on the neuropsychological and social cognition measures were performed using the single case procedure formalized by Crawford et al. (1998) and by Crawford and Garthwaite (2002) to deal with single cases in cognitive neuropsychology appropriately. This comparison was performed twice, before and after the rehabilitation training, to investigate whether individual's scores in the treatment group changed (as compared to the control group) due to the training realized.

Results

Clinical and functional assessment

The two groups of patients were well matched for age (Mann-Whitney U = 8.500, not significant, NS), level of education (Mann-Whitney U = 10.000, NS), duration of illness in years (Mann-Whitney U = 9.500, NS), and duration of treatment in years (Mann-Whitney U = 12.000, NS). The comparisons between the score of all the clinical and functional measures in the two groups of patients did not show any significant result. See **table 1** for details.

Baseline neuropsychological and social cognition assessment

The comparisons between the score of all the neuropsychological and social cognition measures in the two groups of patients before the training did not show any significant result. See **table 2** for details.

Longitudinal effect of the cognitive training on the neuropsychological and social cognition measures

In order to investigate the possible presence of a longitudinal effect due to the cognitive training performed, we calculated the difference for all the measures between the initial and final performances as $(T_1 - T_0) / T_0$ for the two groups, and then we statistically compared these differences by means of Mann-Whitney U tests. Results were as follows: A significant longitudinal effect in the expected direction (improved performance in

Table 1. *Comparison of the demographical, clinical and functional measures in the two groups*

	Treatment group mean (SD) (n = 5)	Control group mean (SD) (n = 5)	Mann-Whitney U
Age	45.40 (8.02)	39.20 (8.29)	8.500 NS
Education	10.40 (3.36)	11.60 (2.19)	10.000 NS
Gender (M:F)	4:1	3:2	-
Duration of illness	20.60 (11.67)	13.80 (8.73)	9.500 NS
Duration of treatment	13.40 (6.11)	13.40 (9.04)	12.000 NS
PANSS – total	78.80 (21.94)	96.60 (39.30)	9.000 NS
PANSS – positive	12.80 (4.82)	21.00 (10.70)	8.000 NS
PANSS – negative	24.40 (12.30)	26.20 (11.23)	11.000 NS
PANSS – general psychopathology	41.60 (10.11)	49.40 (18.56)	8.500 NS
PSP	42.20 (22.11)	45.80 (10.03)	12.000 NS
GAF	38.60 (16.46)	44.20 (14.17)	11.000 NS

GAF = Global assessment of functioning; NS = not significant; PANSS = Positive and negative syndrome scale for schizophrenia; PSP = Personal and social performance scale.

Table 2. *Baseline comparison of the neuropsychological and social cognition variables in the two groups of patients*

	Treatment group mean (SD) (n = 5)	Control group mean (SD) (n = 5)	Mann-Whitney U
Neuropsychological measures			
TIB IQ	106.76 (5.28)	104.03 (5.46)	8.000 NS
FAB	13.20 (1.48)	12.80 (1.92)	8.500 NS
BACS – verbal memory	27.40 (8.20)	36.40 (17.96)	10.000 NS
BACS – token	46.80 (9.68)	53.80 (17.01)	9.500 NS
BACS – sequence of numbers	16.60 (5.55)	16.00 (3.74)	12.000 NS
BACS – verbal fluency	36.60 (7.99)	24.60 (7.30)	9.000 NS
BACS – number-symbol	20.40 (9.45)	22.40 (10.21)	8.000 NS
BACS – tower of London	16.80 (3.42)	11.60 (4.51)	11.000 NS
Social cognition measures			
RME – experimental	18.60 (7.40)	19.60 (6.02)	8.500 NS
RME – control	35.40 (0.89)	34.60 (3.13)	12.000 NS
Comic strip – non-social	9.80 (4.32)	11.80 (2.49)	11.000 NS
Comic strip – social	8.60 (1.14)	8.80 (5.02)	8.000 NS

BACS = Brief assessment of cognition in schizophrenia; FAB = Frontal assessment battery; NS = not significant; RME = Reading the mind in the eyes; TIB IQ = Test di Intelligenza Breve – Intelligence Quotient.

patients undergoing the structured rehabilitation training) was found for the BACS verbal memory (Mann-Whitney U = 1.000, p = 0.016), and for the comic strip task – non-social (Mann-Whitney U = 2.500, p = 0.032). A trend towards a significant effect was found for the FAB (Mann-Whitney U = 3.000, p = 0.056), whereas for all the other measures the results did not show the presence of a statistically significant longitudinal effect.

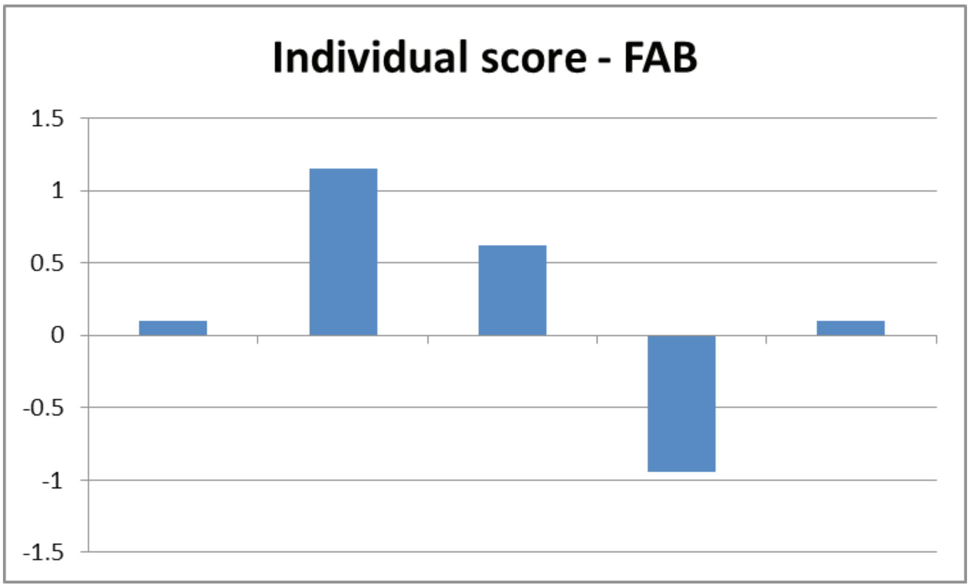
Individual patients' score on neuropsychological and social cognition measures in the treatment group versus controls

Comparison of individual patients' scores on the neuropsychological and social cognition measures with controls' means using a modified t-test procedure (Crawford et al. 1998; Crawford and Garthwaite 2002) was performed twice: before and after the training. Interestingly, the training appeared to have a positive effect (i.e. to allow the patient to get higher scores) for the treated patients in the vast majority of measures, even if in most of the cases the significance threshold ($p < 0.05$) was not reached. See **figures 1-4**.

Regarding the neuropsychological measures, after the training the difference from controls was statistically significant for the BACS – verbal fluency in patients 1 ($t(8) = 2.261$, $p = 0.04$), 2 ($t(8) = 6.100$, $p = 0.001$), 3 ($t(8) = 3.327$, $p = 0.01$), 4 ($t(8) = 6.100$, $p = 0.001$), and 5 ($t(8) = 4.820$, $p = 0.004$). For the BACS – number-symbol in patient 2 ($t(8) = 2.841$, $p = 0.02$). Regarding the social cognition tasks, after the training the difference from controls was statistically significant for the RME – experimental in patient 2 ($t(8) = 2.540$, $p = 0.03$). All of the other comparisons did not reach a statistically significant improvement after training.

Figure 1. *Single case score of treated patients versus controls' mean for the FAB at baseline (a), and after the training (b). Scores expressed as Z scores*

a)



b)

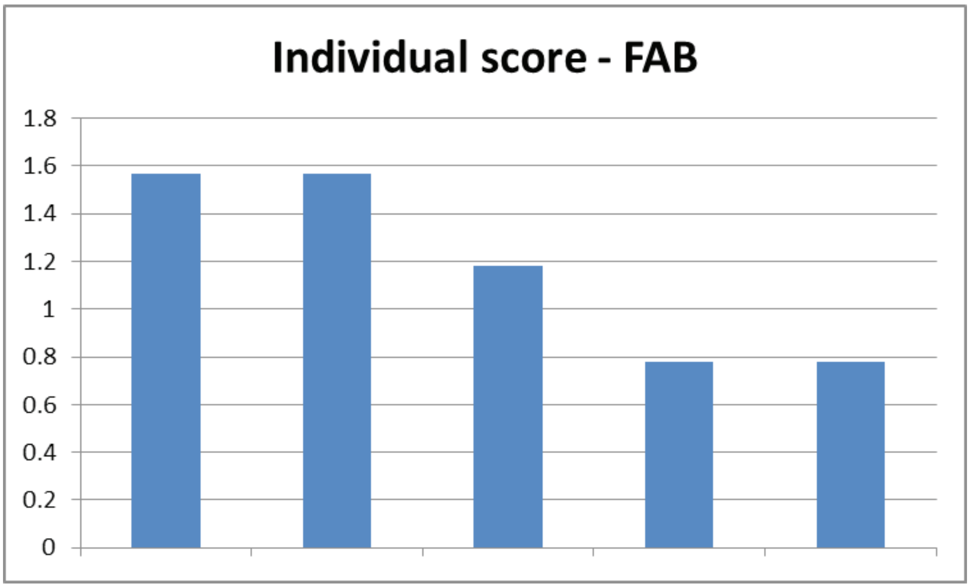
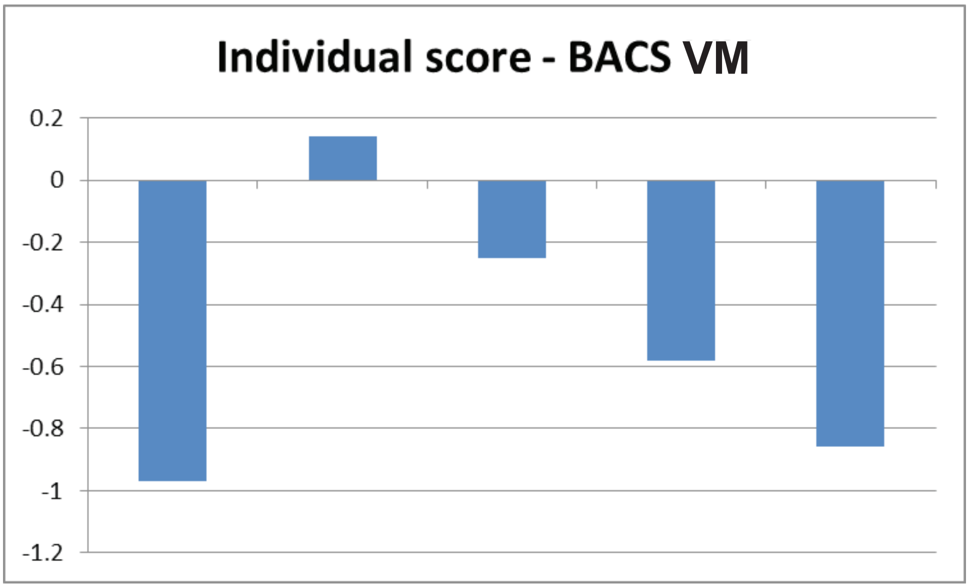
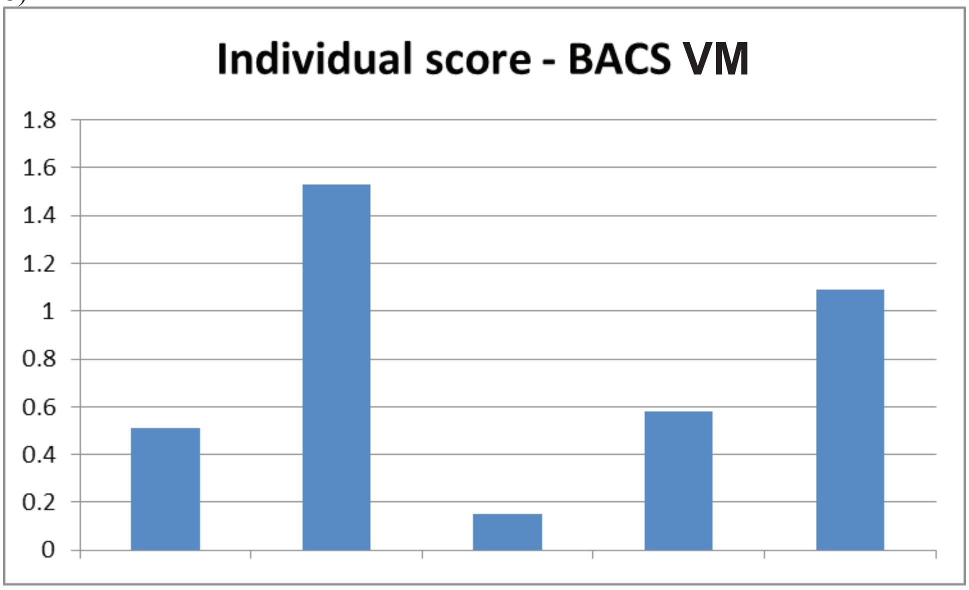


Figure 2. *Single case score of treated patients versus controls' mean for the BACS – verbal memory at baseline (a), and after the training (b). Scores expressed as Z scores*

a)



b)



Discussion

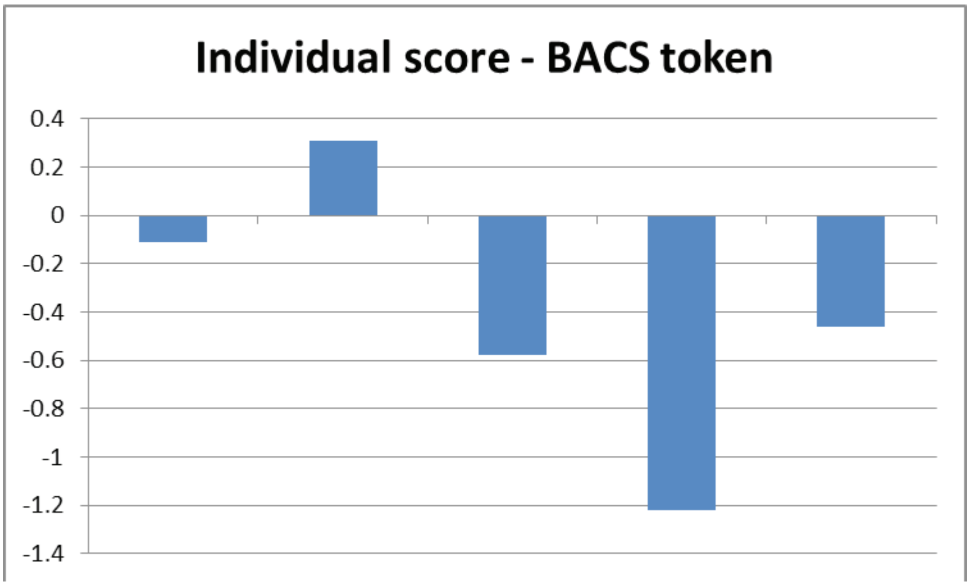
Schizophrenia is a chronic psychiatric condition characterized by a significant impairment in patients' social and cognitive domains that influences seriously their quality of life. Cognitive impairment contributes significantly to the marked psychosocial problems that patients with schizophrenia typically present. Thus, cognitive rehabilitation has recently become an essential component of the rehabilitation process targeting patients with schizophrenia.

In our pilot study, we investigated the effects of an intensive computerized cognitive training on cognitive and social cognition abilities in schizophrenia. Two small groups of patients were involved: a treatment group that underwent three sessions a week for 12 consecutive weeks using the cognitive rehabilitation software Brainer, and a control group that underwent the same number of sessions without using a structured rehabilitation training. It is important to note that all the participants carried out the cognitive training or the control intervention in the presence of a psychiatric rehabilitation therapist, with a twofold aim: clinically speaking, to allow the patients to maintain a supportive relationship with the same therapist throughout the intervention; and, methodologically speaking, to limit as much as possible the diverse influence of nonspecific factors (such as the presence of a therapist) between the two groups. The two groups were well matched for the main demographic and clinical variables. Interestingly, they performed similarly on the neuropsychological and social cognition measures administered at the baseline. So, we were confident that the two groups did not differ significantly to one another before the beginning of the cognitive training.

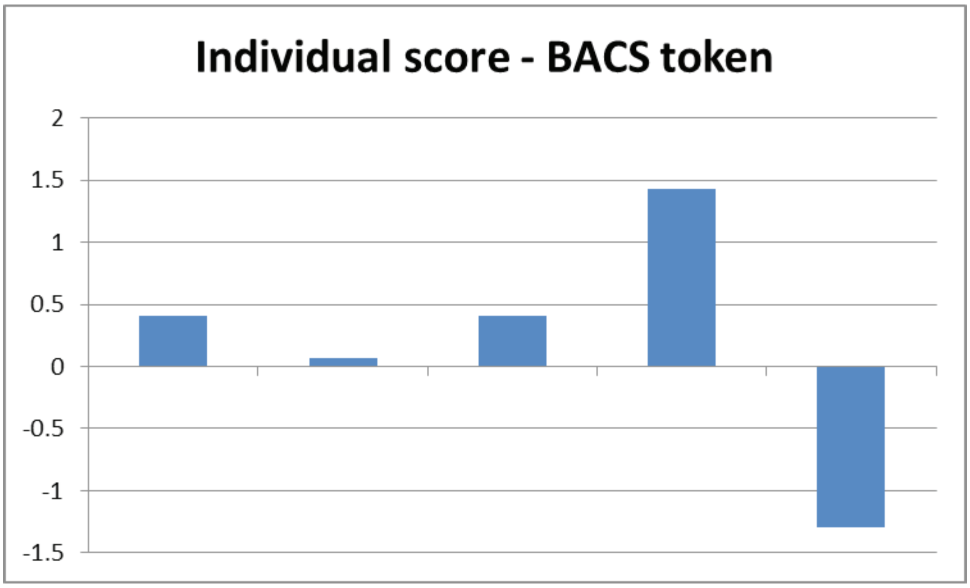
Regarding their neuropsychological profile, in

Figure 3. *Single case score of treated patients versus controls' mean for the BACS – token at baseline (a), and after the training (b). Scores expressed as Z scores*

a)



b)

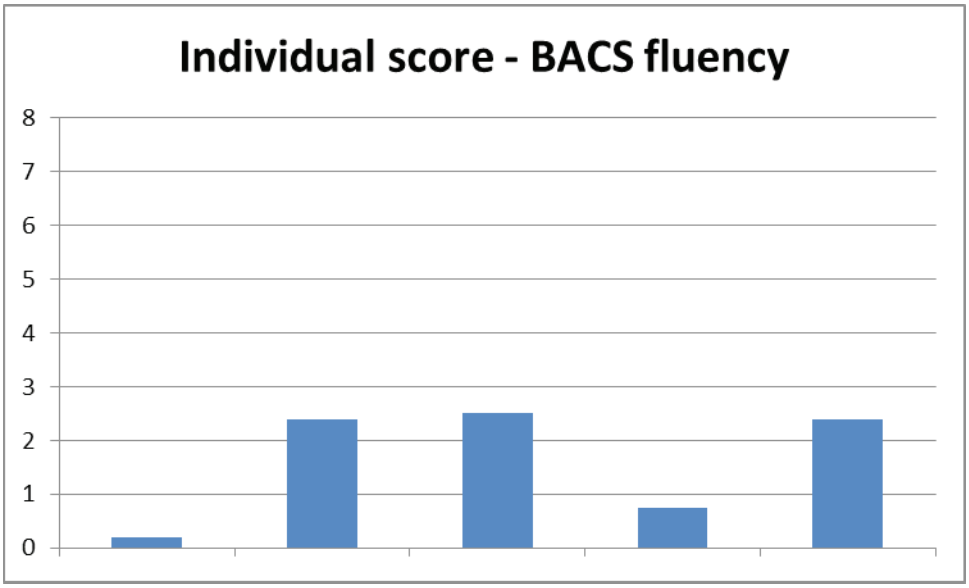


keeping with previous research our patients showed the presence of significant deficits in the cognitive abilities typically affected in schizophrenia, such as attention, memory and executive functions. On the social cognition side, patients showed a lower score on the RME, as compared to published normative data (Baron-Cohen et al. 2001). In addition, patients showed also lower scores on the comic strip task, as compared to other clinical populations and healthy controls (Cavallo et al. 2011a, 2011b).

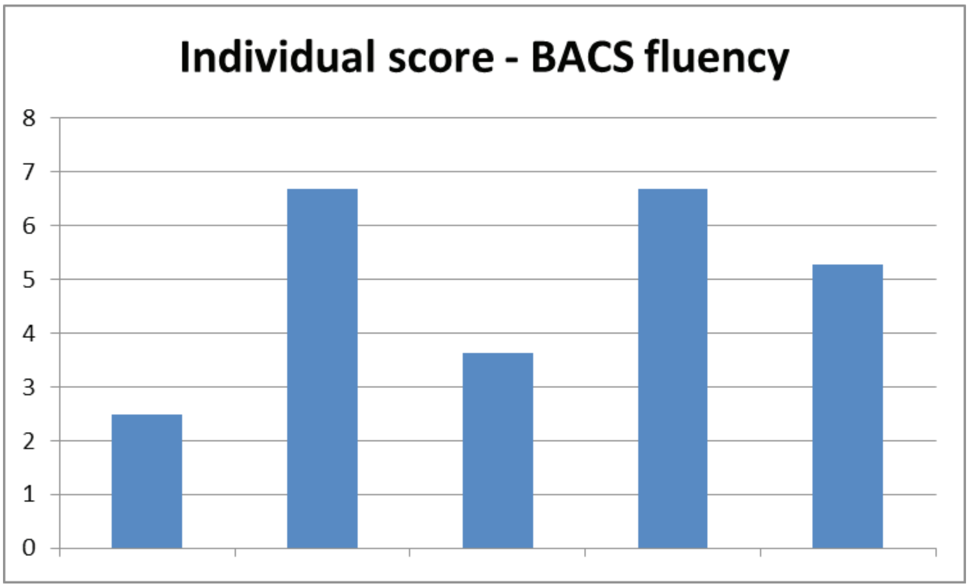
We found a significant longitudinal effect in in the treatment group in patients' performance on some neuropsychological and social cognition tasks, as compared to healthy controls. More specifically, when the differences between final and initial performances were taken into account, we demonstrated that the performance of treated patients during the course of the study significantly improved in the BACS verbal memory and in the comic strip task (non-social dimension), while the performance on the FAB approached statistical significance. This suggests that an intensive cognitive training had a significant effect on some of the dimensions of interest. However, due to the small group size, it is crucial not to limit our view to group comparisons, but focusing on a single-case level too. We then performed comparisons of individual patients' score in the treatment group versus controls' scores on the neuropsychological and social cognition measures using an appropriate single case procedure. This comparison was performed twice, before and after the training, to investigate whether individual's scores in the treatment group changed (as compared to the control group) due to the cognitive training realized. Interestingly, on a single-level basis, we found a positive effect (i.e. patients got higher scores than controls after the training) for the treated patients in

Figure 4. *Single case score of treated patients versus controls' mean for the BACS – verbal fluency at baseline (a), and after the training (b). Scores expressed as Z scores*

a)



b)



the vast majority of measures. It is important to note that in most cases this improvement did not reach statistical significance, but nevertheless a clear pattern of improvement emerged. A significant improvement was reached for the BACS – verbal fluency (in all five patients), for the BACS – number-symbol (in patient 2), and for the RME – experimental (in patient 2).

Overall, these preliminary results are consistent with previous research, that showed a significant improvement in the cognitive domain after a structured cognitive training (McGurk et al. 2007, Wykes et al. 2011). In addition, an improvement in some social cognition abilities was observed too, even if the impact of the cognitive intervention on these abilities was less evident. However, our results did not show the presence of a comparable change in the clinical measures due to the training administered. Thus, we can conclude that while the cognitive training appeared to have a significant positive effect on some cognitive abilities, a less evident effect was found on other domains not directly targeted by the training. Coming back to the question reported above in the Introduction, our preliminary evidence supports a significant effect of the training realized on the abilities targeted by the intervention, whereas other abilities not directly targeted by the intervention were less influenced by the training. As recent literature showed the presence of a generalization of training effects (Subramaniam et al. 2012), future studies should tackle this crucial clinical issue, in order to try and identify trainings which present a wider and more significant positive impact on patients' lives.

A strength of the present study is that the performance of treated patients was compared to a small group of controls via a series of modified t-tests specifically designed to deal with single case studies. This allowed us to directly compare patients' performance with the performance of a control group recruited in the same setting and with similar clinical and cognitive abilities. In addition, the cognitive exercises proposed were tapping all of the cognitive functions known to be affected in schizophrenia, and they were specifically designed having rehabilitation purposes in mind. As the cognitive exercises proposed required only few minutes to be performed, the short duration of training sessions (i.e. 30 minutes each) allowed us to implement an intensive cognitive training that was well accepted by patients. As a result, we did not have drop-out, and patients were highly motivated and presented a high degree of satisfaction during and after the training.

This study also has some limitations. Firstly, the small sample size did not allow us a generalizability of the results to this clinical population. Due to the pilot nature of the study, we intentionally recruited only few patients in order to set up a rehabilitation training that was as much as possible under our control, but obviously future studies should aim at recruiting and treating large number of patients, in order of seeing whether our interesting preliminary results can be confirmed and hopefully corroborated on a large scale. Secondly, our training followed the typical "drill and practice" format, during which various exercises of increasing level of difficulty are repeatedly proposed to the patient, who is invited to try and solve them by trials and errors in order to identify gradually the most efficient ways of solve these problems. While this classical approach has merit, recent evidence has started to show that when the rehabilitation approach consists of focused drill and practice of cognitive skills only, the results of the training typically do not impact significantly on psychosocial outcomes. Conversely, cognitive rehabilitation trainings that incorporate also the teaching of compensatory strategies and/or that explicitly discuss with the patients the generalizability of cognitive acquirements to real-world situations appear to have a more significant impact on patient's life. Future studies should then incorporate the discussion of how the cognitive training performed during the session may help the patient to be more effective in solving real-life problems. Lastly, we did not schedule a follow-up after the end of the intervention, so we did not know whether our results were stable over time or not.

To conclude, the present pilot study supports the view that it is possible to successfully train at least some cognitive and possibly some social cognition abilities in patients affected by schizophrenic disorders. In fact, our preliminary results showed that the treated patients were able to improve their performance on some measures due to the training implemented. However, although our pilot study provided some relevant suggestions about this research topic, further and stronger evidence is urgently required in order to answer more robustly to the important question: Do neuropsychological and social cognition abilities in schizophrenia change after intensive cognitive training? And, more importantly, future research should address the essential question: what rehabilitation trainings may have a significant positive impact on patients' cognitive and social abilities, and not only on the skills specifically targeted by the rehabilitation intervention?

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