



Computerized cognitive remediation training for schizophrenia: An open label, multi-site, multinational methodology study

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ABSTRACT

A recent single-site study (Fisher et al., 2009. *Am J Psychiatry*. 166 (7) 805–11) showed that repeated training with the Brain Fitness Program (BFP) improved performance on a battery of neuropsychological tasks. If replicated these data suggest an important non-pharmacological method for ameliorating cognitive impairment in schizophrenia. Our study evaluated the BFP training effects in an open-label, multi-site, multinational clinical trial. Fifty-five stable adult patients with schizophrenia on regular antipsychotic medication completed ≥ 32 BFP training sessions over 8–10 weeks. Training effects on cognitive performance and functional capacity outcome measures were measured using CogState® schizophrenia battery, UCSD Performance based Skills Assessment (UPSA-2) and Cognitive Assessment Interview (CAI). BFP training showed a large and significant treatment effect on a training exercise task (auditory processing speed), however this effect did not generalize to improved performance on independent CogState® assessment. There were no significant effects on UPSA-2 or CAI scores. Our study demonstrated the feasibility of implementing BFP training in a multi-site study. However, BFP training did not show significant treatment effects on cognitive performance or functional capacity outcome measures despite showing large and significant effects on a training exercise.

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1. Introduction

There is evidence that cognitive remediation and psychological rehabilitation treatments improve performance on selected individual neuropsychological tasks (ES 0.41) and measures of psychosocial functioning (ES 0.36) among patients with schizophrenia (McGurk et al., 2007). It is also known that performance on cognitive tasks included in computerized cognitive remediation programs improves with repeated application (Fisher et al., 2009; Dickinson et al., 2010). More importantly one recent study showed that these practice related effects can generalize beyond the computerized cognitive rehabilitation program tasks and manifest as improvement in performance on a battery of standardized neuropsychological tasks (Fisher et al., 2009). If replicated these data suggest an important non-pharmacological method for ameliorating cognitive impairment in schizophrenia, a major unmet need in treatment of these patients. Combining a novel pharmacological treatment and computerized cognitive remediation may be the most effective way to improve cognitive function in patients with schizophrenia. However, before such

proof-of-concept trials can be conducted it is important to show that cognitive remediation effects previously reported in single site studies can be replicated in multi-site studies.

This study evaluated the feasibility of implementing a computerized cognitive remediation training program in a multi-site, multinational clinical trial. Recently, Keefe et al. (2010) reported the feasibility of implementing BFP in multiple sites in the USA, we evaluate this in a multinational study. The aim of the current study was to determine the nature and magnitude of improvement in cognitive function and functional capacity in adults with stable schizophrenia, who participated in a validated computerized cognitive remediation training, Brain Fitness program (BFP). We also evaluated the practice effects associated with repeated administration of cognitive and functional capacity outcome measures in a 2-week run-in period prior to starting cognitive rehabilitation.

2. Materials and methods

2.1. Clinical trial design

This was an open-label, multi-site, single sequence study. The study was conducted in six sites in two countries (three sites each in the USA and UK). The relevant local institutional review boards approved all procedures, and all participants provided written informed consent. Individuals who agreed to participate in the clinical trial and met the study criteria, attended the clinic three times in the first two weeks, to complete three assessments each of cognitive and functional capacity outcome measures, before starting cognitive remediation training. The training started in the third week and consisted of 40 sessions lasting at least 1 hour each, up to five times per week. Participants received financial compensation for their time in assessments and training sessions, which was contingent upon study participation and not performance.

2.2. Participants

Participation was open to individuals diagnosed with schizophrenia (DSM-IV R) confirmed using the structured clinical interview for DSM disorders (SCID-I/P; First et al., 2002), who were currently clinically stable and without any acute exacerbation in the previous six months. All patients, except one, were within the first 10 years since onset or first treatment for schizophrenia. Eligible individuals were 18–45 years old, on regular regimens of second-generation antipsychotic medication, without a history of significant brain trauma, neurological disorder, mental retardation, other psychiatric disorders, and substance or alcohol dependence within the previous six months. All patients met pre-specified criteria of symptomatic stability including Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) total score of ≤ 75 ; a score of ≤ 2 on all Positive Scale items of the PANSS, except items P1 (delusions), P3 (hallucinatory behavior), and P5 (grandiosity), where they had a score of ≤ 3 ; all Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983) global items ≤ 3 ; Calgary Depression Scale for schizophrenia (CDSS; Addington et al., 1990) total score ≤ 10 ; and a Simpson-Angus Scale total score (SAS; Simpson and Angus, 1970) < 6 .

None of the participants had received ECT in the previous 6 months and none were receiving regular anticholinergic medication. Recruitment for the trial began in 2008 and concluded in 2009.

2.3. Brain fitness program (BFP)

The Brain Fitness Program consisted of six computerized exercises designed to improve the speed and accuracy of auditory information processing. Exercises continuously adjusted difficulty to user performance to maintain an approximately 85% correct rate. Correct trials were rewarded with points and visual animations. Exercises contained

stimulus sets spanning the acoustic organization of speech. The exercises included time order judgment of pairs of frequency-modulated sweeps, discrimination of confusable syllables, recognition of sequences of confusable syllables, matching pairs of confusable syllables, reconstruction of sequences of verbal instructions, and identification of details in a verbally presented story. During the initial stages of training in all exercises, all auditory stimuli were processed to exaggerate the rapid temporal transitions within the sounds by increasing their amplitude and stretching them in time. This exaggeration was gradually removed over the course of the training period such that, by the end of training, all auditory stimuli had temporal characteristics representative of real-world rapid speech. In each training session, a participant worked with four of the six exercises for 15 min per exercise. Adherence was monitored using electronic data upload after each training session.

2.4. Assessments

The participants were assessed before and immediately after BFP training. The assessments included the CogState® schizophrenia battery, a comprehensive computerized battery of cognitive measures (Pietrzak et al., 2009); Digit Span task; two functional capacity outcome measures: UCSD Performance based Skills Assessment (UPSA-2) (Patterson et al., 2001) and Cognitive Assessment Interview (CAI) (Ventura et al., 2010). The Cognitive and functional capacity outcome measures were administered three times in the first two weeks to evaluate their practice effects, if any. Third assessments were chosen a priori as baseline assessments.

2.5. Analyses

Analyses focussed on “completer” population (those who completed at least 32 training sessions and post-training assessments). The difference between the baseline and post treatment measures was evaluated by means of effect size (Becker, 1988) and paired t-test. Effect of training on the BFP exercise was obtained through direct assessment of auditory processing speed on the auditory time-order judgment (ATOJ) task.

3. Results

3.1. Group characteristics and feasibility

Sixty-five patients with schizophrenia were enrolled, of which 55 completed the study. One participant was lost to follow-up, five participants withdrew consent during the study and four participants were dropped because of completing less than 32 training sessions. Table 1

Table 1
Baseline characteristics of patients with schizophrenia who completed at least 32 training sessions of Brain Fitness Program (BFP).

Baseline characteristics	
Numbers	Total enrolled 65 Total completed 55
Age in years [mean (SD)]	31.1 (7)
Males	42 (76%)
Total duration of illness in years [mean (SD)]	6.4 (2.8)
PANSS total score [mean (SD)]	56.4 (12.3)
Pre-morbid IQ range (NART)	86–124
Number of years of education [mean (SD)]	12.3 (2.1)
Educational level	<High school 5 High school or higher 44
Current living arrangement	University 4 Living independently 31 Supported accommodation 23
Employment status	Unemployed 46 Voluntary work 2 Paid job 6

PANSS: Positive and Negative Syndrome Scale; NART: National Adult Reading Test.

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