Cognitive Remediation and Physical Exercise in Multi-Episode Schizophrenia: Study Protocol for a Randomised Controlled Trial

Pujol N; Cortizo R; Ayllon L; Salvador T; Moreno D; Catala F; Chamorro J; Oller S; Polo-Velasco J; Abellanas A; Díez-Aja C; Pérez V; Mané A.

Institute of Neuropsychiatry and Addiction of the Barcelona MAR Health Park, Barcelona, Spain
Hospital del Mar Medical Research Institute. IMIM, Barcelona, Spain. Ciber Salud Mental Group (CIBERSAM), Barcelona, Spain
Corresponding author: Nuria Pujol; npujol@parcdesalutmar.cat

6th Biennial Schizophrenia International Research Society Conference

Background

Cognitive remediation (CR) and physical exercise have separately shown promising results in schizophrenia cognitive improvement, despite this, the impact on daily functionality is still limited. Physical exercise increases Brain Derived Neurotrophic Factor (BDNF) levels, promoting neuronal and cognitive plasticity, which can maximize the impact of CR. Aims: We are conducting a randomised controlled trial to determine the efficacy of an intensive program that combines CR and physical exercise on cognition and related outcomes for patients with chronic schizophrenia. An additional aim of the trial is to investigate functional and structural brain effects of this intervention and its association to BDNF.

Method / Design

This is a single-blind, controlled randomized study with three different groups: patients receiving CR and physical exercise (experimental intervention), patients receiving CR and healthy lifestyle promotion (control intervention) and a healthy control group (no intervention).

- **Participants:**

The patient sample consist of 74 patients fulfilling *Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision* (DSM-IV-TR) criteria for schizophrenia or schizoaffective disorder. The healthy control sample consist of 18 participants which are screened for the presence of lifetime Axis I psychotic disorders and for the presence of a first-degree relative with schizophrenia.

Inclusion criteria:
- Aged 28-60 years
- Do low physical activity (measured by International Physical Activity Questionnaire, IPAQ)

Exclusion criteria:
- Presence of neurological or substance abuse disorders
- Intelligence quotient < 70
- Somatic illnesses that contraindicate physical exercise

- **Interventions:**

The interventions are 12-week long and consist of three weekly sessions (90 min of CR and 40 min of either aerobic exercise or healthy lifestyle promotion). The interventions are delivered in a group format (4–7 patients per group).

Cognitive Remediation:

The REHACOP is a cognitive remediation program designed for patients with psychosis (Ojeda et al., 2012). This program is highly structured and it is based on paper-pencil tasks that are hierarchically organized into 3 levels of difficulty. REHACOP trains patients in several cognitive domains such as attention, memory, processing speed, language, executive functioning and social cognition. REHACOP groups are led by a trained clinical psychologist (RC, LA and NP).

Aerobic exercise:

The program has been designed by an expert in physical activity and sport education (Anita Macedo) and it consists of outdoor group training sessions led by nursing staff (TS, DM, FC, JPV). Each session includes: Stretching exercises (4 min), Aerobic exercise (20 min interval walking), Stretching exercises (5 min) and Relaxation (1 min) (Figures 1-4). The Borg's (0–10) RPE scale is used to assess whole-body perceived exertion during exercise, being the optimal intensity of the exercise program 4–6.

Figure 1. Stretching exercises (5 min)

Figure 2. Aerobic exercise (20 min)

Figure 3. Stretching exercises (4 min)

Figure 4. Relaxation (1 min)

Healthy lifestyle promotion:

This program is an educational intervention focused on healthy lifestyle habits and it has been designed by a clinical nurse specialist (TS). The group program targets the promotion of regular physical activity, sleep quality, healthy eating habits, smoking cessation, stress management and sexual health. These therapeutic groups are led by nursing staff (TS, DM, FC, JPV).

- **Assessments:**

Primary outcome measures are cognitive performance, functional outcome, negative symptoms, BDNF levels and neuroimaging measures. Secondary outcome measures are quality of life and metabolic parameters. All measures are blindly assessed at three time points; baseline (T0), post treatment at 3 months (T1), and follow-up at 12 months (T2) (Table 1).

The study has been approved by the ethics committee of the Hospital del Mar/IMIM (reference number: 2015 /6209/I). All participants sign informed consent prior to enrollment.

Table 1. Study measures and time points

Concept	Measure	T0 Baseline	T1 Post-treatment	T2 FU 12 months
Cognition	MCCB	x	x	x
	Effort-based decision making task	x	x	x
	Reversal learning task	x	x	x
	POFA	x	x	x
	Hinting Task	x	x	x
Functionality and quality of life	UPSA	x	x	x
	WHO-DAS	x	x	x
Psychotic and depressive symptoms	BNSS	x	x	x
	PANSS	x	x	x
	GDS	x	x	x
Physical Health	IPAQ	x	x	x
	ECG	x	x	x
	Anthrometric measures (height, weight, waist, hip perimeter)	x	x	x
	Blood pressure and test (cholesterol, glucose, triglycerides)	x	x	x
	6-minute walk test (blood pressure and heart rate)	x	x	x
Neurotrophins	Serum BDNF level	x	x	x
Neuroimaging	fMRI: 2 back task and resting state	x	x	
	DTI/MRI	x	x	
Other	Sociodemographic information	x		

FU Follow-up; MCCB: Consensus Battery for Clinical Trials in Schizophrenia NIMH-MATRICS; POFA: Emotional perception with Pictures of Facial; WHO-DAS: WHO Disability Assessment Schedule; UPSA: Performance-Based Skills Assessment; EQ-5D: EuroQoL-5D; BNSS: Brief Negative Symptom Scale; PANSS: Positive and Negative Syndrome Scale; GDS: Calgary Depression Scale; IPAQ: Affect International Physical Activity Questionnaire; ECG: electrocardiogram; BDNF: Brain-derived neurotrophic factor; fMRI: functional Magnetic Resonance Imaging; DTI: Diffusion Tensor Imagin

Discussion

The results of this trial will provide valuable information about whether cognitive remediation efficacy for patients with schizophrenia can be enhanced by aerobic exercise-induced BDNF upregulation.

REFERENCES: Ojeda N, Peña J, Bengoetxea E, García A, Sánchez P, Elizagárate E, Segarra R, Ezcurra J, Gutiérrez-Fraile M, Eguíluz JI. REHACOP: a cognitive rehabilitation programme in psychosis. Rev Neurol. 2012;16;54(6):337-42

TRIAL REGISTRATION: The trial is registered at *www.clinicaltrials.gov*, identifier: NCT02864576
FUNDING: This work is funded by the Instituto de Salud Carlos III-Subdirección General de Evaluación y Fomento de la Investigación, with the Research Project PI15/00453.

Hospital del Mar

Parc de Salut MAR Barcelona