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Cortical thickness in regions of frontal and temporal lobes is associated with responsiveness to cognitive remediation therapy in schizophrenia

Rafael Penadés [a,b,c,d,*], Nuria Pujol [a], Rosa Catalán [a,b,c,d], Guillem Masana [b,c,d], Clemente García-Rizo [c,d], Nuria Bargalló [b,e,f], Alexandre González-Rodríguez [d], Dídac Vidal-Piñeiro [a,b], Miquel Bernardo [a,b,c,d], Carme Junqué [a,b]

[a] Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Spain
[b] Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
[c] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain
[d] Barcelona Clinic Schizophrenia Unit (BCSU), Institut Clínic de Neurociències (ICN), Hospital Clinic, Barcelona, Spain
[e] Centre de Diagnòstic per la Imatge (CDIC), Hospital Clinic, Barcelona, Spain
[f] Magnetic Resonance Imaging Core Facility, IDIBAPS, Barcelona, Spain

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ABSTRACT

Background: Despite the evidence for the efficacy of cognitive remediation therapy (CRT) in patients with schizophrenia, comparatively little is known about the potential predictors of good treatment response. We tried to determine whether improvement in cognition following CRT is positively associated with baseline cortical thickness (CTh) or baseline clinical symptoms level or baseline cognitive performance.
Methods: The current work uses data collected in a previous study (Penadés et al., 2013) in which a CRT program was investigated through a controlled randomized trial (NCT 01318850) with three groups: patients receiving cognitive treatment, patients receiving a different psychological intervention as an active and a healthy control groups (HC). CTh was estimated from the T1-weighted MRIs using the FreeSurfer software.
Results: We found that CRT responsiveness was associated with baseline measures of cortical thickness in the frontal and temporal lobes. Positive changes in non-verbal memory were associated with greater initial thickness in cortical regions involving left superior frontal, left caudal middle frontal, left precuneus and paracentral; superior frontal, right caudal middle frontal gyrus and pars opercularis. Additionally, uncorrected data also suggested that verbal memory improvement could be associated with CTh in some areas of the frontal and temporal lobes.
Discussion: Our findings are consistent with the hypothesis that greater CTh in specific brain areas could be associated with better response to CRT. Furthermore, brain areas associated with CRT responsiveness were located mainly in regions of frontal and temporal lobes.

1. Introduction

Cognitive remediation therapy (CRT) has emerged as an effective treatment improving cognition and some aspects of daily functioning in patients with diagnosis of schizophrenia (McGurk et al., 2007; Wykes et al., 2011). Despite this evidence for the efficacy of CRT, comparatively little is known about potential predictors of a good treatment response (Kurtz et al., 2009, Wykes and Spaulding, 2011). Whereas there is some empirical support suggesting that some variables are associated with positive outcomes, for instance the use of strategy learning (Paquin et al., 2014), lower patient age or antipsychotic intake at baseline (Vita et al., 2013), only one study has tested neuroimaging data. In that study, Keshavan et al. (2011) tested the Cognitive Enhancement Therapy (CET) in a sample of patients with schizophrenia who were randomly assigned to CET ($n = 29$) or to an active control group with an Enriched Supportive Therapy ($n = 21$). Results suggested that whole brain cortical surface area and gray matter volume significantly moderated the effects of cognitive treatment on social cognition, but not neurocognition.

Cognitive testing and neuroimaging data are among the strongest candidates for being valid predictors of CRT outcome in schizophrenia for many reasons. Both of them are important in terms of functional outcomes. Thus, convincing evidence suggests that cognitive performance is strongly associated with functional outcomes in general (Green et al., 2000; Keefe et al., 2011). Regarding neuroimaging data, although investigation of the neural correlates of functional disability in schizophrenia is not fully understood yet, some studies suggest that gray matter abnormalities may also be predictive of poorer outcomes (Mathalon et al., 2001; Ho et al., 2003).

* Corresponding author at: Clinical Institute of Neurosciences (ICN), Hospital Clinic, C/ Villarroel 170, 08036 Barcelona, Spain.
E-mail address: rpenades@clinic.ub.es (R. Penadés).

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Moreover, cognitive variables have been posited to be good predictors of outcome for psychological treatments in schizophrenia (Kurtz, 2011). Results revealed that attention and memory measured at baseline were linked to progress in social skill training programs. Additionally, attention, memory and problem-solving measures were linked to progress in work therapy and supported employment programs, and comprehensive, integrated programs of psychosocial rehabilitation. More specifically, Medalia and Richardson (2005) showed that baseline cognitive performance, intrinsic motivation and larger clinical experience of the therapists predicted improvement in cognition after the cognitive remediation program. In addition, measures of sustained visual vigilance and immediate verbal memory have been found to be able to predict normalized performance in memory tasks after the cognitive training (Fiszdon et al., 2005). Finally, measures of auditory attention and working memory are able to predict the cognitive performance of the subjects even after a follow-up period of one year (Kurtz et al., 2009).

Furthermore, several studies reported that neuroimaging data could be used to predict treatment response in patients with schizophrenia. Particularly, cortical thickness (CTh) has been proposed as a good predictor of treatment outcomes and in fact it has been shown in different studies that antipsychotic treatment response was associated with larger brain volume (Molina et al., 2003) and greater regional CTh (Szeszko et al., 2012). Significant cortical thinning has been found in chronic samples and even in first episodes (Kuperberg et al., 2003; Nesvåg et al., 2008; Goldman et al., 2009; Venkatasubramanian et al., 2008; Roiz-Santiáñez et al., 2010; Schultz et al., 2010; Cobia et al., 2011; Crespo-Facorro et al., 2011). Additionally, it also has been found that patients with schizophrenia had reduced prefrontal cortical thinning especially in the lateral prefrontal areas (Glahn et al., 2008; Honea et al., 2005) and those reductions could be linked to impaired executive functions (Crespo-Facorro et al., 2011). Furthermore, it has been suggested that CRT responsiveness might be influenced by the integrity of specific brain regions, precisely those that are shown to be involved in complex top-down processing of information during the intervention (Eack et al., 2010). Unfortunately, only one study has tested directly cortical gray matter integrity as a predictor of CRT responsiveness. Nonetheless, it is an outstanding study in which the same group (Keshavan et al., 2011) was able to show a significant positive association between greater cortical gray matter volume and the prediction of a better response to CRT.

In the current study, we tried to determine whether improvement in cognition following CRT in persons with schizophrenia is associated with baseline CTh measures or baseline symptoms level or baseline cognitive performance. We hypothesized that greater improvement in cognition following CRT would be associated with higher CTh at baseline in the frontal lobes. However, given the lack of studies on both cognitive and neuroimaging predictors of CRT, we explored positive associations between CTh and CRT responsiveness across the whole brain. Finally, positive correlation with some baseline cognition but not with symptoms scores is expected.

2. Materials and methods

This study uses data collected as part of a trial investigating a CRT program in a partner study (Penadés et al., 2013). A controlled, randomized study (NCT 01318850) was carried out with three groups: patients receiving cognitive treatment, patients receiving a different psychological intervention as an active control, and a healthy control group (HC). All participants were assessed 2 to 3 days before the first treatment session and also 2 to 3 days after the last treatment session through symptom scales, neuropsychological battery, and magnetic resonance imaging. HC were assessed at the recruitment and after a period of 4 months.

2.1. Participants

The trial recruited 35 participants by the Schizophrenia Unit at the Hospital Clinic and they were randomized to receive either CRT or a control psychological treatment (Social Skills Training; SST) where cognition was not targeted (Fig. 1). The inclusion criteria were 1) age less than 55 years, 2) diagnosis of schizophrenia confirmed following the Structured Clinical Interview for DSM-IV Axis I Disorders, 3) prevalence of negative symptoms confirmed by the Positive and Negative Syndrome Scale, and 4) presence of cognitive impairments confirmed by a battery of neuropsychological tests. Exclusion criteria were 1) Vocabulary test of the Wechsler Adult Intelligence Scale—Third Edition below 4 (scaled score), 2) organic cerebral diseases or primary diagnosis of substance abuse, 3) psychotic exacerbation in the previous 6 months, and 4) plan to change medication during the intervention phase. Additionally, a sample of 15 participants was recruited for the HC group (Table 1).

2.2. Cognitive assessment

Cognitive domain scores were obtained by calculating the mean of the standardized T-scores (Mean: 50; SD: 10) from the respective subtests of each cognitive domain as following: Working Memory (WM): Digit Span, Letter-Number Sequencing and Arithmetic (WAIS-III). Psychomotor Speed (PS): Digit Symbol-Coding (WAIS-III) and Trail Making Test-A (TMT). Verbal Memory (VM): Rey Auditory Verbal Learning Test, and Logical Memory I and II (WMS-III). Nonverbal Memory (NVM): Visual Reproduction I and II and Faces I and II (WMS-III). Executive Function (EF): Wisconsin Card Sorting Test (WCST) Categories and perseverations, Trail Making Test-B (TMT-B), Tower of London (TOL).

2.3. Treatments

CRT was applied according to the Wykes and Reeder (2005) manual receiving 40 sessions: 1-hour sessions two or three times a week over 4 months. It was implemented on an individual basis using mainly the paper-and-pencil tasks from the Spanish translation of the Frontal/Executive program (Delahunty and Morice, 1993) and was used to facilitate the strategy-learning in tasks of progressive complexity adopting an errorless learning approach. Each task was set at the subject's own pace with scaffolding as the main instructional technique. Patients in the treatment control group received 40 h of treatment based on a behaviorally oriented SST. The intervention was adapted from the manualized therapy protocol Symptom Management Module from the University of California—Los Angeles skills training modules (Liberman and Kopelowicz, 1995). UCLA modules have shown positive results in symptom control (Eckman et al., 1995) but they are not expected to have any effects on cognition.

2.4. Cortical thickness analysis

2.4.1. Image Acquisition

Images were acquired on a 3TMRI scanner (Magnetom Trio Tim, Siemens Medical Systems, Germany). A T1-weighted structural image was acquired for each subject with MPRAGE 3D protocol (TR = 2300 msec, TE = 2.98 msec, 240 slices, slice thickness = 1 mm, FOV = 256 mm, matrix size = 256 × 256).

2.4.2. Surface reconstruction and cortical thickness calculation

Anatomical images were visually inspected for motion artifacts and gross structural abnormalities. Cortical thickness (CTh) was estimated from the T1-weighted MRIs using the FreeSurfer software, a set of automated tools for reconstruction of brain cortical surface (Fischl et al., 1999; Fischl and Dale, 2000). Briefly, the T1-weighted images were used to segment cerebral white matter and to estimate the gray–white matter interface. This gray–white matter estimate was used as the starting point of a deformable surface algorithm searching for the pial surface. Local CTh was measured based on the difference between the positions of equivalent vertices in the pial and gray–white matter surfaces. The surface of the gray–white matter border was inflated and