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Volumetric and morphological characteristics of the hippocampus are associated with progression to schizophrenia in patients with first-episode psychosis

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ABSTRACT

Background: Abnormalities in the hippocampus have been implicated in the pathophysiology of psychosis. However, it is still unclear whether certain abnormalities are a pre-existing vulnerability factor, a sign of disease progression or a consequence of environmental factors. We hypothesized that first-episode psychosis patients who progress to schizophrenia after one year of follow up will display greater volumetric and morphological changes from the very beginning of the disorder.
Methods: We studied the hippocampus of 41 patients with a first-episode psychosis and 41 matched healthy controls. MRI was performed at the time of the inclusion in the study. After one year, the whole sample was reevaluated and divided in two groups depending on the diagnoses (schizophrenia vs. non-schizophrenia).
Results: Patients who progressed to schizophrenia showed a significantly smaller left hippocampus volume than control group and no-schizophrenia group ($F = 3.54$; $df = 2, 77$; $P = 0.03$). We also found significant differences in the morphology of the anterior hippocampus (CA1) of patients with first-episode psychosis who developed schizophrenia compared with patients who did not.
Conclusions: These results are consistent with the assumption of hyperfunctioning dopaminergic cortico-subcortical circuits in schizophrenia, which might be related with an alteration of subcortical structures, such as the hippocampus, along the course of the disease. According with these results, hippocampus abnormalities may serve as a prognostic marker of clinical outcome in patients with a first-episode psychosis.

1. Introduction

Anatomical abnormalities in the hippocampus have been widely reported in schizophrenia. Reduced volume of the hippocampus has been observed in schizophrenia, being up to 7% smaller than in healthy controls (HC) [1–3]. Volumetric decreases have also been described in patients with a first-episode psychosis (FEP) [4] and in high-risk samples [5]; therefore, such differences in the hippocampus would not be explained by antipsychotic treatment or chronic illness, suggesting that smaller hippocampus could be a characteristic of the pathophysiology of psychosis. However, these results are contradictory with other studies in patients at ultra-high risk of psychosis (UHR) that have described larger bilateral hippocampi in the subgroup who developed psychosis [6] or similar size when compared to HCs [7], putting forward that structural changes of the hippocampus may occur during or after the onset of psychotic symptoms.

Surface deformation analysis can contribute to clarify these controversies by providing biological relevant information about the hippocampal neurodevelopment and the neurobiology of

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schizophrenia. It has been proposed that mechanical tension along axons, dendrites and glia during neurodevelopmental processes and neuronal connectivity may lead to shape variations of brain structures [8,9]. Shape analysis may permit the study of isolated abnormalities within a given structure, such as the hippocampus, which consists of different subfields: Cornus Ammonis (CA 1, 2, 3, 4), dentate gyrus (DG), presubiculum and subiculum that have, in turn, well-known attributable functions [10,11]. In this line, some shape deformations in limbic structures, including the hippocampus have been reported in multiplex-multigenerational families with schizophrenia [12]. Shape analyses have reported deformities in left anterior hippocampal region in patients with schizophrenia [13–15] and in anterior and midbody regions in first-episode schizophrenia patients [16]. Deformities in posterior region and in the anterior and posterior regions have also been described in schizophrenia [17,18].

It is still unclear whether certain abnormalities are a pre-existing vulnerability factor or a sign of disease progression. Although, these questions can be better addressed by investigating subjects at the initial stages of psychosis with a presumably lower impact of treatment, a limitation of the existing studies on UHR or FEP samples is that they are focused on heterogeneous groups of patients that can develop different mental disorders such as bipolar disorder or schizophrenia. Existing studies that include a follow-up period have related volume abnormalities with clinical outcome, without distinguishing among diagnoses. Among them, the study by Mamah et al. [19] focused on antipsychotic effects in hippocampus shape changes after 104 weeks of follow-up and reported larger surface deformation over time in patients treated with haloperidol compared with olanzapine without identifying differences in specific hippocampal regions. Another work [20] found increased metabolism in CA1 subregions in absence of structural differences in pre-psychotic stages, but with a reduction of hippocampal volume when patients progressed to a psychotic syndrome. Dean et al. [21] found greater shape inversion in the left ventral posterior hippocampus at baseline in UHR who, 12 months after, displayed more positive and negative symptoms, and greater impairment of tolerance to normal stress. Lastly, Scanlon et al. [22] failed to find significant structural abnormalities in patients' hippocampus compared to HCs after 3 years of follow-up.

The aim of this study is to describe volumetric and morphological alterations in the hippocampus in a sample of patients with FEP and to investigate whether these changes may be associated with progression to schizophrenia after one year of follow-up. We hypothesize that patients who progress to schizophrenia will display greater volumetric and morphological changes from the very beginning of the disorder. Therefore, detection of such abnormalities might help to identify therapeutic targets for the first stages of the illness and to prevent chronic courses.

2. Material and methods

2.1. Participants

We included a total of 41 right-handed patients in their first hospitalization at the acute in-patients ward of the hospital with a diagnosis of FEP. Eligible patients were aged 18 to 35 years with presence of positive and negative psychotic symptoms for less than six months. Patients with neurological disease or head trauma were excluded. The Structured Clinical Interview for Diagnosing DSM-IV Disorders (SCID-I) [23] was administered to confirm diagnosis. At the time of hospitalization, we assessed the psychopathological state with the Positive and Negative Syndrome Scale (PANSS) [24]. All patients were scanned on 3T MRI during the first month of hospitalization. Patients could have started medication with atypical antipsychotics at the time of scanning. We included a group of 41 right-handed HCs from the local community (including students of the surrounding area as well as non-affected friends of the patients) comparable in terms of age, gender and educational level who also underwent a 3T MRI and were screened with the SCID-I to rule out current or past psychiatric illness. After twelve months, the whole sample of patients was re-assessed to ascertain the diagnosis by two clinical experts using SCID-I. Twenty-three patients out of the 41 FEP patients fulfilled the DSM IV-TR criteria for schizophrenia (FEP-SCH), while 18 patients did not (FEP-NoSCH). Among these latter patients, 7 were diagnosed as schizophreniform disorder, 4 patients as brief psychotic disorder, 4 as psychosis not otherwise specified, 2 patients as schizoaffective disorder and 1 patient was fully remitted. The Local Ethics Committee approved the study, which was performed in accordance with the ethical standards of the Declaration of Helsinki (amendment of 2008), and written informed consent was obtained from all participants.

2.2. Image acquisition and processing and data analyses

Participants were scanned on a 3T Philips Achieva Scanner. T1-weighted images were acquired in an axial orientation (TR/TE = 13/7.4 ms, flip angle = 8°, field of view [FOV] 23 cm) with in-plane resolution of 256 × 256 and 1-mm slice thickness. Whole brain volumes were acquired with 40 contiguous 3.5-mm thick transverse slices. The images were processed with the FMRIB Software Library (FSL) 4.1 image analysis. Total intracranial volume and left and right hippocampi were segmented using the FreeSurfer 5.3.0. The shape analysis of the hippocampus was made using the FIRST v5.0 tool [25]. The manual segmentations were parameterized and described as surface meshes from which a point distribution was modelled. FSL-FIRST provided the most probable shape by searching through linear combinations of shape variation modes. Hippocampus meshes were then converted to labelled voxel region of interests (ROI) after a boundary correction using FAST voxel-wise segmentation software. The statistical analysis was made using 'randomize tool', with a cluster-based multiple-comparison-correction, using the null distribution of the maximum cluster size (across the image). The volumetric analysis was calculated using the 'fslstat' tools. Statistical differences were calculated between the FEP and HC groups, and between the HC, FEP-NoSCH and FEP-SCH subgroups by means of ANCOVAs, including TIV as a covariate. Partial correlations (corrected for TIV) of hippocampal volumes with illness severity (measured with PANSS subscales) and with medication (chlorpromazine equivalents) were performed. Statistical significance was set at $P < 0.05$, and all analyses were performed using R language.

3. Results

3.1. Demographic and clinical data

No significant differences between FEP and HC were detected in demographic characteristics (Table 1). At the time of scanning,

Table 1
Demographic data for first-episode of psychosis (FEP) and healthy controls.

Variable	FEP ($n = 41$)	Controls ($n = 41$)	Statistic	P value
Age	26.01 ± 5.49	27.29 ± 5.04	$t = -1.027$	0.15
Gender (M: F)	22: 19	25: 16	$\chi^2 = 0.199$	0.66
Education n (%)[a]			F[b]	0.11
Primary	1 (2.4%)	1 (2.4%)		
Secondary	15 (36.6%)	7 (17.07%)		
Graduate	25 (60.9%)	33 (80.48%)		

Numbers represent mean ± standard deviation; M: male, F: female.
[a] Level of education completed.
[b] Fisher's exact test not provided by the statistical software.