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Association between duration of untreated psychosis and brain morphology in schizophrenia within the Northern Finland 1966 Birth Cohort ☆

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ABSTRACT

Background: Duration of untreated psychosis (DUP) has been linked with poor prognosis and changes in the brain structure in schizophrenia at least at the beginning of the disease, but it is still unknown whether DUP relates to brain morphometry in the longer term. Our aim was to analyze the relation between DUP and the brain structure in schizophrenia in the general population, after several years of illness.
Methods: Brains of subjects with psychosis from the Northern Finland 1966 Birth Cohort (NFBC 1966) were scanned with MRI during 1999–2001 after an 11-year follow-up. DUP was assessed from medical records and regressed against global and local tissue density measurements. The brain morphometric and the DUP information were available for 46 subjects with DSM-III-R schizophrenia.
Results: The DUP did not correlate with volumes of the total gray or white matter or the cerebrospinal fluid. The length of DUP associated positively with reduced densities of the right limbic area and the right hippocampus.
Conclusions: Long DUP was slightly associated with reductions of gray matter densities in the limbic area and especially the hippocampus after several years follow-up, supporting the hypothesis that, compared to short DUP, long DUP might be a marker of different disease trajectories including subtle morphometric changes.

1. Introduction

Since the 1980s there has been growing interest into the duration of untreated illness in schizophrenia. In the early 1990s the definition of duration of untreated psychosis (DUP) was presented (Loebel et al., 1992) accompanied by the first speculations on the possible toxicity, neuronal damage and associated poor prognosis of long DUP (Wyatt, 1991; Olney and Farber, 1995).

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Two reviews (Norman and Malla, 2001; Marshall et al., 2005) and one meta-analysis (Perkins et al., 2005) exist on the association between DUP and the outcome of schizophrenia. They suggest that longer DUP is associated with poorer clinical and social outcome, at least in the first years of illness. DUP might be one of the few modifiable prognostic factors in schizophrenia (Perkins et al., 2005; Melle et al., 2004).

One possible explanation for the association between DUP and poor outcome could be that long DUP might cause toxic structural changes in the brain. This hypothesis has previously been studied with conflicting results, and the association between DUP and the brain structure remains unclear (Perkins et al., 2005). Hoff et al. (2000) did not find any significant relations between DUP and the total volumes of the lateral ventricles, temporal lobe and cortex in a first-episode sample. Another first-episode study (Ho et al., 2003) found no correlation between the length of DUP and volumes in the following areas: total brain tissue, gray and white matter, cerebrospinal fluid (CSF) and measures of brain surface anatomy. In the same sample, there was no significant correlation between the DUP and the neurocognitive functioning. Ho et al. (2005) found no significant association between the DUP and the hippocampal volume.

In other studies of patients with first-episode psychosis, longer DUP was associated with gray matter decrements in the left temporal and occipital cortices (Lappin et al., 2006), and with smaller caudate volume (Crespo-Facorro et al., 2007a). Takahashi et al. (2007) found the volumes of the gray matter in the left planum temporale to be smaller when the DUP was longer. However, negative findings in these studies included total white matter, gray matter and CSF volumes, and other regions of the brain including each subregion of the prefrontal cortex and thalamus (Crespo-Facorro et al., 2007b).

To sum up, it is still unclear whether and how DUP relates to the brain morphometry in schizophrenia. Most earlier studies suffer from methodological flaws, such as lack of unbiased population-based samples. In addition, many previous studies have concerned first-episode psychosis in relatively early phases of illness.

The aim of the current study was to investigate the association between DUP and the brain morphology in schizophrenia in a general population birth cohort sample after an average of 11 years after illness onset. We hypothesized that longer DUP would be related to a greater brain morphological abnormality.

2. Methods

2.1. Sample

The Northern Finland 1966 Birth Cohort (NFBC 1966) is an unselected, general population birth cohort ascertained during mid-pregnancy. It is based on 12,068 women in the area of Oulu and Lapland, and their 12,058 born children. The expected births took place during the year 1966 and they presented 96% of all births (Rantakallio, 1969). The present study is based on 11,017 individuals living in Finland at the age of 16 years. Of these, 83 have denied the use of their data, resulting in 10,934 subjects. Permission to gather data was obtained from the Ministry of Social and Health Affairs, and the study design is under review of the Ethical Committee of the Northern Ostrobothnia Hospital District. A written informed consent was obtained from all the participants.

All 146 living members of the NFBC 1966 who had developed schizophrenia or other psychosis (Isohanni et al., 1997; Moilanen et al., 2003) were invited in 1999–2001 at about the age of 33–35 years to the University Hospital of Oulu for a field survey. Of the 146 subjects invited, 91 participated in the survey including MRI scans of the brain and diagnostic psychiatric interviews (SCID, Structural Clinical Interview for DSM-III-R, Spitzer et al., 1989). The subjects were rated according to PANSS (Positive and Negative Syndrome Scale), CGI (Clinical Global Impressions) and SOFAS (Social and Occupational Functioning Assessment Scale) based on the SCID I-interview in 1999–2001 as presented in Table 1b. PANSS was used to measure symptoms from the period of 1 week before the MRI scan. Separate interviews for PANSS were not used. CGI was used to rate the severity of illness. SOFAS was used to rate the social and occupational functioning. Altogether 61 subjects with schizophrenia were detected and scanned (the other 30 subjects in the field survey were diagnosed with other psychoses), as is described in detail by Haapea et al. (2007) and Tanskanen et al. (2005, 2009a,b). Of these subjects, 54 had a successful MRI of the brain.

2.2. Image acquisition and analysis

Structural MRI data were acquired from all participants by using a GE Signa system (General Electric, Milwaukee, WI) operating at 1.5 Tesla. Dual echo fast spin echo (T2- and proton density-weighted) images of the whole brain were acquired in the coronal plane with slice thickness = 3 mm, repetition time = 4000 ms, and echo time = 24 and 96 ms. MRI data were quality controlled by radiological screening, and the data reported here exclude three scans with poor quality due to subject movement and two scans that showed gross structural lesions (hydrocephalus) (Tanskanen et al., 2009a).

MRI data were segmented and probabilistic maps of gray matter, white matter and CSF were created for each subject using BAMM software (Brammer et al., 1997; Suckling et al., 1999a; Suckling et al., 1999b). Gray matter maps were resliced in the axial orientation and co-registered with the MNI single subject high-resolution T1-weighted image (Montreal Neurological Institute; http://www.bic.mni.mcgill.ca) using an affine transformation implemented in FSL software (Jenkinson and Smith, 2001). The AAL (Automated Anatomical Labeling) regionally parcellated template image (Schmahmann et al., 1999; Tzourio-Mazoyer et al., 2002), also in the space of the MNI T1 image, was then used to estimate regional mean gray matter densities in each of the 116 cortical and subcortical structures for each subject.

To avoid problems posed by multiple testing we did not examine all of these 116 areas Rather, we adopted a two-stage strategy, in which these 116 areas were combined into 17 larger regions (Tzourio-Mazoyer et al., 2002) for the first stage. The larger regions were formed as follows: each hemisphere of cerebral gray matter was divided into eight regions in the right and left hemispheres: pre/post-central,