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Long-term antipsychotic and benzodiazepine use and brain volume changes in schizophrenia: The Northern Finland Birth Cohort 1966 study

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ABSTRACT

High doses of antipsychotics have been associated with loss in cortical and total gray matter in schizophrenia. However, previous imaging studies have not taken benzodiazepine use into account, in spite of evidence suggesting adverse effects such as cognitive impairment and increased mortality. In this Northern Finland Birth Cohort 1966 study, 69 controls and 38 individuals with schizophrenia underwent brain MRI at the ages of 34 and 43 years. At baseline, the average illness duration was over 10 years. Brain structures were delineated using an automated volumetry system, volBrain, and medication data on cumulative antipsychotic and benzodiazepine doses were collected using medical records and interviews. We used linear regression with intracranial volume and sex as covariates; illness severity was also taken into account. Though both medication doses associated to volumetric changes in subcortical structures, after adjusting for each other and the average PANSS total score, higher scan-interval antipsychotic dose associated only to volume increase in lateral ventricles and higher benzodiazepine dose associated with volume decrease in the caudate nucleus. To our knowledge, there are no previous studies reporting associations between benzodiazepine dose and brain structural changes. Further studies should focus on how these observations correspond to cognition and functioning.

1. Introduction

Progressive changes in the brain structures of individuals with schizophrenia compared to healthy controls have been reported especially in frontal and temporal lobes, anterior cingulate, hippocampus, amygdala, thalamus and insula (Shepherd et al., 2012; Torres et al., 2013). The possible effects of antipsychotics on brain structure and functioning have been of intensive study in recent years (Andreasen et al., 2013; Ho et al., 2011; Radua et al., 2012), and a meta-review concluded that previous comparisons between healthy controls and people with schizophrenia may be, at least partly, confounded by the effects of medication (Shepherd et al., 2012). However, in spite of several reviews and meta-analyses (Fusar-Poli et al., 2013; Roiz-Santiáñez et al., 2015; Vita et al., 2015) on the association between antipsychotics and brain volume changes, the results are inconclusive with a need for further studies.

Many imaging studies in schizophrenia are conducted in the early phase of the illness, mostly during the first episode, when the possible

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long-term effects of medications may not yet be noticeable. However, studies in rodents suggest that the effects of antipsychotics on the brain are evident also at later stages of the treatment (Terry et al., 2008, 2007a, 2007b; Terry and Mahadik, 2007). Some studies focus on patients drawn from clinics serving chronic patients, where the patients might be on average sicker and therefore not representative of the great variety of different stages of illness found in entire population suffering from the disease. Clinical trials with strictly defined medication doses over years of follow-up are hard to conduct, and few include imaging measures in their protocol. Therefore the data from naturalistic settings are crucial when examining potential long-term effects and adverse effects of antipsychotic treatment (Wang et al., 2011).

Pharmacological treatment of schizophrenia is not limited to antipsychotic medication. Benzodiazepines are commonly used in schizophrenia as sedatives or anxiolytics and to reduce aggressiveness and ease agitation. In schizophrenia, benzodiazepine use has been associated with increased risk of mortality even after controlling for potential confounders (Fontanella et al., 2016) and, in general, benzodiazepine use has been associated with not only increased mortality (Tiihonen et al., 2016) but also cognitive impairment (Baandrup et al., 2017; Barker et al., 2005, 2004a, 2004b). Although the mechanism of these effects is unknown, adverse effects on brain health such as accelerated ageing (Koutsouleris et al., 2014; Schnack et al., 2016), or individually varying decreases in brain volume (Schnack et al., 2016), are possible candidate mechanisms that merit investigation. In the general population, approximately 3% use benzodiazepines over 6 months, which is defined as long-term treatment (Kurko et al., 2015). Recently chronic benzodiazepine use has been associated with decrease in brain plasticity in mice (Curto et al., 2016), but there are no modern structural imaging studies on benzodiazepine effects on the human brain. Previous studies have used computed tomography (CT) to study the effect of benzodiazepine use mainly on ventricular enlargement (Busto et al., 2000; Lader et al., 1984; Moodley et al., 1993; Perera et al., 1987; Schmauss and Krieg, 1987; Uhde and Kellner, 1987), but to our knowledge there are no previous MRI studies on benzodiazepine effects on brain structures in schizophrenia (or other conditions).

Because antipsychotic medication is the key treatment in schizophrenia and other psychoses, it is highly important to take possible confounding factors into account when studying potentially harmful effects of antipsychotic medications. Important confounding factors are for example illness duration and severity, age, sex, and other long-term medications. Nevertheless, only a few previous studies on long-term follow-ups have taken into account illness severity measures when analyzing antipsychotic effects on brain structures (Huhtaniska et al., 2017).

In this study our aim was to analyze, in a population-based sample of schizophrenia cases with illness duration on average of 10 years at baseline, whether a nine-year scan-interval antipsychotic or benzodiazepine dose would have an effect on brain structural changes. This is the first longitudinal MRI study that we are aware of to investigate the effects of benzodiazepines on brain structure in schizophrenia and to examine the effects of antipsychotic medication on brain structure in schizophrenia whilst controlling for benzodiazepine use.

2. Methods

2.1. Study sample

This study is based on an unselected, general population birth cohort called The Northern Finland Birth Cohort 1966 (NFBC1966). The Ethical Committee of the Northern Ostrobothnia Hospital District has approved the NFBC1966 project and keeps its study design under continuous review. The sample collection is described in more detail in our previous publications using a partly overlapping sample (Guo et al., 2015; Veijola et al., 2014) and in the Supplementary Methods.

Forty-five individuals with schizophrenia spectrum disorder and 77 non-psychotic controls participated in both baseline and follow-up studies when the participants were approximately 34 and 43 years old. At baseline the diagnoses were validated (Isohanni et al., 1997; Moilanen et al., 2003) using the Structured Clinical Interview for DSM-III-R (SCID-I; Spitzer et al., 1989) criteria and anamnestic information including individual hospital medical records. The original diagnoses were confirmed at the follow-up using Structured Diagnostic Interview for DSM-IV (First et al., 2002) and information from medical records. SCID-I was also completed for controls at both time points.

For seven participants with schizophrenia spectrum disorder and seven controls MRI data were incomplete (scans missing or too poor quality at either time-point). One of the controls had a psychotic episode during the follow-up period according to the Care Register for Health Care (CRHC) and was not included in the final study group. Therefore, the final schizophrenia spectrum group included 38 participants and the control group 69 participants. The specific diagnoses for the schizophrenia spectrum group were schizophrenia ($n = 33$), schizophreniform disorder ($n = 1$), schizoaffective disorder ($n = 3$) and delusional disorder ($n = 1$). Hereafter the term schizophrenia is used to refer to schizophrenia and other schizophrenia spectrum disorders. The sample collection is described in more detail in Supplement Fig. 1 and in Supplementary Methods.

In schizophrenia group the participants did not differ statistically significantly from the non-participants and are representative of the entire schizophrenia population in NFBC1966 regarding age, sex and educational level. In the control group, the participants' level of education was higher than of the non-participants (Veijola et al., 2014).

2.2. Data on medication

Lifetime psychiatric medication use was collected using all available medical records (hospital and out-patient care case notes), an interview conducted at both baseline and follow-up, and the register of the Finnish Social Insurance Institution on psychoactive medications consumed during 1997 (Husa et al., 2014; Veijola et al., 2014). The medical records were acquired on the basis of information concerning the subjects' treatment facilities, which we received from the CRHC. If the subject had no information in the CRHC, we requested medical records from the outpatient facilities of the subjects' area of residence. Participants in this study had given their permission to collect medical records by signing the written informed consent. We had permission for collecting the data from the Ministry of Social Affairs and Health.

All medical records were reviewed to record the name of the drug, dose and time period the medication had been used. Drugs were categorized by using the Anatomical Therapeutic Chemical (ATC) classification system (WHO, 2010). Antipsychotics included classes N05A (antipsychotics) and Pertriptyl (N06CA01 combination medicine including perphenazine). Benzodiazepines included ATC classes N05BA (anxiolytics, benzodiazepine derivatives), N05CD (hypnotics and sedatives, benzodiazepine derivatives), and N05CF (hypnotics and sedatives, benzodiazepine-related drugs). For antipsychotic medication, the information was used to calculate the cumulative doses of lifetime and interscan interval antipsychotic doses expressed as dose-years of a daily dose of 100 mg chlorpromazine (CPZy) using several sources, see Moilanen et al. (2015) for details. For benzodiazepines, the information was used to calculate the defined daily doses (DDD) (Nykänen et al., 2016; Rissanen et al., 2015) and these were then expressed as benzodiazepine dose-years (BZDy). One BZDy is equivalent to the amount of benzodiazepine medication, which a person would use if the daily dose was 1 DDD and the duration of treatment would be one year. All the used medications are listed in Supplement Table 1.

2.3. Covariates and background variables

Onset age of the illness was ascertained from medical records and it was defined as the age of first evident psychotic symptoms. Clinical