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Additional Information

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. Though benzodiazepines are also commonly used in schizophrenia, previous imaging studies have not taken this into account. In this study we examined the association between cumulative antipsychotic and benzodiazepine dose and brain volume change in schizophrenia cases with average illness duration over 10 years at baseline. 38 individuals with schizophrenia and 69 controls from the Northern Finland Birth Cohort 1966 went through brain MRI at the ages of 34 and 43 years (nine-year follow-up). Brain structures were delineated from MRIs using an automated volumetry system volBrain. Data on medication use was collected using medical records and interviews. The data were analyzed using linear regression model with intracranial volume and sex as covariates. Additionally, illness severity was also taken into account. Both antipsychotic and benzodiazepine dose during the scan interval associated statistically significantly to volumetric changes in subcortical structures. However, after adjusting for each other and the average PANSS total score, higher scan-interval antipsychotic dose associated only to volume increase in lateral ventricles ($b=0.502$, $p=0.028$) and higher benzodiazepine dose associated with volume decrease in the caudate nucleus ($b=-0.422$, $p=0.029$). To our knowledge, this is the first study to report associations between benzodiazepine dose and brain structural changes in schizophrenia. Further studies should focus on how these structural alterations correspond to cognition, functioning and other outcomes.

Key words: schizophrenia, antipsychotics, benzodiazepines, brain, MRI

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 interest during the last 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.

The results from studies with 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). However, many imaging studies in schizophrenia are made in the early phase of the illness, mostly during the first episode, when the possible long-term effects of medications may not yet be noticeable. 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 is 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 (Barker et al., 2005, 2004a, 2004b). Although the mechanism of these effects is unknown, adverse effects on brain health such as accelerated ageing, or decreases in brain volume, 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 (Bust et al., 2000; Lader et al., 1984; Moodley et al., 1993; Perera et al., 1987; Schmauss and Krieg 1987; Uhde and Keller 1987), but to our knowledge there are no previous MRI studies on benzodiazepine effects on brain structures in schizophrenia (or other conditions).

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. Experimental procedures

Study sample

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

45 individuals with schizophrenia spectrum disorder and 77 controls participated in both studies when the participants were approximately 34 and 43 years old. At baseline the diagnoses were validated using Diagnostic and Statistical Manual of Mental Disorders Third Edition Revised (DSM-III-R) criteria (Isohanni et al., 1997; Moilanen et al., 2003) and confirmed at the follow-up using Structured Diagnostic Interview for DSM-III-R (SCID) (Spitzer et al.) and anamnestic information including individual hospital medical records. SCID was done also for controls. The specific diagnoses for the schizophrenia spectrum group were schizophrenia (N=40), 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.

For seven participants with schizophrenia and seven controls MRI data were incomplete (scans missing or too poor quality at either time-point). One of the controls had 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 group included 38 participants and the control group 69 participants. The sample collection is described in more detail in Supplement Figure 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 NFBC 1966 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).

Data on medication

Life-time psychiatric medication use was collected using all available medical records (hospital and out-patient care case notes), an interview conducted during the field study at both time points, 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 Peritriptyl (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), these were then expressed as dose-years. One DDD dose year (DDy) is equivalent to the amount of medication, which a person would use if the daily dose was 1 DDD and the duration of treatment would be one year.

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 symptoms in participants with schizophrenia at baseline and follow-up were examined using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). In the baseline study, the PANSS was measured based on the SCID I -interview and general psychiatric interview, while in the follow-up study PANSS was defined using a specific PANSS interview. The number of hospital days during the follow-up was collected from the CRHC. Remission was assessed using the Andreasen symptomatic criteria (Andreasen et al., 2005), but the symptoms were only required not to be present at the time of the assessment, and no duration criteria was used since PANSS was done only once at baseline and follow-up.

MRI methods

The participants were scanned with the same 1.5 T GE Signa scanner (General Electric, Milwaukee, Wisconsin) at both baseline and follow-up at the Oulu University Hospital. At baseline T1-weighted high-resolution three dimensional spoiled gradient echo (3D SPGR) images were acquired in the coronal plane covering the whole brain (slice thickness 1.5 mm; in-plane resolution matrix size 256x256; voxel size 1.5 mm x 1 mm x 1 mm; repetition time 35 ms; echo time 5 ms; flip angle = 35). Prior to the follow-up imaging the scanner was up-graded into HDxt with a new gradient system and parallel image data acquisition

with an 8 channel receiving coil. At follow-up, the T1 weighted images were acquired with a 3D fast spoiled gradient echo (FSPGR) sequence (slice thickness = 1 mm; in-plane resolution matrix size 256x256; voxel size 1 mm³; repetition time 12.576 ms; echo time 5.3 ms; flip angle =20).

MRI data processing

To extract the brain tissue volumes from the MRI images we used an online automated MRI brain volumetry system volBrain (<http://volbrain.upv.es/>) (Manjón and Coupe 2016). VolBrain segments the MRI into 15 different brain tissue classes or structures (white matter (WM), gray matter (GM), cerebrospinal fluid (CSF), brain (WM+GM), intracranial cavity, cerebrum, cerebellum, brainstem, lateral ventricles, caudate, putamen, thalamus, globus pallidus, hippocampus, amygdala, accumbens) separated in right and left if applicable. Details on the image processing pipeline are provided in Supplementary Methods. In this study we focused mainly on subcortical structures.

Since there are many concerns regarding the methodology and replicability of measures in longitudinal MRI studies, and as we had a scanner update during the follow-up, we also performed a calibration scan inviting 15 controls to be scanned with both used protocols during the same day to assess the possible effect of the scanner update on our measurements. With the help of these calibration-scans, we measured the inter-scan reliability rates for each extracted brain structure volume and excluded the structures with single measures intraclass correlation poorer than 0.90. For more information on the calibration scan and reliability measures, see Supplementary Methods and Supplement Table 1.

We calculated the annual change of each studied brain region using the total change during the follow-up and the length of follow-up for each individual.

Statistical analyses

The brain structural MRI changes were examined in 10 different measures based on the interest in subcortical structures and our inter-scan reliability measures. These areas were: total brain, total gray matter (GM), cerebrum, cerebral GM, lateral ventricles, caudate nucleus, putamen, thalamus, hippocampus, and nucleus accumbens. We analyzed differences between subjects with schizophrenia and non-psychotic controls and associations between medication doses and brain areas in the schizophrenia group. We used sex and intracranial volume (ICV) at baseline as covariates in all analyses.

We analyzed the association between our two medication variables (cumulative antipsychotic dose in dose years during the scan interval and cumulative benzodiazepine dose in dose years during the scan interval) and structural MRI changes using a linear regression analysis. All analyses were adjusted for sex and baseline ICV. We ran correlations between different covariates and medication variables, and between covariates and brain structural changes to choose potential confounding factors for the analyses. These confounding factors were onset age, average PANSS score between the two time points, and cumulative number of hospital days during the follow-up. In addition, we added benzodiazepine use as a covariate in antipsychotic effect analyses and vice versa.

We applied a logarithmic transformation to medication data and the number of hospital days during the follow-up and used them as continuous variables in analyses.

The analyses were performed using IBM SPSS Statistics version 23 using $p < 0.05$ as a limit for statistical significance.

3. Results

Characteristics of the Sample

The characteristics of the schizophrenia and control samples are described in Table 1. The clinical characteristics of the schizophrenia group are described in Table 2. In schizophrenia group the number of males was 21 (54%), age at baseline was on average 33.7 years and the length of follow-up was 9.1 years. At baseline 13 (34 %) subjects were in remission and at follow-up 12 (32 %). Fourteen (37%) subjects were on disability pension at baseline and the average PANSS score between the two time points was 61.4 (SD 20.7).

Schizophrenia cases showed statistically significant decrease in the volumes of total brain ($t=-2.27$, $p=0.025$), cerebrum ($t=-0.38$, $p=0.019$), caudate nucleus ($t=-4.05$, $p<0.0001$), thalamus ($t=-0.14$, $p=0.035$) and hippocampus ($t=-0.023$, $p=0.028$) when compared to controls. All results on case control differences are presented in Supplement Table 2 and the average volume change in cases and controls is presented in Supplement Table 3.

Medication use characteristics

Medication use characteristics of the schizophrenia group are described in Table 3. Before baseline 37 (97%) schizophrenia subjects had been medicated with antipsychotics. All of them had used typical antipsychotics and 20 (53%) had used atypical antipsychotics. The mean cumulative dose of antipsychotics by baseline was 27.6 (SD 34.9) CPZy.

During the follow-up 34 (90%) subjects used antipsychotics. Five subjects (13%) used only typical antipsychotics and six subjects (15%) used only atypical antipsychotics. Twenty-three (61%) subjects used both typical and atypical antipsychotics during the follow-up. The mean dose of antipsychotics during the follow-up for all medicated subjects was 28.5 (SD 24.8) CPZy, for subjects using only typical antipsychotics 7.7 (SD 9.3) CPZy, and for subjects using only atypical antipsychotics 19.0 (SD 18.7) CPZy.

Before baseline 36 (95%) subjects had used benzodiazepines. Five (14%) subjects had used benzodiazepines only irregularly (prescribed to be taken only when needed). The mean cumulative dose of benzodiazepines by baseline was 3.6 DDDy (SD 4.3 DDDy). During the follow-up 30 (79%) subjects used benzodiazepines. Ten (33 %) subjects used benzodiazepines only irregularly during the follow-up. The mean dose during the follow-up was 6.7 DDDy (SD 8.2 DDDy).

Association between cumulative antipsychotic dose during the follow-up and brain changes

Higher scan interval antipsychotic dose associated with increased lateral ventricle volumes ($b=0.46$, $p=0.012$) and decrease in volumes of total GM ($b=-0.38$, $p=0.012$), cerebral GM ($b=-0.39$, $p=0.012$), thalamus ($b=-0.34$, $p=0.030$), hippocampus ($b=-0.34$, $p=0.040$) and nucleus accumbens ($b=-0.38$, $p=0.018$). After adjusting antipsychotic effects with benzodiazepine use and PANSS average score, only the finding regarding lateral ventricles remained statistically significant ($b=0.50$, $p=0.028$). Even when hospital days during the follow-up was added to the model, the association still remained ($b=0.487$, $p=0.035$).

On the areas where PANSS average score during the follow-up was statistically significantly associated with brain structure volume changes (total GM, cerebral GM and nucleus accumbens), the size of the effect was roughly the same as the association of antipsychotic dose on those brain areas. The effect of onset age was also roughly the same as the effect of antipsychotic dose on the same areas. All results regarding all covariates and brain volumes are presented in Table 4. Tables 5.1 and 5.2 present the results of antipsychotic and benzodiazepine dose effects in adjusted analyses.

Association between cumulative benzodiazepine dose during the follow-up and brain changes

Higher scan interval benzodiazepine dose associated with increase in lateral ventricles ($b=0.35$, $p=0.037$) and decrease in total brain ($b=-0.35$, $p=0.037$), cerebrum ($b=-0.32$, $p=0.048$), caudate nucleus ($b=-0.49$, $p=0.002$), thalamus ($b=-0.36$, $p=0.033$) and nucleus accumbens ($b=-0.40$, $p=0.018$). After adjusting for antipsychotic dose and PANSS average score only the finding regarding caudate nucleus remained ($b=-0.42$, $p=0.029$).

4. Discussion

Main results

In this study, schizophrenia cases showed more increase in lateral ventricles over time than non-psychotic controls and more decrease in the volumes of total brain, caudate nucleus and hippocampus. In subjects with schizophrenia, antipsychotic medication dose during the follow-up related to increase in lateral ventricles when taking into account illness severity measures and benzodiazepine dose. Benzodiazepine use associated with caudate volume reduction after adjusting for average PANSS score and antipsychotic dose.

Antipsychotic use and brain volume change

In the NFBC 1966 we have found that in schizophrenia, higher amount of antipsychotic medication over the 9-year follow-up predicted larger total brain volume loss (Veijola et al., 2014). Consistent with those results, here, using a different image analysis method, we noted associations between antipsychotic medication exposure and decrease in total grey matter (with a marginal effects on total brain volume). These effects were attenuated when we controlled for potential confounding factors including benzodiazepine use, which we and others did not control for in previous studies. However, the association we observed

here between antipsychotic medication exposure and lateral ventricular change was robust to controlling for illness severity and benzodiazepine use. In our previous studies in this sample using the FSL tool SIENA to examine movement over time (atrophy) at the brain edge, we noted an association between antipsychotic medication use and lateral ventricular volume increase (Vejola et al., 2014), and with periventricular brain volume reductions at the fourth ventricular edge (Guo et al., 2015). When viewing these studies using different methods together, it appears in our sample that there is a consistent association between antipsychotic medication exposure and ventricular volume change. However, we recognize that not all other studies have noted similar effects (Ho et al., 2011; Saijo et al., 2001; Puri et al., 2001).

We have also studied cognition in this sample in relation to medication. Higher dose-years of antipsychotics associated with decline in verbal learning and memory between ages 34 and 43 years (Husa et al., 2014), and high lifetime dose and antipsychotic polypharmacy associated also with poorer outcomes in schizophrenia at the age of 43 years (Moilanen et al., 2015). These results are consistent with the possibility that long-term antipsychotic medication has some adverse effects on the brain, although it remains possible that residual confounding may be responsible for these associations. For example, although we adjust for illness severity in our sample, there is no gold standard way to measure illness severity. Patients with the most severe illness may be the ones who are prescribed the most medication by doctors attempting to regain symptom control, but it may be that a more severe disease process results, through unknown mechanisms unrelated to medication, in the most cognitive decline and the most progressive brain atrophy.

The potential antipsychotic effect on brain structures in schizophrenia was suggested already in the 1970's by Marsden (Marsden, 1976) in response to the report on lateral ventricle increase in schizophrenia by Johnstone et al. (1976). Since then the issue has

raised again on the 2000's as second-generation antipsychotics have been studied excessively and been compared with traditional first-generation antipsychotics (e.g. Crespo-Facorro et al., 2008; Lieberman et al., 2005; Mamah et al., 2012; Roiz-Santiáñez et al., 2012). Animal studies have examined different antipsychotic agents and treatments, and the results suggest that antipsychotics may have effects on brain structures even when illness related confounding factors present in human studies are excluded (Dorph-Petersen et al., 2005; Vernon et al., 2014, 2011).

The possible mechanism behind antipsychotic-related structural brain changes is not clear. In striatal areas antipsychotics may increase striatal metabolism as a consequence of neurons trying to overcome antipsychotic induced D2 blockade and therefore lead to increased volumes (Buchsbaum et al., 1992). In literature this has been associated especially to typical antipsychotic use, whereas some studies have found atypical antipsychotics to even reverse the effect after switching (Lang et al., 2004; Scheepers et al., 2001). However, a systematic review on antipsychotic monotherapy effects in basal ganglia reported that no studies found typical antipsychotics to induce basal ganglia volume increases, but atypical antipsychotics have been associated to both increases and decreases (Ebdrup et al., 2013). On cortical volumes, wide-spread reductions in antipsychotic exposed monkeys (Dorph-Petersen et al., 2005) were traced to result from lower astrocyte number that both haloperidol and olanzapine exposure associated with (Konopaske et al., 2007). On the contrary, antipsychotic induced decrease in volume and thickness of anterior cingulate cortex in rats was not associated to decrease in astrocyte number but instead an increase in cell number (Vernon et al., 2014).

Benzodiazepine use and brain volume change

Though the association of antipsychotic medication on structural changes in the brain has gained a lot of attention in the previous years, the effects of benzodiazepines have not

been taken into account. In studies with over 2 year follow-ups looking at associations between antipsychotics and brain MRI findings in schizophrenia only one used benzodiazepine use as an exclusion criteria (Molina et al., 2005), 5 reported in their methods that subjects used also benzodiazepines (Takahashi et al., 2012, 2011a, 2011b, 2010, 2009) and only one study briefly discussed the potential confounding effect of benzodiazepine use and need for further research on how benzodiazepines may affect brain structures (Takahashi et al., 2010).

The results of earlier CT studies on benzodiazepine effects on brain structures are inconsistent, though it has to be noted, that the topic has been studied very little. The most recent studies on benzodiazepine effects on brain structures detected by CT concluded that long-term benzodiazepine use does not result in brain abnormalities (Busto et al., 2000; Lader et al., 1984; Moodley et al., 1993; Perera et al., 1987). However, two studies have found that benzodiazepines associate to ventricle-to-brain ratio (Schmauss and Krieg 1987; Uhde and Kellner 1987) and the other even suggested a dose-dependent effect (Schmauss and Krieg 1987). Since benzodiazepine use has been associated with decline in cognition (Barker et al., 2004a, 2004b) and decreased structural plasticity in pyramidal neurons in mice (Curto et al., 2016), there is a need for understanding the molecular mechanisms behind benzodiazepine effects on the brain.

Knowing the potential effects and adverse effects benzodiazepines may have on brain structure and functioning is essential in schizophrenia, because the prevalence of benzodiazepine use varies from 15% to even 91% (Mundt et al., 2012; Vares et al., 2011; Waterreus et al. 2012). In the Northern Finland Birth Cohort 1966 (NFBC 1966), 42% of individuals with schizophrenia used benzodiazepines at the age of 43 (Nykänen et al. 2016), and in our study, 95% of patients had used benzodiazepines prior to study commencement, with 79% using them in the inter-scan interval. In addition,

benzodiazepines are commonly used in general population: approximately 3% use benzodiazepines over 6 months and in some populations the number is even higher (Kurko et al., 2015). The fact that these medications are so widely used underlines the importance of studying their long-term effects carefully.

Methodological discussion

This study partly demonstrates the importance of using adequate covariates when studying variables that are sensitive to confounding factors. Taking illness related factors into account in this study was challenging, as the used variables correlated with each other (see Supplement Table 4). In previous studies illness severity and potential confounding medication have not been taken into account comprehensively. 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 these medications. Still, only a few previous studies with long-term follow-ups have adjusted their analyses with illness severity measures when analyzing antipsychotic effects on brain structures (Andreasen et al., 2013; Guo et al., 2015; Ho et al., 2011; Veijola et al., 2014).

Imaging studies are often sensitive to confounding effects due to various reasons. To exclude natural variation in brain volumes between two time point images, the protocol before each scan should be as strictly the same as possible, for example the diet and fluid intake should be comparable. The scanner should be the same, it should not be updated and phantoms should be imaged frequently for maximal quality. Issues rising from these factors potentially confound the results of imaging studies and though they are well-known, they are hard to rule out when conducting longitudinal studies.

Strengths and limitations

One strength of this study is the comprehensive, thoroughly collected medication data. To our knowledge, there is no such data on longitudinal use of both antipsychotics and benzodiazepines anywhere in the world. Our data has been collected using several sources: by interviewing the person themselves, interviewing the care takers and by scrutinizing all available medical records and collecting all available information on medication adherence, prescribed doses and duration of treatments.

Another strength is the rare naturalistic setting that is tailor-made for studying long-term associations, effects and adverse effects of medications (Wang et al., 2011). Naturalistic settings may provide novel information and perspective in contrast to clinical studies that are often made with determined objectives and in more strictly defined study populations.

A limitation in our study is the sample size. Though there were 101 identified schizophrenia cases in the NFBC 1966 in the beginning of this study, only 73 of them participated at baseline and 45 at follow-up. Possibly partly because of active home-recruitment in our study, the participants did not differ from the non-participants in terms of age, sex or educational level (Veijola et al., 2014). Still, we cannot be certain this sample represents our study population extensively in all measured domains.

Sample size limits the power to find associations and due to several analyses some associations may be due to chance. Small sample size also affected our decision not to correct for multiple comparisons when analyzing different brain areas, since the size of brain structures are connected to each other and a conservative correction method (e.g. Bonferroni) would probably over-correct the results. Given these facts, the results of this study need to be interpreted cautiously and they need to be replicated especially regarding the findings on benzodiazepines.

Another limitation is the uncertainty regarding the MRI methods used. Though we tried to overcome the possible interference by using test-retest measures, we cannot be sure our findings are a result of true differences between the studied populations. In any case, we emphasize that the results of this study are only observed differences between the MRI measures at two different time points and we do not suggest a causal effect.

Conclusions

Cumulative antipsychotic dose associates to ventricular enlargement in schizophrenia even after controlling for benzodiazepine use and illness related factors. Nevertheless it cannot be concluded that antipsychotics themselves cause the ventricular enlargement found in this study, but rather the use of antipsychotics may be a marker for a factor we are unable to identify, which contributes to ventricular enlargement.

This study assesses the association between benzodiazepine dose and structural brain changes for the first time in schizophrenia and though it was not possible to detect benzodiazepine associated changes with a limited sample size, our results suggest, that in future, studies focusing on antipsychotic effects should take benzodiazepine use into account because of its potential to confound the results.

There is a need for understanding the mechanisms behind antipsychotic and benzodiazepine related structural and functional changes in the brain. Further studies should also focus on how medication related structural alterations correspond to cognition and functioning.

Author Disclosures

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Conflict of Interest

None.

Contributors

S.H., E.J., J.M. and G.K.M. designed the study. S.H. conducted the statistical analyses and wrote the first version of the manuscript. J.S.M, E.J., H.L., S.H. and J.M. collected and modified the medication data. J.T., J.V.M., P.C. and V.K. assisted and guided the MRI segmentation and analyses. T.H. and L.B. performed the MRI modifications and segmentations. H.K., J.V. and M.I. served as specialist consultants. All authors took part in improving and finalizing the manuscript.

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