Huhtaniska, S.; Korkala, L.; Heikka, T.; Björnholm, L.; Lehtiniemi, H.; Hulkko, AP.; Moilanen, JS.... (2018). Antipsychotic and benzodiazepine use and brain morphology in schizophrenia and affective psychoses - Systematic reviews and birth cohort study. Psychiatry Research Neuroimaging. 281:43-52. https://doi.org/10.1016/j.pscychresns.2018.08.015

Antipsychotic and benzodiazepine use and brain morphology in schizophrenia and affective psychoses – systematic reviews and birth cohort study

Huhtaniska Sanna,[a,b,c] Korkala Iikka,[a,c] Heikka Tuomas[a], Björnholm Lassi, [b,c] Lehtiniemi Heli,[a] Hulkko Anja P.,[a,b,c] Moilanen Jani,[b] Tohka Jussi,[d] Manjón José,[e] Coupé Pierrick,[f] Kiviniemi Vesa,[g] Isohanni Matti,[a,c,h] Koponen Hannu,[i] Murray Graham,[j,k] Miettunen Jouko,[a,b] Jääskeläinen Erika[a,b,c,h]

a. Center for Life Course Health Research, University of Oulu, Finland

b. Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Finland

c. Department of Psychiatry, Research Unit of Clinical Neuroscience, University of Oulu, Finland

d. AI Virtanen Institute for Molecular Sciences, University of Eastern Finland, Finland

e. Instituto de Aplicaciones de las Tecnologías de la Información y de las Comunicaciones Avanzadas (ITACA), Universitat Politècnica de València, Spain.

f. Laboratoire Bordelais de Recherche en Informatique, Unité Mixte de Recherche CNRS (UMR 5800), PICTURA Research Group, France

g. Department of Diagnostic Radiology, Oulu University Hospital, Finland

h. Department of Psychiatry, Oulu University Hospital, Finland

i. University of Helsinki, Helsinki University Hospital, Psychiatry, Helsinki, Finland

j. University of Cambridge, Department of Psychiatry, United Kingdom

k. University of Cambridge, Behavioural and Clinical Neuroscience Institute, United Kingdom

Corresponding author:

MD Sanna Huhtaniska

Center for Life Course Health Research

P.O. Box 5000

90014 University of Oulu, Finland

Fax. +358 8 5315037, Tel. +358 40 6742959

Email: sanna.huhtaniska@oulu.fi

Abstract

The aim of this paper was to investigate differences in brain structure volumes between schizophrenia and affective psychoses, and whether cumulative lifetime antipsychotic or benzodiazepine doses relate to brain morphology in these groups. We conducted two systematic reviews on topic and investigated 44 schizophrenia cases and 24 with affective psychoses from the Northern Finland Birth Cohort 1966. The association between lifetime antipsychotic and benzodiazepine dose and brain MRI scans at the age of 43 was investigated using linear regression. Intracranial volume, sex, illness severity, and antipsychotic/benzodiazepine doses were used as covariates. There were no differences between the groups in brain structure volumes. In schizophrenia, after adjusting for benzodiazepine dose and symptoms, a negative association between lifetime antipsychotic dose and the nucleus accumbens (b=-0.397, p=0.024) remained. In affective psychoses, higher lifetime benzodiazepine dose associated with larger volumes of total gray matter (b=0.301, p= 0.020), cerebral gray matter (b=0.291, p= 0.025), and thalamus (b=0.352, p= 0.044) after controlling for antipsychotic use and symptoms. It seems that in addition to antipsychotics, also severity of symptoms, benzodiazepine dose and duration of illness associates to brain structure volumes. These results suggest, that benzodiazepine effect should be investigated independently and not only as a confounder.

Key words: schizophrenia, affective psychoses, brain, MRI, psychopharmacology.

1. Introduction

Though affective psychoses are common, they are much less investigated than schizophrenia. They have been considered distinct disease entities with differing aetiology of schizophrenia, though these psychotic disorders also share some similarities. Structural brain changes are found in both individuals with schizophrenia (Hulshoff Pol and Kahn 2008; Olabi et al., 2011; Vita et al., 2012) and affective psychoses (Bora et al., 2008; Busatto 2013) when compared to controls. In schizophrenia these changes include both gray and white matter reductions (Olabi et al., 2011), especially in gray matter in the frontal and temporal lobes, hippocampus/amygdala, thalamus and insula (Shepherd et al., 2012). Though similarities can be found in the brain structures in psychotic bipolar disorder compared to schizophrenia, gray matter abnormalities and hippocampal volume reductions are more common in schizophrenia (Bora et al., 2008). Likewise, there are abnormalities in brain structures in psychotic depression compared to non-psychotic depression, but less prominently than in schizophrenia (Busatto 2013).

The current key treatment of psychosis, regardless of its aetiology or the underlying illness, is antipsychotic medication. Suggested harmful effects of high dose long-term antipsychotic treatment on brain structure volumes in psychoses are a debated issue with no consensus (Fusar-Poli et al., 2013; Huhtaniska et al., 2017a). Gray matter reductions have been detected also in populations at high risk for psychosis (Wood et al., 2008) and drug naïve first episode schizophrenia patients (Leung et al., 2011), which most likely reflects the pathological process leading to illness onset. However, there are some evidence from animal studies that antipsychotic medications affect brain structures even when illness-related factors are not present (Dorph-Petersen et al., 2005; Vernon et al., 2014, 2011). In addition, as the altered morphological findings are not present in all psychotic individuals across diagnoses, it seems that in addition to neurodevelopmental disturbances, also environmental factors like medication might additionally contribute to their origin.

According to our previous meta-analysis on long-term antipsychotic effects on brain structures, higher antipsychotic doses associated with decrease in parietal lobe volume and increase in basal ganglia volume (Huhtaniska et al., 2017a). Many previous reviews have included both longitudinal and cross sectional studies. In data supplement table 1 we present previous systematic reviews on cross-sectional studies on antipsychotic medication effects on brain structures in schizophrenia. Based on these, higher doses of antipsychotics have been associated with lower total brain and midbrain volumes, higher doses of typical antipsychotics to lower gray matter, larger basal ganglia, and larger thalamic volumes, and higher doses of atypical antipsychotics to a larger volume of caudate nucleus, thalamus, and hippocampus (Haijma et al., 2013; Navari and Dazzan 2009; Scherk and Falkai 2006; Smieskova et al., 2009).

In addition to antipsychotics, individuals with psychosis are often medicated with other psychiatric medications, such as benzodiazepines. When studying medication effects in a non-controlled population, it is important to take into account the possible confounding effects of other medications. To our knowledge, the effect of benzodiazepine use on brain structures has not been studied before in psychoses with the exception of our previous longitudinal study of the Northern Finland Birth Cohort 1966 (NFBC1966) in a smaller sample (Huhtaniska et al., 2017b). Previously benzodiazepine use has been associated with decline in cognition (Baandrup et al., 2017; Fond et al., 2017) and increased mortality (Fontanella et al., 2016) in schizophrenia, and decreased brain plasticity in mice (Curto et al., 2016; Huopaniemi et al., 2004). Therefore, it is interesting to examine, whether there are also effects on brain structures on a macroscopic level.

The naturalistic design of our NFBC1966 data offers an opportunity to study medication effects on brain structures in a population based birth cohort setting during midlife. We are able to analyze data of individuals with psychosis several years after illness onset and several years of treatment. We have previously published longitudinal findings from NFBC1966 follow-up study performed at ages 34 and 43 years for schizophrenia subjects. In these studies, higher doses of antipsychotic

medication over the follow-up was associated with a larger total brain volume loss (Veijola et al., 2014), a degree of periventricular brain reduction at the fourth ventricular edge (Guo et al., 2015), and an increase in lateral ventricles after adjusting for symptom severity (Huhtaniska et al., 2017b). Higher benzodiazepine doses during the follow-up was associated with a volume decrease in the caudate nucleus even after controlling for antipsychotic use and illness severity (Huhtaniska et al., 2017b).

In this study, in addition to analysing associations between lifetime antipsychotic and benzodiazepine doses and brain structures in schizophrenia at early midlife, we wanted to investigate and compare whether these medications would also associate with brain structures in a group of individuals with affective psychoses, a group that has been studied considerably less than schizophrenia. First, we systematically reviewed earlier literature on differences in brain morphology between schizophrenia and affective psychoses and findings regarding antipsychotic or benzodiazepine effects on brain structures in affective psychoses. Then, our main aim was to analyse in a general population-based sample at the age of 43 years, whether there are differences in the brain volumes between schizophrenia and affective psychoses (schizoaffective disorder, psychotic depression or psychotic bipolar disorder) and whether lifetime antipsychotic or benzodiazepine doses associate with brain structure volumes when controlling for illness severity measures. The hypotheses were that 1) individuals with schizophrenia would show larger ventricular size or smaller volumes of brain structures than individuals with affective psychoses, 2) larger lifetime doses of antipsychotics and benzodiazepines would associate with either larger ventricular size or smaller volumes in brain structures, and 3) the effect of medication would not differ between the groups.

2. Methods

2.1 Systematic reviews

To systematically review findings on structural differences in the brain between schizophrenia and affective psychoses, a literature search was conducted the 4th of May 2017 from the database of PubMed. We used the search terms: psychotic and (bipolar or depressive or depression) and MRI and brain, and the search was directed to human studies only. Inclusion criteria were cross-sectional design and brain volume comparisons were made between any affective psychosis group and schizophrenia. Only studies comparing two groups with a history of psychosis were included.

To examine previous findings regarding antipsychotic and benzodiazepine use and brain structures in affective psychoses, a literature search was conducted the 4th of May 2017 from the database of PubMed. We used the search terms: psychotic and (bipolar or depressive or depression or affective) and (antipsychotic or benzodiazepine) and MRI and brain and (structure or structural or morphometry), and the search was directed to human studies only. In addition, we screened previous reviews on topic, references of included studies and all the included studies from the previously described search regarding differences between brain structures in schizophrenia and affective psychoses. Inclusion criteria was that the association between antipsychotic or benzodiazepine medication and brain structures was examined in any sample of affective psychosis.

2.2 Sample of NFBC1966

The participants of this study were members of the Northern Finland Birth Cohort 1966 (NFBC1966), which is an unselected, general population birth cohort identified during mid-pregnancy based on an expected delivery date during 1966 in the provinces of Lapland and Oulu, Finland. The cohort has been described in more detail in previous publications (Husa et al., 2017; Nykänen et al., 2016). Permission to gather data was obtained from the Ministry of Social and Health Affairs and the study design was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District.

This study is based on 68 individuals with psychosis from the NFBC1966, who participated in the brain MRI scan, psychiatric interviews and examinations in 2008-2011, at an average age of 43

years (SD 0.8), and had adequate structural MRI scans. Diagnoses were based on information from national registers, hospital notes and SCID-I interview (First et al., 2002) performed during the study at the age 43 years (hereafter "43-year study"). The sample included 44 cases with schizophrenia (including 2 cases with schizophreniform disorder), and 24 cases with affective psychosis (including 5 cases with schizoaffective disorder, 6 with bipolar psychosis, and 13 with psychotic depression). Written informed consent was obtained from all participants and the participants have the possibility to deny the use of their data at any time.

2.2.1 Data on use of psychiatric medication

Information on lifetime use of psychiatric medications, until the day the person was examined in the 43-year study, was gathered by a careful review of individual hospital, outpatient and health centre notes of all cases from everywhere in Finland. This procedure is described in more detail in previous publications from the NFBC1966 (Husa et al., 2014; Moilanen et al., 2015). Current and earlier use of psychiatric medications and their doses were also ascertained in the interview at 43-year study by asking about the use of psychiatric medications during the previous 3 months and as far as the subjects could remember.

All medical records were reviewed to record the name of the drug, dose and 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 N06CA01 (combination medicine including perphenazine). Benzodiazepines included classes N05BA (anxiolytics, benzodiazepine derivatives), N05CD (hypnotics and sedatives, benzodiazepine derivatives), and N05CF (hypnotics and sedatives, benzodiazepine-related drugs). The information was used to calculate the cumulative dose of lifetime medication in defined daily doses (DDD) and these were then expressed as dose-years. One DDD year (DDDy) is equivalent to using one DDD daily for a year.

2.2.3 Covariates

As a marker of illness severity, we used Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), which was assessed at the 43-year study using a specific interview. The age at onset of the illness was ascertained from medical records and it was defined as the age of first evident psychotic symptoms. Due to the birth cohort design, age of illness onset reflects also duration of illness. Also sex and intracranial volume (ICV) were used as covariates.

2.2.4 Imaging data

The participants were scanned with the same 1.5 T GE Signa scanner (General Electric, Milwaukee, Wisconsin) at the Oulu University Hospital at the 43-year study. 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 mm^3; repetition time 12.576 ms; echo time 5.3 ms; flip angle =20º).

To extract the brain structure volumes from the MRI images we used an online automated MRI brain volumetry system volBrain (http://volbrain.upv.es/) (Manjón and Coupé 2016). Based on previously reported reliability measures (Huhtaniska et al., 2017b) and previous brain imaging findings in psychoses, we selected 10 brain areas to be examined: total brain, total gray matter (GM), cerebrum, cerebral GM, lateral ventricles, caudate, putamen, thalamus, hippocampus, accumbens). Details on the reliability measures and image processing pipeline are described in our previous publication (Huhtaniska et al., 2017b) and briefly in supplementary material.

2.2.5 Statistical analyses

Independent samples t-test was used to assess the differences between the background variables of the groups. Differences between brain areas of subjects with schizophrenia and affective psychoses and associations between lifetime and medication doses and brain areas were analysed in both groups. A logarithmic transformation was applied to medication data because of the skewness of the

variables and these were used as continuous variables in analyses. All confounders were analysed as continuous variables.

We used several models to investigate the associations between lifetime medication doses and brain structures in both groups. All analyses were made using linear regression with sex and intracranial volume (ICV) as covariates. The medication analyses were additionally adjusted for PANSS total score and onset age. Benzodiazepine DDDy were added as a covariate in analyses of antipsychotic DDDy, and vice versa. In addition, we analysed the group × medication interactions in models with group + group × medication interaction + medication dose (antipsychotic or benzodiazepine) + ICV + sex. No corrections for multiple comparisons were made due to the possibility of overcorrecting the results. The analyses were performed using IBM SPSS Statistics version 23 using $p<0.05$ as a limit for statistical significance.

3. Results

3.1 Systematic reviews

3.1.1. Differences in brain structures between schizophrenia and affective psychoses

The search located 291 studies and after abstract and title review 94 articles were evaluated in detail. The final number of included studies was 30. The data collection in presented in data supplement figure 1 and detailed information on included studies are presented in data supplement table 2.

Of the found 30 studies, 15 examined differences between schizophrenia and psychotic bipolar disorder cases. Only six studies investigated differences between mixed mood disorder group and schizophrenia and only two studies differences between psychotic depression and schizophrenia. A summary of the findings of the review is presented in Table 1. In the studies with statistically significant findings, the cortical volumes were smaller in the schizophrenia group compared to affective psychoses groups, and the only findings with larger volumes in schizophrenia were found

in putamen, caudate and globus pallidus when compared to psychotic bipolar disorder (Mamah et al., 2016; Rimol et al., 2010). Regarding lateral ventricles, the size was larger in schizophrenia than in psychotic bipolar disorder (McDonald et al., 2006), but larger in psychotic depression than in schizophrenia (Salokangas et al., 2002). Of the found 30 studies, 9 did not find any differences between these groups in their regions of interest (Cui et al., 2001; Janssen et al., 2014; Koo et al., 2008; Morgan et al., 2007; Radonic et al., 2008; Reite et al., 2010; Rosa et al., 2010; Rosa et al., 2015; Strasser et al., 2004).

Table 1. Summary of the findings in schizophrenia based on the systematic review of differences in brain volumes between schizophrenia and affective psychoses.

Finding	Studies
Statistically significant findings between schizophrenia and psychotic bipolar disorder:	
- Smaller volumes in cerebellum	Ivleva et al., 2012; Ivleva et al., 2013
- Gray matter deficits in cerebellum	Nenadic et al., 2015b
- Widespread cortical and subcortical gray matter volume reductions	Brown et al., 2011; Ivleva et al., 2012; Ivleva et al., 2013; Mamah et al., 2016; McDonald et al., 2005; Nenadic et al., 2015a, 2015b; Salokangas et al., 2002; Harvey et al., 1994
- Smaller cerebral gray matter volume	Harvey et al., 1994
- Smaller total gray matter volume	Mamah et al., 2016
- Smaller gray matter volume in subgenual cortex	Yüksel et al., 2012
- Smaller hippocampal volumes	Arnold et al., 2015; McDonald et al., 2006; Radonic et al., 2011; GM: Brown et al., 2011; Nenadic et al., 2015
- Larger volume of putamen	Mamah et al., 2016; RImol et al., 2010
- Smaller volume of putamen	Brown et al., 2011
- Different shape of amygdala	Mahon et al., 2015
- Smaller amygdala	Mahon et al., 2012
- Smaller gray matter volume in amygdala	Brown et al., 2011
- Larger volumes of caudate and globus pallidus	Mamah et al., 2016
- Larger ventricle volumes	Mc Donald et al., 2006
Statistically significant findings between schizophrenia and schizoaffective disorder	
- Smaller gray matter volumes in frontotemporal, cingulate, parietal and occipital cortices	Ivleva et al., 2012
Statistically significant findings between schizophrenia and psychotic depression	
- Smaller volume in left posterior subgenual cortex	Coryel et al., 2005
- Smaller ventricular CSF volumes	Salokangas et al., 2002
Statistically significant findings between schizophrenia and combined affective psychoses group	
- Smaller total brain and total gray matter volumes	El-Sayed et al., 2010
- Smaller insular gray matter volume	Kasai et al., 2003
- Higher rate of cavum septum pellucidum	Jurjus et al., 1993
No differences between schizophrenia and psychotic bipolar disorder	
- Gray matter VBM	Cui et al., 2011
- Lobar cortical thickness, surface are, gyrification index and sulcal width	Janssen et al., 2014
- Intracranial volume, white matter volume, nucleus accumbens and thalamic volumes	Mamah et al., 2016
- Cerebral volume	Mc Donald et al., 2006
- Temporal lobe volume and asymmetry	Radonic et al., 2008
- Superior temporal gyrus laminar thickness	Ratnanather et al., 2013
- Lateral ventricles	Rosa et al., 2010
- Cortical thickness, hippocampus, amygdala, thalamus, ventricles, nucleus accumbens, ventral diencephalon, cerebellar cortex or white matter, caudate, pallidum or brainstem	Rimol et al., 2010
- Left hippocampus, lateral ventricles	Strasser et al., 2004
No differences between schizophrenia and schizoaffective disorder	

- gray matter VBM	Ivleva et al., 2013
- Intracerebral volume, total brain volume, ventricular volume	Reite et al., 2010
- Temporal lobe volume and asymmetry	Radonic et al., 2008
No differences between schizophrenia and combined affective psychoses group	
- Frontal lobes, superior temporal cortices, hippocampus, insula, whole brain VBM	Rosa et al., 2015
- Temporal pole gray matter volume	Kasai et al., 2003
- VBM	Morgan et al., 2007
- Cingulate gyrus gray matter volumes in 3 anterior subregions and 1 posterior subregion	Koo et al., 2008

VBM= voxel-based morphometry
*=smaller

3.1.2 Associations between antipsychotic and benzodiazepine use in affective psychoses

The search located 18 studies, of which 8 fulfilled our inclusion criteria. In addition, 63 full text articles from other sources were investigated. In total, 71 articles were assessed in detail, and 15 studies were included in the systematic review. The data collection is described in data supplement figure 2 and detailed information on all included studies in data supplement table 3.

Of the 15 included studies, the majority did not find associations between medication and brain structures. Only two studies found statistically significant associations: one found an association between antipsychotics and positive vertex displacement in right pallidum in psychotic bipolar disorder (Liberg et al., 2015), and another between longer duration of antipsychotic exposure and increased ventricular volumes in affective psychoses but not in schizophrenia (Morgan et al., 2007). A summary of the findings of the review is presented in Table 2.

Table 2 Summary of the systematic review of associations between medication and brain volumes in affective psychoses.

Finding	Studies
- Longer duration of antipsychotic exposure correlated with increased third ventricle and lateral ventricle volumes in affective psychoses group	Morgan et al., 2007
- Significant association between antipsychotics and positive vertex displacement in the right pallidum in psychotic bipolar disorder	Liberg et al., 2015
- No association between antipsychotic medication and investigated brain volumes	Arnold et al., 2015; Giakoumatos et al., 2015; Ivleva et al., 2012; Ivleva et al., 2013; Janssen et al., 2014; Kasai et al., 2003; Koo et al., 2008; Mathew et al., 2014; Rimol et al., 2010; Rosa et al., 2010; Strakowski et al., 1999; Woodward and Heckers 2015; Yüksel et al., 2012

3.2 Characteristics of the sample

The characteristics of the sample are described in Table 3. The schizophrenia group included more males (61%) than the affective psychoses group (29%). Only 10% of the schizophrenia group were married/cohabited compared to the 50% in affective psychoses group. The PANSS total and subscores were also higher in the schizophrenia group and fewer individuals were in remission (21%) than in the affective psychoses group (88%). The onset age was significantly lower in the schizophrenia group compared to the affective psychoses group. However, there were no significant differences in educational level or the number of people on disability pension between the groups.

There were no statistically significant differences between brain volumes of the two groups in any studied brain areas, see data supplement table 4 for details.

3.2.1 Characteristics of lifetime medication use

The characteristics of medication use in the sample are presented in Table 4. In the schizophrenia group 42 (96%) individuals had used antipsychotics during lifetime, and the cumulative mean dose was 20.1 DDDy. Thirty-nine (88%) individuals had used typical and 35 (80%) individuals atypical antipsychotics. Thirty-three (75%) individuals had used benzodiazepines (mean dose 9.1 DDDy). Thirty-two (73%) individuals had used both antipsychotics and benzodiazepines. In the affective psychoses group 20 (83%) individuals had used antipsychotics (mean dose 4.7 DDDy). Fifteen (63%) individuals had used typical and 16 (67%) individuals atypical antipsychotics. Ten (41%) individuals had used benzodiazepines (mean dose 6.6 DDDy). Nine (38%) had used both benzodiazepines and antipsychotics. All the used medications are listed in data supplement table 5. Many of the study subjects had used several different antipsychotics during their lifetime, especially those with schizophrenia.

Table 3. Characteristics of the sample.

	Schizophrenia (N=44)	Affective psychoses (N=24)
Gender* N (%)		
Male	27 (61)	7 (29)
Age at the study moment, years (SD)		
Mean age, Range	43.1 (0.7), 41.8 – 44.5	43.6 (0.7), 41.9 – 44.7
Marital status at the study moment * N (%)		
Married or cohabiting	10 (23)	12 (50)
Single	34 (77)	12 (50)
Educational level at the study moment N (%)		
Low	24 (55)	15 (63)
Middle	10 (23)	6 (25)
High	10 (23)	3 (13)
Work status at the study moment N (%)		
Disability pension	26 (60)	12 (50)
Employed	12 (27)	8 (33)
Other[a]	5 (11)	3 (13)
Current alcohol abuse N (%)	4 (9)	5 (21)
Diagnosis N (%)		
Schizophrenia	42 (96)	
Schizophreniform disorder	2 (4)	
Schizoaffective disorder		5 (21)
Psychotic bipolar disorder		6 (25)
Psychotic depression		13 (54)
Lifetime hospital treatment days		
Mean (SD) median, range	579 (899) 213, 1-5093	162 (122) 146, 2-399
PANSS* mean (SD) median, range		
Total symptoms score	70 (27), 26, 30-130	43 (9.7), 11, 31-75
Positive symptoms score	17 (8) 16, 6-32	9 (3) 9, 4-16
Negative symptoms score	19 (10) 17, 8-43	12 (4) 10, 8-21
Emotional symptoms score	18 (7) 16, 8-33	12 (3) 10, 8-19
Excitement symptoms score	15 (5) 14, 8-29	10 (2) 10, 8-14
Disorganized symptoms score	25 (12) 23, 10-59	16 (6) 14, 9-36
Remission* N (%)	11 (25)	21 (88)
Onset age* mean (SD), Range	25 (6.3), 16.7–42.0	32 (6.3), 21.4–41.2
Current use of medication N (%), mean DDD (SD)		
Antipsychotics	35 (80), 203 (218)	17 (71), 280 (192)
Benzodiazepines	20 (45), 33 (21)	5 (21), 28 (11)

a= unemployed or not in working life due to other reasons than disability pension
PANSS= Positive And Negative Syndrome Scale, DDD= defined daily dose.
*=statistically significant differences between the groups.
The cumulative number of hospital days since illness onset until the 43-years study was collected from the Care Register for Health Care. Remission was assessed using the remission criteria by Andreasen et al., (2005), and based on PANSS interview. The symptoms were only required not to be present during the period of one week before the assessment, and no duration criteria was used since PANSS was done only once.

Table 4. Number of persons using antipsychotics and benzodiazepines during their lifetime and lifetime doses of medication.

	Schizophrenia (N=44) N (%[a]), mean DDDy (SD)	Affective psychoses (N=24) N(%[a]), mean DDDy (SD)
Use of antipsychotics in DDDy		
Use of antipsychotics	42 (96), 20.1 (20.5)	20 (83), 4.7 (5.2)
Use of typical antipsychotics	39 (88), 11.3 (14.9)	15 (63), 1.8 (2.7)
Use of atypical antipsychotics	35 (80), 11.5 (9.4)	16 (67), 4.2 (4.4)
Use of benzodiazepines in DDDy		
Use of benzodiazepines	33 (75) 9.1 (10.5)	10 (41), 6.6 (8.0)
Use of benzodiazepines only irregularly	5 (11)	2 (8)
Use of both antipsychotics and benzodiazepines	32 (73), ap 23.5 (22.4), bzd 9.4 (10.6)	9 (38), ap 6.6 (6.9), bzd 7.1 (8.4)

a= the percentage of cases that have had the medication at any point of their illness
N= number of cases, SD= Standard Deviation, DDDy= dose years in defined daily dose, ap= antipsychotic, bzd= benzodiazepine.

3.2.3 Association between lifetime cumulative antipsychotic doses and brain volumes

In schizophrenia, higher cumulative lifetime antipsychotic doses were associated with brain volumes in several areas (see data supplement table 6 for details), and after adjusting the analyses for benzodiazepine use (see Table 5), the associations remained in total GM (b= -0.25, p= 0.017), cerebral GM (b= -0.25 p= 0.024), thalamus (b= -0.39 p= 0.014) and nucleus accumbens (b= -0.40, p= 0.014). After adding onset age to the model, the statistically significant associations still remained in total GM (b= -0.26, p= 0.025), cerebral GM (b= -0.29, p= 0.019), thalamus (b= -0.42, p=0.016), nucleus accumbens (b= -0.46, p= 0.011), and the lateral ventricles (b= 0.39, p= 0.046). When replacing onset age with PANSS total score as a marker of illness severity, only the association in nucleus accumbens remained (b= -0.38, p= 0.033) statistically significant, though the finding in thalamus almost reached significance as well (b= -0.34, p= 0.050). However, in the PANSS adjusted analyses, PANSS total score did not either associate to the structure volumes with the exception of lateral ventricles (b= 0.43, p= 0.018). The results of the analyses with both medication types are presented in Table 5 and the results of further adjusted analyses in Table 6.

There were no associations between lifetime antipsychotic doses and volumes of brain structures in affective psychoses (Tables 5 and 6, data supplement table 6).

3.2.4 Association between lifetime cumulative benzodiazepine dose and brain volumes

In schizophrenia higher lifetime benzodiazepine doses associated with lower volumes of total brain (b= -0.23, p= 0.002) and cerebrum (b= -0.21, p= 0.006). After adjusting the analysis for antipsychotic doses, no associations remained. When onset age was added to the model, there was again a significant association between higher benzodiazepine doses and lower volumes in total brain (b= -0.17, p= 0.044), but this association did not remain when adjusting for PANSS total score instead of onset age (Tables 5 and 6, data supplement table 6).

In affective psychoses, higher lifetime doses of benzodiazepines were associated with larger volumes in total GM (b= 0.30, p= 0.020), cerebral GM (b= 0.29, p= 0.025) and thalamus (b= 0.35, p= 0.044) after adjusting the analyses for cumulative antipsychotic dose and PANSS total score (Tables 5 and 6, data supplement table 6).

3.2.5 Interaction analyses

There were no statistically significant associations between group × antipsychotic interaction and brain volumes or between group × benzodiazepine interaction and brain volumes (data supplement table 7).

Table 5. Association between antipsychotic DDDy, benzodiazepine DDDy and brain volumes in the same model in schizophrenia cases and cases with affective psychoses. Sex and ICV as covariates. Statistically significant findings in **bold.**

		Antipsychotic dose and benzodiazepine in the same model			
Brain area		**Schizophrenia (N=44)**		**Affective psychoses (N=24)**	
		b	**p**	**b**	**p**
Total Brain	ap	-0.128	0.118	-0.398	0.695
	bzd	-0.154	0.062	0.134	0.136
Total GM	ap	**-0.251**	**0.017**	0.060	0.626
	bzd	0.028	0.786	**0.325**	**0.014**
Cerebrum	ap	-0.134	0.125	-0.018	0.835
	bzd	-0.138	0.115	0.160	0.072
Cerebrum GM	ap	**-0.247**	**0.024**	0.084	0.482
	bzd	0.044	0.682	**0.315**	**0.014**
Lateral ventricles	ap	0.325	0.061	0.250	0.274
	bzd	0.064	0.699	-0.221	0.331
Caudate	ap	0.002	0.990	0.626	0.114
	bzd	0.121	0.471	0.217	0.184
Putamen	ap	0.169	0.282	0.069	0.711
	bzd	0.004	0.980	0.219	0.247
Thalamus	ap	**-0.387**	**0.014**	-0.269	0.089
	bzd	0.005	0.971	**0.361**	**0.026**
Hippocampus	ap	-0.255	0.113	-0.213	0.154
	bzd	-0.077	0.627	0.299	0.051
Accumbens	ap	**-0.396**	**0.014**	0.146	0.396
	bzd	0.134	0.390	-0.475	0.068

ICV= intracranial volume, b= standardized beta, ap= antipsychotic, bzd= benzodiazepine.

Table 6. Statistically significant associations between antipsychotic doses, benzodiazepine doses, total PANSS score or onset age and brain volumes in the same model in schizophrenia cases and cases with affective psychoses. Sex and ICV as covariates in all analyses. Statistically significant findings in **bold**.

		Antipsychotic dose, benzodiazepine dose and PANSS in the same model		Antipsychotic dose, benzodiazepine dose and onset age in the same model	
Brain area		**Schizophrenia (N=44)**	**Affective psychoses (N=24)**	**Schizophrenia (N=44)**	**Affective psychoses (N=24)**
Total Brain	AP	b=-0.078 p=0.387	b=-0.012 p= 0.910	b= -0.165 p= 0.070	b= -0.013 p=0.870
	BZD	b= -0.113 p= 0.204	b= 0.117 p= 0.200	**b= -0.171 p= 0.044**	**b= 0.199 p= 0.030**
	PANSS/onset age	b= -0.127 p= 0.163	b= -0.074p= 0.461	b= -0.082 p= 0.334	**b= 0.188 p= 0.047**
Total GM	AP	b= -0.171 p= 0.120	b= 0.142 p= 0.312	**b= -0.263 p=0.025**	b= 0.076 p=0.537
	BZD	b= 0.079 p= 0.453	**b= 0.301 p= 0.020**	b= 0.022 p= 0.831	**b= 0.375 p= 0.009**
	PANSS/onset age	b=-0.202 p= 0.066	b= -0.194p= 0.153	b= -0.026 p= 0.808	b= 0.146 p= 0.291
Cerebrum	AP	b= -0.073 p= 0.445	b= -0.005 p= 0.962	b= -0.183 p= 0.060	b= 0.001 p= 0.991
	BZD	b= -0.091 p= 0.329	b= 0.148 p= 0.105	b= -0.160 p= 0.075	**b= 0.218 p= 0.018**
	PANSS/onset age	b= -0.157 p= 0.104	b= -0.054p= 0.579	b= -0.107 p= 0.237	b= 0.168 p= 0.072
Cerebrum GM	AP	b= -0.159 p= 0.157	b= 0.161 p= 0.261	**b= -0.286 p=0.019**	b= 0.094 p=0.440
	BZD	b= 0.097 p= 0.375	**b= 0.291 p= 0.025**	b= 0.027 p= 0.808	**b= 0.347 p= 0.013**
	PANSS/onset age	b= -0.221 p= 0.052	b= -0.170 p= 0.213	b= -0.085 p= 0.444	b= 0.094 p= 0.488
Lateral ventricles	AP	b= 0.160 p= 0.363	b= 0.195 p= 0.479	**b= 0.388 p= 0.046**	b= 0.206 p= 0.349
	BZD	b= -0.060 p= 0.725	b=-0.174 p= 0.463	b= 0.069 p= 0.692	b= -0.358 p= 0.132
	PANSS/onset age	**b= 0.432 p= 0.018**	b= 0.225 p= 0.393	b= 0.137 p= 0.444	b= -0.396 p= 0.113
Caudate	AP	b= 0.031 p= 0.867	b= 0.296 p= 0.157	b= -0.078 p= 0.674	b= 0.299 p=0.057
	BZD	b= 0.157 p= 0.391	b= 0.205 p= 0.249	b= 0.086 p= 0.614	**b= 0.333 p= 0.046**
	PANSS/onset age	b= -0.062 p= 0.738	b= -0.067 p= 0.730	b= -0.175 p= 0.319	b= 0.337p= 0.053
Putamen	AP	b= 0.168 p= 0.324	b= 0.108 p= 0.627	b= 0.008 p=0.962	b= 0.058 p= 0.761
	BZD	b= -0.033 p= 0.840	b= 0.229 p= 0.237	b= -0.067 p= 0.662	b= 0.186 p= 0.366
	PANSS/onset age	b= -0.022 p= 0.894	b= -0.020 p= 0.926	**b= -0.352 p= 0.028**	b= -0.095 p= 0.656
Thalamus	AP	b= -0.336 p= 0.050	b= -0.261 p= 0.185	**b= -0.421 p=0.016**	b= -0.252 p= 0.115
	BZD	b= 0.043 p= 0.794	**b= 0.352 p= 0.044**	b= -0.011 p= 0.941	**b= 0.414 p= 0.019**
	PANSS/onset age	b= -0.111 p= 0.508	b= -0.043 p= 0.813	b= -0.085 p= 0.592	b= 0.154 p= 0.374
Hippocampus	AP	b= -0.232 p= 0.201	b=-0.121 p= 0.500	b=-0.317 p= 0.078	b= -0.196 p= 0.193
	BZD	b= -0.055 p= 0.755	b= 0.268 p= 0.093	b= -0.105 p= 0.523	**b= 0.352 p= 0.035**
	PANSS/onset age	b= -0.061 p= 0.734	b= -0.176 p= 0.306	b= -0.136 p= 0.416	b= 0.154 p=0.352
Accumbens	AP	**b= -0.375 p= 0.033**	b= 0.332 p= 0.066	**b= -0.460 p=0.011**	b=0.178 p= 0.289
	BZD	b= 0.132 p= 0.430	b= -0.397 p= 0.538	b= 0.106 p= 0.505	b= 0.108 p= 0.540
	PANSS/onset age	b= -0.048 p=0.777	**b= -0.397 p= 0.024**	b= -0.139 p= 0.393	b= 0.287 p= 0.130

ICV= intracranial volume, b= standardized beta, ap= antipsychotic, bzd= benzodiazepine

4. Discussion

4.1 Main results

We found no differences in brain structure volumes at the age of 43 years between the two diagnostic groups, even though onset age (which corresponds to duration of illness in this sample) and illness severity (PANSS total score) were significantly different between the groups. Likewise, many earlier studies have neither found differences (Table 1).

In the schizophrenia group, higher cumulative lifetime antipsychotic doses associated with smaller volumes of total GM, cerebral GM, thalamus, and nucleus accumbens, and after adding PANSS total score to the model, the association in nucleus accumbens still remained, and the association in thalamus almost reached significance. Higher cumulative doses of benzodiazepines associated with smaller volumes of total brain after controlling for antipsychotic doses and onset age (i.e. illness duration), but the association did not remain when adjusted for PANSS total score instead of onset age.

In the affective psychoses group, there were no associations between lifetime antipsychotic doses and volumes of brain structures. Surprisingly, higher lifetime doses of benzodiazepines were associated with larger volumes in total GM, cerebral GM and thalamus after controlling for antipsychotic dose and PANSS total score. There were no statistically significant associations between group × medication dose and brain volumes in interaction analyses.

In the systematic reviews, the differences in brain structures between schizophrenia and affective psychoses are not clear, since there are both since there are both studies reporting differences and no differences. The differences are reported mainly in gray matter volumes and basal ganglia structures. There are no previous studies on the association between benzodiazepine use and brain structures in affective psychoses, and of the studies focusing on the association between antipsychotic use and brain structures, there were only two statistically significant findings.

4.2 Antipsychotic use and brain volumes

In previous studies of an overlapping NFBC1966 sample, a higher amount of antipsychotic medication predicted total brain volume loss and lateral ventricular volume increase (Veijola et al., 2014), as well as periventricular brain volume reductions at the fourth ventricular edge (Guo et al., 2015) over a 9-year follow-up. In addition to brain findings, in the NFBC1966, higher doses of antipsychotics associated with decline in verbal learning and memory (Husa et al., 2014), and high lifetime doses and antipsychotic polypharmacy associated with poorer outcomes in schizophrenia (Moilanen et al., 2016). These previous findings and the findings of this study are somewhat consistent and suggest that high-dose long-term antipsychotic medications may have some non-profitable effects on the brain in schizophrenia.

Our results regarding the association of antipsychotics and lower gray matter volumes in schizophrenia are in line with the previous review of Haijma et al. (2013). However, the findings regarding associations between antipsychotic doses and smaller volumes in thalamus and nucleus accumbens in schizophrenia have not been reported by previous reviews, but instead they have reported larger volumes of thalamus and basal ganglia (Navari and Dazzan 2009; Scherck and Falkai 2006; Smieskova et al., 2009).

Though the associations between higher lifetime doses of antipsychotics and brain structures in schizophrenia were confounded by PANSS total score, the overall estimates of the models including PANSS, sex, and ICV and antipsychotic dose, sex, and ICV were of the same magnitude (see data supplement table 8). Therefore, it seems, that antipsychotics, benzodiazepines, age of illness onset or duration of illnes and severity of symptoms all may have an effect on brain structures.

In this study we wanted to expand the focus of antipsychotic effects also to affective psychoses, in which we hypothesized, that the effect would be similar to that of schizophrenia. However, we failed to detect any associations related to antipsychotic medication in the affective psychoses group. This may be due to the fact that the individuals with affective psychoses in our sample had

higher onset age (i.e. shorter duration of illness) and partly because of this, the duration of medication and lifetime antipsychotic doses were much lower than in the schizophrenia group.

Based on our systematic review, several previous studies have not found associations between antipsychotics and brain morphology in affective psychoses (Table 2). The only positive findings were from studies by Liberg et al., 2015, where they found an association between antipsychotic medication and positive vertex displacement in the right pallidum in psychotic bipolar disorder, and Morgan et al., 2007, who found that longer duration of antipsychotic treatment was associated with an increased ventricular volume in the affective psychoses group. Though not many studies focus on affective psychoses and antipsychotic medications, there are studies on medication effects in affective disorders in general. A review on medication effects on neuroimaging findings in bipolar disorder concluded that the effects of psychotrophic medications such as lithium or antipsychotics are predominantly normalizing and do not seem to affect the differences observed in volumes, white matter tracts or BOLD signal between bipolar disorder patients and healthy controls (Hafeman et al., 2012).

4.3 Benzodiazepine use and brain volumes

There are no previous cross-sectional studies on the association between benzodiazepine doses or use and brain structures measured with MRI in psychoses. In previous computed tomography studies, benzodiazepine use has not been associated with brain volumes (Busto et al., 2000; Lader et al., 1984; Moodley et al., 1993; Perera et al., 1987), with the exception of an association between benzodiazepines and increased ventricle-to-brain ratio (Schmauss and Krieg 1987; Uhde and Kellner 1987). In our previous longitudinal study on NFBC1966 data including a partly overlapping sample, we found that higher benzodiazepine doses during the 9-year follow-up were associated with a decrease in volume of the caudate nucleus after controlling for antipsychotic doses and PANSS average score (Huhtaniska et al., 2017b).

In this study, lifetime benzodiazepine doses did not associate with any brain structures in schizophrenia at the age of 43 years, when antipsychotic doses were taken into account. In this sample, individuals with schizophrenia had used much more antipsychotics (mean dose 20.1 DDDy) than benzodiazepines (mean dose 9.1 DDDy), and thus it might be hard to distinguish the effect of these two medications. Also, in schizophrenia, the lifetime benzodiazepine doses may indicate a more severe illness (Takita et al., 2016), since polypharmacy including antipsychotics and benzodiazepines has been linked to poorer outcome (Längle et al., 2012).

On the other hand, in the affective psychoses group, higher lifetime benzodiazepine doses associated with larger volumes in total gray matter, cerebral gray matter and thalamus even after controlling for antipsychotic dose and PANSS total score or onset age. In this group, the lifetime use of antipsychotics was lower (mean dose 4.7 DDDy) than lifetime use of benzodiazepines (mean dose 6.6 DDDy), which may partly explain this finding. It might even be, that in affective psychoses, benzodiazepine use with appropriate doses may help maintaining a better level of functioning after eliminating excess anxiety and hence associate with greater gray matter volumes. The practices for prescribing benzodiazepines might also be different in these two patient groups (Clark et al,. 2004).

4.4 Strengths and limitations

This study utilizes naturalistic birth cohort data, thus the sample is not selected and it may represent the clinical variability more realistically. In this natural setting it was possible to compare schizophrenia cases with cases with history of affective psychoses and to study both subgroups for association of lifetime antipsychotic or benzodiazepine doses with brain structure measurements at the age of 43 years. Our data is very heterogenous representing different stages of the disease including individuals in remission, more severely ill and with active psychosis.

To our knowledge, there are no other studies with data on lifetime use of antipsychotics and benzodiazepines in individuals with schizophrenia or affective psychoses. The medication data has

been collected very comprehensively by scrutinizing all available medical records and interviewing all subjects carefully at the time of the study.

The main limitation of this study is the small sample size and the different number of cases in patient groups. Acknowledging the small sample size and the fact that we did not correct for multiple comparisons our findings may be by chance and the results must be considered exploratory. However, the findings regarding schizophrenia cases are in line with our previous longitudinal studies (Guo et al., 2015; Huhtaniska et al., 2017b; Veijola et al., 2014).

The differences in background variables may also affect our results. The gender distribution was significantly different between the groups: in the affective psychoses 71% of the subjects were female vs. 39% in the schizophrenia group. In addition, the differences in marital status, age at illness onset, and severity of illness between the groups may affect the results. There were also differences in the background variables between the groups that we could not control for in our analyses due to the lack of power. We had no data on symptom severity covering the whole illness, which could have provided a more reliable measure of illness severity.

The cross-sectional design cannot answer the question whether there is an actual change in the brain structure volumes associated to medication, but unfortunately we do not have longitudinal data on brain changes in affective psychoses, though we have reported longitudinal findings in schizophrenia cases from this sample (Huhtaniska et al., 2017b). However, it could be presumed, that if these medications associate to brain structures in a longitudinal design, we would also detect associations when examining lifetime medication exposure in a cross sectional design.

Though the medication data was collected very thoroughly, we cannot exclude the potential confounding effects of other psychotropic or somatic medications. Especially the use of lithium could confound the results, but since there had been only a few cases on lithium treatment during their whole lifetime and none at the time of the study, we did not find it relevant to include lithium use in our analyses. For the confounding effect of other mood stabilizers, we did not have the data.

In addition, many individuals had used several different antipsychotics, and we could not study the effects of independent drugs.

4.5. Conclusions

At middle age (age of 43 years) there were no differences in brain structure volumes between schizophrenia and affective psychoses. There were many associations between larger lifetime doses of antipsychotics and lower volumes of brain structures in schizophrenia, but after adjusting for lifetime benzodiazepine doses, few of them remained. After additionally adjusting the analyses for PANSS total score only the association in nucleus accumbens remained. There were no associations between lifetime benzodiazepine doses and brain structures in schizophrenia after taking into account lifetime antipsychotic doses. In affective psychoses, there were no associations between lifetime antipsychotic doses and brain structures, but there was a positive association between lifetime benzodiazepine doses and total and cerebral gray matter and thalamus after controlling for antipsychotic dose and PANSS total score or onset age.

Our findings underline the importance of taking benzodiazepine use and illness severity measures into account when studying antipsychotic effects on the brain. In addition, benzodiazepines and their effects on brain structures should be studied independently. More studies focusing on affective psychoses and medication effects are necessary. Further studies should also focus on how these findings correspond to cognition and functioning.

Funding sources

This work was supported by unrestricted grants from the Academy of Finland (grant numbers 132 071, 278 286, 268 336), the Sigrid Jusélius Foundation, the Brain & Behavior Research Foundation, the Orion Research Foundation sr, the Foundation for Psychiatric Research, The scholarship Fund of the University of Oulu - Tyyni Tani Found, the University of Oulu Scholarship Foundation, the Jalmari and Rauha Ahokas Foundation, The Maud Kuistila Memorial Foundation, the jane and

Aatos Erkko Foundation, and the Oy H Lundbeck Ab. The funders had no role in the study design, data collection, data analysis, interpreting the results or the decision to publish the article.

Conflicts of interest

None.

References

Arnold, S.J., Ivleva, E.I., Gopal, T.A., Reddy, A.P., Jeon-Slaughter, H., Sacco, C.B., Francis, A.N., Tandon, N., Bidesi, A.S., Witte, B., Poudyal, G., Pearlson, G.D., Sweeney, J.A., Clementz, B.A., Keshavan, M.S., Tamminga, C.A., 2015. Hippocampal volume is reduced in schizophrenia and schizoaffective disorder but not in psychotic bipolar I disorder demonstrated by both manual tracing and automated parcellation (FreeSurfer). Schizophr Bull. 41, 233-49. doi: 10.1093/schbul/sbu009.

Baandrup, L., Fagerlund, B., Glenthoj, B., 2017. Neurocognitive performance, subjective well-being, and psychosocial functioning after benzodiazepine withdrawal in patients with schizophrenia or bipolar disorder: a randomized clinical trial of add-on melatonin versus placebo. Eur Arch Psychiatry Clin Neurosci. 267, 163-171. doi: 10.1007/s00406-016-0711-8

Bora, E., Yucel, M., Fornito, A., Berk, M., Pantelis, C., 2008. Major psychoses with mixed psychotic and mood symptoms: are mixed psychoses associated with different neurobiological markers? Acta Psychiatr Scand. 118, 172-87. doi: 10.1111/j.1600-0447.2008.01230.x.

Brown, G.G., Lee, J.S., Strigo, I.A., Caligiuri, M.P., Meloy, M.J., Lohr, J., 2011. Voxel-based morphometry of patients with schizophrenia or bipolar I disorder: a matched control study. Psychiatry Res. 194, 149-56. doi: 10.1016/j.pscychresns.2011.05.005.

Busatto, G.F., 2013. Structural and functional neuroimaging studies in major depressive disorder with psychotic features: a critical review. Schizophr Bull. 39, 776-86. doi: 10.1093/schbul/sbt054.

Busto, U.E., Bremner, K.E., Knight, K., Brugge, K., Sellers, E.M., 2000. Long-term benzodiazepine therapy does not result in brain abnormalities. J Clin Psychopharmacol. 20, 2-6.

Clark, R.E., Xie, H., Brunette, M.F., 2004. Benzodiazepine prescription practices and substance abuse in persons with severe mental illness. J Clin Psychiatry. 65, 151-5.

Coryell, W., Nopoulos, P., Drevets, W., Wilson, T., Andreasen, N.C., 2005. Subgenual prefrontal cortex volumes in major depressive disorder and schizophrenia: diagnostic specificity and prognostic implications. Am J Psychiatry. 162, 1706-12. doi: 10.1176/appi.ajp.162.9.1706.

Cui, L., Li, M., Deng, W., Guo, W., Ma, X., Huang, C., Jiang, L., Wang, Y., Collier, D.A., Gong, Q., Li, T., 2011. Overlapping clusters of gray matter deficits in paranoid schizophrenia and psychotic bipolar mania with family history. Neurosci Lett. 489, 94-8. doi: 10.1016/j.neulet.2010.11.073.

Curto, Y., Garcia-Mompo, C., Bueno-Fernandez, C., Nacher, J., 2016. Chronic benzodiazepine treatment decreases spine density in cortical pyramidal neurons. Neurosci Lett. 613, 41-46. doi: 10.1016/j.neulet.2015.12.048.

Dorph-Petersen, K.A., Pierri, J.N., Perel, J.M., Sun, Z., Sampson, A.R., Lewis, D.A., 2005. The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: A comparison of haloperidol and olanzapine in macaque monkeys. Neuropsychopharmacology 30, 1649–1661.

El-Sayed, M., Steen, R.G., Poe, M.D., Bethea, T.C., Gerig, G., Lieberman, J., Sikich, L., 2010. Brain volumes in psychotic youth with schizophrenia and mood disorders. J Psychiatry Neurosci. 35, 229-36.

First M., Spitzer R., Gibbon M., Williams J., 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition With Psychotic Screen (SCID-I/P W/PSYSCREEN). New York: BiometricsResearch, New York State Psychiatric Institute.

Fond, G., Berna, F., Boyer, L., Godin, O., Brunel, L., Andrianarisoa, M., Aouizerate, B., Capdevielle, D., Chereau, I., Danion, JM., Dubertret, C., Dubreucq, J., Faget, C., Gabayet, F., Le Gloahec, T., Llorca, PM., Mallet, J., Misdrahi, D., Rey, R., Richieri, R., Passerieux, C., Portalier, C., Roux, P., Vehier, A., Yazbek, H., Schürhoff, F., Bulzacka, E, FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) group, 2017. Benzodiazepine long-term administration is associated with impaired attention/working memory in schizophrenia: results from the national multicentre FACE-SZ data set. Eur Arch Psychiatry Clin Neurosci. doi: 10.1007/s00406-017-0787-9. [Epub ahead of print]

Fontanella, C.A., Campo, J.V., Phillips, G.S., Hiance-Steelesmith, D.L., Sweeney, H.A., Tam, K., Lehrer, D., Klein, R., Hurst, M., 2016. Benzodiazepine use and risk of mortality among patients with schizophrenia: a retrospective longitudinal study. Benzodiazepine use and risk of mortality among patients with schizophrenia: a retrospective longitudinal study. J Clin Psychiatry. 77, 661-667. doi: 10.4088/JCP.15m10271.

Fusar-Poli, P., Smieskova, R., Kempton, M.J., Ho, B.C., Andreasen, N.C., Borgwardt, S., 2013. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. Neurosci Biobehav Rev. 37, 1680–1691. doi: 10.1016/j.neubiorev.2013.06.001.

Giakoumatos, C.I., Nanda, P., Mathew, I.T., Tandon, N., Shah, J., Bishop, J.R., Clementz, B.A., Pearlson, G.D., Sweeney, J.A., Tamminga, C.A., Keshavan, M.S., 2015. Effects of lithium on cortical thickness and hippocampal subfield volumes in psychotic bipolar disorder. J Psychiatr Res. 61, 180-7. doi: 10.1016/j.jpsychires.2014.12.008.

Guo, J., Huhtaniska, S., Miettunen, J., Jääskeläinen, E., Kiviniemi, V., Nikkinen, J., Moilanen, J., Haapea, M., Mäki, P., Jones, P.B., Veijola, J., Isohanni, M., Murray, G.K., 2015. Longitudinal regional brain volume loss in schizophrenia: Relationship to antipsychotic medication and change in social function. Schizophr Res 168, 297–304. doi: 10.1016/j.schres.2015.06.016.

Hafeman, D.M., Chang, K.D., Garrett, A.S., Sanders, E.M., Phillips, M.L., 2012. Effects of medication on neuroimaging findings in bipolar disorder: an updated review. Bipolar Disord. 14, 375-410. doi: 10.1111/j.1399-5618.2012.01023.x.

Haijma, S.V., Van Haren, N., Cahn, W., Koolschijn, P.C., Hulshoff Pol, H.E., Kahn, R.S., 2013. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. Schizophr Bull. 39, 1129-38. doi: 10.1093/schbul/sbs118.

Harvey, I., Persaud, R., Ron, M.A., Baker, G., Murray, R.M., 1994. Volumetric MRI measurements in bipolars compared with schizophrenics and healthy controls. Psychol Med. 24, 689-99.

Huhtaniska, S., Jääskeläinen, E., Heikka, T., Moilanen, J.S., Lehtiniemi, H., Tohka, J., Manjón, J.V., Coupé, P., Björnholm, L., Koponen, H., Veijola, J., Isohanni, M., Kiviniemi, V., Murray, G.K., Miettunen, J., 2017b. Long-term antipsychotic and benzodiazepine use and brain volume

changes in schizophrenia: The Northern Finland Birth Cohort 1966 study. Psychiatry Res. 266, 73-82. doi: 10.1016/j.pscychresns.2017.05.009.

Huhtaniska, S., Jääskeläinen, E., Hirvonen, N., Remes, J., Murray, G.K., Veijola, J., Isohanni, M., Miettunen, J., 2017a. Long-term antipsychotic use and brain changes in schizophrenia - a systematic review and meta-analysis. Hum Psychopharmacol. 32. doi: 10.1002/hup.2574.

Hulshoff Pol, H.E., Kahn, R.S., 2008. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. Schizophr Bull 34, 354–366. doi: 10.1093/schbul/sbm168.

Huopaniemi, L., Keist, R., Randolph, A., Certa, U., Rudolph, U., 2004. Diazepam-induced adaptive plasticity revealed by alpha1 GABAA receptor-specific expression profiling. J Neurochem. 88, 1059-1067.

Husa, A.P., Moilanen, J., Murray, G.K., Marttila, R., Haapea, M., Rannikko, I., Barnett, J.H., Jones, P.B., Isohanni, M., Remes, A.M., Koponen, H., Miettunen, J., Jääskeläinen, E., 2017. Lifetime antipsychotic medication and cognitive performance in schizophrenia at age 43 years in a general population birth cohort. Psychiatry Res. 247, 130-138. doi: 10.1016/j.psychres.2016.10.085.

Husa, A.P., Rannikko, I., Moilanen, J., Haapea, M., Murray, G.K., Barnett, J., Jones, P.B., Isohanni, M., Koponen, H., Miettunen, J., Jääskeläinen, E., 2014. Lifetime use of antipsychotic medication and its relation to change of verbal learning and memory in midlife schizophrenia - An observational 9-year follow-up study. Schizophr Res. 158, 134-141. doi: 10.1016/j.schres.2014.06.035.

Ivleva, E.I., Bidesi, A.S., Keshavan, M.S., Pearlson, G.D., Meda, S.A., Dodig, D., Moates, A.F., Lu, H., Francis, A.N., Tandon, N., Schretlen, D.J., Sweeney, J.A., Clementz, B.A., Tamminga, C.A., 2013. Gray matter volume as an intermediate phenotype for psychosis: Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). Am J Psychiatry. 170, 1285-96. doi: 10.1176/appi.ajp.2013.13010126.

Ivleva, E.I., Bidesim A.S., Thomas, B.P., Meda, S.A., Francis, A., Moates, A.F., Witte, B., Keshavan, M.S., Tamminga, C.A., 2012. Brain gray matter phenotypes across the psychosis dimension. Psychiatry Res. 204, 13-24. doi: 10.1016/j.pscychresns.2012.05.001.

Janssen, J., Alemán-Gómez, Y., Schnack, H., Balaban, E., Pina-Camacho, L., Alfaro-Almagro, F., Castro-Fornieles, J., Otero, S., Baeza, I., Moreno, D., Bargalló, N., Parellada, M., Arango, C., Desco, M., 2014. Cortical morphology of adolescents with bipolar disorder and with schizophrenia. Schizophr Res. 158, 91-9. doi: 10.1016/j.schres.2014.06.040. Epub 2014 Jul 29

Jurjus, G.J., Nasrallah, H.A., Olson, S.C., Schwarzkopf, S.B., 1993. Cavum septum pellucidum in schizophrenia, affective disorder and healthy controls: a magnetic resonance imaging study. Psychol Med. 23, 319-22.

Kasai, K., Shenton, M.E., Salisbury, D.F., Onitsuka, T., Toner, S.K., Yurgelun-Todd, D., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2003. Differences and similarities in insular and temporal pole MRI gray matter volume abnormalities in first-episode schizophrenia and affective psychosis. Arch Gen Psychiatry. 60, 1069-77. doi: 10.1001/archpsyc.60.11.1069.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bull 13, 261-76.

Koo, M.S., Levitt, J.J., Salisbury, D.F., Nakamura, M., Shenton, M.E., McCarley, R.W. 2008. A cross-sectional and longitudinal magnetic resonance imaging study of cingulate gyrus gray matter volume abnormalities in first-episode schizophrenia and first-episode affective psychosis. Arch Gen Psychiatry. 65, 746-60. doi: 10.1001/archpsyc.65.7.746.

Lader, M.H., Ron, M., Petursson, H., 1984. Computerized axial brain tomography in longterm benzodiazepine users. Psychol. Med. 14, 203–206.

Längle, G., Steinert, T., Weiser, P., Schepp, W., Jaeger, S., Pfiffner, C., Frasch, K., Eschweiler, G.W., Messer, T., Croissant, D., Becker, T., Kilian, R., 2012. Effects of polypharmacy on outcome in patients with schizophrenia in routine psychiatric treatment. Acta Psychiatr Scand. 125, 372-81. doi: 10.1111/j.1600-0447.2012.01835.x.

Leung, M., Cheung, C., Yu, K., Yip, B., Sham, P., Li, Q., Chua, S., McAlonan, G., 2011. Gray matter in first-episode schizophrenia before and after antipsychotic drug treatment. Anatomical likelihood estimation meta-analyses with sample size weighting. Schizophr Bull 37, 199–211. doi: 10.1093/schbul/sbp099.

Liberg, B., Ekman, C.J., Sellgren, C., Johansson, A.G., Landén, M., 2015. Subcortical morphometry and psychomotor function in euthymic bipolar disorder with a history of psychosis. Brain Imaging Behav. 9, 333-41. doi: 10.1007/s11682-014-9313-0.

Mahon, P.B., Eldridge, H., Crocker, B., Notes, L., Gindes, H., Postell, E., King, S., Potash, J.B., Ratnanather, J.T., Barta, P.E., 2012. An MRI study of amygdala in schizophrenia and psychotic bipolar disorder. Schizophr Res. 138, 188-91. doi: 10.1016/j.schres.2012.04.005.

Mahon, P.B., Lee, D.S., Trinh, H., Tward, D., Miller, M.I., Younes, L., Barta, P.E., Ratnanather, J.T., 2015. Morphometry of the amygdala in schizophrenia and psychotic bipolar disorder. Schizophr Res. 164, 199-202. doi: 10.1016/j.schres.2015.02.011.

Mamah, D., Alpert, K.I., Barch, D.M., Csernansky, J.G., Wang, L., 2016. Subcortical neuromorphometry in schizophrenia spectrum and bipolar disorders. Neuroimage Clin. 11, 276-86. doi: 10.1016/j.nicl.2016.02.011.

Manjón, J. V., Coupé, P., 2016. volBrain: an online MRI brain volumetry system. Front Neuroinform. 10:30. doi: 10.3389/fninf.2016.00030.

Mathew, I., Gardin, T.M., Tandon, N., Eack, S., Francis, A.N., Seidman, L.J., Clementz, B., Pearlson, G.D., Sweeney, J.A., Tamminga, C.A., Keshavan, M.S., 2014. Medial temporal lobe structures and hippocampal subfields in psychotic disorders: findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. JAMA Psychiatry. 71, 769-77. doi: 10.1001/jamapsychiatry.2014.453.

McDonald C1, Bullmore E, Sham P, Chitnis X, Suckling J, MacCabe J, Walshe M, Murray RM. Regional volume deviations of brain structure in schizophrenia and psychotic bipolar disorder: computational morphometry study. Br J Psychiatry. 2005 May;186:369-77.

McDonald, C., Marshall, N., Sham, P.C., Bullmore, E.T., Schulze, K., Chapple, B., Bramon, E., Filbey, F., Quraishi, S., Walshe, M., Murray, R.M., 2006. Regional brain morphometry in patients with schizophrenia or bipolar disorder and their unaffected relatives. Am J Psychiatry. 163, 478-87. doi: 10.1176/appi.ajp.163.3.478.

Moilanen, J., Huhtaniska, S., Haapea, M., Jääskeläinen, E., Veijola, J., Isohanni, M., Koponen, H., Miettunen, J., 2015. Brain morphometry of individuals with schizophrenia with and without antipsychotic medication – The Northern Finland Birth Cohort 1966 Study. Eur Psychiatry. 30, 598-605. doi: 10.1016/j.eurpsy.2015.02.009.

Moilanen, J.M., Haapea, M., Jääskeläinen, E., Veijola, J.M., Isohanni, M.K., Koponen, H.J., Miettunen, J., 2016. Long-term antipsychotic use and its association with outcomes in schizophrenia - the Northern Finland Birth Cohort 1966. Eur Psychiatry. 36, 7-14. doi: 10.1016/j.eurpsy.2016.03.002. Epub 2016 Jun 13.

Moodley, P., Golombok, S., Shine, P., Lader, M., 1993. Computed axial brain tomograms in long-term benzodiazepine users. Psychiatry Res. 48, 135-144.

Morgan, K.D., Dazzan, P., Orr, K.G., Hutchinson, G., Chitnis, X., Suckling, J., Lythgoe, D., Pollock, S.J., Rossell, S., Shapleske, J., Fearon, P., Morgan, C., David, A., McGuire, P.K., Jones, P.B., Leff, J., Murray, R.M., 2007. Grey matter abnormalities in first-episode schizophrenia and affective psychosis. Br J Psychiatry Suppl. 51, 111-6. doi: 10.1192/bjp.191.51.s111.

Navari, S., Dazzan, P., 2009. Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. Psychol Med. 39, 1763–1777. doi: 10.1017/S0033291709005315

Nenadic, I., Maitra, R., Dietzek, M., Langbein, K., Smesny, S., Sauer, H., Gaser, C., 2015a. Prefrontal gyrification in psychotic bipolar I disorder vs. schizophrenia. J Affect Disord. 185, 104-7. doi: 10.1016/j.jad.2015.06.014.

Nenadic, I., Maitra, R., Langbein, K., Dietzek, M., Lorenz, C., Smesny, S., Reichenbach, J.R., Sauer, H., Gaser, C., 2015b. Brain structure in schizophrenia vs. psychotic bipolar I disorder: A VBM study. Schizophr Res. 165, 212-9. doi: 10.1016/j.schres.2015.04.007.

Nykänen, S., Puska, V., Tolonen, J.P., Salo, H., Isohanni, M., Koponen, H., Pirkola, S., Penttilä, M., Haapea, M., Moilanen, J., Miettunen, J., Jääskeläinen, E., 2016. Use of psychiatric medications in schizophrenia and other psychoses in a general population sample. Psychiatry Res.235, 160-168. doi: 10.1016/j.psychres.2015.11.013.

Olabi, B., Ellison-Wright, I., McIntosh, A.M., Wood, S.J., Bullmore, E., Lawrie, S.M., 2011. Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. Biol Psychiatry 70, 88–96. doi: 10.1016/j.biopsych.2011.01.032.

Perera, K.M.H., Powell, T., Jenner, F.A., 1987. Computerized axial tomographic studies following long-term use of benzodiazepines. Psychol Med. 17, 775-777.

Radonić, E., Henigsberg, N., Rados, M., Mimica, N., Folnegović-Smalc, V., 2008. Temporal lobe volume in disorders with psychotic features. Coll Antropol. 32, 139-42.

Radonić, E., Rados, M. Kalember, P., Bajs-Janović, M., Folnegović-Smalc, V., Henigsberg, N., 2011. Comparison of hippocampal volumes in schizophrenia, schizoaffective and bipolar disorder. Coll Antropol. 35 Suppl 1, 249-52.

Ratnanather, J.T., Poynton, C.B., Pisano, D.V., Crocker, B., Postell, E., Cebron, S., Ceyhan, E., Honeycutt, N.A., Mahon, P.B., Barta, P.E., 2013. Morphometry of superior temporal gyrus and planum temporale in schizophrenia and psychotic bipolar disorder. Schizophr Res. 150, 476-83. doi: 10.1016/j.schres.2013.08.014.

Reite, M., Reite, E., Collins, D., Teale, P., Rojas, D.C., Sandberg, E., 2010. Brain size and brain/intracranial volume ratio in major mental illness. BMC Psychiatry. 10, 79. doi: 10.1186/1471-244X-10-79.

Rimol, L.M., Hartberg, C.B., Nesvåg, R., Fennema-Notestine, C., Hagler, D.J. Jr., Pung, C.J., Jennings, R.G., Haukvik, U.K., Lange, E., Nakstad, P.H., Melle, I., Andreassen, O.A., Dale, A.M., Agartz, I., 2010. Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. Biol Psychiatry. 68, 41-50. doi: 10.1016/j.biopsych.2010.03.036.

Rosa, P.G., Schaufelberger, M.S., Uchida, R.R., Duran, F.L., Lappin, J.M., Menezes, P.R., Scazufca, M., McGuire, P.K., Murray, R.M., Busatto, G.F., 2010. Lateral ventricle differences between first-episode schizophrenia and first-episode psychotic bipolar disorder: A population-based morphometric MRI study. World J Biol Psychiatry. 11, 873-87. doi: 10.3109/15622975.2010.486042.

Rosa, P.G., Zanetti, M.V., Duran, F.L., Santos, L.C., Menezes, P.R., Scazufca, M., Murray, R.M., Busatto, G.F., Schaufelberger, M.S., 2015. What determines continuing grey matter changes in first-episode schizophrenia and affective psychosis? Psychol Med. 45, 817-28. doi: 10.1017/S0033291714001895.

Salokangas, R.K., Cannon, T., Van Erp, T., Ilonen, T., Taiminen, T., Karlsson, H., Lauerma, H., Leinonen, K.M., Wallenius, E., Kaljonen, A., Syvälahti, E., Vilkman, H., Alanen, A., Hietala, J., 2002. Structural magnetic resonance imaging in patients with first-episode schizophrenia, psychotic and severe non-psychotic depression and healthy controls. Results of the schizophrenia and affective psychoses (SAP) project. Br J Psychiatry Suppl. 43, 58-65.

Scherk, H., Falkai, P., 2006. Effects of antipsychotics on brain structure. Curr Opin Psychiatry. 19, 145-50. doi: 10.1097/01.yco.0000214339.06507.d8

Schmauss, C., Krieg, J.C., 1987. Enlargement of cerebrospinal fluid spaces in long-term benzodiazepine abusers. Psychol Med. 17, 869-873.

Shepherd, A.M., Laurens, K.R., Matheson, S.L., Carr, V.J., Green, M.J., 2012. Systematic meta-review and quality assessment of the structural brain alterations in schizophrenia. Neurosci Biobehav Rev. 36, 1342–1356. doi: 10.1016/j.neubiorev.2011.12.015.

Smieskova, R., Fusar-Poli, P., Allen, P., Bendfeldt, K., Stieglitz, R.D., Drewe, J., Radue, E.W., McGuire, P.K., Riecher-Rössler, A., Borgwardt, S.J., 2009. The effects of antipsychotics on the brain: What have we learnt from structural imaging of schizophrenia? - A systematic review. Curr. Pharm. Des. 15, 2535–2549.

Strakowski, S.M., DelBello, M.P., Sax, K,W., Zimmerman, M.E., Shear, P.K., Hawkins, J.M., Larson, E.R., 1999. Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. Arch Gen Psychiatry. 1999 Mar;56(3):254-60.

Strasser, H.C., Lilyestrom, J., Ashby, E.R., Honeycutt, N.A., Schretlen, D.J., Pulver, A.E., Hopkins, R.O., Depaulo, J.R., Potash, J.B., Schweizer, B., Yates, K.O., Kurian, E., Barta, P.E., Pearlson, G.D., 2005. Hippocampal and ventricular volumes in psychotic and nonpsychotic bipolar patients compared with schizophrenia patients and community control subjects: a pilot study. Biol Psychiatry. 57, 633-9. doi: 10.1016/j.biopsych.2004.12.009.

Takita, Y., Takaesu, Y., Ono, K., Futenma, K., Shimura, A., Murakoshi, A., Komada, Y., Inoue, Y., Inoue, T., 2016. Association between the high-dose use of benzodiazepines and rehospitalization in patients with schizophrenia: a 2-year naturalistic study. Neuropsychiatr Dis Treat. 12, 3243-3247. doi: 10.2147/NDT.S118759.

Uhde, T.W., Kellner, C.H., 1987. Cerebral ventricular size in panic disorder. J Affect Disord. 12, 175-178.

Veijola, J., Guo, J.Y., Moilanen, J.S., Jääskeläinen, E., Miettunen, J., Kyllönen, M., Haapea, M., Huhtaniska, S., Alaräisänen, A., Mäki, P., Kiviniemi, V., Nikkinen, J., Starck, T., Remes, J.J., Tanskanen, P., Tervonen, O., Wink, A.M., Kehagia, A., Suckling, J., Kobayashi, H., Barnett, J.H., Barnes, A., Koponen, H.J., Jones, P.B., Isohanni, M., Murray, G.K., 2014. Longitudinal changes in total brain volume in schizophrenia: Relation to symptom severity, cognition and antipsychotic medication. PLoS One 9: e101689. doi: 10.1371/journal.pone.0101689.

Vernon, A.C., Crum, W.R., Lerch, J.P., Chege, W., Natesan, S., Modo, M., Cooper, J.D., Williams, S.C., Kapur, S., 2014. Reduced cortical volume and elevated astrocyte density in rats chronically treated with antipsychotic drugs-linking magnetic resonance imaging findings to cellular pathology. Biol Psychiatry. 75, 982-890. doi: 10.1016/j.biopsych.2013.09.012.

Vernon, A.C., Natesan, S., Modo, M., Kapur, S., 2011. Effect of chronic antipsychotic treatment on brain structure: a serial magnetic resonance imaging study with ex vivo and postmortem confirmation. Biol Psychiatry. 69, 936-944. doi: 10.1016/j.biopsych.2010.11.010.

Vita, A., De Peri, L., Deste, G., Barlati, S., Sacchetti, E., 2015. The effect of antipsychotic treatment on cortical gray matter changes in schizophrenia: Does the class matter? A meta-analysis and meta-regression of longitudinal magnetic resonance imaging studies. Biol Psychiatry. 78, 403-412. doi: 10.1016/j.biopsych.2015.02.008.

WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2011. Norwegian Institute of Public Health; 2010 (Oslo).

Wood, S.J., Pantelis, C., Velakoulis, D., Yücel, M., Fornito, A., 2008. Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risk. Schizophr Bull. 34, 322–329. doi: 10.1093/schbul/sbm149.

Woodward, N.D., Heckers, S., 2015. Brain Structure in Neuropsychologically Defined Subgroups of Schizophrenia and Psychotic Bipolar Disorder. Schizophr Bull. 41, 1349-59. doi: 10.1093/schbul/sbv048.

Yüksel, C., McCarthy, J., Shinn, A., Pfaff, D.L., Baker, J.T., Heckers, S., Renshaw, P., Ongür, D., 2012. Gray matter volume in schizophrenia and bipolar disorder with psychotic features. Schizophr Res. 138, 177-82. doi: 10.1016/j.schres.2012.03.003.