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Sanna Huhtaniska

THE ASSOCIATION BETWEEN ANTIPSYCHOTIC AND BENZODIAZEPINE USE WITH BRAIN MORPHOLOGY AND ITS CHANGES IN SCHIZOPHRENIA

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
MEDICAL RESEARCH CENTER OULU;
OULU UNIVERSITY HOSPITAL

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Abstract

The association between antipsychotics and brain volume changes in schizophrenia is not clear. Previous imaging studies have not examined benzodiazepine use, though it has been linked to cognitive impairment. The aim of this thesis was to examine the association between long-term antipsychotic and benzodiazepine use and brain structures in schizophrenia.

Based on a systematic review and meta-analysis of previous studies on long-term antipsychotic use and brain changes in schizophrenia, a higher antipsychotic exposure associated with parietal lobe decrease and basal ganglia increase. Previous data on the topic is very heterogenous and the overall number of studies is small (N=34). Most reported findings were non-significant.

In the Northern Finland Birth Cohort 1966, 38 cases with schizophrenia spectrum disorder participated in the longitudinal study at the ages of 34 and 43. In the cross-sectional study, 44 cases with schizophrenia and 24 cases with affective psychoses participated at the age of 43. Structural brain MRI scans were acquired from all participants and data on antipsychotic and benzodiazepine dose was collected using medical records and interviews. Illness severity and antipsychotic/ benzodiazepine dose were included as confounders in the analyses.

Higher scan-interval antipsychotic dose associated to volume increase in lateral ventricles and higher benzodiazepine dose associated to volume decrease in the caudate nucleus during the 9-year follow-up. In the 43-year study, higher lifetime antipsychotic dose associated to smaller nucleus accumbens volume in schizophrenia. In comparison, higher lifetime benzodiazepine dose associated to larger volumes of total gray matter, cerebral gray matter, and thalamus in affective psychoses. In analyses without illness severity and other medication as confounders, there were several statistically significant associations.

It seems that long-term antipsychotic use may associate to structural brain changes in schizophrenia and some associations may be confounded by symptoms and the use of benzodiazepines. These findings underline the importance of taking benzodiazepine use and other confounding factors into account when studying the effects of antipsychotics on the brain. Further studies should focus on how these findings relate to cognition and functioning.

Keywords: antipsychotics, benzodiazepines, brain structures, MRI, schizophrenia

Huhtaniska, Sanna, Psykoosilääkkeiden ja bentsodiatsepiinien yhteys aivojen rakenteellisiin muutoksiin skitsofreniassa.

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Tiivistelmä

Psykoosilääkityksen yhteys skitsofreniassa tapahtuviin aivomuutoksiin on epäselvä. Aiemmat kuvantamistutkimukset eivät ole tutkineet bentsodiatsepiinien käyttöä, vaikka niiden käyttö on yhdistetty heikompaan kognititioon. Tämän tutkimuksen tarkoituksena oli selvittää pitkäaikaisen psykoosi- ja bentsodiatsepiinlääkityksen yhteyttä aivojen rakenteisiin skitsofreniassa.

Systemaattisen katsauksen ja meta-analyysin perusteella suurempi psykoosilääkeannos liittyi päälakilohkon tilavuuden pienenemiseen sekä tyvitumakkeiden koon kasvuun skitsofreniassa pitkäaikaisseurannoissa. Aikaisempi kirjallisuus on erittäin heterogeenistä ja tutkimusten kokonaismäärä on pieni (N=34). Suurin osa löydöksistä ei ollut tilastollisesti merkitseviä.

Pohjois-Suomen syntymäkohortti 1966 aineistossa 38 skitsofreniaspektrin psykoosia sairastavaa henkilöä osallistui pitkittäistutkimukseen 34 vuoden ja 43 vuoden iässä. Poikkileikkaustutkimuksessa 44 skitsofreniaa ja 24 mielialapsykoosia sairastavaa henkilöä osallistui tutkimukseen 43 vuoden iässä. Pään rakenteellinen magneettikuvaus tehtiin kaikille osallistujille. Tiedot psykoosilääkkeiden ja bentsodiatsepiinien annoksista kerättiin sairauskertomusmerkinnöistä ja haastatteluista. Taudin vakavuus ja psykoosilääkkeiden/bentosidatsepiinien annos huomioitiin sekoittavina tekijöinä.

Korkeampi psykoosilääkeannos liittyi aivokammioiden koon kasvuun ja korkeampi bentsodiatsepiiniannos häntätumakkeen koon pienenemiseen 9 vuoden seurannassa. Poikkileikkaustutkimuksessa korkeampi elinaikainen psykoosilääkeannos liittyi pienempään makaavan tumakkeen tilavuuteen skitsofreniassa. Mielialapsykooseissa korkeampi elinaikainen bentsodiatsepiiniannos liittyi suurempaan koko aivojen harmaan aineen, isoaivojen harmaan aineen ja talamuksen tilavuuteen. Kun sekoittavia tekijöitä ei otettu huomioon, tilastollisesti merkitseviä yhteyksiä löytyi useammilta aivoalueilta

Tutkimuksen perusteella psykoosilääkkeiden pitkäaikaiskäyttö saattaa liittyä aivojen rakenteellisiin muutoksiin skitsofreniassa. Bentsodiatsepiinien käyttö ja oireet voivat toimia sekoittavina tekijöinä. Löydökset korostavat sekoittavien tekijöiden huomioimisen tärkeyttä tutkittaessa psykoosilääkkeiden vaikutuksia aivoihin. Tulevaisuudessa tutkimusten tulisi selvittää, miten löydökset liittyvät kognitioon ja toimintakykyyn.

Asiasanat: aivot, bentsodiatsepiinit, MRI, psykoosilääkkeet, skitsofrenia

To my family

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Oulu, November 2017 Sanna Huhtaniska

Abbreviations

BDNF	Brain derived neurotropthic factor
BMI	Body mass index
BZDy	Benzodiazepine dose-year
CNS	Central nervous system
CPZy	Chlorpromazine equivalent dose-year
CRHC	Care Register for Health Care
CSF	Cerebrospinal fluid
CT	Computed tomography
D2	Dopamine receptor 2
DDDy	Defined daily dose-year
DSM	Diagnostic and Statistical Manual of Mental Disorders
GABA	Gamma-aminobutyric acid
GM	Gray matter
ICD	International Statistical Classification of Diseases and Related Health Problems
ICV	Intra cranial volume
MRI	Magnetic Resonance Imaging
NFBC1966	Northern Finland Birth Cohort 1966
NMDA	N-methyl-D-aspartate
PANSS	Positive and Negative Syndrome Scale
SCID	The Structured Clinical Interview for DSM disorders
SII	Social Insurance Institution of Finland
SOFAS	Social and Occupational Functioning Assesment Scale
TNF-alpha	Tumor necrosis factor alpha
VBM	Voxel-based morphometry
WHO	World Health Organization
WM	White matter

List of original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:

I Huhtaniska S, Jääskeläinen E, Hirvonen N, Remes J, Murray GK, Veijola J, Isohanni M & Miettunen J (2017) Long-term antipsychotic use and brain changes in schizophrenia - a systematic review and meta-analysis. Hum Psychopharmacol, 32(2).

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Contents

1 Introduction

Schizophrenia is one of the most serious psychiatric disorders if not the most severe. The outcome is often unfavorable and the recovery rate has not improved during last decades (Jääskeläinen *et al*. 2013) regardless of the advances in the treatment. The prevalence of schizophrenia is 0.46 % worldwide (Saha *et al*. 2005), but in Northern Finland the prevalence is as high as 1.8 % (Perälä *et al*. 2008).

Schizophrenia is a psychotic illness with both neurodevelopmental and suggested neurodegenerative disturbances of the brain (Isohanni *et al*. 2005). The size of the whole brain is smaller and the size of the ventricles is larger in patients with schizophrenia than in controls (Kempton *et al*. 2010, Wright *et al*. 2000). Differences in brain volume have been detected particularly in frontal and temporal lobes, anterior cingulate, hippocampus, amygdala, thalamus, and insula, and these changes have been considered progressive (Honea *et al*. 2005, Hulshoff Pol & Kahn 2008, Navari & Dazzan 2009, Shepherd *et al*. 2012, Torres *et al*. 2013). Though these structural brain changes are confirmed by many case-control studies, factors associating to these changes have not been examined thoroughly especially in longitudinal designs.

Antipsychotic medication is the key treatment to decrease positive symptoms in schizophrenia and other psychoses. Though antipsychotics are effective in preventing relapses during the first two years and when treating the positive symptoms (Leucht *et al*. 2009), their effectiveness and the adverse effects after the first few years of illness onset are not clear (Sohler *et al*. 2015). Antipsychotics also have significant side effects, such as hypertriglyceridemia (Saari *et al*. 2004) and excess metabolic syndrome (Koponen *et al*. 2002, Vancampfort *et al.* 2015).

In addition to antipsychotic medication, people with psychotic disorders are often prescribed benzodiazepines as sedatives, anxiolytics, to reduce aggressiveness, or to ease agitation. Benzodiazepine use has been associated to increased risk of mortality both in general population (Tiihonen *et al*. 2016) and in schizophrenia (Fontanella *et al*. 2016), and to decline in cognition (Baandrup *et al*. 2017, Barker *et al*. 2004a, 2004b, 2005). Despite these findings, benzodiazepine effects on brain structures have not been studied previously in schizophrenia or other psychiatric disorders through using MRI, though there are a few computed tomography (CT) studies on benzodiazepine effects on ventricular enlargement (Busto *et al*. 2000, Lader *et al*. 1984, Moodley *et al*. 1993, Perera *et al*. 1987, Schmauss & Krieg, 1987, Uhde & Kellner 1987).

The possible effect of antipsychotic medication on the brain changes detected in schizophrenia was suggested already in the 1970's (Marsden 1976), but only recently researchers have begun to focus more on the possible effects antipsychotic medication might have on the brain morphology and functioning. The relationship is debatable, and it has been of great interest in schizophrenia research during the past years (Andreasen *et al*. 2013, Fusar-Poli *et al*. 2013, Ho *et al*. 2011, Radua *et al*. 2012, Roiz-Santiañez *et al*. 2015). Earlier reviews have suggested, that some of the regional brain volume changes in schizophrenia may be related to illness stage or medication status (Shepherd *et al*. 2012) and comparisons between schizophrenia cases and controls may be confounded by medication effects (Navari & Dazzan 2009). Long-term use of antipsychotics on high doses has also been found to be associated with unfavorable changes in brain functioning (Radua *et al*. 2012).

Previous studies and reviews on medication effects on brain structures in schizophrenia have mainly focused on short follow-ups (1-2 years), and the associations have been studied mostly with cross-sectional variables or brain volumes have been compared between groups using or not using antipsychotics. Only a few studies have taken potential confounders, such as illness stage or severity, into account in their analyses.

Since the use of antipsychotics and benzodiazepines is often long-term (even life-long in case of antipsychotics), and they have both been associated with unfavorable outcomes associated with brain functioning, it is important to clarify, whether there are associations between these medications and brain structures on macroscopic level. Naturalistic studies offer important information on long-term medication effects, since it is very hard to conduct randomized controlled trials lasting several years (Wang *et al*. 2011). The objective of this study was to focus on the effects of long-term antipsychotic and benzodiazepine use on brain structures in schizophrenia and affective psychoses in a population-based sample.

2 Review of the literature

2.1 Schizophrenia

Schizophrenia is a severe psychotic disorder, in which the ability to distinguish internal stimuli from actual stimuli is disturbed and the relationship with reality is impaired. The symptoms of schizophrenia are divided into positive symptoms including hallucinations, delusions and disorganized speech and behavior, and negative symptoms including apathy, social withdrawal and anhedonia (APA 2013). The symptoms vary between patients and even within the same patient in different phases of the illness. Schizophrenia is also characterized with cognitive impairment.

In Finland, the diagnosis of schizophrenia is based on structured diagnostic criteria according to the International Classification of Diseases, Revision 10 (ICD-10; WHO 1992). More detailed diagnostic criteria based on Diagnostic and Statistical Manual of Mental Disorders (DSM – American Psychiatric Association, APA) and its different updated versions are also used especially for research purposes. The differences between these two diagnostic criteria are mainly in the duration of the symptoms – according to ICD the symptoms are required to last at least for a month and according to DSM six months. The diagnostic criteria for DSM-IV (Americal Psychiatric Association 1994), which have been used in this thesis, are presented in Table 1.

Table 1. The diagnostic criteria of schizophrenia according to DSM-IV (APA 1994).

Diagnostic criteria	Description
Symptoms	Criterion A Two or more of the following: 1. Delusions (e.g. being controlled, thought broadcasting, thought insertion or withdrawal) 2. Hallucinations 3. Disorganized speech 4. Grossly disorganized or catatonic behavior 5. Negative symptoms, i.e. affective flattening, alogia or, avolition Exception: Only one criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts or two or more voices communicating with each other. Criterion B Social or occupational dysfunction One or more major areas of functioning such as work, relations or self-care are markedly below the level achieved prior to the onset Criterion C Duration: Continuous signs of the disturbance persist for at least 6 months, including at least 1 month of symptoms (or less if successfully treated) that meet Criterion A and may include periods of prodromal or residual symptoms.
Exclusion criteria or other specific criteria	Criterion D Schizoaffective and Mood Disorder exclusion: No major depressive, manic or mixed episodes have occurred concurrently with the active-phase symptoms, and if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods. Criterion E Substance/general medical condition exclusion: The disturbance is not due to direct physiological effects of a substance or a general medical condition. Criterion F Relationship to a pervasive developmental disorder: If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

In addition to schizophrenia, there are also other *schizophrenia spectrum disorders,* which include schizophreniform disorder, delusional disorder and schizoaffective disorder. These disorders include similar symptoms, but their duration may be shorter and the disorder might not be as severe as in schizophrenia. Based on DSM criteria, *schizophreniform disorder* has the same symptoms as schizophrenia, but the duration of the symptoms is shorter: symptoms should last at least 1 month but under 6 months. In *delusional disorder* the main feature is the presence of delusions, that are not completely culturally inadequate and the duration of these delusions is required to be at least three months. In addition, no other psychotic symptoms should be present for the diagnosis of delusional disorder. *Schizoaffective disorder* includes symptoms from both schizophrenia and affective disorders: the psychotic symptoms resemble schizophrenia and the symptoms also fulfil diagnostic criteria for moderate or severe depression or mania. The mood disorder should be present for at least half of the illness duration in schizoaffective disorder. Other schizophrenia spectrum disorders are often studied as a part of a group of cases with schizophrenia.

Schizophrenia is not only the most severe psychotic disorder, but also a major public health burden that affects both those who have fallen ill and also their families and friends. The course of illness varies between individuals, and the outcomes range from recovery to difficult disability. Symptomatic remission is achieved by 7-52% of the individuals in the long-term (Lang *et al*. 2013). Regardless of the advances in pharmacological and psychosocial interventions, the recovery has stayed at the same level or even decreased during the last decades (Jääskeläinen *et al*. 2013). The functional outcomes are not satisfactory either (Schennach *et al*. 2012) and the rate of employment is as low as 10-20% (Marwaha & Johnson 2004). In addition, medication adherence is often poor (Phan 2016, García *et al*. 2016) and only a minority of the patients has regular contact with the health care providers (Nykänen *et al*. 2016).

2.1.1 Epidemiology and etiology of schizophrenia

The incidence of schizophrenia varies around the world over five-fold (McGrath *et al*. 2008), and the prevalence is on average 0.46 % (Saha *et al*. 2005). In Northern Finland the prevalence is as high as 1.8 % (Perälä *et al*. 2008). The incidence peaks at early adulthood, at around 18-25 years of age (Jackson *et al*. 2013), but schizophrenia can occur at all ages. The hypothesis behind the increased incidence in early adulthood is based on neurodevelopmental factors and altered functioning

of the maturing brain (Keshavan 1999, Keshavan & Hogarty 1999, Owen *et al.* 2011).

Schizophrenia is considered as a neurodevelopmental disorder with genetic risk factors, and the pathway leading to illness onset is also regulated by various different environmental factors. The heritability is high (Cardno & Gottesman 2000, Kendler *et al*. 1993), and there are various genes that are linked to the risk of schizophrenia (Tandon *et al*. 2008), though no individual gene accounts for the onset of the disease. Also several environmental risk factors from prenatal period to adolescence and adulthood have been found to increase the risk of schizophrenia. These include e.g. abnormal fetal growth and complications in delivery (Cannon *et al*. 2002, Matheson *et al*. 2014), delayed motor development (Filatova *et al*. 2017), childhood adverse events (Matheson *et al*. 2014, Mayo *et al*. 2017), poor school performance (MacCabe *et al*. 2008) and cannabis (Matheson *et al*. 2014, Wilkinson *et al*. 2014) and tobacco use (Gurillo *et al*. 2015). In addition, immunological and inflammation related processes increase the risk of schizophrenia and may affect disease onset (Brown 2006, Karlsson *et al*. 2001, Matheson *et al*. 2014). There is an increased incidence of gastrointestinal barrier dysfunction, food antigen sensitivity, inflammation and metabolic syndrome in schizophrenia and the proinflammatory cytokine levels in serum are higher in schizophrenia cases than in controls (Nemani *et al*. 2015). Schizophrenia cases also have a higher risk for developing autoimmune diseases than normal populations (Strous & Shoenfeld 2006).

The aetiology of schizophrenia is still unknown, though there are several aetiological models that try to explain the pathogenetic processes behind the illness onset. One of the major pathological features is the disturbance of synaptic connectivity due to risk gene expression (e.g. DISC-1), which is known to regulate neurotransmitter systems and signaling pathways in the brain (Balu & Coyle 2011).

In the *stress-vulnerability model* (van Os *et al*. 2010) the underlying sensitivity to schizophrenia is triggered to illness onset by psychological stress (e.g. traumatic events or regular stress during maturation). The *gene-interaction model* differs from the latter in the sense that the effects of environmental risk factors depend on genetic liability and both of them are needed for illness onset (Maynard *et al*. 2001, Mittal *et al*. 2008, Tsuang *et al*. 2004).

The *neurodevelopmental hypothesis* is based on three facts: an existing association between pre- and perinatal adverse events and later schizophrenia; developmental motor, physical and other challenges in children that later develop schizophrenia; and imaging studies showing that structural brain alterations are

already present at the onset of schizophrenia (Howes & Murray 2014, Murray & Lewis 1987, Weinberger 1987). According to the hypothesis, schizophrenia occurs as a result of disturbed maturation of the brain due to various risk factors, it starts already in the prenatal period and continues as the brain develops towards adulthood (Rapoport *et al*. 2012). Critique towards the neurodevelopmental hypothesis has been raised since it does not account for all the features of schizophrenia, for example the progressive deterioration and progressive changes observed in brain imaging (Fatemi & Folsom 2009, Pantelis *et al.* 2005).

Based on the *neurodegenerative hypothesis* schizophrenia is a chronic, progressive disorder that results in biochemical changes, which lead to different clinical syndromes (Pino *et al*. 2014). The progressive neuroanatomical changes observed in schizophrenia and the often deteriorating course of illness suggest the idea of a continuous process in the brain. A novel suggestion, *progressive neurodevelopmental hypothesis* combines both neurodevelopmental and neurodegenerative hypotheses as an integrated model (Pino *et al*. 2014).

To summarize, several factors, such as genetic predisposition, disruptions in brain development, neuroimmunological processes and environmental factors result in disturbances of the normal synaptic connectivity, which leads to the onset of schizophrenia (Faludi & Mirnicks 2011). Since there is evidence for many different aetiological theories, the truth is most likely a combination of these different models and might vary between individuals. The complex pathophysiology has even been suggested to be individual (Faludi & Mirnicks 2011).

The neurobiology behind schizophrenia is not clear either. The role of *dopamine* seems to be essential, since a hyperdopaminergic state induced by stimulants leads to psychotic symptoms. Individuals at high risk for schizophrenia, that later develop psychosis, show higher dopamine synthesis capacity (Howes *et al*. 2011). In addition, the effects of antipsychotics on positive symptoms are mediated through dopamine receptor 2 (D2). It has been suggested that the onset of psychosis is preceded by excessive dopaminergic activity in the mesolimbic pathway (Howes et al. 2017, Miyamoto *et al*. 2012, Weinberger 1987) and the negative symptoms are thought to be the result of a reduced dopaminergic signalling in the mesocortical pathways (Hensler *et al*. 2013, Toda & Abi-Dargham 2007). In addition to the dopamine hypothesis, the dysfunction of glutamatergic, serotonergic and gamma-aminobutyric acid (GABA) signalling may also lead to aberrant functioning of interneurons and manifest as cognitive, behavioral and social dysfunction (Yang & Tsai 2017). Glutamate is the primary excitatory

neurotransmitter in the brain, and its effects are controlled by N-methly-D-aspartate (NMDA) receptors. NMDA receptor antagonists have induced schizophrenia-like positive, negative and cognitive symptoms in healthy individuals (Insel 2010), and thus these receptors are also being investigated for new antipsychotic agents (Javitt *et al*. 2012).

2.1.2 Brain structures in schizophrenia

Johnstone *et al*. (1976) conducted the first study which compared brain structures between schizophrenia cases and controls. Ventricular size was found to be larger in schizophrenia cases and it correlated with poorer cognitive measures (Johnstone *et al*. 1976). The first MRI study with a very small sample was published in 1984 (Smith *et al*. 1984) and since then MRI studies have become the primary method for investigating brain abnormalities in schizophrenia.

By now, it is clear, that there are progressive structural changes in the brain in schizophrenia in comparison with the healthy controls, and these changes have been reported especially in frontal and temporal lobes, anterior cingulate, hippocampus, amygdala, thalamus, and insula (Shepherd *et al*. 2012, Torres *et al*. 2013). Brain grey matter (GM) reductions have also been found in first episode, drug naïve schizophrenia patients (Leung *et al*. 2011) as well as in populations at high risk for psychosis (Wood *et al*. 2008). Since some of the findings occur before the actual illness onset, it leads us to think that they are related to developmental factors. On the other hand, as the changes may be progressive already from before illness onset and continue to progress over time, it points to a degenerative process (Job *et al.* 2005, Pantelis *et al.* 2003). However, the findings vary greatly between studies and not all individuals with schizophrenia seem to manifest these alterations, so it is likely, that some environmental factors such as medications, alcohol or drug use, or dietary factors also affect these structural alterations. The possible effects of confounding factors are not often taken into account in case control studies, and thus, the effects of medication may be a confounding factor in comparisons between controls and individuals with schizophrenia (Shepherd *et al*. 2012).

2.1.3 Treatment of schizophrenia

According to the Finnish Schizophrenia Current Care Guidelines (Schizophrenia (online). Current Care Guidelines, 2015) the treatment of schizophrenia is based on long-lasting, confidential relationship with the medical staff. Every individual

should have their own personalized treatment plan, which is made in co-operation with the patients themselves. The treatment should be a combination, which includes antipsychotic medication with lowest possible dose to reduce symptoms, psychosocial treatments such as cognitive behavioral therapy, psychoeducation, and occupational and vocational rehabilitation. Due to significant relapse risk, antipsychotic treatment should be continued for at least 2-5 years after the first psychotic episode and even longer based on symptoms and individual risks for relapses. The course of schizophrenia is very heterogenic varying from one psychotic episode to several relapses or continuous symptoms, so the treatment may last for a few years or it may be life-long. The aim is to reduce symptoms and achieve remission or even recovery. There is only evidence for add-on benzodiazepine treatment in acute phase of schizophrenia (Volz *et al*. 2007). However, there is no evidence of its additional effectivity in the long-term treatment, but instead adverse effects are reported (Tiihonen *et al*. 2012). Still, they are quite commonly used to treat anxiety, agitation or for their sedative effects (Schizophrenia (online). Current Care Guidelines, 2015).

2.2 Association between antipsychotics and benzodiazepines and brain structures

2.2.1 Association between antipsychotics and brain structures in schizophrenia

The relationship between antpsychotics and brain structures in schizophrenia has been of much interest during recent years. Antipsychotics are used in all psychotic disorders and they are the main pharmacological treatment in schizophrenia.

The exact mechanisms of antipsychotics are still not completely established. It is thought that their efficacy for psychotic symptoms is achieved by blocking D2, which are thought to mediate the positive symptoms (Miyamoto *et al*. 2012, Seeman 1992). Antipsychotics are traditionally divided into two subgroups based on their D2 binding potential and side effect profiles.

Typical antipsychotics were developed first and created the foundation for antipsychotic treatment in psychoses. After the difficult side effects of strong D2 blocking were recognized, new agents with better tolerance were invented. These second generation antipsychotics are called atypical antipsychotics, and one definition for them is that they produce minimal extrapyramidal symptoms while

acting clinically effectively on psychotic symptoms (Meltzer 2000), though this definition is not completely accurate (Farah 2005). Atypical antipsychotics have lower D2 blocking ability, but they are also much more effective in blocking dopamine-4 receptors in the GABA regulated interneurons and 5-HT_{2A} serotonergic receptors (Heckers 2000, Kusumi *et al.* 2015). Though the division between the two medication groups is also criticized, it is commonly used both in clinical practice and for research purposes.

Antipsychotics are effective for the treatment of acute psychosis and particularly positive symptoms (Leucht *et al*. 2017). It has also been shown that antipsychotics prevent relapses (Leucht *et al*. 2012) and may reduce mortality in schizophrenia (Tiihonen *et al*. 2009, 2016, Torniainen *et al*. 2015), but their effectiveness during years of treatment is not fully known (Sohler *et al*. 2015). In addition to their efficacy for treating psychosis, antipsychotics have also some major somatic side effects such as hypertriglyceridemia (Saari *et al*. 2004) and excess metabolic syndrome (Koponen *et al*. 2002, Vancampfort *et al.* 2015), which are associated to worse cardiovascular health and premature mortality (Laursen *et al*. 2014). The metabolic side effects have also been linked to cognitive dysfunction, which is linked to lower BDNF levels and higher TNF-alpha levels (Zhang *et al*. 2017).

A systematic search for reviews and meta-analyses on the association between antipsychotics and brain structures in schizophrenia were conducted in January 2015, August 2015 and updated in July 2017. The search located 9 systematic reviews examining longitudinal associations and 3 reviews examining cross-sectional associations between antipsychotics and brain structures in schizophrenia. These studies are presented in Table 2. The results of the reviews are not conclusive.

The longitudinal reviews report decreased GM volumes (Aderhold *et al*. 2015, Fusar-Poli *et al*. 2013, Smieskova *et al*. 2009, Torres *et al*. 2013, Vita *et al*. 2015), mixed resuls on GM, WM and basal ganglia (Roiz-Santiañez *et al*. 2015), basal ganglia volume increase (Ebdrup *et al*. 2013, Torres *et al*. 2013), increase in lateral ventricles (Fusar-Poli *et al*. 2013), no effect on lateral ventricles (Roiz-Santiañez *et al*. 2015) and mixed results (Moncrieff & Leo 2010). Based on these previous reviews on longitudinal studies, typical antipsychotics seem to associate to decrease in the volumes of the whole brain, frontal, temporal and parietal GM (Vita *et al*. 2015) and increased GM volume in the basal ganglia (Smieskova *et al*. 2009), and one suggests the effect of typical antipsychotics to be of greater magnitude than the effect of atypical antipsychotics (Navari & Dazzan 2009). On the other hand, in another review cases treated with only atypical antipsychotics did not show

decrease in whole brain or parietal GM (Vita *et al*. 2015) and atypical antipsychotics were associated with basal ganglia volume increases non-consistently (Ebdrup *et al*. 2013). Two studies reported no clear differences between typical and atypical antipsychotics (Aderhold *et al*. 2015, Roiz-Santiañez *et al*. 2015).

According to the previous systematic reviews on cross-sectional studies higher doses of antipsychotics associate to lower total (Haijma *et al*. 2013) and midbrain volumes (Navari & Dazzan 2009). Typical antipsychotics associate to lower gray matter (Haijma *et al*. 2013), larger basal ganglia and thalamic volumes (Navari & Dazzan 2009, Scherck & Falkai 2006, Smieskova *et al*. 2009), and atypical antipsychotics associate to larger volume of caudate nucleus (Haijma *et al*. 2013), thalamus (Navari & Dazzan 2009, Scherck & Falkai 2006, Smieskova *et al*. 2009) and hippocampus (Navari & Dazzan 2009). The potential mechanisms how antipsychotics may affect brain structures are presented in the discussion.

Previous studies of antipsychotics and brain structures in the NFBC1966

There are also previous studies in the Northern Finland Birth Cohort 1966 regarding antipsychotics and brain structures in schizophrenia. Higher amount of antipsychotic medication over the 9-year follow-up associated to total brain volume loss and ventricular enlargement (Veijola *et al*. 2014, Guo *et al*. 2015). At the age of 34, individuals with antipsychotic medication had lower total GM volumes than those without medication, and the time spent without antipsychotic medication associated with larger total GM volume (Moilanen *et al*. 2015). Lifetime cumulative antipsychotic dose or type of antipsychotic medication did not associate to brain morphometry at the age of 34 years (Moilanen *et al*. 2015).

Though this thesis focuses on the same subject as these previously published studies, the methods used are different. At the time these previous studies were conducted, data on separate brain structure volumes were not yet available for the sample. In the previous follow-up studies (Veijola *et al*. 2014, Guo *et al*. 2015), we used a different analyzing method, FSL tool SIENA, to examine brain edge movement over time (indicating atrophy), and SIENA focuses only on the surface of the brain (cortex and ventricular edges). In the cross-sectional study (Moilanen *et al*. 2015) the focus was on comparing individuals with or without medication and only the volume of total gray matter was examined in addition to a voxel-based morphometry (VBM) approach.

Table 2. Earlier systematic reviews and meta-analyses on the association between antipsychotics and brain volumes. Studies are presented in chronological order from most recent to older ones.

Author, year	Study type Time of the collection of studies Number of studies	Follow-up	Main results[1]	Comment
Longitudinal reviews				
Vita *et al.* 2015	Meta-analysis, meta-regression Studies were collected until March 31, 2014 18 longitudinal studies	7.3 months to 7.2 years	Treatment with first-generation antipsychotics or mixed antipsychotic treatment associated to decrease in volumes of whole-brain, frontal, temporal and parietal GM. Cases treated with only second-generation antipsychotics did not show decrease in whole-brain or parietal GM, and for frontal and temporal GM there was even an increase, though not statistically significant.	Focused on studies on cortical GM Authors of the original publications were contacted if the studies did not report the data required on antipsychotic dose and only if a response was not received, the study was excluded.
Roiz- Santiáñez *et al.* 2015	Systematic review Studies were collected from 1994 to 2014. 41 longitudinal studies	4 weeks to 7.2 years	Mixed results regarding white and gray matter, whole brain, cortical thickness and basal ganglia. No effect on lateral ventricles. No clear differences between typical and atypical antipsychotics	Broad inclusion criteria. Most studies enrolled first episode patients. Results of studies with years of follow-up were not presented separately from shorter-term studies.
Aderhold *et al.* 2015	Systematic review Studies were published between 1995 and mid-2013. 15 longitudinal studies	10 months to 7.2 years	There is evidence for grey and white matter volume changes of the frontal brain, which cannot be explained by the severity of the disease alone.	Article in German. Included only studies with a follow-up of maximum 10 months Focused on frontal brain areas.

Author, year	Study type Time of the collection of studies Number of studies	Follow-up	Main results[1]	Comment
			No clear difference between atypical and typical antipsychotics.	
Ebdrup *et al*. 2013	Systematic review Studies were collected until June 2012. 13 longitudinal studies	3-24 months	No evidence that first generation antipsychotic monotherapy (specifically haloperidol and zuclopenthizol) induces significant basal ganglia volume increases. Basal ganglia volume increases associated with second-generation antipsychotics (olanzapine and risperidone), although not consistently so.	Focus on basal ganglia only, strict inclusion criteria. Studies with relatively short follow-up. Results of studies with years of follow-up were not presented separately from shorter-term studies.
Fusar-Poli *et al*. 2013	Meta-analysis Studies were collected until end of April 2012. 30 longitudinal studies	Median 72.4 weeks, range 4-520 weeks	Higher cumulative antipsychotic dose associate to more pronounced average gray matter volume decrease and lateral ventricle increase within time. Gray matter volume decrease correlated to higher cumulative exposure to antipsychotics, while there were no effects of duration of illness or illness severity.	Associations between the mean antipsychotic dose of the study sample and mean brain volume loss of the study sample was analyzed, so no conclusions on associations between brain volume change and antipsychotics *within* samples can be made. In 16/30 studies the length of follow-up was over two years. Results of studies with years of follow-up were not presented separately from shorter-term studies.

Author, year	Study type Time of the collection of studies Number of studies	Follow-up	Main results[1]	Comment
Torres *et al.* 2013	Meta-analysis Studies were collected until August 2012. 5 longitudinal and 5 cross-sectional studies	Not reported	Patients using antipsychotics had significant clusters of deficits in left lateral temporal cortex, left inferior frontal gyrus, left superior trontal fyrus (extending to te left middle frontal gyrus) and right rectal gyrus compared to controls. There were significant clusters of excess volumes in left dorsal anterior cingulate cortex, left ventral anterior cingulate cortex and right putamen.	Associations between dose of antipsychotics and brain volume were not analyzed. Cases with antipsychotics were compared to controls. Most of the patients (78.5%) used atypical antipsychotics. Only VBM studies were included. Only in 3/10 studies the length of illness was over two years, the length of follow-ups were not reported. The results were not presented separately for cross-sectional and longitudinal studies.
Moncrieff & Leo, 2010	Systematic review Studies were collected between 1995 and April 2009. 26 longitudinal studies	Mean 34 months, range 8 months to 10 years	Mixed results. Authors' conclusions: "Some evidence points towards the possibility that antipsychotic drugs reduce the volume of brain matter and increase ventricular or fluid volume. Antipsychotics may contribute to the genesis of some of the abnormalities usually attributed to schizophrenia."	No results on association between dose of antipsychotics and brain volume change were presented. In 16/26 studies the length of follow-up was over two years. Results of studies with long (over 2 years) follow-up were not presented separately.

Author, year	Study type Time of the collection of studies Number of studies	Follow-up	Main results[1]	Comment
				A review table of 21 studies comparing brain structure between drug- naïve FEP patients and controls cross-sectionally was presented.
Navari & Dazzan, 2009	Systematic review. Studies were collected until January 2007. 23 longitudinal and 10 cross-sectional studies	Not reported	Antipsychotics act regionally rather than globally on the brain. Based on effect sizes, the effect of typical antipsychotics is of greater magnitude than that of atypicals.	The length of follow-ups of the studies was not reported. Results on association between dose of antipsychotics and brain volume change were not presented. Mostly results about the effect of switching antipsychotics were presented. Included also 9 cross-sectional studies, only the results on longitudinal studies are reported here.
Smieskova *et al.* 2009	Systematic review. Studies were collected until November 2008. 24 longitudinal studies	Not reported	Treatment with typical and atypical antipsychotics may affect regional gray matter volume. Typical antipsychotics led to increased gray matter volume of the basal ganglia, atypical antipsychotics reversed this effect after switching. Atypical antipsychotics seem not to have effect on basal ganglia structure.	Only results on differences in typical vs. atypical antipsychotics were presented. No results on association between dose of antipsychotics and brain volume change were presented. Mostly results concerning studies with short (maximum 1 year) follow-up were presented. Also childhood onset schizophrenia samples were included.

Author, year	Study type Time of the collection of studies Number of studies	Follow-up	Main results[1]	Comment
				Included also cross-sectional studies, only the results regarding longitudinal studies are reported here.
Cross-sectional reviews				
Haijma *et al*. 2013	Meta-analysis Medicated sample collection 1998-2012, antipsychotic-naïve sample collection until January 2012. 283 studies on medicated patients, 33 studies on antipsychotic-naïve patients, quantity of cross-sectional studies not reported	n.a.	Higher doses of both antipsychotic types associated with lower total brain volume. Higher doses of atypical antipsychotics associated to lower total grey matter volume. Higher doses of atypical antipsychotics associated with larger volume of caudate nucleus. No associations between total white matter volume and dose of the antipsychotic medication.	Included mainly cross-sectional studies, although study designs were not mentioned.
Smieskova *et al*. 2009	Systematic review. Studies collected from 1996 to 2008. 4 cross-sectional studies	n.a.	Higher typical antipsychotic doses associated with larger volumes in basal ganglia and thalamus. Higher atypical antipsychotic doses associated with larger volume in thalamus. Higher hippocampal volume in first-episode cases treated with atypicals vs haloperidol. A cluster of gray matter deficit in left middle temporal gyrus in cases treated with typical antipsychotics vs atypical antipsychotics	Systematic review that also included 24 longitudinal studies. Only the results regarding cross-sectional studies are reported here.

Author, year	Study type Time of the collection of studies Number of studies	Follow-up	Main results[1]	Comment
Navari & Dazzan 2009	Systematic review. Studies were collected until January 2007 9 cross-sectional studies.	n.a.	Higher antipsychotic exposure correlated with lower midbrain volumes. No correlation between thalamic volume and current antipsychotic dose. No associations between whole-brain volume or hippocampal volumes and medication dose. Higher doses of typicals associated with larger volumes in caudate, putamen, globus pallidus, and thalamus Higher doses of atypicals associated with larger thalamic volumes. Smaller cortical grey matter volumes associated to higher dose of haloperidol use when compared to lower dose of haloperidol use. Smaller volume in left middle temporal gyrus in cases treated with typicals when compared to cases treated with atypicals. Mixed results regarding antipsychotic type and hippocampal volumes.	Systematic review which also included 23 longitudinal follow-up studies. Only the results regarding cross sectional studies are reported here.

VBM=Voxel Based Morphometry, n.a.= not applicable

2.2.2 Association between benzodiazepines and brain structures

Though long-term use of benzodiazepines is not recommended in clinical treatment guidelines of schizophrenia, the prevalence of benzodiazepine use varies from 15% to even 91% (Mundt *et al*. 2012, Vares *et al*. 2011, Waterreus *et al*. 2012). At the age of 43 years, 42% of schizophrenia cases used benzodiazepines in Northern Finland Birth Cohort 1966 (Nykänen *et al*. 2016). Benzodiazepines are also commonly used in the general population - approximately 3% use benzodiazepines over 6 months, which is defined as long-term treatment, and in some populations the number is even higher (Kurko *et al*. 2015).

Benzodiazepines are mainly used as anxiolytics and sedatives. They bind allosterically to specific $GABA_A$ receptor subtypes increasing the inhibitory neurotransmission in the brain (Griebel & Holmes 2013). They are effective in the acute treatment of anxiety symptoms, but their long-term use is related to several side effects such as sedation, memory disturbances, tolerance and dependence (Hoffman & Mathew 2008, Lader 2011). In addition to benzodiazepines, benzodiazepine derivatives, also called the z-drugs, act on the same mechanism, but have shorter elimination half-lives, and are thus used to treat insomnia (Lader 2011).

There are several studies on the effects of long-term benzodiazepine use on cognition, in which it has been linked to cognitive dysfunction (Baandrup *et al*. 2017, Barker *et al*. 2004a, 2005) that may not be reversible (Barker *et al*. 2004b). However, only one of the above-mentioned studies included schizophrenia cases (Baandrup *et al*. 2017). In schizophrenia, tapering off benzodiazepines improved cognitive performance in addition to improving quality of life and decreasing Positive and Negative Sydrome Scale (PANSS) total scores (Kitajima *et al*. 2011). Benzodiazepine use has also been associated with increased risk of mortality both in schizophrenia (Fontanella *et al*. 2016, Tiihonen *et al*. 2012) and in general population (Tiihonen *et al*. 2016).

In schizophrenia, benzodiazepines are used in addition to antipsychotic medications as sedatives or anxiolytics and in order to reduce aggressiveness and ease agitation. The need of benzodiazepines in the treatment may reflect a more difficult illness (Takita *et al*. 2016), and polypharmacy including antipsychotics and benzodiazepines has been linked to a poorer outcome (Längle *et al*. 2012).

Though chronic benzodiazepine use has been associated with decrease in brain plasticity in mice (Curto *et al*. 2016), there are no MRI studies on benzodiazepine

effects on the human brain in any disease category to my knowledge. Previous studies on humans are conducted with CT, analysing the effect of benzodiazepine use on ventricular enlargement (Busto *et al*. 2000, Lader *et al*. 1984, Moodley *et al*. 1993, Perera *et al*. 1987, Schmauss & Krieg 1987, Uhde & Kellner 1987). The results of these earlier studies are inconsistent; The most recent studies have 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), but two studies have found that benzodiazepines associate to increased ventricle-to-brain ratio (Schmauss & Krieg 1987, Uhde & Kellner 1987) and one even suggested a dose-dependent effect (Schmauss & Krieg 1987). These previous studies are mostly made on general benzodiazepine using or abusing populations (Busto *et al*. 2000, Moodley *et al*. 1993, Perera *et al*. 1987, Schmauss & Krieg 1987), with the exception of Lader *et al*. (1984), which studied alcoholics with benzodiazepines and Uhde & Kellner (1987), which studied individuals with panic disorder. The potential mechanisms behind benzodiazepine effects on brain structures are presented in the discussion.

2.2.3 Medication effects on brain structures in affective psychoses

Affective psychoses include psychotic bipolar disorder and psychotic depression and, sometimes, schizoaffective disorder. In affective psychoses psychosis is the extreme point of mood disorder either in the manic phase in psychotic bipolar disorder or in the depressive phase in psychotic depression. For the diagnosis of affective psychosis, the diagnostic criteria for schizophrenia or schizoaffective disorder must not be fulfilled.

Structural brain changes are also found in cases with affective psychoses (Bora *et al*. 2008, Busatto 2013) when compared to controls. Though there are some similarities in the brain structural alterations between psychotic bipolar disorder and schizophrenia and psychotic depression and schizophrenia, the findings seem to be more prominent in the schizophrenia group (Bora *et al*. 2008, Busatto 2013). A systematic literature search from Pubmed targeted on studies comparing brain structure findings in schizophrenia and affective psychoses located 30 studies. Of these, nine did not find differences between the brain structure volumes in the two earlier-mentioned groups (Cui *et al*. 2001, Janssen *et al*. 2014, Koo *et al*. 2008, Morgan *et al*. 2007, Radonić *et al*. 2008, Reite *et al.* 2010, Rosa *et al*. 2010, Rosa *et al*. 2015, Strasser *et al*. 2005). In the studies with statistically significant findings, cortical volumes were smaller in schizophrenia when compared to affective

psychoses and the findings with larger volumes in schizophrenia were found in the putamen, caudate and globus pallidus when compared to psychotic bipolar disorder (Mamah *et al*. 2016, Rimol *et al*. 2010). The findings regarding lateral ventricles were inconclusive: one study found the ventricles to be larger in schizophrenia than in psychotic bipolar disorder (McDonald *et al*. 2006), one study found the ventricles to be larger in psychotic depression than in schizophrenia (Salokangas *et al*. 2002), and one study did not find a difference between schizophrenia and psychotic bipolar groups (Rosa *et al*. 2010).

A systematic literature search on antipsychotic and benzodiazepine effects on brain structures in affective psychoses was conducted in December 2016 and updated in July 2017. The search located 15 original studies, of which 13 did not find any association between antipsychotic exposure and brain structures. One study of psychotic bipolar disorder cases found an association between antipsychotics and positive vertex displacement in right pallidum (Liberg *et al*. 2015) and another found that longer duration of antipsychotic exopure associated to increased ventricular volumes in affective psychoses but not in schizophrenia (Morgan *et al*. 2007). To my knowledge, ther are no previous studies on benzodiazepine effects on brain structures in affective psychoses.

2.2.4 Summary of earlier literature

Schizophrenia is a disorder of the brain, and several factors seem to contribute to the illness onset. Gray matter deficits and ventricular enlargement are the most commonly reported brain structural alterations in schizophrenia when compared to controls. The key treatment for schizophrenia is antipsychotic medication, which reduces positive symptoms, but is not as effective against negative symptoms and cognitive deficits. There is evidence suggesting that antipsychotics associate to lower cortical gray matter volume and higher basal ganglia structure volumes in schizophrenia. Though benzodiazepines are commonly used as add-on treatment, and there is evidence of adverse effects on cognition, the relationship between benzodiazepines and brain structures has not been studied before in schizophrenia. In comparison to schizophrenia, affective psychoses are studied far less regarding brain structures and medication effects. In general, previous studies on the association between antipsychotics and brain structure change are inconclusive.

3 Aims of the study

The aim of this doctoral study was to analyse associations between long-term antipsychotic and benzodiazepine use and brain structures in schizophrenia. The spesific aims of the original studies were:

1. To conduct the first systematic review on the associations between antipsychotic dose and brain volumes focusing on long-term (over 2 years) follow-ups in schizophrenia. (Original study I)
2. To analyze in the NFBC1966 sample whether scan-interval antipsychotic or benzodiazepine dose associates to structural changes in the brain between ages 34 and 43. (Original study II)
3. To analyze in the NFBC1966 if lifetime antipsychotic or benzodiazepine doses associate to brain structure volumes in schizophrenia and compare these findings with a group of affective psychoses. (Original study III)

4 Materials and methods

4.1 Systematic review and meta-analysis (I)

4.1.1 Data search

In the systematic review and meta-analysis, the guidelines of Meta-analysis Of Observational Studies in Epidemiology (MOOSE) (Stroup *et al*. 2000) were followed. The literature search was performed on August 28th 2015 with the search strategy (MRI OR "magnetic resonance imaging") AND (longitudinal OR follow-up OR repeated) AND (schizophreni* OR psychoses OR psychosis OR schizoaffective OR "psychotic disorders") using the databases of PubMed, Scopus, Web of Knowledge, and PsycINFO. There were no restrictions on language, publication date or publication status, and the search was directed to all fields. In addition, manual searches were done by investigating the references of previous reviews and the included studies. If the data was not presented in detail in the original studies, the authors were contacted in order to receive unpublished data. All found articles were evaluated by two researchers (Sanna Huhtaniska and Jouko Miettunen) and the data from the included studies were extracted in consensus within the research team. All studies with an MRI follow-up of at least 2 years were scrutinized regardless of title or abstract information on antipsychotic medication, which also enabled us to find the studies, which looked at antipsychotic associations as secondary analyses only.

4.1.2 Inclusion and exclusion criteria

In order to be included in the systematic review, the original studies had to fulfill the following inclusion criteria: subjects were scanned twice, the average scanning interval was at least two years, at least 80% of the subjects had a schizophrenia spectrum diagnosis, and antipsychotic medication data was used as a predictor for volumetric changes in brain structures.

The exclusion criteria were: follow-up under 2 years, all subjects had childhood/adolescent onset schizophrenia, or antipsychotic medication variable was expressed only as “yes/no”, “duration of treatment”, or “duration of untreated psychosis”. No restrictions regarding the patients’ illness status or the brain areas studied were applied.

4.1.3 Data collection

The information on study location, sample size (males/females), follow-up time, illness stage (time since onset), diagnoses and diagnostic criteria, scanner information, studied brain regions, used covariates, medication data, and information on how the regions of interest were traced and how the imaging change score was calculated in the study (if reported) were collected from all original studies. A quality score was calculated for all included studies based on a modified version of the quality assessment criteria introduced by McGrath *et al*. (2004). Studies were categorized into two groups based on whether they examined dose of antipsychotic medication or compared typical and atypical antipsychotic medications.

The brain regions were categorized into 9 brain areas based on anatomical location according to Tzourio-Mazoyer *et al.* (2002). These were total brain, cerebrum, frontal lobe, temporal lobe, parietal lobe, occipital lobe, cerebellum, limbic area, and basal ganglia. CSF and ventricles were studied together. In case some specific brain areas were not clearly part of any of the anatomical locations listed above; they were not included in the meta-analysis, but instead, as part of the systematic review. For the systematic review, the regions were further classified based on brain tissue types into gray matter (GM) and white matter (WM), and different tissue types were analysed separately. For the meta-analysis, the studies on volume and grey matter were combined in each area. An exception was cerebrospinal fluid (CSF) and ventricles, which were studied together in one analysis.

4.2 The Northern Finland Birth Cohort 1966 (II, III)

The Northern Finland Birth Cohort 1966 (NFBC1966) is an unselected, general population birth cohort ascertained during mid-pregnancy. The cohort represents 96% (N=12 058) of the live born children in the Finnish provinces of Lapland and Oulu with an expected delivery date during 1966. Data on biological, socioeconomic, and health conditions, living habits, and family characteristics of cohort members have been collected prospectively from pregnancy. More information on the Northern Finland Birth Cohorts can be found in http://www.oulu.fi/nfbc.

4.2.1 Sample (II, III)

In this thesis, the term ”NFBC1966 follow-up study” refers to the NFBC1966 study with two brain MRI images and two psychiatric examinations done at the ages of 34 years and 43 years. The term “NFBC1966 43-year study” refers to the cross-sectional study conducted at the age of 43 years including psychiatric examination and brain MRI scan. The sample collection is described in Figure 1.

NFBC1966 follow-up study (II)

The first psychosis study was conducted in 1999-2001 when the cohort members were on average 34 years. The nationwide Care Register for Health Care (CRHC) was used to identify all NFBC1966 members with a history of any psychotic episode. The case records were scrutinized and the diagnoses validated using Diagnostic and Statistical Manual of Mental Disorders Third Edition Revised (DSM-III-R) criteria (Isohanni *et al*. 1997, Moilanen *et al*. 2003). Since the majority of patients experiencing a first episode of psychoses were hospitalized in Finland until recent years (Arajärvi *et al*. 2005), this method most likely identified a large majority of individuals with a history of psychosis in the NFBC1966.

In total 146 NFBC1966 members with a history of at least one known psychotic episode by the end of 1997 were invited to participate in 1999-2001. Of the invited individuals, 101 had diagnosis of schizophrenia. Ninety-two (63%) of the invited participated, and based on Structured Diagnostic Interview for DSM-III-R (SCID-I) (Spitzer *et al*. 1989), there were 61 individuals diagnosed with schizophrenia and 11 individuals diagnosed with other schizophrenia spectrum disorder. The average illness duration was 10.0 (SD 4.0) at the baseline study.

Control participants were randomly selected from the NFBC1966 living in the Oulu area and not having had a psychotic episode by 1997 according to the CRCH. Altogether 187 control subjects were invited for the follow-up study in 1999-2001 and 104 (56%) of them participated.

All participants, who had a baseline MRI scan were invited to a follow-up examination after a nine-year interval at the age of 43 years on average including a repeat MRI scan (43-year study). The follow-up study was conducted during the years 2008-2011. Thirty-eight (62%) of the participants with schizophrenia, 7 (64%) of the participants with schizophrenia spectrum disorder, and 77 (74%) of the controls participated in the follow-up. The original diagnoses were confirmed at

follow-up for all participants using SCID-I (Fris *et al*. 2002) and SCID-I was also done for controls at both timepoints.

In the longitudinal study (II), forty-five individuals with schizophrenia spectrum disorder and 77 non-psychotic controls participated in both baseline and follow-up studies at the approximate ages of 34 and 43 years. For seven participants with schizophrenia spectrum disorder and seven controls the 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 hence was not included in the final study group. The final groups, in which the analyses were made, included 38 participants with schizophrenia spectrum disorder and 69 controls. The specific diagnoses for the schizophrenia spectrum group were schizophrenia (n=33), schizophreniform disorder (n=1), schizoaffective disorder (n=3) and delusional disorder (n=1). In this dissertation, regarding the study II, the term schizophrenia is used to refer to schizophrenia and other schizophrenia spectrum disorders.

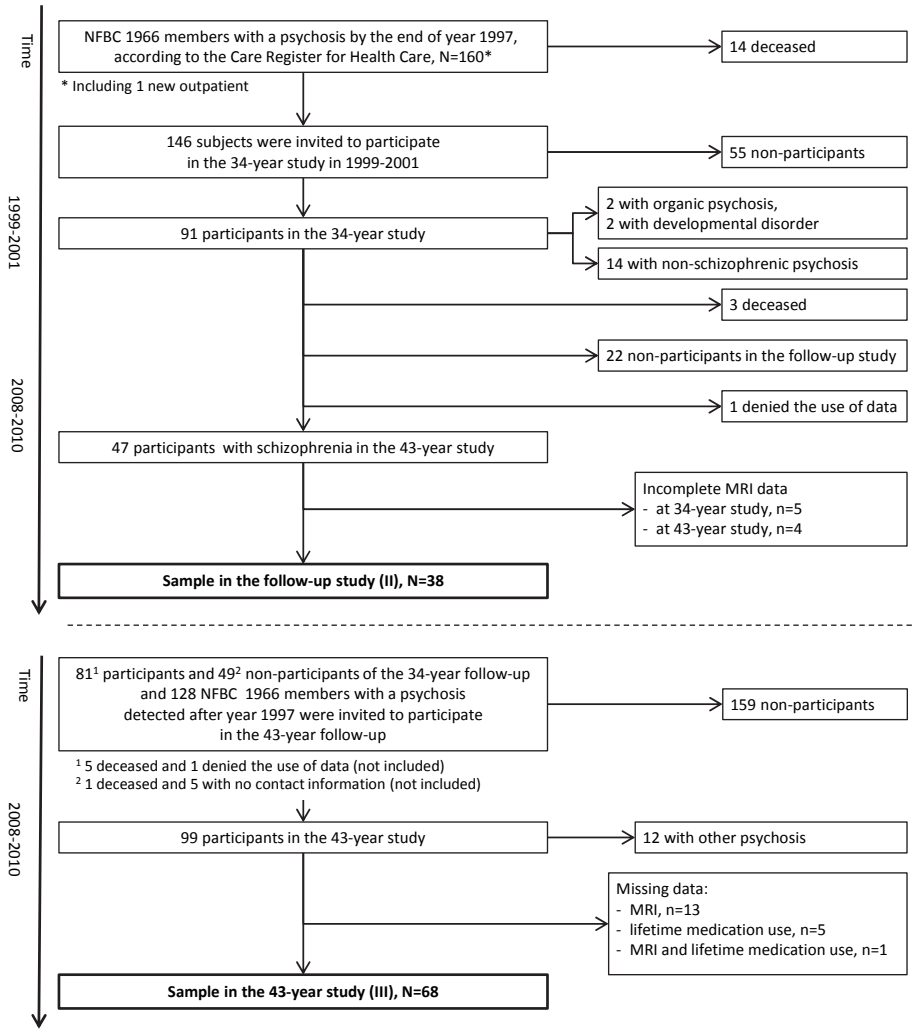


Fig. 1. Data collection of the NFBC1966 studies.

NFBC1966 43- year study (III)

In addition to the individuals, who participated in the NFBC1966 follow-up study, cohort members who had developed psychosis at any time by the end of 2008 were invited to participate in the NFBC1966 43-year study. The diagnoses were collected

through CRHC and Social Insurance Institution of Finland's (SII) register on sick leaves, disability pensions and the reimbursement data due to psychosis by the end of 2008. Also every individual, who had reported psychosis or current antipsychotic use in 1997 in a questionnaire data collection were included (Nykänen *et al.* 2016).

Forty-seven participants from the NFBC1966 follow-up study and 52 individuals with any psychosis participated at the age of 43. Of these, 59 had diagnosis of schizophrenia and 28 had diagnosis of affective psychosis (8 cases with schizoaffective disorder, 7 cases with bipolar psychosis, and 13 cases with psychotic depression). In this study, schizoaffective disorder was included in the affective psychoses in the cross-sectional study (III), with the idea of separating individuals with affective symptoms from schizophrenia and balancing the two groups, since the number of schizophrenia cases was high compared to other diagnostic groups. To be included in the study, the participants must have had gone through psychiatric examinations, had adequate brain MRI scans, and available lifetime medical data. Diagnoses were based on information from registers, hospital notes and SCID-I interview (First *et al*. 2002) for DSM-IV.

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).

4.3 Imaging data

The participants were scanned with the same 1.5 T GE Signa scanner (General Electric, Milwaukee, Wisconsin) at both 34 years and 43 years of age at the Oulu University Hospital. At 34 years, 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 256×256; voxel size 1.5 mm × 1 mm × 1 mm; repetition time 35 ms; echo time 5 ms; flip angle = 35). Before the 43-year 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 43 years, the T1 weighted images were acquired with a 3D fast spoiled gradient echo (FSPGR) sequence (slice thickness = 1 mm; in-plane resolution matrix size 256×256 voxel size 1 mm3; repetition time 12.576 ms; echo time 5.3 ms; flip angle =20).

4.3.1 Brain structural measurements

To extract the brain structures and tissue volumes from the MRI images, the images were processed with an automated volumetry system called volBrain (Manjón and Coupé 2016). It is based on an advanced pipeline that provides automatic segmentation of brain tissue types and 11 brain structures (divided in right/left if applicable, additional information on asymmetry) from T1-weighted MRI images.

The images are first preprocessed to normalize and register them into the MNI space (MNI stands for Montreal Neurological Institute, and the MNI space is a brain 3D coordinate system based on 152 normal MRI scans). At the first preprocessing step the images are denoised with the adaptive nonlocal mean filter (Manjón *et al*. 2010a). These denoised images are then corrected for inhomogeneity with an N3 method (Tustison *et al*. 2010) and registered to MNI space using the ANTS algorithm (Avants *et al*. 2010). In the MNI space the images are corrected for inhomogeneity using SPM8 routines (Ashburner & Friston 2005). Finally, an intensity normalization procedure is applied to the images (Manjón *et al*. 2010b).

After the preprocessing, the images are segmented using non-local patch-based multi-atlas methods (Coupé *et al*. 2011). A dedicated adaptation is used separately for each structure. Intracranial cavity is extracted using NICE (Manjón *et al*. 2014) and hemispheres are extracted based on NABS (Romero *et al*. 2015). Brain tissue types are classified using a procedure described in Coupé *et al*. (2011). Eight subcortical structures (lateral ventricles, caudate nucleus, putamen, thalamus, globus pallidus, hippocampus, amygdala and nucleus accumbens) are segmented with the method described in Coupé *et al*. (2011). All segmentations are based on volBrain experts' definition with the exception of hippocampus, which is segmented follwing the EADC protocol (Boccardi *et al*. 2015).

Since the scanner was updated during the follow-up, a calibration scan was performed with 15 controls. These 15 controls were scanned with both used protocols during the same day in order to assess the possible effect of the scanner update on the MRI measurements. With the help of these calibration-scans, the inter-scan reliability rates were measured for each extracted brain structure volume and the structures with single measures intraclass correlation poorer than 0.90 were excluded from the analyses. Most structures were highly correlated and exceeded the 0.90 limit, and of the structures we were interested in looking at, only amygdala and globus pallidus did not reach the limit of 0.90.

Based on these reliability measures and the previous brain imaging findings in psychoses, 10 brain areas of all 61 available measures were selected to be examined

in the analyses (II and III): total brain, total GM, cerebrum, cerebral GM, lateral ventricles, caudate, putamen, thalamus, hippocampus and accumbens.

For the follow-up study (II), the annual change of each studied brain region was calculated using the total change during the follow-up and the length of the follow-up for each individual. In the 43-year study (III), the volumes of each region were used as they were calculated by volBrain.

4.4 Medication data

Information on lifetime use of psychiatric medications, until the day the person was examined in the 43-year study, was collected through a careful review of individual hospital, outpatient and health centre medical records from everywhere in Finland. The data was collected for all cases with a history of psychosis, who participated in the follow-up and 43-year studies. The name of the drug, dose and time period during which the medication had been used were collected from the medical records. In addition, the use of current and earlier psychiatric medications during the last 3 months or as far as the subjects could remember, was asked in interviews at both time points.

All medicines were categorized using the Anatomical Therapeutic Chemical (ATC) classification system (WHO 2010). Antipsychotics included classes N05A (antipsychotics) and 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).

This information was then used to calculate the cumulative doses of lifetime (III) and interscan interval (follow-up) (II) doses. For antipsychotics, the interscan interval dose was expressed as dose-years of a daily dose of 100 mg chlorpromazine (CPZy) (II) using several sources (Moilanen *et al*. 2015). The lifetime antipsychotic dose was expressed as defined daily dose (DDD) and these were then expressed as DDD years (DDDy) (III). For benzodiazepines, both interscan interval and lifetime doses were expressed as DDD years (BZDy in II, DDDy in III). One DDDy is equivalent to the amount of medication a person would use, if the daily dose were 1 DDD and the duration of treatment would be one year.

4.5 Background variables and covariates

Clinical symptoms were examined both at the ages of 34 and 43 years using the PANSS (Kay *et al*. 1987). At baseline, the PANSS was measured based on the SCID I -interview and general psychiatric interview, and at follow-up using a specific PANSS interview. In study II the average of these measures was used to estimate the illness severity during the follow-up. In study III only the PANSS score from the 43-year study was used to assess illness severity during the MRI scan.

Onset age of the illness was ascertained from medical records and from the CRHC for the schizophrenia cases in the follow-up study, and from the CRHC for the schizophrenia cases and affective psychoses cases that participated only in the 43-year study. Onset age was defined as the age of first evident psychotic symptoms. Since this study is based on a birth cohort, and the subjects were examined on the average at the same age, onset age represents also the duration of illness in the NFBC1966 samples.

The number of hospital days during the follow-up (II) and lifetime (III) was collected from the CRHC. This measure was used as an additional measure of illness severity in the follow-up study, because it is the only available variable that reflects the illness severity status over the entire follow-up period.

Remission was assessed at both time points using the Andreasen criteria (Andreasen *et al*. 2005), but 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 the PANSS was done only once at baseline and follow-up.

Marital status and educational level were collected from questionnaire data at both studies. Working status was collected from questionnaire data and the information from SII and Finnish Centre for Pensions. Comorbid diagnose of alcohol use disorder was ascertained by SCID-I interviews at both time points.

4.6 Statistical analyses

4.6.1 Systematic review and meta-analysis (I)

The effect of antipsychotic dose was estimated using correlation coefficients. If the original studies presented other effect measures, these were transformed to correlations (Rosenthal, 1994, Rosenthal *et al*. 2000). When there was an overlap in the studies from same samples analyzing the same brain areas, the larger sample was included. Also studies that reported results only as non-significant without

presenting numeric results were included in order to minimize the risk of bias across studies. Heterogeneity was estimated using the I2 statistic (excluding studies, which did not report numerical results). The statistical significance in heterogeneity was tested using the chi-square test. Values of I2 range from 0% to 100% reflecting the proportion of the total variation across studies beyond chance. A value of 25% describes low, 50% moderate, and 75% high heterogeneity or major excessive variation across studies (Higgins *et al*. 2003).

If only one antipsychotic dose was studied, that correlation was included in the meta-analysis, but if there were several different doses for different antipsychotics, the mean of those correlations was used in the meta-analysis. If any of the previously defined 9 brain areas (total brain, cerebrum, frontal lobe, temporal lobe, parietal lobe, occipital lobe, cerebellum, limbic area, or basal ganglia) were studied, that correlation was included in the analyses, but if several smaller areas within the defined areas were studied, the mean of the correlations was used in the analyses. If only one smaller area within the larger defined areas was studied, those correlations were included in the corresponding larger areas. All the studies focusing on volume were combined and if the total volumes of the structure were not presented, the results on GM volumes were included.

The effect of antipsychotic medication dose was studied using random effect meta-analyses if at least three studies focused on the same brain area in their analyses. Tests of overall effect were based on z-tests where $p<0.05$ was considered statistically significant. In the random-effects analysis, each study was weighted by the inverse of its variance and the between-studies variance.

To see whether adjusting the results in the original analyses would affect the results of the meta-analyses, meta-analyses were also conducted using only those studies that had used covariates in their analyses. In addition, to see if the quality of the original studies affected the results of the meta-analyses, the analyses were performed using only the studies exceeding the median quality score.

As sensitivity analyses, meta-analyses were also conducted including the studies that had not reported numerical data in their analyses, in which case the correlation was estimated to be null. Publication bias was assessed using Egger's test for small-study effects, but since the test is not very good with a small number of studies, the results were reported with a significance level of $p<0.10$.

All analyses were conducted using STATA 11.0 software (StataCorp, Stata Statistical Software: Release 11. College Station, TX: Stata Corp, Lp 2009).

4.6.2 NFBC1966 follow-up study (II)

The structural MRI changes of the brain were examined in 10 different measures based on the interest in subcortical structures and the inter-scan reliability measures. These areas were: total brain, total GM, cerebrum, cerebral GM, lateral ventricles, caudate nucleus, putamen, thalamus, hippocampus, and nucleus accumbens.

The differences in longitudinal brain volume change between subjects with schizophrenia and non-psychotic controls and associations between medication doses during the scan interval and brain structure volume change in the schizophrenia group were analyzed using linear regression with sex and baseline intracranial volume (ICV) as covariates. In medication analyses, benzodiazepine DDDy was added as a covariate in analyses of antipsychotic CPZy, and vice versa. Also the average PANSS score between the two time points and hospital treatment days during the follow-up were added as additional covariates in medication analyses.

Since the medication data and number of hospital treatment days during the follow-up were skewed, a logarithmic transformation was applied to these variables and they were used as continuous variables in analyses.

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

4.6.3 NFBC1966 cross-sectional study (III)

The differences between brain structure volumes between schizophrenia and affective psychoses groups were analysed in all 10 brain measures (total brain, total GM, cerebrum, cerebral GM, lateral ventricles, caudate nucleus, putamen, thalamus, hippocampus, and nucleus accumbens). The associations between lifetime medication dose and brain structures were analysed in both groups separately. A logarithmic transformation was applied to the medication data due to its skewness, and the transformed variables were used as continuous in the analyses.

All analyses were made using linear regression with sex and ICV as covariates. Again, in medication analyses, benzodiazepine DDDy was added as a covariate in analyses of antipsychotic DDDy and vice versa. The medication analyses were also adjusted with the PANSS total score, and onset age. In addition, the group × medication interactions were analysed in models including group, group × medication interaction, medication dose (antipsychotic or benzodiazepine), and ICV and sex as covariates.

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

5 Ethical considerations and personal involvement

5.1 Ethical considerations

The permission to gather the NFBC1966 data has been obtained from the Ministry of Social Affairs and Health in 1993. The Ethics Committee of the Northern Ostrobothnia Hospital District has accepted the study design of the NFBC1966 and keeps it under review. The research plan for NFBC1966 34-year follow-up study was accepted in the Ethical Committee of Oulu University, Faculty of Medicine in 30 March 1998, and for the 43-year follow-up in the regional Ethics Committee of the Northern Ostrobothnia Hospital District 18 February 2008. Data protection has been scrutinized by the Privacy Protection Agency, as well as by the principles from the Ministry of Social Affairs and Health. Regarding both studies, written informed consent was obtained from all participants. Study subjects were assigned an ID-number and their identities are not revealed to anyone working with the data. The medical records were collected with the consent of the participants. All cohort subjects have the right to deny the use of information concerning themselves at any time.

5.2 Personal involvement

I have started my doctoral studies in 2011 with a two-month research exchange to the Brain Mapping Unit of the University of Cambridge, UK. I received the doctoral study rights in the University of Oulu in June 2011 and afterwards became a student in the University of Oulu Graduate School. I have worked on the structural imaging data of the NFBC1966 since 2010 and participated in the numerous phases of pre-processing and data quality control with different MRI analysis software using most of my summers and spare time as a researcher during 2010-2012. Afterwards I have trained other students to preprocess and analyse the data and continued my work in planning and figuring out the possible ways to deal with our data. The search for suitable analysing methods and modifying the data to be more easily processible was a laborious and time-consuming work that lasted for several years, and I was involved in the process already from the beginning of my studies. In addition to the original articles included in my thesis, I have been a co-author in seven publications on the NFBC1966 mainly performing the analysing and

processing of the MRI data, and in two of them I have been the second author. During 2013-2015 I continued my work on this thesis data and thesis part-time, and for the year 2016 I received a doctoral student's position in the Medical Research Center Oulu. Since April 2016 I have worked as a full time researcher in the Center for Life Course Health Research in the University of Oulu.

I have designed the original studies in collaboration with my supervisors Professor Jouko Miettunen, Adjunct Professor Erika Jääskeläinen, and Ph.D., MRCPsych Graham Murray. Since the collection of the data had mainly been done before I joined the research group, I have not participated in the data collection. However, I have been actively involved in the data processing and analysing of the imaging data and I have participated in the evaluation and collection of the medication data. I have performed the statistical analyses in the original publications II and III by myself with the guidance of statisticians. I screened through all the search results in the original publication I and extracted the data and assessed the quality ratings of the studies. I have written the first versions of all the original publications as the first author and finalized the manuscripts in collaboration with other authors.

6 Results

6.1 Systematic review and meta-analysis (I)

6.1.1 Search results and included studies

The search located 1815 studies, and after reviewing the abstracts and titles, 125 studies were included in more detailed evaluation. In total 34 publications from 16 different samples fulfilled the inclusion criteria. Of those, 31 studies presented results only on dose effect, three studies focused only on comparisons between typical and atypical edications, and two studied both of these. The data collection is described in Figure 2.

The included studies were highly heterogenous in their methods and focused on different subregions of the brain. The focus was rarely on antipsychotics and brain volume change, but the association was studied as a secondary analysis. Six studies from four different samples had a follow-up of over five years (Andreasen *et al*. 2013, Guo *et al*. 2015, Ho *et al*. 2011, Nesvåg *et al*. 2012, Saijo *et al*. 2001, Veijola *et al*. 2014). Only 11 studies used covariates in their analyses (e.g. age or total GM) and only four studies from two different samples took into account illness severity measures in their analyses (Andreasen *et al*. 2013, Guo *et al*. 2015, Ho *et al*. 2011, Veijola *et al*. 2014).

The scores of the quality assessment ranged from 7 to 18 points with a median of 11 points.

6.1.2 Associations between dose of antipsychotic medication and brain structural changes

Most of the reported correlations in the original studies were statistically non-significant. Of all the reported associations, half were reported only as non-significant without numerical details. The statistically significant findings are summarized in Table 3. In addition to a study by Ho *et al*. (2011) with a sample of 211 cases, studies with small sample sizes reported large correlations.

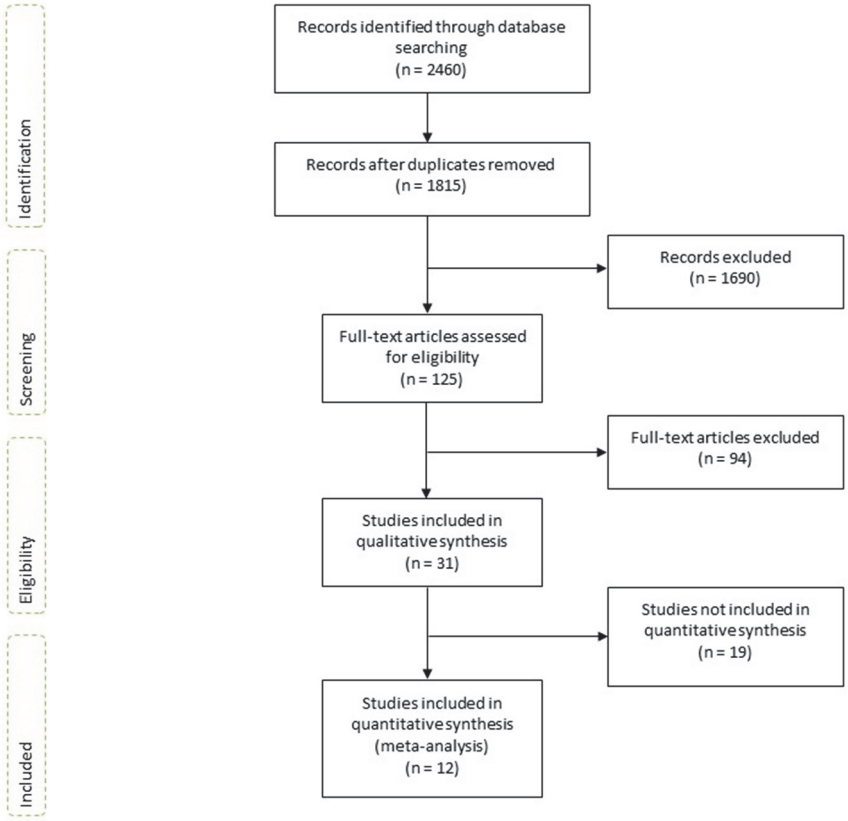


Fig. 2. Data collection of the systematic review and meta-analysis (I). Based on Figure 1 from original study I.

Table 3. Summary of results on associations between higher antipsychotic medication dose and brain morphometric changes by brain regions. Based on Table 3 from original study I.

Brain Areas	Statistically significant findings	Non-significant findings
Total brain	*** total and atypical dose associated with larger decrease (Veijola et al. 2014)	Brans et al. 2008, Collin et al. 2012, Ho et al. 2003, Nesvåg et al. 2012, Roiz-Santiáñez et al. 2014, Takahashi et al. 2010
Cerebrum	*** atypical dose associated with less progressive decrease of GM (Brans et al. 2008) * clozapine dose associated with reduction and typical and clozapine dose associated with reduction of GM (Ho et al. 2011)	Nesvåg et al. 2012, van Haren et al. 2008
Frontal lobe	*** total dose associated with reduction in first episode patients (Gur et al. 1998) ** clozapine associated with reduction of GM (Ho et al. 2011) and with increase of right superior and right and left medial frontal cortex (van Haren et al. 2011), non-clozapine atypical dose associated with increase of right medial frontal cortex (van Haren et al. 2011), and typical dose associated with reduction of left precentral cortex (van Haren et al. 2011) * total, typical and nonclozapine atypical dose associated with reduction of GM (Ho et al. 2011) and total dose associated with volume decrease (Andreaen et al. 2013), olanzapine and clozapine increased volume in a cluster in superior frontal gyrys (van Haren et al. 2007)	Cobia et al. 2012, Gur et al. 1998, Ho et al. 2003, Nesvåg et al. 2012, Roiz-Santiáñez et al. 2014, Takahashi et al. 2013b, Veijola et al. 2014
Temporal lobe	*** total dose associated with reduction in first episode patients (Gur et al. 1998), total and atypical dose associated with less reduction of right and left caudal superior temporal gyrys, total dose with less reduction of left planum temporale (Takahashi et al. 2010) and of whole fusiform gyrus (Takahashi et al. 2011a), atypical dose associated with less reduction (Nesvåg et al. 2012) ** total dose associated with reduction (Veijola et al. 2014), clozapine dose associated with decrease of GM (Ho et al. 2011) * total dose associated with decrease of GM (Ho et al. 2011) and decrease of volume (Andreasen et al. 2013)	Hedman et al. 2016, Ho et al. 2003, Roiz-Santiáñez et al. 2014, Takahashi et al. 2009, van Haren et al. 2011, van Haren et al. 2007

Brain Areas	Statistically significant findings	Non-significant findings
Parietal lobe	** total dose associated with reduction (Veijola et al. 2014) * total, clozapine and nonclozapine atypical dose associated with GM reduction and nonclozapine atypical dose with WM increment (Ho et al. 2011)	Andreasen et al. 2013, Ho et al. 2003, Nesvåg et al. 2012, Roiz-Santiáñez et al. 2014, van Haren et al. 2011
Occipital lobe	- no significant findings	Ho et al. 2007, Ho et al. 2011, Nesvåg et al. 2012, Roiz-Santiáñez et al. 2014, Veijola et al. 2014
Cerebellum	- no significant findings	Brans et al. 2008, Collin et al. 2012, Ho et al. 2003, Ho et al. 2011, Nesvåg et al. 2012, van Haren et al. 2008, Veijola et al. 2014
CSF and ventricles	*** total dose associated with increase (Veijola et al. 2014) * total dose associated with increase in parietal lobe CSF (Andreasen et al. 2013) ^ clozapine associated with reduction of sulcal CSF (Ho et al. 2011)	Collin et al. 2012, Ho et al. 2003, Ho et al. 2007, Nesvåg et al. 2012, Roiz-Santiáñez et al. 2014, Saijo et al. 2001, van Haren et al. 2007, van Haren et al. 2008
Limbic system	*** typical dose associated with increase and atypical and risperidone dose with decrease of anterior cingulate cortex (Ho et al. 2007) ** clozapine associated with increase in right cingulate cortex (Ho et al. 2011) * clozapine associated with decrease of thalamus (Ho et al. 2011)	McCormick et al. 2005, Roiz-Santiáñez et al. 2014, van haren et al. 2007, van Haren et al. 2011
Basal ganglia	*** typical dose increased and atypical dose decreased globus pallidus (McCormick et al. 2005), clozapine increased putamen (Ho et al. 2011) ** typical dose increased putamen (McCormick et al. 2005), total dose increased putamen (Ho et al. 2011)	Heitmiller et al. 2004, Nesvåg et al. 2012, Roiz-Santiáñez et al. 2014, Westmoreland Corson et al. 1999

Brain Areas	Statistically significant findings	Non-significant findings
	* clozapine decreased and nonclozapine atypical increased caudate volume, typical dose and nonclozapine atypical dose increased putamen (Ho et al. 2011), typical dose increased volume in selected voxels in caudate (van Haren et al. 2007)	
Other	- no significant findings	Davidson et al. 2012, Hedman et al. 2016, Takahashi et al. 2011b, Takahashi et al. 2012, Takahashi et al. 2013a

Correlations: *=small (0.1 < r < 0.3) **=moderate (0.3 ≤ r < 0.5) ***=large (r ≥ 0.5) ^=smaller than 0.1.

After combining correlations from different brain areas according to the anatomical locations, meta-analyses were conducted in areas, which were studied in at least three samples. In meta-analyses, higher antipsychotic exposure associated statistically significantly with decrease in parietal lobe volume (studies, n=4; r=-0.14, z=2.70, p=0.007) and with increase in basal ganglia volume (n=4; r=0.10, z=2.01, p=0.044). Similar effect sizes were also found for decreases in total brain (n=3, r=-0.15, z=0.82, p=0.411), frontal lobe (n=7; r=-0.14, z=1.45, p=0.15), temporal lobe (n=8; r=-0.12, z=1.13, p=0.26), occipital lobe (n=3, r=-0.14, z=1.94, p=0.052) and increase in CSF and ventricles (n=5; r=0.13, z=1.21, p=0.23), although these were not statistically significant. Heterogeneity was high ($I2 > 75\%$) for total brain and cerebral volumes. The results of the meta-analysis are presented in Figure 3.

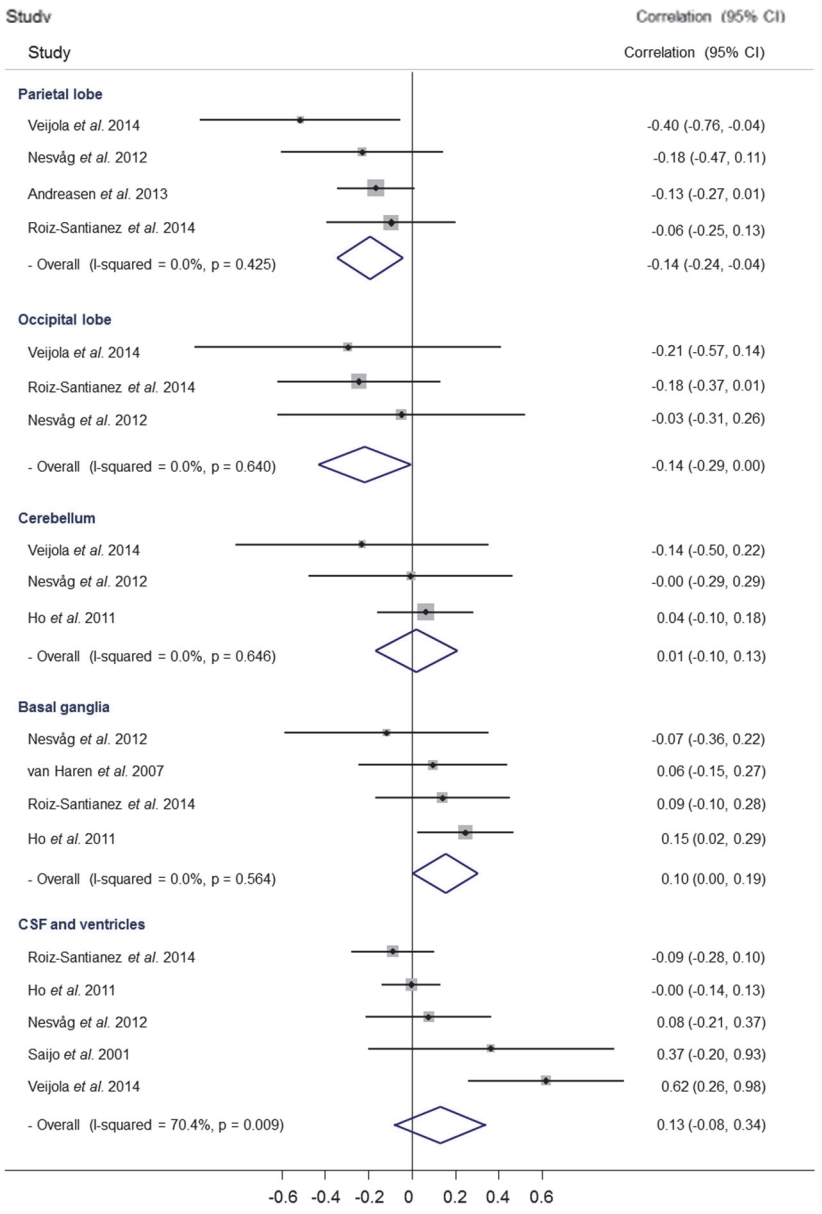
In sensitivity analyses, including studies with non-numerical results did not change the results. There was an indication of publication bias in Egger's test for small-study effects in the basal ganglia (p=0.005, for other areas p>0.19).

When the meta-analyses were conducted with studies, that exceeded the median in quality score points (frontal lobe, temporal lobe, parietal lobe, basal ganglia, CSF and ventricles), the results were statistically significant in parietal lobe (z=2.04, p=0.04) and basal ganglia (z=2.29, p=0.02), and the overall effect sizes for all analysed areas were of the same magnitude as with meta-analysis with all studies. Based on these findings, it seems that the quality of original studies did not affect the results of the meta-analysis.

For studies with adjusted analyses, the meta-analysis was possible for 3 areas: frontal lobe, temporal lobe and basal ganglia. In meta-analyses with studies with

adjusted analyses, the findings regarding basal ganglia remained the same ($z=2.29$, $p=0.02$).

Only 5 studies fulfilling the inclusion criteria, compared typical and atypical antipsychotics in the same sample. There were mostly no differences between these two classes, except for the finding in one study showing that cumulative dose of typical medication was associated with more increase in basal ganglia volume (McCormick *et al*. 2005).


Study
Correlation (95% CI)
Parietal lobe
Veijola et al. 2014
-0.40 (-0.76, -0.04)
Nesvåg et al. 2012
-0.18 (-0.47, 0.11)
Andreasen et al. 2013
-0.13 (-0.27, 0.01)
Roiz-Santianez et al. 2014
-0.06 (-0.25, 0.13)
- Overall (I-squared = 0.0%, p = 0.425)
-0.14 (-0.24, -0.04)
Occipital lobe
Veijola et al. 2014
-0.21 (-0.57, 0.14)
Roiz-Santianez et al. 2014
-0.18 (-0.37, 0.01)
Nesvåg et al. 2012
-0.03 (-0.31, 0.26)
- Overall (I-squared = 0.0%, p = 0.640)
-0.14 (-0.29, 0.00)
Cerebellum
Veijola et al. 2014
-0.14 (-0.50, 0.22)
Nesvåg et al. 2012
-0.00 (-0.29, 0.29)
Ho et al. 2011
0.04 (-0.10, 0.18)
- Overall (I-squared = 0.0%, p = 0.646)
0.01 (-0.10, 0.13)
Basal ganglia
Nesvåg et al. 2012
-0.07 (-0.36, 0.22)
van Haren et al. 2007
0.06 (-0.15, 0.27)
Roiz-Santianez et al. 2014
0.09 (-0.10, 0.28)
Ho et al. 2011
0.15 (0.02, 0.29)
- Overall (I-squared = 0.0%, p = 0.564)
0.10 (0.00, 0.19)
CSF and ventricles
Roiz-Santianez et al. 2014
-0.09 (-0.28, 0.10)
Ho et al. 2011
-0.00 (-0.14, 0.13)
Nesvåg et al. 2012
0.08 (-0.21, 0.37)
Saijo et al. 2001
0.37 (-0.20, 0.93)
Veijola et al. 2014
0.62 (0.26, 0.98)
- Overall (I-squared = 70.4%, p = 0.009)
0.13 (-0.08, 0.34)
-0.6 -0.4 -0.2 0 0.2 0.4 0.6

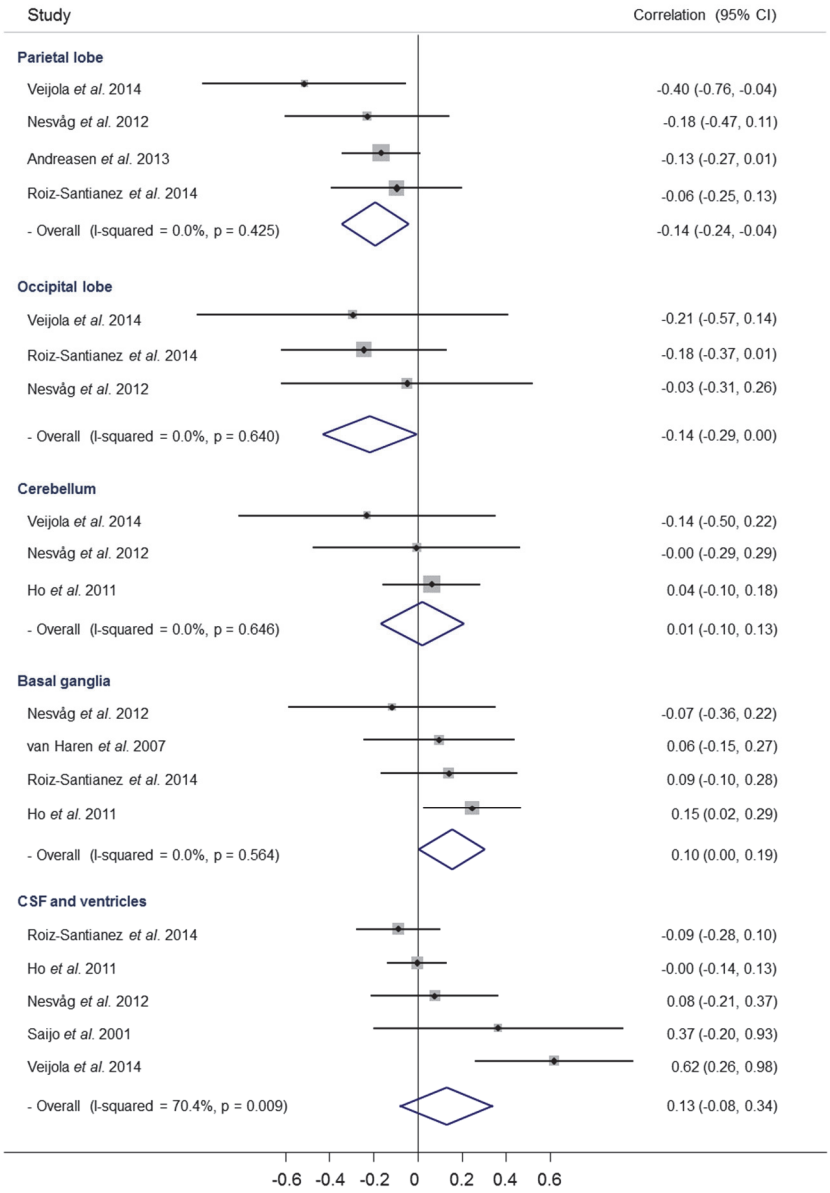


Fig. 3. Results of the meta-analysis. Based on Figure 2 in original study I.

6.2 Characteristics of the NFBC1966 samples (II, III)

The characteristics of the sample are presented in Table 4. In the follow-up study (II), 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. The onset age was 23.1 years on average. 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).

In the cross-sectional study (III), in the schizophrenia group, the number of males was 27 (61%) and the average age was 43.1 years. Onset age was 25 years on average. Eleven (25%) were in remission during the study and the average PANSS score was 70 (SD 27). In the affective psychoses group, 7 (29%) were male and the average age was 43.6 years. The onset age was 32 years on average. Twenty-one (88%) were in remission during the study and the average PANSS score was 43 (SD 9.7).

6.2.1 Medication use characteristics of the follow-up sample (II)

The medication use of the follow-up sample (II) is presented in Table 5. 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.

During the follow-up, 34 (90%) schizophrenia subjects used antipsychotics. Twenty-three (61%) used both typical and atypical antipsychotics, five subjects (13%) used only typical antipsychotics and six subjects (15%) used only atypical antipsychotics. The mean dose 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 the baseline study, 36 (95%) schizophrenia subjects had used benzodiazepines. Five (14%) of them had used benzodiazepines only irregularly (prescribed to be taken only when needed). During the follow-up, 30 (79%) schizophrenia subjects used benzodiazepines. Ten (33 %) of them used benzodiazepines only irregularly. The mean dose during the follow-up was 6.7 (SD 8.2) DDDy.

Table 4. Characteristics of the sample. Modified from Table 1 in original study II and Table 3 in original study III.

	Follow-up study	43-year study	
Variable	Schizophrenia (n=38)	Schizophrenia (n=44)	Affective psychoses (n=24)
Gender* n (%)			
Male	21 (55%)	27 (61%)	7 (29%)
Age, years (SD)	Baseline/follow-up		
Mean age, Range	33.7 (0.7), 32.6- 35.4 / 42.8 (0.5), 41.8- 44.0	43.1 (0.7), 41.8 – 44.5	43.6 (0.7), 41.9 – 44.7
Marital status* n (%)	At baseline		
Married or cohabited	11 (29 %)	10 (23%)	12 (50%)
Single	27 (71%)	34 (77%)	12 (50%)
Educational level n (%)	At baseline		
Low	20 (53%)	24 (55%)	15 (63%)
Middle	9 (24%)	10 (23%)	6 (25%)
High	9 (24%)	10 (23%)	3 (13%)
Working status n (%)	At baseline		
Disability pension	14 (37%)	26 (60%)	12 (50%)
Employed	14 (37%)	12 (27%)	8 (33%)
Other[a]	10 (26%)	5 (11%)	3 (13%)
Comorbid diagnose of alcohol use disorder n (%)	9 (24 %)	40 (91 %)	19 (79%)
Diagnosis n (%)			
Schizophrenia	33 (87%)	42 (96%)	-
Schizophreniform disorder	1 (3%)	2 (4%)	-

	Follow-up study	43-year study	
Variable	Schizophrenia (n=38)	Schizophrenia (n=44)	Affective psychoses (n=24)
Delusional disorder	1 (3%)	-	-
Schizoaffective disorder	3 (8%)	-	5 (21%)
Psychotic bipolar disorder	-	-	6 (25%)
Psychotic depression	-	-	13 (54%)
Lifetime hospital treatment days	At baseline		
Mean (SD) median, range	514, (892) 151, 0-4702	579 (899) 213, 1-5093	162 (122) 146, 2-399
PANSS total score	Average		
Mean (SD) median, range	61.4 (20.7), 30–95	70 (27), 30-130	43 (9.7), 31-75
Remission* n (%)	Baseline/Follow-up		
	13 (34%)/12 (32%)	11 (25%)	21 (88%)
Onset age* mean (SD), Range	23.1 (4.4), 16.7–31.0	25 (6.3), 16.7–42.0	32 (6.3), 21.4–41.2

a= unemployed or not in working life due to other reasons than disability pension, PANSS= Positive And Negative Syndrome Scale.

Table 5. Medication use characteristics of the follow-up sample, N=38 schizophrenia cases. Modified from Table 2 in original study II.

Medication use	N (%)	Mean dose (Median)
Use of antipsychotics before baseline in CPZy		
Use of antipsychotics	37 (97.4)	27.6 (14.0)
Use of typical antipsychotics	37 (97.4)	21.6 (8.7)
Use of atypical antipsychotics	20 (52.6)	11.0 (5.9)
Use of clozapine	9 (23.7)	16.7 (9.8)
Use of antipsychotics during follow-up in CPZy		
Use of antipsychotics	34 (89.5)	28.5 (20.8)
Use of typical antipsychotics	28 (73.7)	9.4 (6.1)
Use of atypical antipsychotics	29 (76.3)	24.3 (20.3)
Using typical antipsychotics only	5 (13.2)	7.7 (4.5)
Using atypical antipsychotics only	6 (15.8)	19.0 (12.5)
Using both typical and atypical antipsychotics	23 (60.5)	35.5 (38.2)
Use of clozapine	7 (18.4)	3.2 (3.6)
Use of benzodiazepines in BZDy		
Use of benzodiazepines before baseline scan	36 (94.7)	3.6 (2.5)
Use of benzodiazepines only irregularly before baseline	5 (13.8)	1.1 (0.6)
Use of benzodiazepines during follow-up	30 (78.9)	4.1 (3.3)
Use of benzodiazepines only irregularly during follow-up	10 (33.3)	1.6 (1.1)
Use of both antipsychotics and benzodiazepines during the follow-up	30 (78.9)	4.1 (3.3) BZDy 28.7 (20.8) CPZy

CPZy = antipsychotic dose years in chlorpromazine equivalents, BZDy = benzodiazepine dose years in defined daily dose N= number of cases, SD= Standard Deviation, DDDy= dose years in defined daily dose, ap= antipsychotic, bzd= benzodiazepine.

Table 6. Lifetime medication use characteristics. Modified from Table 4 in original study III.

Medication use	Schizophrenia N (%[a]), mean DDDy (SD)	Affective psychoses 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)
Current use of medication		
Antipsychotics	35 (80%), 203 (218)	17 (71%), 280 (192)
Benzodiazepines	20 (%), 33 (21)	5 (%), 28 (11)

N= number of cases, SD= Standard Deviation, DDDy= dose years in defined daily dose, ap= antipsychotic, bzd= benzodiazepine

6.2.2 Lifetime medication use characteristics (III)

The lifetime medication use in schizophrenia and affective psychoses by the age of 43 years are presented in Table 6. In the schizophrenia group, 42 (96%) individuals had used antipsychotics during lifetime, and the mean dose was 20.1 DDDy. Thirty-nine (88%) individuals had used typical antipsychotics and 35 (80%) individuals had used atypical antipsychotics. Thirty-three (75%) had used benzodiazepines and the mean dose was 9.1 DDDy.

In affective psychoses, 20 (83%) individuals had used antipsychotics and the mean dose was 4.7 DDDy. Fifteen (63%) individuals had used typical antipsychotics and 16 (67%) individuals had used atypical antipsychotics. Ten (41%) individuals had used benzodiazepines and the mean dose was 6.6 DDDy. Many of the study subjects had used several different antipsychotics during their lifetime.

6.2.3 Differences between groups regarding brain structures

In the follow-up study (II), when compared to non-psychotic controls, schizophrenia cases showed statistically significant decreases 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).

There were no statistically significant differences between brain volumes in schizophrenia and affective psychoses in the cross-sectional study (III).

6.3 Associations between medication and structural brain change during the follow-up (II)

6.3.1 Associations between antipsychotic dose and brain volume change during the follow-up

Higher cumulative antipsychotic dose during the follow-up 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 the analyses with cumulative benzodiazepine dose and PANSS average score as illness severity measure, the finding regarding lateral ventricles remained statistically significant (b=0.50, p=0.028). The results regarding all covariates and brain volumes are presented in Table 7.

Table 7. Associations between CPZy, BZDy and PANSS and brain structural changes during the follow-up, and associations between CPZy, BZDy and PANSS and brain structural changes in the same model. Modified from Table 4.1 in original study II.

		Independent model		CPZy, BZDy and PANSS in the same model	
Brain area	Variable	b	p	b	p
Total Brain	CPZy	-0.27	0.088		
	BZDy	**-0.35**	**0.037**	-0.23	0.252
	PANSS	-0.09	0.590		
Total GM	CPZy	**-0.38**	**0.012**	-0.24	0.252
	BZDy	-0.15	0.367		
	PANSS	**-0.37**	**0.013**		
Cerebrum	CPZy	-0.26	0.092		
	BZDy	**-0.32**	**0.048**	-0.21	0.296
	PANSS	-0.08	0.607		
Cerebrum GM	CPZy	**-0.39**	**0.012**	-0.25 p	0.242
	BZDy	-0.15	0.376		
	PANSS	**-0.37**	**0.015**		
Lateral ventricles	CPZy	**0.46**	**0.003**	**0.50**	**0.028**
	BZDy	**0.36**	**0.037**	0.13	0.517
	PANSS	0.21	0.211		
Caudate	CPZy	-0.29	0.062		
	BZDy	**-0.49**	**0.002**	**-0.42**	**0.029**
	PANSS	-0.25	0.117		
Putamen	CPZy	-0.30	0.074		
	BZDy	-0.27	0.144	-0.08	0.703
	PANSS	-0.25	0.154		
Thalamus	CPZy	**-0.34**	**0.030**	-0.19	0.419
	BZDy	**-0.36**	**0.033**	-0.24	0.233
	PANSS	-0.26	0.121		
Hippocampus	CPZy	**-0.34**	**0.040**	-0.33	0.176
	BZDy	-0.18	0.306		
	PANSS	-0.16	0.337		

		Independent model		CPZy, BZDy and PANSS in the same model	
Brain area	Variable	b	p	b	p
Accumbens	CPZy	**-0.38**	**0.018**	-0.35	0.727
	BZDy	**-0.40**	**0.018**	-0.24	0.270
	PANSS	**-0.37**	**0.023**		

ICV and sex as covariates in all analyses. CPZy = antipsychotic dose years in chlorpromazine equivalents during follow-up, BZDy = benzodiazepine dose years in defined daily dose during follow-up, ICV = intracranial volume, GM = grey matter, b = standardized beta, PANSS = The average score of Positive and Negative Syndrome Scale total score at 34 years and 43 years.

6.3.2 Associations between benzodiazepine dose and brain volume change during the follow-up (II)

Higher scan interval cumulative benzodiazepine dose associated with increase in the volume of the 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 cumulative antipsychotic dose and PANSS average score, the finding in the caudate nucleus remained statistically significant (b=-0.42, p=0.029). The results regarding all covariates and brain volumes are presented in Table 7.

6.4 Association between medication and brain volumes at the age of 43 years (III)

6.4.1 Associations between lifetime antipsychotic dose and brain volumes

In schizophrenia, higher cumulative lifetime antipsychotic dose associated to smaller volumes of total brain, total GM, cerebrum, cerebral GM, thalamus, hippocampus and accumbens, and larger volumes of lateral ventricles. After adjusting the analyses with lifetime benzodiazepine dose, 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). When onset age was added to the model, the statistically significant associations were found 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 the level of significance as well (b=-0.34, p=0.050). However, in the PANSS adjusted analyses, PANSS total score did not associate to the structure volumes either with the exception of lateral ventricles (b=0.43, p=0.018).

There were no associations between lifetime antipsychotic dose and volumes of brain structures in affective psychoses. In addition, there were no statistically significant associations between group × lifetime antipsychotic dose and brain volumes in interaction analyses. The results of lifetime antipsychotic and benzodiazepine doses in the same model are presented in Table 8.

6.4.2 Associations between lifetime benzodiazepine dose and brain volumes

In schizophrenia, higher cumulative lifetime benzodiazepine dose associated to lower volumes of total brain (b=-0.23, p=0.002) and cerebrum (b=-0.21, p=0.006). When adjusting the analysis with cumulative lifetime antipsychotic dose, no associations remained. However, after adding onset age to the model, there was a significant association between higher benzodiazepine dose and lower volume in total brain (b=-0.17, p=0.044), but this association did not remain when the model was adjusted with PANSS total score instead of onset age.

In affective psychoses, higher cumulative lifetime benzodiazepine dose associated to 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) even after the analyses were adjusted with cumulative lifetime antipsychotic dose and PANSS total score or onset age.

The results of lifetime antipsychotic and benzodiazepine doses in the same model are presented in Table 8. There were no statistically significant associations between group × lifetime benzodiazepine dose and brain volumes in interaction analyses.

Table 8. Associations between lifetime antipsychotic and benzodiazepine dose and the same model including PANSS as an additional covariate. ICV and sex as covariates in all analyses. Modified from Tables 5 and 6 in original study III.

		Antipsychotic and benzodiazepine dose in the same model				Antipsychotic and benzodiazepine dose and PANSS in the same model			
		Schizophrenia		Affective psychoses		Schizophrenia		Affective psychoses	
Brain area	Variable	b	p	b	p	b	p	b	p
Total Brain	AP	-0.13	0.118	-0.40	0.695	-0.08	0.387	-0.01	0.910
	BZD	-0.15	0.062	0.13	0.136	-0.11	0.204	0.12	0.200
	PANSS					-0.13	0.163	-0.07	0.461
Total GM	AP	**-0.25**	**0.017**	0.06	0.626	-0.17	0.120	0.14	0.312
	BZD	0.03	0.786	**0.33**	**0.014**	0.08	0.453	**0.30**	**0.020**
	PANSS					-0.20	0.066	-0.19	0.153
Cerebrum	AP	-0.13	0.125	-0.02	0.835	-0.07	0.445	-0.005	0.962
	BZD	-0.14	0.115	0.16	0.072	-0.09	0.329	0.15	0.105
	PANSS					-0.167	0.104	-0.05	0.579
Cerebrum GM	AP	**-0.25**	**0.024**	0.08	0.482	-0.16	0.157	0.16	0.261
	BZD	0.04	0.682	**0.32**	**0.014**	0.10	0.375	**0.29**	**0.025**
	PANSS					-0.22	0.052	-0.17	0.213
Lateral ventricles	AP	0.33	0.061	0.25	0.274	0.16	0.363	0.20	0.479
	BZD	0.04	0.804	-0.22	0.331	-0.06	0.725	-0.17	0.463
	PANSS					**0.43**	**0.018**	0.23	0.393
Caudate	AP	0.002	0.990	0.63	0.114	0.03	0.867	0.30	0.157
	BZD	0.12	0.471	0.22	0.184	0.16	0.391	0.21	0.249
	PANSS					-0.06	0.738	-0.07	0.730
Putamen	AP	0.17	0.282	0.07	0.711	0.17	0.324	0.11	0.627
	BZD	0.004	0.980	0.22	0.247	-0.03	0.840	0.23	0.237
	PANSS					-0.02	0.894	-0.02	0.926
Thalamus	AP	**-0.39**	**0.014**	-0.27	0.089	-0.34	0.050	-0.26	0.185
	BZD	0.005	0.971	**0.36**	**0.026**	0.04	0.794	**0.35**	**0.044**

		Antipsychotic and benzodiazepine dose in the same model				Antipsychotic and benzodiazepine dose and PANSS in the same model			
		Schizophrenia		Affective psychoses		Schizophrenia		Affective psychoses	
Brain area	Variable	b	p	b	p	b	p	b	p
	PANSS					-0.11	0.508	-0.04	0.813
Hippocampus	AP	-0.26	0.113	-0.21	0.154	-0.23	0.201	-0.12	0.500
	BZD	-0.08	0.627	0.30	0.051	-0.06	0.755	0.27	0.093
	PANSS					-0.06	0.734	-0.18	0.306
Accumbens	AP	**-0.40**	**0.014**	0.15	0.396	**-0.38**	**0.033**	0.33	0.066
	BZD	0.13	0.390	-0.48	0.068	0.13	0.430	-0.40	0.538
	PANSS					-0.05	0.777	**-0.40**	**0.024**

ICV= intracranial volume, b= standardized beta, ap= antipsychotic, bzd= benzodiazepine, PANSS= Positive and Negative Syndrome Scale

7 Discussion

7.1 Main findings

According to the meta-analysis (I), higher long-term antipsychotic exposure associated with decrease in parietal lobe volume and increase in basal ganglia volume. The original studies were very heterogenous in their methods and most reported statistically non-significant correlations. Based on the systematic review, there were no clear differences between typical and atypical medication exposure and brain volume changes in long-term use.

In the NFBC1966 follow-up study, higher antipsychotic medication dose during a 9-year follow-up associated to increase in lateral ventricular volume when the average illness duration was 10 years already at baseline and even after taking illness severity measures and benzodiazepine dose into account (II). Higher benzodiazepine dose associated to reduction in caudate nucleus volume after adjusting with illness severity and antipsychotic dose (II).

In the NFBC1966 43-year study, higher lifetime antipsychotic dose associated to smaller volume in nucleus accumbens after controlling for illness severity and lifetime benzodiazepine dose, and higher lifetime benzodiazepine dose associated to smaller volume of total brain after controlling for antipsychotic dose and illness duration (onset age) in the schizophrenia group. In affective psychoses, higher lifetime benzodiazepine dose associated to larger volumes of total GM, cerebral GM and thalamus after controlling for antipsychotic dose and illness severity.

Summary of the main findings is presented in Table 9.

Table 9. Summary of the statistically significant findings.

	Meta-analysis (I)	Follow-up study (II)		43-year study (III)			
				Schizophrenia		Affective psychoses	
Brain area	Antipsychotics	Antipsychotics	Benzodiazepines	Antipsychotics	Benzodiazepines	Antipsychotics	Benzodiazepines
Total brain			Decrease	Smaller volume	Smaller volume[a]		
Total GM		Decrease		Smaller volume[a]			**Larger volume**
Cerebrum			Decrease	Smaller volume	Smaller volume		
Cerebral GM		Decrease		Smaller volume[a]			**Larger volume**
Lateral ventricles		**Increase**	Increase	Larger volume[a]			
Parietal lobe*	Decrease	-	-	-	-	-	-
Basal ganglia*	Increase	-	-	-	-	-	-
Caudate nucleus			**Decrease**				
Thalamus		Decrease	Decrease	Smaller volume[a]			**Larger volume**
Hippocampus		Decrease		Smaller volume			
Nucleus accumbens		Decrease	Decrease	**Smaller volume**			

All NFBC1966 analyses were adjusted with ICV and sex. All statistically significant results in bold were analysed using PANSS score as illness severity measure. a= statistically significant findings using onset age as alternative illness severity measure instead of PANSS. *= areas were studied in the meta-analysis (I) but not in the NFBC1966 studies (II, III).

7.2 Comparison with earlier studies

7.2.1 Systematic review and meta-analysis (I)

The findings of the systematic review and meta-analysis are partly similar, but also differ from the previous reviews, which have also included studies with shorter follow-ups. Previous reviews have not reported antipsychotic effects in the parietal lobe, but effects on basal ganglia volumes have been reported often, as well as effects on frontal and temporal lobes and CSF/ventricles. However, most previous reviews have also included studies investigating differences between schizophrenia cases using antipsychotics and being drug-naïve.

There are several reviews (see Table 2) on associations between antpsychotic medication and brain volume change over time, but none of them have focused on the long term follow-ups. The current results extend the findings of associations between antipsychotic dose and brain volume changes (Fusar-Poli *et al*. 2013, Roiz-Santiáñez *et al*. 2015, Vita *et al*. 2015). The findings are independent instead of replications, since the methods used in the study I differ from the previous studies: Vita *et al*. (2015) analysed effects only on the cortical gray matter, Roiz-Santiáñez *et al*. (2015) included also studies with shorter follow-ups, and Fusar-Poli *et al*. (2013) analysed associations between antipsychotic dose and brain volumes only at study level (i.e. between the mean antipsychotic dose of the study sample and mean of brain volume loss of the study sample).

A previous systematic review on antipsychotic monotherapy effects in basal ganglia reported that there were no effects of typical antipsychotics on basal ganglia volume increase, but atypical antipsychotics were associated to both increases and decreases (Ebdrup *et al*. 2013). In this review and meta-analysis (I) typical antipsychotics were more often associated with basal ganglia volume increments than atypical antipsychotics (Ho *et al*. 2011, van Haren *et al*. 2011, Westmoreland Corson *et al*. 1999). However, the difference between the effects of typical and atypical antipsychotics is not clear (I), and earlier reviews have also reported heterogenous findings regarding differences between typical and atypical antipsychotic effects (Ebdrup *et al*. 2013, Navari & Dazzan 2009, Smieskova *et al*. 2009). A meta-analysis of antipsychotic effects on cortical gray matter reported that more progressive loss was found in patients treated with at least one first-generation

antipsychotic and less progressive in those treated only with second-generation antipsychotics (Vita *et al*. 2015).

Though the evidence of the association between long-term use of antipsychotics and brain structures in schizophrenia is not strong, it still cannot be concluded, that the association does not exist.

7.2.2 Comparison with earlier studies on antipsychotic effects on brain structures (II, III)

In a partly overlapping NFBC1966 schizophrenia sample, with a different method based on brain surface movement (atrophy) over time (FSL SIENA), we found that higher amount of antipsychotic medication over the 9-year follow-up predicted larger total brain volume loss and ventricular enlargement (Veijola *et al*. 2014, Guo *et al*. 2015). Therefore, it seems that in this sample, the association between larger antipsychotic exposure and ventricular enlargement is consistent. However, not all other studies have found similar associations with long-term antipsychotic use (Ho *et al*. 2011, Puri *et al*. 2001, Saijo *et al*. 2001), and there was no association between CSF and ventricles in the meta-analysis (I).

In addition to ventricular enlargement, total brain volume loss has also been associated to higher antipsychotic exposure during the follow-up in NFBC1966 (Veijola *et al*. 2014). In this study (II), with a different image analysis method, decrease in total gray matter volume was associated to larger antipsychotic dose as well, though the association was attenuated after adjusting with benzodiazepine dose and illness severity.

The results regarding the association between higher lifetime antipsychotic dose and lower gray matter volumes in schizophrenia in cross-sectional analyses (III), though not statistically significant after several adjustments, are in line with the findings of a previous review on cross-sectional studies (Haijma *et al*. 2013). Previous reviews have not reported associations between smaller volumes in thalamus and nucleus accumbens, but instead they have reported larger volumes of thalamus and basal ganglia associated to antipsychotic use, though the findings of original studies are varied (Navari & Dazzan 2009, Scherck & Falkai 2006, Smieskova *et al*. 2009).

Regarding affective psychoses, the findings are mostly in line with previous literature with no significant associations between antipsychotic dose and brain structures (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 & Heckers 2015, Yüksel *et al*. 2012). The only previous positive findings, to my knowledge, have been found by Liberg *et al*. (2015), who found an association between antipsychotic medication and positive vertex displacement in the pallidum in psychotic bipolar disorder, and Morgan *et al*. (2009), who found that longer duration of antipsychotic treatment associated to increased ventricular volumes in a group with affective psychoses. Though there are only a few studies focusing on medication effects in affective psychoses, a review on medication effects in bipolar disorder concluded that the effects of psychotrophic medications, such as lithium or antipsychotics, seem to be more normalizing and do not seem to affect the differences observed in volumes (Hafeman *et al*. 2012).

7.2.3 Comparison with earlier studies on benzodiazepine effects on brain structures (II, III)

To my knowledge, there are no previous MRI studies on benzodiazepine effects on brain structures in schizophrenia or affective psychoses. In earlier CT studies the findings are inconsistent, though the topic has not been studied extensively. Most studies 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), but two studies have found that benzodiazepines associate to increased ventricle-to-brain ratio (Schmauss & Krieg 1987, Uhde & Kellner, 1987) and one even suggested a dose-dependent effect (Schmauss & Krieg, 1987). However, these studies were made mostly in general population samples (Busto *et al*. 2000, Moodley *et al*. 1993, Perera *et al*. 1987, Schmauss & Krieg 1987), in addition to a sample of alcoholics (Lader *et al*. 1984) and a sample with panic disorder (Uhde & Kellner 1987).

7.3 Possible mechanisms behind antipsychotic induced brain volume changes

The mechanism behind the possible effects of antipsychotics on brain volumes is not clear, though there are some potential suggestions. Antipsychotics have effects on regional cerebral blood flow in several regions, particularly in frontal regions and basal ganglia (Goozée *et al*. 2014). They have been found to cause several changes in rodent nerve cells indicating potential to associate with changes in the cell functioning and morphology in humans as well (Dean 2006). Structural effects

of antipsychotics in the rodent brain are detectable already after eight weeks of treatment (Vernon *et al*. 2011). Though some effects seem to be reversed after discontinuation (Vernon *et al*. 2012), a variety of neurobiological changes in rats have been observed after three to six months of treatment, indicating that these medications may also have long-term consequences in addition to their acute effects (Terry & Mahadik 2007).

Antipsychotics seem to increase striatal metabolism as a consequence of presynaptic D2 blocking (Buchsbaum *et al*. 1992, Eisenberg *et al*. 2017), which may lead to increased volumes in the striatum. Reductions in cortical volumes in antipsychotic exposed monkeys compared to placebo (Dorph-Petersen *et al*. 2005) resulted from lower astrocyte number in the antipsychotic treated groups (Konopaske *et al*. 2007). However, antipsychotic induced decrease in volume and thickness of anterior cingulate cortex in rats was not associated to a decrease in the astrocyte number but instead to a decrease in the neuropil (Vernon *et al*. 2014). Antipsychotics may also induce autophagy, which is related to neurodegeneration and cell death, and thus contribute to volumetric changes (Shin *et al*. 2012). The metabolic side effects of antipsychotics have also been linked to cognitive dysfunction, which again was linked to lower BDNF levels and higher TNF-alpha levels (Zhang *et al*. 2017), which may contribute to plasticity in the brain.

One possible theory explaining antipsychotic-related structural changes could be through alterations in the gut-brain axis (Kanji et al. 2017), which is a bidirectional connection between the central nervous system (CNS) and gut, where the CNS regulates gut functioning and homeostasis, and in turn the gut microbiome affect the brain's physiological, behavioral and cognitive functions (Wang & Wang 2016). Micro-organisms can regulate BDNF and NMDA receptors and thus contribute to brain development and neural plasticity (Sudo *et al*. 2004). In female rats, administration of olanzapine changed the gut bacteria significantly and increased the levels of systemic inflammatory markers (Davey *et al*. 2012), which in turn correlate positively with clinical symptoms (Fan *et al*. 2007a, 2007b, Hope *et al*. 2013).

7.4 Possible mechanisms behind benzodiazepine induced brain volume changes

Since there are not many studies investigating the potential effects of benzodiazepines on brain structures, there is no current knowledge on the mechanism how benzodiazepines could affect brain structures in humans either.

However, in animal studies BDNF levels decreased after acute, but not repeated administration of the benzodiazepine triazolam and closely related drug zolpidem in the mouse hippocampus (Licata *et al*. 2013b). BDNF regulates neuronal connectivity and synaptic efficacy (Lu 1999) and plays a key role in neural plasticity (Duman 2004, Zagrebelsky & Korte 2014), and thus it could be a mediator in structural alterations as well. Benzodiazepine exposure also decreased the density of the spines of pyramidal neurons in mice (Curto *et al*. 2016), and diazepam reduced the level of transcripts involved in synaptic functions and neural plasticity (Huopaniemi *et al*. 2004). Zolpidem has also been found to alter the function of resting-state networks in healthy individuals (Licata *et al*. 2013a), and functional aberration often leads to structural changes as well (Keck *et al*. 2011).

7.5 Other factors associated with structural changes in the brain in schizophrenia

Though the results of this study suggest that antipsychotic medications and benzodiazepines might affect brain structures in long-term use, it is possible, that the detected associations are due to confounding factors that were not easily identified in these studies. In addition to antipsychotic medication, relapse duration has been associated to gray and white matter decrease in schizophrenia, though in different brain areas (Andreasen *et al*. 2013). Poorer functional outcome is also related to more pronounced brain volume loss (van Haren *et al*. 2013). Though individuals with more severe illness course may also be prescribed larger doses of antipsychotics, the relationship between both relapses and functional outcome and brain volume seem to be independent of antipsychotic intake (Andreasen *et al*. 2013, van Haren *et al*. 2013). In the study (II) on the brain 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 effect size of PANSS was roughly the same as the effect size of cumulative antipsychotic dose on those brain areas. The effect of onset age (illness duration) was also roughly the same as the effect of cumulative antipsychotic dose on the same areas.

Illness duration is one key confounder that should be taken into account in the studies examining brain structures in schizophrenia. The timing of the brain changes in schizophrenia is not clear and it has been argued that the rate of volume decrease is highest in the first year of illness (van Haren *et al*. 2013), at least with respect to gray matter changes (Pantelis *et al.* 2005). However, recently it was

reported, that white matter changes occur more evidently at later stages of the illness after gray matter reductions (Cropley *et al.* 2017). It has also been suggested, that the effect of antipsychotic medication on symptoms and functioning may be different in the first years of the illness than later during the illness, and that greater medication dose might relate to poorer outcome after several years of follow-up (Wunderink *et al*. 2013). In addition, the findings between antipsychotics and brain structures may be stronger in the early phase compared to a more chronic stage: Gur *et al.* (1998) found that higher medication dose associated to greater reduction in frontal and temporal volumes in first-episode schizophrenia group, but not in a previously treated group. However, in the systematic review (I), both first-episode and previously treated samples reported statistically significant associations. Though brain changes during the early phase of the illness are most likely crucial for the understanding of these associations, it is also important to clarify the association between antipsychotic medication and brain structures in more chronic patients in longer follow-ups.

Apart from illness related factors, continuous use of cannabis has been associated to gray matter deficits in schizophrenia (van Haren *et al*. 2013). Body mass index (BMI) and dietary profile have also been suggested to affect brain volumes and confound the effects of medication (when weight gain is one of the most common adverse effects of antipsychotic medication), but a recent study by Jørgensen *et al*. 2016) found that antipsychotic related brain volume loss was independent of BMI change, and that BMI change correlated negatively on brain volume change in both first-episode psychosis cases and controls. The effect of gender should also be taken into account since females are often underrepresented in schizophrenia studies and antipsychotic effects and associations with brain volumes may differ between the sexes (Crawford & DeLisi 2016, Heitmiller *et al*. 2004).

A study on IQ and brain measures in schizophrenia concluded that progressive brain tissue loss is related to relative cognitive decline during the early course of illness (Kubota *et al*. 2015). On the other hand, cognitive enhancement therapy has been shown to preserve gray matter volumes in schizophrenia compared to matched individuals without cognitive therapy (Eack *et al*. 2010). Also functional MRI studies refer to increased activation due to cognitive rehabilitation (Penadés *et al*. 2013, Wexler *et al*. 2000, Wykes *et al*. 2002). Physical exercise has been shown to both improve cognition and increase brain volume in schizophrenia cases, though the brain regions with positive findings vary (Firth *et al*. 2017). In addition, BDNF

levels increase due exercise thus possibly explaining the previously mentioned associations (Firth *et al*. 2017).

In addition to several environmental and illness related factors, normal ageing also degenerates the brain. A review exploring the accelerated aging hypothesis of schizophrenia reported decreased BDNF levels in the frontal regions in schizophrenia similar to those in older individuals compared to a younger cohort (Islam *et al*. 2017) thus supporting the accelerated aging hypothesis.

7.6 Association between antipsychotic medication and brain functioning in schizophrenia

The meaning of the structural changes related to antipsychotic treatment is unclear. Increase in volume is not automatically a positive measure and decrease a negative measure regarding the brain functioning: basal ganglia increments may be associated with more extrapyramidal symptoms (Tost *et al*. 2010) and on the other hand, antipsychotic associated cortical thinning has been linked to improved cognitive function in first episode schizophrenia in a short-term study (Lesh *et al*. 2015). On the other hand, poorer outcome and more severe illness seem to associate to decrease in brain volumes as well (Andreasen *et al*. 2013, Gur *et al*. 1998, Ho *et al*. 2011, Nesvåg *et al*. 2012, van Haren *et al*. 2013).

Larger doses of antipsychotics have been associated to poorer cognition (Faber *et al*. 2012, Husa *et al*. 2014, Torniainen *et al*. 2012), poorer somatic health (Barnett *et al*. 2007, Steylen *et al.* 2013) and poorer social functioning (Moilanen *et al*. 2016, Wunderink *et al*. 2013) in schizophrenia. Long-term use of antipsychotics on high doses has also been found to associate with unfavorable changes in the brain functioning (Radua *et al*. 2012).

In NFBC1966 higher dose-years of antipsychotics associated with decline in verbal learning and memory between ages 34 and 43 (Husa *et al*. 2014) and high lifetime dose and antipsychotic polypharmacy associated with poorer outcomes at the age of 43 years (Moilanen *et al*. 2016). These results are consistent with the structural findings suggesting potential adverse effects of long-term antipsychotic use in the NFBC1966 sample.

7.7 The function of brain areas with significant findings in this study

The brain areas antipsychotics were associated to in this study link to several important functions, which are often impaired in schizophrenia. Several cognitive and motor functions, such as attention, working and long-term memory, numerical processing, tool use and sensorimotor transformations for action planning, are processed in the parietal lobe. It is also the key area in tasks involving integration of different stimuli (Teixeira *et al*. 2014). A large resting state fMRI study identified key functional circuitry alterations in parietal regions instead of frontal regions in medicated schizophrenia cases (Guo *et al*. 2014). A study with macaque monkeys reported glial loss in the parietal lobe associated with antipsychotic exposure (Konopaske *et al*. 2007), which suggests that antipsychotics may play a role in the structural changes in the parietal lobe.

The term basal ganglia refer to a group of subcortical nuclei, which are primarily responsible for motor control, and involved in motor learning, executive functions and emotions (Lanciego *et al*. 2012). In addition, the basal ganglia play a significant role in attention, time estimation, habit formation and reward-related behavior (Lanciego *et al.* 2012). In detail, nucleus accumbens plays a key role in reward circuitry and action selection, integrating cognitive and affective information (Floresco 2015) and the caudate nucleus is responsible for planned goal directed action (Grahn *et al*. 2008). A review on motor abnormalities and basal ganglia structure in schizophrenia (Hirjak *et al*. 2015) concluded, that especially caudate nucleus, globus pallidus and putamen morphology are associated with involuntary movements, negative symptoms and neurological soft signs, which are minor neurological signs indicating non-specific cerebral dysfunction such as clumsiness and motor incoordination. These findings were partly determined by psychopathology, and not entirely explained by antipsychotic medication effects, as has often been thought.

7.8 General and methodological discussion

In general, the understanding of the brain as a continuously changing and partly regenerating plastic organ is not complete. Several different factors are associated to brain volume change both in brain disorders and normal population. Some of the observed changes seem to be reversible. Though some associations seem logical, the mechanisms behind them are not clear. As an example outside of schizophrenia,

post traumatic stress disorder is associated with hippocampus volume decrease, which complicates the processing of the trauma (Hull 2002, Woon *et al*. 2010), and physical exercise has been shown to increase brain volumes and improve cognition as well as to prevent age related deterioration (Batouli & Saba 2017). Similar structure-function associations are being examined and found in schizophrenia.

It is not easy to conduct longitudinal structural MRI studies. To minimize the effects of potential confounders, the conditions before each scan should be as similar as possible. Not only the scanner should be the same, but also the individuals entering the scanner should be in the same condition each time, e.g. diet and hydration levels should be comparable. Though these issues are well acknowledged, they are very hard to control in real life settings. Another confounding effect in imaging studies is the diversity in the segmentation and analysing techniques used, which may also result in differences between the findings in different studies (Honea *et al*. 2005).

The results of this study suggest that there are antipsychotic related changes in the brain in individuals with schizophrenia. These findings support the conclusions of neuropathological (Iritani 2007) and animal studies (Dorph-Petersen *et al*. 2005, Vernon *et al*. 2011, 2014) concluding that antipsychotic drugs are not neuroprotective. Animal studies have found medication related changes even when the illness related factors and other confounders often present in human studies are excluded.

Though the results of the meta-analysis (I) were non-significant regarding total brain, frontal and temporal lobe decrease and ventricular increase, the pooled effect sizes were similar in these regions compared to parietal lobe and basal ganglia, but the findings were heterogenous. Further studies are needed to examine whether there are regional differences on lobar level associated to antipsychotic effects.

The effects of antipsychotics may vary in different brain regions and across species. Widespread reductions in cortical volumes in antipsychotic exposed monkeys resulted from lower astrocyte number (Dorph-Petersen *et al*. 2005) which was associated with both haloperidol and olanzapine exposure (Konopaske *et al*. 2007). However, in rats, antipsychotic induced decrease in volume and thickness of anterior cingulate cortex was not associated to decrease in astrocyte number but instead to an increase in cell number (Vernon *et al*. 2014).

Most schizophrenia studies are made in selected populations drawn from hospitals and other institutions, in which patients may be more ill than in population based settings. Samples are small and methods heterogenous. Illness related confounders are rarely used: based on the systematic review (I), only 4 studies

adjusted their analyses for illness severity measures. However, the quality of the original studies or the use of covariates did not affect the results of the meta-analysis (I).

Ideally, all brain MRI studies in schizophrenia should take into account at least some basic confounding factors that are known to affect brain volumes. These include gender, age, illness stage (duration of illness), illness severity and substance use. These confounders may also affect the associations between medications and brain volumes. The follow-up study of the NFBC1966 sample partly demonstrates the importance of using covariates in the analyses when studying variables that are sensitive to confounding factors. Illness related factors were difficult to control, since the interscan interval variables correlated strongly with each other. In the NFBC1966 follow-up study (II) it was not possible to control illness severity throughout the follow-up as well as desired, since there were only two separate measures, which of course is not ideal and might affect the results.

A randomized controlled trial would be the optimal method for studying associations between long-term use of these medications and brain structures in theory, but these trials are difficult or even impossible to put into practice. Clinical trials regarding long-term antipsychotic treatment are very hard to conduct and the dropout rates can be significant in long-term follow-ups. In addition, since the treatment should be personalized, it is not ethical to make strictly defined trials that last for several years. In clinical trials the samples are often even more highly selected than in observational studies. However, since the use of antipsychotics in psychotic disorders, especially in schizophrenia, is often long-term in clinical practice, it is also important to examine long-term associations in naturalistic studies (Wang *et al*. 2011).

7.9 Strengths and limitations

7.9.1 Systematic review and meta-analysis (I)

This systematic review and meta-analysis is the first to focus on long-term effects of antipsychotics on brain volumes in schizophrenia. Previous reviews have included also cross-sectional studies or studies with short follow-ups. In addition, the previous studies have not focused on antipsychotic dose effects but also studied the use (or absence) of antipsychotics or study level correlations.

The interpreation of the data from original studies is difficult, since most sample sizes are small and the studies may be underpowered to detect subtle associations. To be able to detect a moderate correlation of r= 0.3, the sample size should be 67 (β=80%, α=5%). On the other hand, small and medium correlations from studies with small samples do not reach statistical significance. Most of the statistically significant findings of the review and meta-analysis came from the two largest samples, the IOWA Longitudinal Study (Andreasen *et al*. 2013, Ho *et al*. 2003, 2007, 2011, McCormick *et al*. 2005, Westmoreland Corson *et al*. 1999) and the Utrech Schizophrenia Project (Collin *et al*. 2012, van Haren *et al*. 2007, 2008, 2011).

The original studies rarely took into account confounding factors. Of the 34 included studies, 11 used covariates such as age or total gray matter in their analyses. Only 4 studies took illness severity measures into account. The quality scores varied from 7 to 18 points with a median of 11 points. When conducting the meta-analysis with studies with lower or better quality scores, it did not affect the results.

One challenge with interpreting the results was that the studies rarely focused on associations between antipsychotics and brain volume changes as their main aim. Also the regions of interest varied greatly and not many studies focused on the same areas.

The decision to exclude studies focusing on adolescents and children based on the fact, that the use of antipsychotics is different in those groups than in adults. In addition, the brain is still developing in adolescence and it would be hard to compare the results to studies with adults or chronic illness states. The review by Roiz-Santiáñez *et al*. (2015) reported that studies focusing on adolescents did not find associations between antipsychotic exposure and whole brain volume. Likewise, in a study of young individuals at clinical high risk for psychosis, gray matter loss was not associated to antipsychotic medication status among those, who converted to psychosis (Cannon *et al*. 2015).

Observational studies are prone to publication bias, but the intention was to overcome the problem with a wide search strategy that was not directed to find only antipscychotic-associated findings. All studies with a follow up of over two years were scrutinized without prior knowledge on whether they had studied antipsychotic effects or not. In addition, many authors of the original studies were contacted in person to obtain previously unpublished data. Due to these procedures I am confident that the most related articles were included in the review. There was no clear evidence of publication bias, though there was a significant finding in Egger's test for small-study effects in the basal ganglia (p= 0.005 for other areas

p>0.19). Heterogeneity was high, indicating high variation in the results of the original studies. Thus it is hard to make definitive conclusions due to heterogenic results.

As a limitation, it was not possible to perform meta-analyses regarding different classes of antipsychotics or illness stage due to paucity of original studies. Another limitation was the lack of validated measures in the original studies to estimate antipsychotic exposure. Eight of the included 16 projects reported that they had used several sources for estimating antipsychotic exposure, but five did not report their protocol at all.

7.9.2 The NFBC1966 (II, III)

The most significant strength in the NFBC1966 study is the comprehensive, thoroughly collected medication data. It is unique with both antipsychotic and benzodiazepine lifetime use history, and it has been collected by interviews and by scrutinizing all available medical records in order to collect the prescribed doses and duration of treatments. To my knowledge, this work has been the first to investigate benzodiazepine dose effects on brain structure volumes in schizophrenia and affective psychoses. However, it was not possible to study the effects of independent drugs, since many subjects had used many different antipsychotics and benzodiazepines during their medication history. It also has to be acknowledged, that data collected mainly from medical records is susceptible for errors regarding adherence, thus possibly leading to over estimation of the used doses. However, whenever there was indication of a person not taking their medication or quitting it, this was taken into account in the calculations of medication doses.

Another strength is the naturalistic setting. This kind of approach is ideal for studying long-term associations, effects and adverse effects of medications (Wang *et al*. 2011). Compared to clinical trials, which are often made in strictly selected and controlled settings, studies made in naturalistic settings may provide additional information and new perspectives, since the subjects come from general population with relatively low doses of medication. This NFBC1966 sample is very heterogeneous and represents different stages of psychotic disorders including individuals in remission, more severely ill and with active psychosis. This sample is different from most study samples, since it also includes schizophrenia cases in remission and individuals from different hospital districts from a wide geographical area. The individuals are of same age, but in different stages of the illness.

Two different variables for antipsychotic doses were used in this study. In the follow-up study (II) CPZ was used since the previous longitudinal studies in NFBC1966 had used the same variable. In the cross-sectional 43-year study I used the DDD variable, since it might be a more modern option to assess the total exposure of antipsychotic medication based on its frequent updates regarding different medications (Rijcken *et al*. 2003). In addition, the DDD variable was more easily comparable with the benzodiazepine DDD variable. In this sample, the correlations between the CPZ and DDD variables regarding both follow-up and lifetime antipsychotic doses were highly correlated with each other (0.95-0.97 in longitudinal doses and 0.97-0.99 in lifetime doses), and therefore the results should not be influenced by the choice of medication variable (CPZ or DDD).

For the parcellation of brain structures, the automated brain volumetry system volBrain was the easiest and most reliable option regarding subcortical volumes for the data used in this study. Also other methods and segmentation programs were explored, but since the quality of the structural MRI scans at the age of 43 in the NFBC1966 study was not optimal, other segmentation programs were not as successfull as volBrain. In addition, the use of volBrain is efficient, since it does not need additional work regarding image processing. Unfortunately, volBrain does not parcellate cortical structures, thus it was not possible to study them in our sample. The scanner update during the follow-up may of course affect the brain structural measures. However, based on the calibration scan results, I am confident that the measures used in this study are reliable.

A major limitation of these NFBC1966 samples is the sample size. Of the 101 identified schizophrenia cases in the beginning of the follow-up study, only 73 participated at baseline and 45 at follow-up. Due to small number of affective psychoses cases in the follow-up study, it was not possible to make longitudinal analyses on affective psychoses. Because of active home-recruitment, the participants in the follow-up study did not differ from the non-participants in terms of age, sex or educational level (Veijola *et al*. 2014). Nevertheless, these NFBC1966 samples may not represent the whole schizophrenia population in the NFBC1966 in all measured domains. In general, the results of this NFBC1966 study are restricted between the ages of 34 and 43 years.

Also the samples in the follow-up study and 43-year study differ significantly regarding illness duration and severity: in the follow-up study (II) also very severely ill patients were actively recruited from their homes to participate in the study, whereas in the 43-year study (III), only the individuals actively willing to participate participated. In the 43-year study, the schizophrenia and affective

psychoses groups were not even, and the demographic characteristics including male/female ratio were significantly different between the groups, thus therefore they were not ideally comparable. The lifetime doses of medications were also significantly different between the groups and may partly epxplain the lack of findings regarding antipsychotic dose and brain volumes in the affective psychoses group.

One uncertainty in this study is also the lack of correction for multiple comparisons. The small sample size reduces statistical power to detect subtle associations, but also increases the likelihood of chance findings. Still, since conservative correction methods may overcorrect the results, it was a consious choice not to use them. There was a possibility to study 61 different brain measures produced by volBrain, but only 10 measures were selected for the analyses in the studies II and III based on previous findings and the reliability measure results.

Another limitation is the fact that it was impossible to control all potential confounding factors in the analyses. These include, for example, other medication use, dietary profile or physical activity. One important issue is that mood stabilizer use was not studied or taken into account, though the use of these medications is common especially in affective psychoses and known to associate positively with brain structure volumes (Manji *et al.* 2000). We were unable to examine the effect of lithium on brain structures in affective psychoses, because only a few individuals had been using it during lifetime and there were no individuals on lithium treatment at the study moment. In addition, it was not possible to take into account non-pharmacological therapies, since the data for psychosocial interventions has not been collected for this sample.

The scanner update during the follow-up may have also affected the results (II), though the study group and I tried to do our best to overcome the effect by using test-retest measures. However, it is a common problem in the follow-up imaging studies and multicenter studies, where the subjects are scanned with different scanners in different locations. Another limitation regarding imaging is the lack of structural MRI in the first episode of psychosis, thus making it impossible to evaluate the structural changes throughout the illness.

8 Conclusions

8.1 Conclusions

Previous data on the association between long-term antipsychotic use and studies on structural brain changes with at leat 2 years of follow-up are very heterogenous, and the overall number of studies is very small. However, there is evidence that antipsychotic medication may contribute to changes in at least some areas of the brain. The results of the meta-analysis complement the previous findings and clarify the findings between long-term use of antipsychotics and brain structures in schizophrenia. Future studies should be conducted in order to find out, whether the findings in parietal lobe accentuate in more chronic patients or if changes in other brain areas emerge in studies with larger samples.

In the NFBC1966 schizophrenia sample, higher cumulative antipsychotic dose associated to ventricular enlargement over a 9-year follow-up even after controlling for benzodiazepine use and illness related factors. In addition, higher cumulative benzodiazepine dose associated to decrease in caudate nucleus volume after taking antipsychotic dose into account in the follow-up study. In the cross-sectional 43-ear study, there was an association between higher lifetime antipsychotic dose and smaller nucleus accumbens volume after adjusting with lifetime benzodiazepine use and illness severity. In the group of affective psychoses in NFBC1966, higher lifetime benzodiazepine dose associated with larger volumes in total and cerebral gray matter and thalamus even after controlling for antipsychotic dose and illness severity measures. These results underline the importance of confounding factors in brain imaging studies, and suggest that both illness severity and benzodiazepine use should be taken into account in future studies investigating antipsychotic medication effects on the brain.

Regardless of these findings, it is possible, that there are unidentified factors that lead to both larger doses of medidcations and structural changes in the brain. It is important to acknowledge that the results of structural imaging studies are only observed differences between measures and though the relationship is possible, the existence of causal effect cannot be definitely concluded.

8.2 Future research

There is a need to understand the mechanisms how antipsychotics and benzodiazepines might alter brain funtioning and structure. Future studies should also focus on the effects of these medications on cognition and functioning and how the observed structural changes correspond to cognition and functioning of the brain.

It is also possible to continue the research on the theme of this thesis in the NFBC samples. Currently there exists data on fMRI tasks and resting state fMRI, and a possibility to study whether there are findings related to different psychiatric medication use. There is also a possibility to continue research on different antipsychotic and benzodiazepine related questions in the NFBC1966. One interesting aspect is the association between long-term antipsychotic use and somatic health and cognition. There exists register data on prescription medications of those NFBC1966 members, who participated at a 46-year study. With the help of this data, it would be possible to assess, e.g. how well the previously collected medication data reflects the reality of the prescribed medication use.

An ideal study design for clarifying the possible link between medications and brain structure changes could be one including initial brain MRI scans during the prodrome and first episode psychosis before antipsychotic treatment and having continuous long-term follow-up including MRI scans during different stages of illness. Also studies examining the association between other treatments and brain structure and functioning are needed.

In general, to make more definitive conclusions, large samples are needed to clarify associations. Large imaging samples are more easily collected from multicenter studies, which require collaboration between different study groups and even different countries. To assess the potential effects of antipsychotics as well as other medications on brain structures or any other measure, perhaps the aspect should be slightly different: maybe we should investigate the use of medications and their effects regardless of diagnoses in order to rule out most of the specific illness related factors.

References

Aderhold V, Weinmann S, Hägele C, Heinz A (2015). Frontal brain volume reduction due to antipsychotic drugs? [Article in German] Nervenarzt 86: 302–323. doi: 10.1007/s00115-014-4027-5.

American Psychiatric Association (APA) (1994). American Diagnostic and Statistical Manual of Mental disorders. 4th ed. American Psychiatric Association, Washington.

American Psychiatric Association (APA) (2013). Diagnostic and statistical manual of mental disorders, 5th edition: DSM-5. American Psychiatric Publishing, Arlington, VA.

Andreasen NC, Carpenter WT, Kane JM, Lasser RA, Marder SR, Weinberger DR (2005). Remission in schizophrenia: Proposed criteria and rationale for consensus. Am J Psychiatry 162, 441–449. doi: 10.1176/appi.ajp.162.3.441.

Andreasen NC, Liu D, Ziebell S, Vora A, Ho BC (2013). Relapse duration, treatment intensity, and brain tissue loss in schizophrenia: A prospective Longitudinal MRI study. Am J Psychiatry 170, 609–615. doi: 10.1176/appi.ajp.2013.12050674.

Arajärvi R, Suvisaari J, Suokas J, Schreck M, Haukka J, Hintikka J, Partonen T, Lönnqvist J (2005). Prevalence and diagnosis of schizophrenia based on register, case record and interview data in an isolated Finnish cohort born 1940–1969. Soc Psychiatry Psychiatr Epidemiol 40, 808–816. doi: 10.1007/s00127-005-0951-9.

Arnold SJ, Ivleva EI, Gopal TA, Reddy AP, Jeon-Slaughter H, Sacco CB, Francis AN, Tandon N, Bidesi AS, Witte B, Poudyal G, Pearlson GD, Sweeney JA, Clementz BA, Keshavan MS, Tamminga CA (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, 233–249. doi: 10.1093/schbul/sbu009.

Ashburner J, Friston KJ (2005). Unified segmentation. Neuroimage 26, 839–851. doi: 10.1016/j.neuroimage.2005.02.018.

Avants BB, Tustison NJ, Song G, Cook PA, Klein A, Gee JC (2010). A reproducible evaluation of ANTs similarity metric performance in brain image registration. Neuroimage 54, 2033–2044. doi: 10.1016/j.neuroimage.2010.09.025.

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.

Balu DT, Coyle JT (2011). Neuroplasticity signaling pathways linked to the pathophysiology of schizophrenia. Neurosci Biobehav Rev 35, 848–870. doi: 10.1016/j.neubiorev.2010.10.005.

Barker MJ, Greenwood KM, Jackson M, Crowe SF (2004a). Cognitive effects of long-term benzodiazepine use: A meta-analysis. CNS Drugs 18, 37–48.

Barker MJ, Greenwood KM, Jackson M, Crowe SF (2004b). Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: A meta-analysis. Arch Clin Neuropsychol 19, 437–454. doi: 10.1016/S0887-6177(03)00096-9.

Barker MJ, Greenwood KM, Jackson M, Crowe SF (2005). An evaluation of persisting cognitive effects after withdrawal from long-term benzodiazepine use. J Int Neuropsychol Soc 11, 281–289. doi: 10.1017/S1355617705050332.

Barnett AH, Mackin P, Chaudhry I, Farooqi A, Gadsby R, Heald A, Hill J, Millar H, Peveler R, Rees A, Singh V, Taylor D, Vora J, Jones PB (2007). Minimising metabolic and cardiovascular risk in schizophrenia: diabetes, obesity and dyslipidaemia. J Psychopharmacol 21, 357-373. doi: 10.1177/0269881107075509.

Batouli SAH, Saba V (2017). At least eighty percent of brain grey matter is modifiable by physical activity: A review study. Behav Brain Res 14, 204–217. doi: 10.1016/j.bbr.2017.06.002.

Boccardi M, Bocchetta M, Morency FC, Collins DL, Nishikawa M, Ganzola R, Grothe MJ, Wolf D, Redolfi A, Pievani M, Antelmi L, Fellgiebel A, Matsuda H, Teipel S, Duchesne S, Jack CR Jr, Frisoni GB; EADC-ADNI Working Group on The Harmonized Protocol for Manual Hippocampal Segmentation and for the Alzheimer's Disease Neuroimaging Initiative (2015). Training labels for hippocampal segmentation based on the EADC-ADNI harmonized hippocampal protocol. Alzheimers Dement 11, 175–183. doi: 10.1016/j.jalz.2014.12.002.

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, 172–187. doi: 10.1111/j.1600-0447.2008.01230.x.

Brans RG, van Haren NE, van Baal GC, Staal WG, Schnack HG, Kahn RS, Hulshoff Pol HE (2008). Longitudinal MRI study in schizophrenia patients and their healthy siblings. Br J Psychiatry 193, 422–423. doi: 10.1192/bjp.bp.107.041467.

Brown AS (2006). Prenatal infection as a risk factor for schizophrenia. Schizophr Bull 32, 200–202. doi: 10.1093/schbul/sbj052.

Buchsbaum MS, Potkin SG, Siegel BV Jr, Lohr J, Katz M, Gottschalk LA, Gulasekaram B, Marshall JF, Lottenberg S, Teng CY, Abel L, Plon L, Bunney WE Jr. (1992). Striatal metabolic rate and clinical response to neuroleptics in schizophrenia. Arch Gen Psychiatry 49, 966–974.

Busatto GF (2013). Structural and functional neuroimaging studies in major depressive disorder with psychotic features: A critical review. Schizophr Bull 39, 776–786. doi: 10.1093/schbul/sbt054.

Busto UE, Bremner KE, Knight K, Brugge K, Sellers EM (2000). Long-term benzodiazepine therapy does not result in brain abnormalities. J Clin Psychopharmacol 20, 2–6.

Cannon M, Jones PB, Murray RM (2002). Obstetric complications and schizophrenia: Historical and meta-analytic review. Am J Psychiatry 159, 1080–1092. doi: 10.1176/appi.ajp.159.7.1080.

Cannon TD, Chung Y, He G, Sun D, Jacobson A, van Erp TG, McEwen S, Addington J, Bearden CE, Cadenhead K, Cornblatt B, Mathalon DH, McGlashan T, Perkins D, Jeffries C, Seidman LJ, Tsuang M, Walker E, Woods SW, Heinssen R; North American Prodrome Longitudinal Study Consortium (2015). Progressive reduction in cortical thickness as psychosis develops: A multisite longitudinal neuroimaging study of youth at elevated clinical risk. Biol Psychiatry 77, 147–157. doi: 10.1016/j.biopsych.2014.05.023.

Cardno AG, Gottesman II (2000). Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and functional genomics. Am J Med Genet 97, 12-17.

Cobia DJ, Smith MJ, Wang L, Csernansky JG (2012). Longitudinal progression of frontal and temporal lobe changes in schizophrenia. Schizophr Res 139, 1–6. doi: 10.1016/j.schres.2012.05.002.

Collin G, Derks EM, van Haren NE, Schnack HG, Hulshoff Pol HE, Kahn RS, Cahn W (2012). Symptom dimensions are associated with progressive brain volume changes in schizophrenia. Schizophr Res 138, 171–176. doi: 10.1016/j.schres.2012.03.036.

Coupé P, Manjón JV, Fonov V, Pruessner J, Robles M, Collins DL (2011). Patch-based segmentation using expert priors: Application to hippocampus and ventricle segmentation. Neuroimage 54, 940–954. doi: 10.1016/j.neuroimage.2010.09.018.

Crawford MB, DeLisi LE (2016). Issues related to sex differences in antipsychotic treatment. Curr Opin Psychiatry 29, 211–217. doi: 10.1097/YCO.0000000000000243.

Cropley VL, Klauser P, Lenroot RK, Bruggemann J, Sundram S, Bousman C, Pereira A, Di Biase MA, Weickert TW, Weickert CS, Pantelis C, Zalesky A (2017). Accelerated Gray and White Matter Deterioration With Age in Schizophrenia. Am J Psychiatry 174, 286-295. doi: 10.1176/appi.ajp.2016.16050610.

Cui L, Li M, Deng W, Guo W, Ma X, Huang C, Jiang L, Wang Y, Collier DA, Gong Q, Li T (2011). Overlapping clusters of gray matter deficits in paranoid schizophrenia and psychotic bipolar mania with family history. Neurosci Lett 489, 94–98. 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.

Davey KJ, O'Mahony SM, Schellekens H, O'Sullivan O, Bienenstock J, Cotter PD, Dinan TG, Cryan JF (2012). Gender-dependent consequences of chronic olanzapine in the rat: Effects on body weight, inflammatory, metabolic and microbiota parameters. Psychopharmacology 221, 155–169. doi: 10.1007/s00213-011-2555-2.

Davidson CA, Kuroki N, Alvarado JL, Niznikiewicz MA, McCarley RW, Levitt JJ (2012). An MRI study of septi pellucidi in relation to hippocampus volume and fornix integrity in schizophrenia. Schizophr Res 134, 165–170. doi: 10.1016/j.schres.2011.11.012.

Dean CE (2006). Antipsychotic-associated neuronal changes in the brain: toxic, therapeutic, or irrelevant to the long-term outcome of schizophrenia? Prog Neuropsychopharmacol Biol Psychiatry 30, 174–189. doi: 10.1016/j.pnpbp.2005.08.019.

Dorph-Petersen KA, Pierri JN, Perel JM, Sun Z, Sampson AR, Lewis DA (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. doi: 10.1038/sj.npp.1300710.

Duman RS (2004). Neural plasticity: consequences of stress and actions of antidepressant treatment. Dialogues Clin Neurosci 6, 157–169.

Eack SM, Hogarty GE, Cho RY, Prasad KM, Greenwald DP, Hogarty SS, Keshavan MS (2010). Neuroprotective effects of cognitive enhancement therapy against gray matter loss in early schizophrenia: Results from a 2-year randomized controlled trial. Arch Gen Psychiatry 67, 674–682. doi: 10.1001/archgenpsychiatry.2010.63.

Ebdrup BH, Nørbak H, Borgwardt S, Glenthøj B (2013). Volumetric changes in the basal ganglia after antipsychotic monotherapy: A systematic review. Curr Med Chem 20, 438–447.

Eisenberg DP, Yankowitz L, Ianni AM, Rubinstein DY, Kohn PD, Hegarty CE, Gregory MD, Apud JA, Berman KF (2017). Presynaptic Dopamine Synthesis Capacity in Schizophrenia and Striatal Blood Flow Change During Antipsychotic Treatment and Medication-Free Conditions. Neuropsychopharmacology 42, 2232-2241. doi: 10.1038/npp.2017.67.

Faber G, Smid HG, Van Gool AR, Wiersma D, Van Den Bosch RJ (2012). The effects of guided discontinuation of antipsychotics on neurocognition in first onset psychosis. Eur Psychiatry 27, 275–280. doi: 10.1016/j.eurpsy.2011.02.003.

Faludi G, Mirnics K (2011). Synaptic changes in the brain of subjects with schizophrenia. Int J Dev Neurosci 29, 305–309. doi: 10.1016/j.ijdevneu.2011.02.013.

Farah A (2005). Atypicality of atypical antipsychotics. Prim Care Companion J Clin Psychiatry 7, 268-274.

Fatemi SH, Folsom TD (2009). The neurodevelopmental hypothesis of schizophrenia, revisited. Schizophr Bull 35, 528–548. doi: 10.1093/schbul/sbn187.

Fan X, Goff DC, Henderson DC (2007a). Inflammation and schizophrenia. Expert Rev Neurother 7, 789–796. doi: 10.1586/14737175.7.7.789.

Fan X, Pristach C, Liu EY, Freudenreich O, Henderson DC, Goff DC (2007b). Elevated serumlevels of C-reactive protein are associatedwithmore severe psychopathology in a subgroup of patients with schizophrenia. Psychiatry Res 149, 267–271. doi: 10.1016/j.psychres.2006.07.011.

Filatova S, Koivumaa-Honkanen H, Hirvonen N, Freeman A, Ivandic I, Hurtig T, Khandaker GM, Jones PB, Moilanen K, Miettunen J (2017). Early motor developmental milestones and schizophrenia: A systematic review and meta-analysis. Schizophr Res Res 188, 13-20. doi: 10.1016/j.schres.2017.01.029.

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). BiometricsResearch, New York State Psychiatric Institute, New York.

Firth J, Cotter J, Carney R, Yung AR (2017). The pro-cognitive mechanisms of physical exercise in people with schizophrenia. Br J Pharmacol [Epub ahead of print]. doi: 10.1111/bph.13772.

Floresco SB (2015). The nucleus accumbens: An interface between cognition, emotion, and action. Annu Rev Psychol 66, 25–52. doi: 10.1146/annurev-psych-010213-115159.

Fontanella CA, Campo JV, Phillips GS, Hiance-Steelesmith DL, Sweeney HA, Tam K, Lehrer D, Klein R, Hurst M (2016). 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.

Fris 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/SPYSCREEN). Biometrics Research, New York State Psychiatric Institute, New York.

Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, 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.

García S, Martínez-Cengotitabengoa M, López-Zurbano S, Zorrilla I, López P, Vieta E, González-Pinto A (2016). Adherence to antipsychotic medication in bipolar disorder and schizophrenic patients: A systematic review. J Clin Psychopharmacol 36, 355–371. doi: 10.1097/JCP.0000000000000523.

Giakoumatos CI, Nanda P, Mathew IT, Tandon N, Shah J, Bishop JR, Clementz BA, Pearlson GD, Sweeney JA, Tamminga CA, Keshavan MS (2015). Effects of lithium on cortical thickness and hippocampal subfield volumes in psychotic bipolar disorder. J Psychiatr Res 61, 180–187. doi: 10.1016/j.jpsychires.2014.12.008.

Goozée R, Handley R, Kempton MJ, Dazzan P (2014). A systematic review and meta-analysis of the effects of antipsychotic medications on regional cerebral blood flow (rCBF) in schizophrenia: Association with response to treatment. Neurosci Biobehav Rev 43, 118–136. doi: 10.1016/j.neubiorev.2014.03.014.

Grahn JA, Parkinson JA, Owen AM (2008). The cognitive functions of the caudate nucleus. Prog Neurobiol 86, 141–155. doi: 10.1016/j.pneurobio.2008.09.004.

Griebel G, Holmes A (2013). 50 years of hurdles and hope in anxiolytic drug discovery. Nat Rev Drug Discov 12, 667–687. doi: 10.1038/nrd4075.

Guo J, Huhtaniska S, Miettunen J, Jääskeläinen E, Kiviniemi V, Nikkinen J, Moilanen J, Haapea M, Mäki P, Jones PB, Veijola J, Isohanni M, Murray GK (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.

Guo S, Kendrick KM, Yu R, Wang HL, Feng J (2014). Key functional circuitry altered in schizophrenia involves parietal regions associated with sense of self. Hum Brain Mapp, 35, 123–139. doi: 10.1002/hbm.22162.

Gur RE, Cowell P, Turetsky BI, Gallacher F, Cannon T, Bilker W, Gur RC (1998). A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. Arch Gen Psychiatry 55, 145–152.

Gurillo P, Jauhar S, Murray RM, MacCabe JH (2015). Does tobacco use cause psychosis? Systematic review and meta-analysis. Lancet Psychiatry 2, 718–725. doi: 10.1016/S2215-0366(15)00152-2.

Hafeman DM, Chang KD, Garrett AS, Sanders EM, Phillips ML (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 SV, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE, Kahn RS (2013). Brain volumes in schizophrenia: A meta-analysis in over 18 000 subjects. Schizophr Bull 39, 1129–1138. doi: 10.1093/schbul/sbs118.

Heckers S (2000). Neural models of schizophrenia. Dialogues Clin Neurosci 2, 267–279.

Hedman AM, van Haren NE, van Baal GC, Brouwer RM, Brans RG, Schnack HG, Kahn RS, Hulshoff Pol HE (2016). Heritability of cortical thickness changes over time in twin pairs discordant for schizophrenia. Schizophr Res 173, 192–199. doi: 10.1016/j.schres.2015.06.021.

Heitmiller DR, Nopoulos PC, Andreasen NC (2004). Changes in caudate volume after exposure to atypical neuroleptics in patients with schizophrenia may be sex-dependent. Schizophr Res 66, 137–142. doi: 10.1016/j.schres.2003.08.008.

Hensler J, Artigas F, Bortolozzi A, Daws L, De Deurwaerdère, Milan L, Navailles S, Koek W (2013). Catecholamine/serotonin interactions: Systems thinking for brain function and disease. Adv Pharmacol 68, 167–197. doi: 10.1016/B978-0-12-411512-5.00009-9.

Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003). Measuring inconsistency in meta-analyses. BMJ 327, 557–560.

Hirjak D, Wolf RC, Wilder-Smith EP, Kubera KM, Thomann PA (2015). Motor abnormalities and basal ganglia in schizophrenia: Evidence from structural magnetic resonance imaging. Brain Topogr 28, 135–152. doi: 10.1007/s10548-014-0377-3.

Ho BC, Andreasen NC, Dawson JD, Wassink TH (2007). Association between brain-derived neurotrophic factor Val66Met gene polymorphism and progressive brain volume changes in schizophrenia. Am J Psychiatry 164, 1890–1809. doi: 10.1176/appi.ajp.2007.05111903.

Ho BC, Andreasen NC, Nopoulos P, Arndt S, Magnotta V, Flaum M (2003). Progressive structural brain abnormalities and their relationship to clinical outcome: A longitudinal magnetic resonance imaging study early in schizophrenia. Arch Gen Psychiatry 60, 585–594. doi: 10.1001/archpsyc.60.6.585.

Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V (2011). Long-term antipsychotic treatment and brain volumes: A longitudinal study of first-episode schizophrenia. Arch Gen Psychiatry 68, 128–137. doi: 10.1001/archgenpsychiatry.2010.199.

Hoffman EJ, Mathew SJ (2008). Anxiety disorders: A comprehensive review of pharmacotherapies. Mt Sinai J Med 75, 248–262. doi: 10.1002/msj.20041.

Honea R, Crow TJ, Passingham D, Mackay CE (2005). Regional deficits in brain volume in schizophrenia: A meta-analysis of voxel-based morphometry studies. Am J Psychiatry 162, 2233–2245. doi: 10.1176/appi.ajp.162.12.2233.

Hope S, Ueland T, Steen NE, Dieset I, Lorentzen S, Berg AO, Agartz I, Aukrust P, Andreassen OA (2013). Interleukin 1 receptor antagonist and soluble tumor necrosis factor receptor 1 are associated with general severity and psychotic symptoms in schizophrenia and bipolar disorder. Schizophr Res 145, 36–42. doi: 10.1016/j.schres.2012.12.023.

Howes OD, Bose SK, Turkheimer F, Valli I, Egerton A, Valmaggia LR, Murray RM, McGuire P (2011). Dopamine synthesis capacity before onset of psychosis: A prospective [18]-DOPA PET imaging study. Am J Psychiatry 168, 1311–1317. doi: 10.1176/appi.ajp.2011.11010160.

Howes OD, McCutcheon R, Owen MJ, Murray RM (2017). The Role of genes, stress, and dopamine in the development of schizophrenia. Biol Psychiatry 81, 9–20. doi: 10.1016/j.biopsych.2016.07.014.

Howes OD, Murray RM (2014). Schizophrenia: An integrated sociodevelopmental-cognitive model. Lancet 383, 1677–1687. doi: 10.1016/S0140-6736(13)62036-X.

Hull AM (2002). Neuroimaging findings in post-traumatic stress disorder. Systematic review. Br J Psychiatry 181, 102–110.

Hulshoff Pol HE, Kahn RS (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 AP, Rannikko I, Moilanen J, Haapea M, Murray GK, Barnett J, Jones PB, 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.

Insel TR (2010). Rethinking schizophrenia. Nature 468, 187–193. doi: 10.1038/nature09552

Iritani S (2007). Neuropathology of schizophrenia: A mini review. Neuropathology 27, 604–608. doi: 10.1111/j.1440-1789.2007.00798.x.

Islam F, Mulsant BH, Voineskos AN, Rajji TK (2017). Brain-derived neurotrophic factor expression in individuals with schizophrenia and healthy aging: Testing the accelerated aging hypothesis of schizophrenia. Curr Psychiatry Rep 19, 36. doi: 10.1007/s11920-017-0794-6.

Isohanni M, Lauronen E, Moilanen K, Isohanni I, Kemppainen L, Koponen H, Miettunen J, Mäki P, Räsänen S, Veijola J, Tienari P, Wahlberg KE, Murray GK (2005). Predictors of schizophrenia: Evidence from the Northern Finland 1966 Birth Cohort and other sources. Br J Psychiatry Suppl 48, 4–7. doi: 10.1192/bjp.187.48.s4.

Isohanni M, Mäkikyrö T, Moring J, Räsänen P, Hakko H, Partanen U, Koiranen M, Jones P (1997). A comparison of clinical and research DSM-III-R diagnoses of schizophrenia in a Finnish national birth cohort. Clinical and research diagnoses of schizophrenia. Soc Psychiatry Psychiatr Epidemiol 32, 303–308.

Ivleva EI, Bidesi AS, Keshavan MS, Pearlson GD, Meda SA, Dodig D, Moates AF, Lu H, Francis AN, Tandon N, Schretlen DJ, Sweeney JA, Clementz BA, Tamminga CA (2013). Gray matter volume as an intermediate phenotype for psychosis: Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). Am J Psychiatry 170, 1285–1296. doi: 10.1176/appi.ajp.2013.13010126.

Ivleva EI, Bidesi AS, Thomas BP, Meda SA, Francis A, Moates AF, Witte B, Keshavan MS, Tamminga CA (2012). Brain gray matter phenotypes across the psychosis dimension. Psychiatry Res 204, 13–24. doi: 10.1016/j.pscychresns.2012.05.001.

Jääskeläinen E, Juola P, Hirvonen N, McGrath J, Saha S, Isohanni M, Veijola J, Miettunen J (2013). A systematic review and meta-analysis of recovery in schizophrenia. Schizophr Bull 39, 1296–1306. doi: 10.1093/schbul/sbs130.

Jackson D, Kirkbride J, Croudace T, Morgan C, Boydell J, Errazuriz A, Murray RM, Jones PB (2013). Meta-analytic approaches to determine gender differences in the age-incidence characteristics of schizophrenia and related psychoses. Int J Methods Psychiatr Res 22, 36–45. doi: 10.1002/mpr.1376.

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, 91–99. doi: 10.1016/j.schres.2014.06.040.

Javitt DC, Zukin SR, Heresco-Levy U, Umbricht D (2012). Has an angel shown the way? Etiological and therapeutic implications of the PCP/NMDA model of schizophrenia. Schizophr Bull 38, 958–966. doi: 10.1093/schbul/sbs069.

Job DE, Whalley HC, Johnstone EC, Lawrie SM (2005). Grey matter changes over time in high risk subjects developing schizophrenia. Neuroimage 25, 1023-1030. doi: 10.1016/j.neuroimage.2005.01.006.

Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L (1976). Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet 2, 924–926.

Jørgensen KN, Nesvåg R, Nerland S, Mørch-Johnsen L, Westlye LT, Lange EH, Haukvik UK, Hartberg CB, Melle I, Andreassen OA, Agartz I (2017). Brain volume change in first-episode psychosis: An effect of antipsychotic medication independent of BMI change. Acta Psychiatr Scand 135, 117–126. doi: 10.1111/acps.12677.

Kanji S, Fonseka TM, Marshe VS, Sriretnakumar V, Hahn MK, Müller DJ (2017). The microbiome-gut-brain axis: implications for schizophrenia and antipsychotic induced weight gain. Eur Arch Psychiatry Clin Neurosci doi: 10.1007/s00406-017-0820-z. [Epub ahead of print].

Karlsson H, Bachmann S, Schröder J, McArthur J, Torrey EF, Yolken RH (2001). Retroviral RNA identified in the cerebrospinal fluids and brains of individuals with schizophrenia. Proc Natl Acad Sci U S A 98, 4634–4639. doi: 10.1073/pnas.061021998.

Kasai K, Shenton ME, Salisbury DF, Onitsuka T, Toner SK, Yurgelun-Todd D, Kikinis R, Jolesz FA, McCarley RW (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, 1069–1077. doi: 10.1001/archpsyc.60.11.1069.

Kay SR, Fiszbein A, Opler LA (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bull 13, 2612–276.

Keck T, Scheuss V, Jacobsen R, Wierenga CJ, Eysel UT, Bonhoeffer T, Hübener M (2011). Loss of sensory input causes rapid structural changes of inhibitory neurons in adult mouse visual cortex. Neuron 71, 869–882. doi: 10.1016/j.neuron.2011.06.034.

Kempton MJ, Stahl D, Williams SC, DeLisi LE (2010). Progressive lateral ventricular enlargement in schizophrenia: A meta-analysis of longitudinal MRI studies. Schizophr Res 120, 54–62. doi: 10.1016/j.schres.2010.03.036.

Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D (1993). The Roscommon family study. 1. Methods, diagnosis of probands, and risk of schizophrenia in relatives. Arch. Gen. Psychiatry 50, 527–540.

Keshavan MS, Hogarty GE (1999). Brain maturational processes and delayed onset in schizophrenia. Dev Psychopathol 11, 525–543.

Kitajima R, Miyamoto S, Tenjin T, Ojima K, Ogino S, Miyake N, Fujiwara K, Funamoto Y, Arai J, Tsukahara S, Ito Y, Tadokoro M, Anai K, Kaneda Y, Yamaguchi N (2012). Effects of tapering of long-term benzodiazepines on cognitive function in patients with schizophrenia receiving a second-generation antipsychotic. Prog Neuropsychopharmacol Biol Psychiatry 36, 300–306. doi: 10.1016/j.pnpbp.2011.11.008.

Konopaske GT, Dorph-Petersen KA, Pierri JN, Wu Q, Sampson AR, Lewis DA (2007). Effect of chronic exposure to antipsychotic medication on cell numbers in the parietal cortex of macaque monkeys. Neuropsychopharmacology 32, 1216–1223. doi: 10.1038/sj.npp.1301233.

Koo MS, Levitt JJ, Salisbury DF, Nakamura M, Shenton ME, McCarley RW (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, 746–760. doi: 10.1001/archpsyc.65.7.746.

Koponen H, Saari K, Savolainen M, Isohanni M (2002). Weight gain and glucose and lipid metabolism disturbances during antipsychotic medication: A review. Eur Arch Psychiatry Clin Neurosci 252, 294–298. doi: 10.1007/s00406-002-0394-1.

Kubota M, van Haren NE, Haijma SV, Schnack HG, Cahn W, Hulshoff Pol HE, Kahn RS (2015). Association of IQ changes and progressive brain changes in patients with schizophrenia. JAMA Psychiatry 72, 803–812. doi: 10.1001/jamapsychiatry.2015.0712.

Kurko TA, Saastamoinen LK, Tähkäpää S, Tuulio-Henriksson A, Taiminen T, Tiihonen J, Airaksinen MS, Hietala J (2015). Long-term use of benzodiazepines: Definitions, prevalence and usage patterns - a systematic review of register-based studies. Eur Psychiatry 30, 1037–1047. doi: 10.1016/j.eurpsy.2015.09.003.

Kusumi I, Boku S, Takahashi Y (2015). Psychopharmacology of atypical antipsychotic drugs: From the receptor binding profile to neuroprotection and neurogenesis. Psychiatry Clin Neurosci 69, 243-258. doi: 10.1111/pcn.12242.

Lader M (2011). Benzodiazepines revisited--will we ever learn? Addiction 106, 2086–2109. doi: 10.1111/j.1360-0443.2011.03563.x.

Lader MH, Ron M, Petursson H (1984). Computerized axial brain tomography in long-term benzodiazepine users. Psychol Med 14, 203–206.

Lanciego JL, Luquin N, Obeso JA (2012). Functional neuroanatomy of the basal ganglia. Cold Spring Harb Perspect Med 2, a009621. doi: 10.1101/cshperspect.a009621.

Lang FU, Ko□sters M, Lang S, Becker T, Ja□ger M (2013). Psychopathological long-term outcome of schizophrenia – a review. Acta Psychiatr Scand 127, 173–182. doi: 10.1111/acps.12030.

Längle G, Steinert T, Weiser P, Schepp W, Jaeger S, Pfiffner C, Frasch K, Eschweiler GW, 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, 372–281. doi: 10.1111/j.1600-0447.2012.01835.

Laursen TM, Nordentoft M, Mortensen PB (2014). Excess early mortality in schizophrenia. Annu Rev Clin Psychol 10, 425–448. doi: 10.1146/annurev-clinpsy-032813-153657

Lesh TA, Tanase C, Geib BR, Niendam TA, Yoon JH, Minzenberg MJ, Ragland JD, Solomon M, Carter CS (2015). A multimodal analysis of antipsychotic effects on brain structure and function in first-episode schizophrenia. JAMA Psychiatry 72, 226–234. doi: 10.1001/jamapsychiatry.2014.2178.

Leucht S, Kissling W, Davis JM (2009). Second-generation antipsychotics for schizophrenia: Can we resolve the conflict? Psychol Med 39, 1591–1602. doi: 10.1017/S0033291709005455.

Leucht S, Leucht C, Huhn M, Chaimani A, Mavridis D, Helfer B, Samara M, Rabaioli M, Bächer S, Cipriani A, Geddes JR, Salanti G, Davis JM (2017). Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: Systematic review, Bayesian meta-analysis, and meta-regression of efficacy predictors. Am J Psychiatry [Epub ahead of print] appiajp201716121358. doi: 10.1176/appi.ajp.2017.16121358.

Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Salanti G, Davis JM (2012). Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: A systematic review and meta-analysis. Lancet 379, 2063–2071. doi: 10.1016/S0140-6736(12)60239-6.

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 CJ, Sellgren C, Johansson AG, Landén M (2015). Subcortical morphometry and psychomotor function in euthymic bipolar disorder with a history of psychosis. Brain Imaging Behav 9, 333–341. doi: 10.1007/s11682-014-9313-0.

Licata SC, Nickerson LD, Lowen SB, Trksak GH, Maclean RR, Lukas SE (2013a). The hypnotic zolpidem increases the synchrony of BOLD signal fluctuations in widespread brain networks during a resting paradigm. Neuroimage 70, 211–222. doi: 10.1016/j.neuroimage.2012.12.055.

Licata SC, Shinday NM, Huizenga MN, Darnell SB, Sangrey GR, Rudolph U, Rowlett JK, Sadri-Vakili G (2013b). Alterations in brain-derived neurotrophic factor in the mouse hippocampus following acute but not repeated benzodiazepine treatment. PLoS One 8, e84806. doi: 10.1371/journal.pone.0084806.

Lu B, Chow A (1999). Neurotrophins and hippocampal synaptic transmission and plasticity. J Neurosci Res 58, 76–87. .

MacCabe JH, Lambe MP, Cnattingius S, Torra□ng A, Bjo□rk C, Sham PC, David AS, Murray RM & Hultman CM (2008). Scholastic achievement at age 16 and risk of schizophrenia and other psychoses: a national cohort study. Psychol Med 38, 1133–1140. doi: 10.1017/S0033291707002048.

Mamah D, Alpert KI, Barch DM, Csernansky JG, Wang L (2016). Subcortical neuromorphometry in schizophrenia spectrum and bipolar disorders. Neuroimage Clin 11, 276–286. doi: 10.1016/j.nicl.2016.02.011.

Manji HK, Moore GJ, Chen G (2000). Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: implications for the pathophysiology and treatment of manic-depressive illness. Biol Psychiatry 48, 740-754.

Manjón JV, Coupé P, Martí-Bonmatí L, Collins DL, Robles M (2010a). Adaptive non-local means denoising of MR images with spatially varying noise levels. J Magn Reson Imaging 31, 192–203. doi: 10.1002/jmri.22003.

Manjón JV, Coupé P (2016). volBrain: An online MRI brain volumetry system. Front Neuroinform 10, 30. doi: 10.3389/fninf.2016.00030.

Manjón JV, Eskildsen SF, Coupé P, Romero JE, Collins DL, Robles M (2014). Nonlocal intracranial cavity extraction. Int J Biomed Imaging 2014:820205. doi: 10.1155/2014/820205.

Manjón JV, Tohka J, Robles M (2010b). Improved estimates of partial volume coefficients from noisy brain MRI using spatial context. Neuroimage 53, 480–490. doi: 10.1016/j.neuroimage.2010.06.046.

Marsden CD (1976). Cerebral atrophy and cognitive impairment in chronic schizophrenia. Lancet 2; 1079.

Marwaha S, Johnson S (2004). Schizophrenia and employment - a review. Soc Psychiatry Psychiatr Epidemiol 39, 337–349. doi: 10.1007/s00127-004-0762-4.

Matheson SL, Shepherd AM, Carr VJ (2014). How much do we know about schizophrenia and how well do we know it? Evidence from the Schizophrenia Library. Psychol Med 44, 3387–3405. doi: 10.1017/S0033291714000166.

Mathew I, Gardin TM, Tandon N, Eack S, Francis AN, Seidman LJ, Clementz B, Pearlson GD, Sweeney JA, Tamminga CA, Keshavan MS (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, 769–777. doi: 10.1001/jamapsychiatry.2014.453.

Maynard TM, Sikich L, Lieberman JA, LaMantia AS (2001). Neural development, cell- cell signaling, and the ”two-hit” hypothesis of schizophrenia. Schizophr Bull 27, 457–476.

Mayo D, Corey S, Kelly LH, Yohannes S, Youngquist AL, Stuart BK, Niendam TA, Loewy RL (2017). The role of trauma and stressful life events among individuals at clinical high risk for psychosis: A review. Front Psychiatry 20, 55. doi: 10.3389/fpsyt.2017.00055.

McCormick L, Decker L, Nopoulos P, Ho BC, Andreasen N (2005). Effects of atypical and typical neuroleptics on anterior cingulate volume in schizophrenia. Schizophr Res 80, 73–84. doi: 10.1016/j.schres.2005.06.022.

McDonald C, Marshall N, Sham PC, Bullmore ET, Schulze K, Chapple B, Bramon E, Filbey F, Quraishi S, Walshe M, Murray RM (2006). Regional brain morphometry in patients with schizophrenia or bipolar disorder and their unaffected relatives. Am J Psychiatry 163, 478–487. doi: 10.1176/appi.ajp.163.3.478.

McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D (2004). A systematic review of the incidence of schizophrenia: The distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Med 2, 13. doi: 10.1186/1741-7015-2-13.

McGrath J, Saha S, Chant D, Welham J (2008). Schizophrenia: A concise overview of incidence, prevalence and mortality. Epidemiol Rev 8, 67–76. doi: 10.1093/epirev/mxn001.

Meltzer HY (2000). An atypical compound by any other name is still a. Psychopharmacology 148, 16–19.

Mittal VA, Ellman LM, Cannon TD (2008). Gene-environment interaction and covariation in schizophrenia: The role of obstetric complications. Schizophr Bull 34, 1083–1094. doi: 10.1093/schbul/sbn080.

Miyamoto S, Miyake N, Jarskog LF, Fleischhacker WW, Lieberman JA (2012). Pharmacological treatment of schizophrenia: A critical review of the pharmacology and clinical effects of current and future therapeutic agents. Mol Psychiatry 17, 1206–1227. doi: 10.1038/mp.2012.47.

Moilanen JM, Haapea M, Jääskeläinen E, Veijola JM, Isohanni MK, Koponen HJ, 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.

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 K, Veijola J, Läksy K, Mäkikyrö T, Miettunen J, Kantojärvi L, Kokkonen P, Karvonen JT, Herva A, Joukamaa M, Järvelin M-R, Moring J, Jones, PB, Isohanni M (2003). Reasons for the diagnostic discordance between clinicians and researchers in schizophrenia in the Northern Finland 1966 Birth Cohort. Soc Psychiatry Psychiatr Epidemiol 38, 305–310. doi: 10.1007/s00127-003-0638-z.

Moncrieff J, Leo J (2010). A systematic review of the effects of antipsychotic drugs on brain volume. Psychol Med 40, 1409–1422. doi: 10.1017/S0033291709992297.

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

Morgan KD, Dazzan P, Orr KG, Hutchinson G, Chitnis X, Suckling J, Lythgoe D, Pollock SJ, Rossell S, Shapleske J, Fearon P, Morgan C, David A, McGuire PK, Jones PB, Leff J, Murray RM (2007). Grey matter abnormalities in first-episode schizophrenia and affective psychosis. Br J Psychiatry Suppl 51, s111–s116. doi: 10.1192/bjp.191.51.s111.

Mundt AP, Aichberger MC, Fakhriddinov S, Fayzirahmanova M, Grohmann R, Heinz A, Ivens S, Magzumova S, Sartorius N, Ströhle A (2012). Prescription patterns of patients diagnosed with schizophrenia in mental hospitals in Tashkent/Uzbekistan and in four German cities. Pharmacoepidemiol Drug Saf 21, 145–151. doi: 10.1002/pds.2166.

Murray RM, Lewis SW (1987). Is schizophrenia a neurodevelopmental disorder? Br Med J (Clin Res Ed) 295, 681-682.

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.

Nemani K, Hosseini Ghomi R, McCormick B, Fan X (2015). Schizophrenia and the gut-brain axis. Prog Neuropsychopharmacol Biol Psychiatry 56, 155-160. doi: 10.1016/j.pnpbp.2014.08.018.

Nesvåg R, Bergmann Ø, Rimol LM, Lange EH, Haukvik UK, Hartberg CB, Fagerberg T, Söderman E, Jönsson EG, Agartz I (2012). A 5-year follow-up study of brain cortical and subcortical abnormalities in a schizophrenia cohort. Schizophr Res 142; 209–216. doi: 10.1016/j.schres.2012.10.004.

Nykänen S, Puska V, Tolonen JP, 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.

Owen MJ, O'Donovan MC, Thapar A, Craddock N (2011). Neurodevelopmental hypothesis of schizophrenia. Br J Psychiatry 198, 173-175. doi: 10.1192/bjp.bp.110.084384.

Pantelis C, Velakoulis D, McGorry PD, Wood SJ, Suckling J, Phillips LJ, Yung AR, Bullmore ET, Brewer W, Soulsby B, Desmond P, McGuire PK (2003). Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. Lancet 361, 281-288. doi: 10.1016/S0140-6736(03)12323-9.

Pantelis C, Yücel M, Wood SJ, Velakoulis D, Sun D, Berger G, Stuart GW, Yung A, Phillips L, McGorry PD (2005). Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. Schizophr Bull 31, 672-696 doi: 10.1093/schbul/sbi034.

Penadés R, Pujol N, Catalán R, Massana G, Rametti G, García-Rizo C, Bargalló N, Gastó C, Bernardo M, Junqué C (2013). Brain effects of cognitive remediation therapy in schizophrenia: a structural and functional neuroimaging study. Biol Psychiatry 73, 1015-1023. doi: 10.1016/j.biopsych.2013.01.017.

Perälä J, Saarni SI, Ostamo A, Pirkola S, Haukka J, Harkanen T, Koskinen S, Lönnqvist J, Suvisaari J (2008). Geographic variation and sociodemographic characteristics of psychotic disorders in Finland. Schizophr Res 106, 337–347. doi: 10.1016/j.schres.2008.08.017.

Perera KMH, Powell T, Jenner FA (1987). Computerized axial tomographic studies following long-term use of benzodiazepines. Psychol Med 17, 775–777.

Phan SV (2016). Medication adherence in patients with schizophrenia. Int J Psychiatry Med 51, 211–219. doi: 10.1177/0091217416636601.

Pino O, Guilera G, Gómez-Benito J, Najas-García A, Rufián S, Rojo E (2014). Neurodevelopment or neurodegeneration: Review of theories of schizophrenia. Actas Esp Psiquiatr 42, 185–195.

Puri BK, Hutton SB, Saeed N, Oatridge A, Hajnal JV, Duncan L, Chapman MJ, Barnes TR, Bydder GM, Joyce EM (2001). A serial longitudinal quantitative MRI study of cerebral changes in first-episode schizophrenia using image segmentation and subvoxel registration. Psychiatry Res 106, 141–150.

Radonić E, Henigsberg N, Rados M, Mimica N, Folnegović-Smalc V (2008). Temporal lobe volume in disorders with psychotic features. Coll Antropol Suppl 1 32, s139–s142.

Radua J, Borgwardt S, Crescini A, Mataix-Cols D, Meyer-Lindenberg A, McGuire PK, Fusar-Poli P (2012). Multimodal meta-analysis of structural and functional brain changes in first episode psychosis and the effects of antipsychotic medication. Neurosci Biobehav Rev 36, 2325–2333. doi: 10.1016/j.neubiorev.2012.07.012.

Rapoport JL, Giedd JN, Gogtay N (2012). Neurodevelopmental model of schizophrenia: Update 2012. Mol Psychiatry 17, 1228–1238. doi: 10.1038/mp.2012.23.

Reite M, Reite E, Collins D, Teale P, Rojas DC, 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.

Rijcken CA, Monster TB, Brouwers JR, de Jong-van den Berg LT (2003). Chlorpromazine equivalents versus defined daily doses: How to compare antipsychotic drug doses? J Clin Psychopharmacol 23, 657–659. doi: 10.1097/01.jcp.0000096247.29231.3a.

Rimol LM, Hartberg CB, Nesvåg R, Fennema-Notestine C, Hagler DJ Jr, Pung CJ, Jennings RG, Haukvik UK, Lange E, Nakstad PH, Melle I, Andreassen OA, Dale AM, 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.

Roiz-Santiáñez R, Ayesa-Arriola R, Tordesillas-Gutiérrez D, Ortiz-García de la Foz V, Pérez-Iglesias R, Pazos A, Sánchez E, Crespo-Facorro B (2014). Three-year longitudinal population-based volumetric MRI study in first-episode schizophrenia spectrum patients. Psychol Med 44, 1591–1604. doi: 10.1017/S0033291713002365.

Roiz-Santiañez R, Suarez-Pinilla P, Crespo-Facorro B (2015). Brain Structural Effects of Antipsychotic Treatment in Schizophrenia: A Systematic Review. Curr Neuropharmacol 13, 422-434.

Romero JE, Manjón JV, Tohka J, Coupé P, Robles M (2015). NABS: non-local automatic brain hemisphere segmentation. Magnetic resonance imaging 33, 474-484. doi: 10.1016/j.mri.2015.02.005.

Rosa PG, Schaufelberger MS, Uchida RR, Duran FL, Lappin JM, Menezes PR, Scazufca M, McGuire PK, Murray RM, Busatto GF (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, 873-887. doi: 10.3109/15622975.2010.486042.

Rosa PG, Zanetti MV, Duran FL, Santos LC, Menezes PR, Scazufca M, Murray RM, Busatto GF, Schaufelberger MS (2015). What determines continuing grey matter changes in first-episode schizophrenia and affective psychosis? Psychol Med 45, 817-828. doi: 10.1017/S0033291714001895.

Rosenthal R, Rosnow RL, Rubin DB (2000). Contrasts and effect sizes in behavioral research: A correlational approach. Cambridge, UK: Cambridge University Press; 212. doi: 10.1016/j.beth.2006.05.002.

Rosenthal R (1994). Parametric measures of effect size. In The handbook of research synthesis, Cooper H, Hedges LV (eds). Russell Sage Foundation: New York; 231–244.

Saari K, Koponen H, Laitinen J, Jokelainen J, Lauren L, Isohanni M, Lindeman S (2004). Hyperlipidemia in persons using antipsychotic medication: a general population-based birth cohort study. J Clin Psychiatry. 65, 547-550.

Saha S, Chant D, Welham J, McGrath J (2005). A systematic review of the prevalence of schizophrenia. PLoS Med 2, e141.

Saijo T, Abe T, Someya Y, Sassa T, Sudo Y, Suhara T, Shuno T, Asai K, Okubo Y (2001). Ten year progressive ventricular enlargement in schizophrenia: An MRI morphometrical study. Psychiatry Clin Neurosci 55: 41–47. doi: 10.1046/j.1440-1819.2001.00783.x.

Salokangas RK, Cannon T, Van Erp T, Ilonen T, Taiminen T, Karlsson H, Lauerma H, Leinonen KM, 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.

Schennach R, Musil R, Möller HJ, Riedel M (2012). Functional outcomes in schizophrenia: employment status as a metric of treatment outcome. Curr Psychiatry Rep 14, 229-236. doi: 10.1007/s11920-012-0261-3.

Scherk H1, Falkai P (2006). Effects of antipsychotics on brain structure. Curr Opin Psychiatry 19, 145-150. doi: 10.1097/01.yco.0000214339.06507.d8.

Schizophrenia (online). Current Care Guidelines, 2015. Working group set up by the Finnish Medical Society Duodecim and the Finnish Psychiatric Association. The Finnish Medical Society Duodecim, Helsinki. (referred to 27.08.2017, www.kaypahoito.fi).

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

Seeman P (1992). Dopamine receptor sequences. Therapeutic levels of neuroleptics occupy D2 receptors, clozapine occupies D4. Neuropsychopharmacology 7(4): 261–284.

Shepherd AM, Laurens KR, Matheson SL, Carr VJ, Green MJ (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.

Shin JH, Park SJ, Kim ES, Jo YK, Hong J, Cho DH (2012). Sertindole, a potent antagonist at dopaminen D2 receptors, induces autophagy by increasing reactive oxygen species in SH-SY5Y neuroblastoma cells. Biol Pharm Bull. 35, 1069-1075.

Smieskova R, Fusar-Poli P, Allen P, Bendfeldt K, Stieglitz RD, Drewe J, Radue EW, McGuire PK, Riecher-Rössler A, Borgwardt SJ (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.

Smith RC, Calderon M, Ravichandran GK, Largen J, Vroulis G, Shvartsburd A, Gordon J, Schoolar JC (1984). Nuclear magnetic resonance in schizophrenia: a preliminary study. Psychiatry Res. 12, 137-147.

Sohler N, Adams BG, Barnes DM, Cohen GH, Prins SJ & Schwartz S (2015). Weighing the evidence for harm from long-term treatment with antipsychotic medications: a systematic review. Am J Orthopsychiat 86, 477-485. doi: 10.1037/ort0000106.

Spitzer L, Williams JBW, Gibbon M, First MB (1989). Structured Clinical Interview for DSM-III-R - Patient Edition (SCID-P, 9/1/89 Version). NewYork: Biometrics Research Department, New York State Psychiatric Institute.

Steylen PM, van der Heijden FM, Kok HD, Sijben NA, Verhoeven WM (2013). Cardiometabolic comorbidity in antipsychotic treated patients: need for systematic evaluation and treatment. Int J Psychiatry Clin Pract 17, 125-130. doi: 10.3109/13651501.2013.779000.

Strakowski SM, DelBello MP, Sax KW, Zimmerman ME, Shear PK, Hawkins JM, Larson ER (1999). Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. Arch Gen Psychiatry 56, 254-260.

Strasser HC, Lilyestrom J, Ashby ER, Honeycutt NA, Schretlen DJ, Pulver AE, Hopkins RO, Depaulo JR, Potash JB, Schweizer B, Yates KO, Kurian E, Barta PE, Pearlson GD (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, 633-639. doi: 10.1016/j.biopsych.2004.12.009.

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB (2000). Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283: 2008–2012.

Strous RD, Shoenfeld Y (2006). Schizophrenia, autoimmunity and immune system dysregulation: a comprehensive model updated and revisited. J Autoimmun 27, 71–80. doi: 10.1016/j.jaut.2006.07.006.

Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu XN, Kubo C, Koga Y (2004). Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. J Physiol 558, 263-75. doi: 10.1113/jphysiol.2004.063388 .

Takahashi T, Kido M, Nakamura K, Furuichi A, Zhou SY, Kawasaki Y, Noguchi K, Seto H, Kurachi M, Suzuki M (2012). Longitudinal MRI study of the pituitary volume in chronic schizophrenia: A preliminary report. Psychiatry Res 202: 84–87. doi: 10.1016/j.pscychresns.2011.11.008.

Takahashi T, Nakamura K, Ikeda E, Furuichi A, Kido M, Nakamura Y, Kawasaki Y, Noguchi K, Seto H, Suzuki M (2013a). Longitudinal MRI study of the midline brain regions in first-episode schizophrenia. Psychiatry Res 212, 150–153. doi: 10.1016/j.pscychresns.2012.12.001.

Takahashi T, Nakamura Y, Nakamura K, Ikeda E, Furuichi A, Kido M, Kawasaki Y, Noguchi K, Seto H, Suzuki M (2013b). Altered depth of the olfactory sulcus in first-episode schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 40, 167–172. doi: 10.1016/j.pnpbp.2012.10.001.

Takahashi T, Suzuki M, Zhou SY, Tanino R, Nakamura K, Kawasaki Y, Seto H, Kurachi M (2010). A follow-up MRI study of the superior temporal subregions in schizotypal disorder and first-episode schizophrenia. Schizophr Res 119, 65–74. doi: 10.1016/j.schres.2009.12.006.

Takahashi T, Wood SJ, Soulsby B, M.cGorry PD, Tanino R, Suzuki M, Velakoulis D, Pantelis C (2009). Follow-up MRI study of the insular cortex in first-episode psychosis and chronic schizophrenia. Schizophr Res 108, 49–56. doi: 10.1016/j.schres.2008.12.029.

Takahashi T, Zhou SY, Nakamura K, Tanino R, Furuichi A, Kido M, Kawasaki Y, Noguchi K, Seto H, Kurachi M, Suzuki M (2011a). A follow-up MRI study of the fusiform gyrus and middle and inferior temporal gyri in schizophrenia spectrum. Prog Neuropsychopharmacol Biol Psychiatry 35, 1957–1964. doi: 10.1016/j.pnpbp.2011.07.009.

Takahashi T, Zhou SY, Nakamura K, Tanino R, Furuichi A, Kido M, Kawasaki Y, Noguchi K, Seto H, Kurachi M, Suzuki M (2011b). Longitudinal volume changes of the pituitary gland in patients with schizotypal disorder and first-episode schizophrenia. Prog Neuropsychopharmaco Biol Psychiatry 35, 177–183. doi: 10.1016/j.pnpbp.2010.10.023.

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.

Tandon R, Keshavan MS, Nasrallah HA (2008). Schizophrenia, ”just the facts” what we know in 2008. 2. Epidemiology and etiology. Schizophr Res 102, 1–18. doi: 10.1016/j.schres.2008.04.011.

Teixeira S, Machado S, Velasques B, Sanfim A, Minc D, Peressutti C, Bittencourt J, Budde H, Cagy M, Anghinah R, Basile LF, Piedade R, Ribeiro P, Diniz C, Cartier C, Gongora M, Silva F, Manaia F, Silva JG (2014). Integrative parietal cortex processes: Neurological and psychiatric aspects. J Neurol Sci 338, 12–22. doi: 10.1016/j.jns.2013.12.025.

Terry AV, Mahadik SP (2007). Time-dependent cognitive deficits associated with first and second generation antipsychotics: Cholinergic dysregulation as a potential mechanism. J Pharmacol Exp Ther 320: 961–968. doi: 10.1124/jpet.106.106047.

Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, Haukka J (2009). 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). Lancet 374, 620-627. doi: 10.1016/S0140-6736(09)60742-X.

Tiihonen J, Mittendorfer-Rutz E, Torniainen M, Alexanderson K, Tanskanen A (2016). Mortality and Cumulative Exposure to Antipsychotics, Antidepressants, and Benzodiazepines in Patients With Schizophrenia: An Observational Follow-Up Study. Am J Psychiatry 173, 600-606. doi: 10.1176/appi.ajp.2015.15050618.

Tiihonen J, Suokas JT, Suvisaari JM, Haukka J, Korhonen P (2012). Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. Arch Gen Psychiatry 69, 476-483. doi: 10.1001/archgenpsychiatry.2011.1532.

Toda M, Abi-Dargham A (2007). Dopamine hypothesis of schizophrenia: Making sense of it all. Curr Psychiatry Rep 9, 329–336.

Torniainen M, Mittendorfer-Rutz E, Tanskanen A, Björkenstam C, Suvisaari J, Alexanderson K, Tiihonen J (2015). Antipsychotic treatment and mortality in schizophrenia. Schizophr Bull 41, 656-63. doi: 10.1093/schbul/sbu164 Erratum in: Schizophr Bull. 2016 42, 528. doi: 10.1093/schbul/sbu164.

Torniainen M, Suvisaari J, Partonen T, Castaneda AE, Kuha A, Suokas J, Perälä J, Saarni SI, Lönnqvist J, Tuulio-Henriksson A (2012). Cognitive impairments in schizophrenia and schizoaffective disorder: relationship with clinical characteristics. J Nerv Ment Dis 200, 316-322. doi: 10.1097/NMD.0b013e31824cb359.

Torres US, Portela-Oliveira E, Borgwardt S, Busatto GF (2013). Structural brain changes associated with antipsychotic treatment in schizophrenia as revealed by voxel-based morphometric MRI: An activation likelihood estimation meta-analysis. BMC Psychiatry 13, 342. doi: 10.1186/1471-244X-13-342.

Tost H, Braus DF, Hakimi S, Ruf M, Vollmert C, Hohn F, Meyer-Lindenberg A (2010). Acute D2 receptor blockade induces rapid, reversible remodeling in human cortical-striatal circuits. Nat Neurosci 13, 920–922. doi: 10.1038/nn.2572.

Tsuang MT, Taylor L & Faraone SV (2004). An overview of the genetics of psychotic mood disorders. J Psychiatr Res 38: 3–15.

Tustison NJ, Avants BB, Cook PA, Zheng Y, Egan A, Yushkevich PA, Gee JC (2010). N4ITK: improved N3 bias correction. IEEE Trans Med Imaging 29, 1310-1320. doi: 10.1109/TMI.2010.2046908.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15, 273–289. doi: 10.1006/nimg.2001.0978.

Uhde TW, Kellner CH (1987). Cerebral ventricular size in panic disorder. J Affect Disord. 12, 175-178.

van Haren NE, Hulshoff Pol HE, Schnack HG, Cahn W, Brans R, Carati I, Rais M, Kahn RS (2008). Progressive brain volume loss in schizophrenia over the course of the illness: Evidence of maturational abnormalities in early adulthood. Biol Psychiatry 63, 106–113. doi: 10.1016/j.biopsych.2007.01.004.

van Haren NE, Hulshoff Pol HE, Schnack HG, Cahn W, Mandl RC, Collins DL, Evans AC, Kahn RS (2007). Focal gray matter changes in schizophrenia across the course of the illness: A 5-year follow-up study. Neuropsychopharmacology 32, 2057–2066. doi: 10.1038/sj.npp.1301347.

van Haren NE, Schnack HG, Cahn W, van den Heuvel MP, Lepage C, Collins L, Evans AC, Hulshoff Pol HE, Kahn RS (2011). Changes in cortical thickness during the course of illness in schizophrenia. Arch Gen Psychiatry 68, 871–880. doi: 10.1001/archgenpsychiatry.2011.88.

van Haren NE, Cahn W, Hulshoff Pol HE, Kahn RS (2013). Confounders of excessive brain volume loss in schizophrenia. Neurosci Biobehav Rev 37, 2418-2423. doi: 10.1016/j.neubiorev.2012.09.006.

Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, Rosenbaum S, Correll CU (2015). Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry 14, 339-347. doi: 10.1002/wps.20252.

van Os J, Kenis G, Rutten BP (2010). The environment and schizophrenia. Nature 468, 203–212. doi: 10.1038/nature09563.

Vares M, Saetre P, Strålin P, Levander S, Lindström E, Jönsson EG (2011). Concomitant medication of psychoses in a lifetime perspective. Hum Psychopharmacol 26, 322-331. doi: 10.1002/hup.1209.

Veijola J, Guo JY, Moilanen JS, Jääskeläinen E, Miettunen J, Kyllönen M, Haapea M, Huhtaniska S, Alaräisänen A, Mäki P, Kiviniemi V, Nikkinen J, Starck T, Remes JJ, Tanskanen P, Tervonen O, Wink AM, Kehagia A, Suckling J, Kobayashi H, Barnett JH, Barnes A, Koponen HJ, Jones PB, Isohanni M, Murray GK (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 AC, Natesan S, Crum WR, Cooper JD, Modo M, Williams SC, Kapur S (2012). Contrasting effects of haloperidol and lithium on rodent brain structure: a magnetic resonance imaging study with postmortem confirmation. Biol Psychiatry 71, 855–863. doi: 10.1016/j.biopsych.2011.12.004.

Vernon AC, 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.

Vernon AC, Crum WR, Lerch JP, Chege W, Natesan S, Modo M, Cooper JD, Williams SC, 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.

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.

Volz A, Khorsand V, Gillies D, Leucht S (2007). Benzodiazepines for schizophrenia. Cochrane Database Syst Rev, CD006391.

Wang P, Brookhart A, Ulbricht C, Schneeweiss S (2011), in: Tsuang, M. Tohen, M. Jones, P. (Eds.), The Pharmacoepidemiology of Psychiatric Medications. Textbook in Psychiatric Epidemiology (3rd ed.). Wiley-Blackwell, Oxford, pp. 155–165.

Wang HX, Wang YP (2016). Gut Microbiota-brain Axis. Chin Med J (Engl) 129, 2373-2380. doi: 10.4103/0366-6999.190667.

Waterreus A, Morgan VA, Castle D, Galletly C, Jablensky A, Di Prinzio P, Shah S (2012). Medication for psychosis - consumption and consequences: The second Australian national survey of psychosis. Aust N Z J Psychiatry 46, 762-773. doi: 10.1177/0004867412450471.

Weinberger DR (1987). Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 44, 660–69.

Westmoreland Corson PW, Nopoulos P, Miller DD, Arndt S, Andreasen NC (1999). Change in basal ganglia volume over 2 years in patients with schizophrenia: Typical versus atypical neuroleptics. Am J Psychiatry 156, 1200–1204. doi: 10.1176/ajp.156.8.1200.

Wexler BE, Anderson M, Fulbright RK, Gore JC (2000). Preliminary evidence of improved verbal working memory performance and normalization of task-related frontal lobe activation in schizophrenia following cognitive exercises. Am J Psychiatry 157, 1694–1697. doi: 10.1176/appi.ajp.157.10.1694.

WHO (1992) International Classification of Diseases and Related Health Problems. 10th revision. World Health Organization, Geneva.

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

Wilkinson ST, Radhakrishnan R, D'Souza DC (2014). Impact of cannabis use on the development of psychotic disorders. Curr Addict Rep 1, 115–128. doi: 10.1007/s40429-014-0018-7

Wood SJ, 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 ND, Heckers S (2015). Brain Structure in Neuropsychologically Defined Subgroups of Schizophrenia and Psychotic Bipolar Disorder. Schizophr Bull 41, 1349-1359. doi: 10.1093/schbul/sbv048.

Woon FL, Sood S, Hedges DW (2010). Hippocampal volume deficits associated with exposure to psychological trauma and posttraumatic stress disorder in adults: a meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 34, 1181-8. doi: 10.1016/j.pnpbp.2010.06.016.

Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET (2000). Meta-analysis of regional brain volumes in schizophrenia. Am J Psychiatry 157, 16-25.

Wunderink L, Nieboer RM, Wiersma D, Sytema S, Nienhuis FJ (2013). Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: Long-term follow-up of a 2-year randomized clinical trial. JAMA Psychiatry 70, 913–920. doi: 10.1001/jamapsychiatry.2013.19

Wykes T, Brammer M, Mellers J, Bray P, Reeder C, Williams C, Corner J (2002). Effects on the brain of a psychological treatment: cognitive remediation therapy Functional magnetic resonance imaging in schizophrenia. Br J Psychiatry 181, 144–152.

Yang AC, Tsai SJ (2017). New Targets for Schizophrenia Treatment beyond the Dopamine Hypothesis. Int J Mol Sci 18, pii: E1689. doi: 10.3390/ijms18081689.

Yüksel C, McCarthy J, Shinn A, Pfaff DL, Baker JT, Heckers S, Renshaw P, Ongür D (2012). Gray matter volume in schizophrenia and bipolar disorder with psychotic features. Schizophr Res 138, 177-182. doi: 10.1016/j.schres.2012.03.003

Zagrebelsky M, Korte M (2014). Form follows function: BDNF and its involvement in sculpting the function and structure of synapses. Neuropharmacology 76 Pt C:628-38. doi: 10.1016/j.neuropharm.2013.05.029.

Zhang C, Fang X, Yao P, Mao Y, Cai J, Zhang Y, Chen M, Fan W, Tang W, Song L (2017). Metabolic adverse effects of olanzapine on cognitive dysfunction: A possible relationship between BDNF and TNF-alpha. Psychoneuroendocrinology 81, 138-143. doi: 10.1016/j.psyneuen.2017.04.014.

List of original publications

I Huhtaniska, S. Jääskeläinen, E. Hirvonen, N. Remes, J. Murray, G.K. Veijola, J. Isohanni, M. Miettunen, J. (2017) Long-term antipsychotic use and brain changes in schizophrenia - a systematic review and meta-analysis. Hum Psychopharmacol, 32(2).

II 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. (2017) Long-term antipsychotic and benzodiazepine use and brain volume changes in schizophrenia: The Northern Finland Birth Cohort 1966 study. Psychiatry Res, 266, 73-82

III Huhtaniska, S. Korkala, I. Heikka, T. Lehtiniemi, H. Hulkko, A. Moilanen, J.S. Tohka, J. Manjón, J.V. Coupé, P. Kiviniemi, V. Isohanni, M. J. Koponen, H. Murray, G.K. Miettunen, J. Jääskeläinen, E. Antipsychotic and benzodiazepine use and brain morphology in schizophrenia and affective psychoses – a systematic review and birth cohort study. Manuscript.

Original publications are not included in the electronic version of the dissertation.

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