Psychiatry & Mental Disorders

Global Scientific Library

Review Article

Shrinking Brain and Schizophrenia: A Review of Current Studies on the Effect of Antipsychotic Medication on Gray Matter Volume

Daniela Krause[1]* and Oliver Pogarell[1]

[1]Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Germany

Abstract

Objectives: Recent research has shown that before the onset of schizophrenia, there are neurodevelopmental changes and abnormalities in the brain volumes of the prospective patients. Yet the reason for this change in gray matter remains unclear: Is it a result of the psychiatric disease - or could it be a result of the antipsychotic medication?

Methods and main results: This review aims to shed some light on the precise influence of different classes of antipsychotic medication on basal ganglia and gray matter brain volumes in schizophrenia. It also highlights possible mechanisms and clinical consequences of these changes in brain volume. Apart from that, the review points out alternative therapies to prevent brain volume loss in schizophrenia.

To date many studies suggest that typical and atypical antipsychotics might have agonistic effects on brain volume loss, indicating a protective impact of atypical antipsychotics on gray matter volume and basal ganglia.

Principal conclusion: Taken this together, brain volume changes in schizophrenia might be a relevant disease pathology that deserves further investigation and could lead to new preventive therapies.

Introduction

In the early 1980's it was first detected that brain volume from patients with schizophrenia was reduced in comparison to the healthy population [1]. Since then research has been trying to explore causes, mechanisms and consequences of different brain volume distributions. To date, there is broad agreement that the pathology of schizophrenia starts years before the first symptoms are diagnosed. One of the pathologies involved in the pathophysiology of schizophrenia are changes in brain volumes. Regarding volume changes in the gray and white matter as well as in the basal ganglia, it seems likely that these changes occur before and/or during the early years of the disease process of schizophrenia [2]. The underlying mechanisms, however, of these brain volume changes remain an ongoing discussion. Yet further questions arise and are to be addressed: what happens to brain volumes over the course of the disease? And what about the influence of antipsychotics on different brain volumes (especially gray matter)? The goal of this review is to shed light on structural brain abnormalities in schizophrenia and to explore, if and how antipsychotics are involved in brain volume changes.

***Corresponding author:** Daniela Krause, Ludwig-Maximilians University, Department of Psychiatry, Department of Neurophysiology and Functional Neuroimaging, Nußbaumstr. 7, 80336 Munich, Germany, Email: Daniela.Krause@med.uni-muenchen.de

Received: August 06, 2017; **Accepted:** September 15, 2017; **Published:** September 22, 2017

Brain Volume Changes in Drug-Naïve Patients with Schizophrenia

In order to address the question of the causes and mechanisms of brain volume loss in schizophrenia, it is required to explore patients that have never received any anti-psychotic treatment. With the help of studies that investigate drug-naïve, ideally first-episode patients with schizophrenia it might be possible to differentiate whether brain volume changes are a disease process or are rather attributable to medication effects. In this respect several studies revealed that first-episode patients with schizophrenia present with a different distribution of brain volumes before the onset of their treatment:

A very recent fMRI study identified that drug-naïve first-episode patients with schizophrenia (n=18) had less gray matter volume in the left superior temporal gyrus, frontal regions, cerebellum and caudate compared to healthy controls. Especially those patients who suffered from acoustic hallucinations showed a reduced thalamic volume, supporting a clinical relevance of the gray matter changes [3]. Another study compared antipsychotic-naïve patients with schizophrenia to healthy controls and demonstrated a significantly reduced gray matter volume of the left and right hippocampal volumes in the group of patients. These results remained stable even after controlling for confounding factors like age, sex and total brain volume [4]. The data were supported by a study by van Erp et al. The authors compared individuals with schizophrenia to healthy controls and showed that patients had significantly smaller hippocampus, amygdala, thalamus, accumbens and intracranial volumes, and significantly larger pallidum and lateral ventricle volumes. In addition putamen and pallidum volume enlargements were associated with duration of illness whereas age and hippocampal volume deficits were more severe in samples with a higher proportion of unmedicated patients [5]. Also a sample of first-episode drug-naïve patients with schizophrenia showed a significantly reduced gray matter volume in the right middle/superior temporal gyrus, the right anterior cingulate gyrus compared to matched controls [6].

The previous studies have shown abnormalities in regard to different brain volumes, mainly present in the gray matter in symptomatic patients. However, there is one study that investigated changes in the brain volume before the onset of schizophrenia symptoms. Finding of abnormalities before the onset of symptoms could help to distinguish whether brain volume changes are likely associated with the disease pathology. First ideas have been pronounced that the outcome of prodromal psychosis can be predicted at the single-subject level with the help of multivariate neuroanatomical risk stratification methods [7]. Takahashi et al. investigated 35 individuals at high risk for schizophrenia (12 of them later developed schizophrenia) and 23 patients with first-episode schizophrenia compared to healthy controls. For the individuals that later had a diagnosis of schizophrenia and the first-episode patients, significant gray matter loss was identified in a longitudinal comparison with about two to six percent per year. In addition the first-episode patients with schizophrenia had a more pronounced gray matter loss in the left Heschl gyrus and the rostral region [8]. These findings indicate brain volume abnormalities before the onset of schizophrenia symptoms.

Citation: Krause D, Pogarell O. Shrinking Brain and Schizophrenia: A Review of Current Studies on the Effect of Antipsychotic Medication on Gray Matter Volume. Psych Mental Disord. 2017; 1:102.

Another study found that schizophrenia spectrum disorder patients who were between 15 and 20 years at their first episode showed significant volume and thickness deficits in the frontal lobe, volume deficits in temporal lobe, and volume enlargements in ventricular system and basal ganglia [9]. Though these patients were medicated, the findings point towards an early onset of structural changes in the whole course of the disease.

But not only clinical studies have shown an abnormal distribution of brain volumes: A large meta-analysis with over 18000 subjects investigated 771 antipsychotic-naïve patients with schizophrenia and identified a volume decrease in the caudate nucleus and thalamus in this group compared to medicated patients with schizophrenia. White matter reductions were found in both groups and did not differ between medicated and anti-psychotic-naive patients, whereas gray matter loss was only found to be increased in the medicated patient group [10].

Taken all these studies together, the results still seem to be preliminary and not overall consistent. Gray matter loss and volume reduction of some basal ganglia structure have been identified in antipsychotic-naïve patients with schizophrenia. However, the reported brain areas differ substantially between studies. The findings of this section are summarized in Table 1.

The Role of Typical and Atypical Antipsychotics on Brain Volume

There has been an ongoing debate whether antipsychotics have an impact on brain volume and if there are differences between atypical and typical antipsychotics. To date, there are already several studies including meta-analyses that try to address these questions.

A meta-analysis by Haijma et al. investigated studies with antipsychotic-naïve patients and medicated patients. In the medicated sample they analyzed the comparison of 8327 antipsychotic-naïve patients with schizophrenia to healthy controls respectively and showed an intracranial and total brain volume reduction of 2% and 2.6%. The effects were most prominent in the gray matter brain structures. Also the longer the duration of illness and the higher the dose of antipsychotics, the more gray matter reduction was identified. However, higher doses of antipsychotic medication were associated with volume increase of the caudate nucleus, an effect only observed for atypical antipsychotics. On the other hand total gray matter loss was more pronounced in patients using a higher dose of antipsychotic medication at time of scanning. This association was significant only for atypical antipsychotics [10]. These results indicate a role of antipsychotic medication in regard to brain volume changes.

Similar findings were reported in another meta-analysis that identified a strong effect of antipsychotics on the gray matter volume over time when 1046 patients were compared to 780 controls. In a longitudinally perspective the authors observed a progressive reduction of gray matter volume and an increase in left ventricular volume in patients compared to controls. In addition a higher cumulative dose of antipsychotics was associated with longitudinal gray matter volume loss over time in the patient group [11].

What makes this study a little bit less convincing is the fact that it did not differentiate between treatments with atypical or typical antipsychotics. Though, there are studies which make this distinction. One analysis found that risperidone and clozapine had an augmentative effect on gray matter volume in chronic schizophrenic patients compared to controls. Study participants had two brain scans, one at baseline and the second one after two years of atypical antipsychotic treatment. Patients received either risperidone when they were treatment-naïve or when patients were chronic-treatment resistant they received clozapine [12].

The influence of atypical antipsychotics on gray matter brain volume has been investigated: Patients diagnosed with schizophrenia received either an atypical antipsychotic drug (risperidone or ziprasidone) or the typical antipsychotic haloperidol. A control group of schizophrenic patients remained untreated. The gray matter volume was measured twice: before the onset of the treatment and 28 days later. An increase in the gray matter volume was found only in the group treated with atypical antipsychotics. No change was reported for patients receiving haloperidol or who were untreated [13]. In conclusion, these studies revealed that there are differences between atypical and typical antipsychotics considering their influence on gray matter volumes.

In line with these findings is a study on cortical thickness. When cortical thickening was investigated over a five year course, it has been found that patients with a higher intake of typical antipsychotics showed a more pronounced cortical thinning, though patients that received atypicals had a lower cortical thinning [14]. In addition, another study corroborates the difference between antipsychotic drug classes. Only atypical antipsychotics were identified to reverse the gray matter loss, which is possibly caused by the disease pathology of schizophrenia. In a longitudinal study over five years it was shown that the cumulative dose per year of clozapine and olanzapine was significantly associated with less decrease in the gray matter in the frontal lobe. In contrast, the opposite was found for typical antipsychotics: These drugs provoked an increase in gray matter loss in the right caudate nucleus and left superior frontal gyrus [2]. In line with the previous findings is a study by Liebermann et al. who reported that haloperidol and not olanzapine is associated with gray matter decrease over time. They included 161 first-episode patients with schizophrenia who received two MRI scans, both at baseline and after 104 weeks of treatment with either haloperidol or olanzapine. In addition healthy controls were also investigated. Similar to the control group, the group treated with olanzapine showed no change in gray matter brain volume, whereas the haloperidol group presented with a significant decrease in gray matter volume at follow-up [15].

However, not all studies conclude that atypical antipsychotics reverse

Authors, year	Number of participants	Main findings in the patient group	Brain region
Huang et al., 2015	n=36 antipsychotic-naïve patients and controls	Less gray matter volume	Left superior temporal gyrus, frontal regions, cerebellum, caudate
Kalmady et al., 2014	n=65 antipsychotic-naïve patients and controls	Reduced gray matter volume	Left and right hippocampus
Van Erp et al., 2015 (Meta-analysis)	n=4568 in total n= unclear of antipsychotic-naïve patients	Reduced volume	Hippocampus
Lui et al., 2009	n=136 antipsychotic-naïve patients and controls	Reduced gray matter volume	right middle/superior temporal gyrus, right anterior cingulate gyrus
Takahashi et al., 2009	n=35 antipsychotic-naïve patients and controls	Reduced gray matter volume	Left Heschl gyrus and rostral region
Haijma et al., 2013 (Meta-analysis)	n=771 antipsychotic-naïve patients	Reduced volume	Caudate nucleus and thalamus

Table 1: Studies on brain volume changes in drug-naïve patients with schizophrenia.

Citation: Krause D, Pogarell O. Shrinking Brain and Schizophrenia: A Review of Current Studies on the Effect of Antipsychotic Medication on Gray Matter Volume. Psych Mental Disord. 2017; 1:102.

gray matter volume loss. Ahmed et al. found that patients treated with the atypical antipsychotic clozapine showed an ongoing decline in gray matter. Switching patients with schizophrenia from an antipsychotic drug to clozapine treatment showed progressive gray matter loss over a six to nine month period. Regardless of symptom improvement patients showed a significant decrease in the volumes of the right and left prefrontal cortex and in the periventricular area. Therefore the authors concluded that clozapine was not able to stop the progressive gray matter loss. Nevertheless, as patients showed a clinical improvement of their symptoms under clozapine therapy, eventually gray matter loss might not directly translate to a bad clinical course [16].

Not only gray matter volume has been identified to be dependent of antipsychotic treatment, also other brain structures like the basal ganglia seem to be involved. Gur et al. found that medicated patients with schizophrenia had an increased volume in the putamen and globus pallidus compared to healthy controls and antipsychotic-naïve patients and a higher dose of an atypical antipsychotic was associated with higher thalamic volume [17].

In a study with drug-naïve patients with schizophrenia, antipsychotic treatment was administered for six weeks. Compared to healthy controls, the volume of the putamen was increased in the patient population after six weeks of treatment. However, in this study the authors did not differentiate between typical and atypical antipsychotics [18].

A typical and an atypical antipsychotic were compared in a study by Glenthoj et al. They investigated 19 first-episode patients with schizophrenia and 19 matched controls which were medicated either with risperidone or zuclopenthixol over the course of three months. No differences were found between the two medication groups regarding volume changes of the basal ganglia. When only risperidone was investigated, a higher volume was found in the putamen, indicating different impact on basal ganglia volumes of typical and atypical drugs [19].

It seems likely that antipsychotics are involved in brain volume changes. However, typical and atypical antipsychotics might have different effects, pointing towards a potentially protective effect of atypical antipsychotics on gray matter volume and basal ganglia. Table 2 summarizes the findings of this section.

Controversy: Are Antipsychotics Responsible for Further Brain Volume Loss?

An important approach was chosen by Boonstra et al. who investigated the effect of discontinuation of atypical antipsychotics on brain volume changes. Therefore from sixteen remitted and stable patients with schizophrenia magnetic resonance imaging brain scans were obtained at baseline and after 16 weeks of either discontinuation (n=8) or continuation (n=8) of antipsychotics. The authors detected an increase in the volumes of nucleus accumbens and putamen in patients who stayed on their atypical medication whereas the discontinuation group presented with a reduction of these volumes [20].

One hypothesis is that gray matter loss is associated with the disease pathology and that atypical antipsychotics can prevent further gray matter loss. This means that gray matter protection could be a possible mode of action of atypicals. Atypical antipsychotics have been proposed to be involved in neuroplasticity [21], and could therefore possibly influence certain brain volumes.

However, brain volume is influenced by many factors. Brain volume changes could also be associated with age. One study showed that before the age of 26 years patients with schizophrenia had a higher brain volume loss then controls, whereas after the age of 40 years healthy controls showed higher brain volume loss over a five year course [22].

One recent study pointed out the relevance of the Intelligence Quotient (IQ). 84 patients with schizophrenia were compared to 116 healthy controls and received brain scans over a three year period. The authors identified a positive correlation between changes in the IQ and cortical volume and thickness globally and in the frontal, temporal and parietal cortices. No influence of symptom severity, cannabis use or the cumulative dose of antipsychotic medication was found [23]. Rais et al. reported that 20 antipsychotic-naïve patients with schizophrenia had a reduced whole-brain volume and gray/white volumes compared to controls and that these abnormalities might be associated with differences in the IQ [24].

All these confounding factors make it difficult to precisely interpret the heterogeneous studies on antipsychotic drugs and brain volume.

Possible responsible mechanisms for brain volume changes

If antipsychotic drugs have an impact on brain volumes, one key question remains: are there explanations for their possible mechanism of action in this respect?

An animal study by Cotel et al. showed that rats chronically exposed to antipsychotic treatment presented an increased activity of microglia in certain brain regions. These findings indicate an association between the antipsychotics haloperidol/ olanzapine and markers of neuroinflammation in the brain [25]. Therefore altered brain volumes could be caused by increased neuroinflammation, different structural remodelings, including apoptosis and cell migration.

Another mechanism could be a regulation of free radicals. These reactive oxygen species have been identified to contribute to neuronal damage and to play a role in the pathophysiology of schizophrenia (reviewed in [26]). However it has been shown, mainly in animal models that antipsychotics impact on the free radical metabolism and that there are differences of atypical and typical antipsychotics regarding the levels of antioxidant enzymes. Only haloperidol and not risperidone, clozapine or olanzapine significantly decreased manganese-superoxide dismutase, copper-zinc superoxide dismutase and lipid peroxidation in rat brain [27]. The same authors reported in a follow-up study that it was possible to reverse the above effects caused of haloperidol on antioxidant enzymes by switching to atypical antipsychotic drugs (olanzapine, clozapine or risperidone) [28].

Also other enzymes related to the free radical generation such as nitric oxide synthase were found to be inhibited by typical antipsychotics [29], although atypical antipsychotics did not alter or reversed the levels of these enzymes [29, 30].

Do Brain Volume Changes Caused by Disease or Drugs Matter Clinically?

Regarding the question whether schizophrenia symptoms are affected by changes of gray matter or basal ganglia volumes, it is helpful to identify structural abnormalities in the brain that may have a functional counterpart.

A recently published study pronounced evidence that gray matter volume loss in schizophrenia is associated with treatment response: The group of schizophrenic patients that were resistant to first-line atypical antipsychotic therapy or did not even respond to clozapine had a significantly greater reduction of gray matter volume compared to both controls and patients who responded to atypical antipsychotics [31]. In addition, it has been shown in a five year longitudinal study that the patients with the most unfavorable course (indicated by the number of hospitalizations) had the largest loss in gray matter of the frontal lobe [2]. During the course of a six week trial, Li et al. found an increase of the volume of the putamen in treated patients with schizophrenia compared to controls, which was positively correlated with the reduction of positive symptoms assessed by the Positive and Negative Syndrome Scale (PANSS) [18]. Huang et al. reported that patients with schizophrenia suffering from acoustic hallucinations showed a correlation between PANSS

Authors, year	Number of participants	Main findings	Type of medication
Haijma et al., 2013 (meta-analysis)	n> 18000 in total	volume increase in the caudate nucleus	only for atypical antipsychotics
		total gray matter loss	only in medicated patients with schizophrenia
Fusar-Poli et al., 2013	n= 10826	reduced gray matter volume; increase in left ventricular volume and higher cumulative dose of antipsychotics associated with gray matter volume loss	patients with schizophrenia treated with antipsychotics
Molina et al., 2005	n= 40	augmentative effect on gray matter volume	patients treated with risperidone and clozapine
Graver et al., 2005	n= 26	increase in the gray matter volume	only in patients treated with risperidone or ziprasidone
		no volume change	patients receiving haloperidol or untreated
Van Haren et al., 2011	n= 182	lower cortical thinning	patients with atypical antipsychotics compared to typicals
Van Haren et al., 2008	n= 209	less decrease in the gray matter in the frontal lobe	patients with
			clozapine and olanzapine
		increase in gray matter loss in the right caudate nucleus and left superior frontal gyrus	patients with
			typical antipsychotics
Liebermann et al., 2005	n= 161	decrease in gray matter volume	patients treated with haloperidol
		no change in gray matter brain volume	patients treated with olanzapine
Ahmed et al., 2015	n= 64	ongoing decline in gray matter of the right and left prefrontal cortex and in the periventricular area	patients treated clozapine
Gur et al., 1998	n= 224	increased volume in the putamen and globus pallidus	patients treated with antipsychotics
		higher thalamic volume	patients with higher dose of an atypical antipsychotic drug
Li et al., 2012	n= 89	increased volume of the putamen	patients treated with antipsychotics
Glenthoj et al., 2007	n= 38	no differences in volume changes of the basal ganglia	patients treated with risperidone or zuclopenthixol
		higher volume in the putamen	patients treated with risperidone

Table 2: Studies on brain volume in patients treated with antipsychotic drugs.

total scores and thalamic volumes, indicating that the thalamic volume could distinguish healthy controls from patients with schizophrenia with acoustic hallucinations [3]. In a sample of drug-naïve first-episode patients with schizophrenia, the decease of gray matter in certain brain regions correlated with total PANSS score and were therefore associated with clinical symptom severity [6]. Especially the total brain volume and the volume of the cerebellum were found to be associated with the schizophrenia symptom "disorganization" over a five year course [32]. Neckelmann et al. also investigated whether hallucinations as a core symptom of schizophrenia are associated with brain volume. They compared 12 patients with schizophrenia (treated either with atypical or typical antipsychotics) to 12 healthy controls and demonstrated that gray matter loss in the left temporal lobe was significantly associated with the frequency of hallucinations. However differences between the classes of antipsychotics were not reported [33].

Altogether these findings indicate that clinical symptoms of schizophrenia may be associated with changes in brain volume, but with all these equivocal results especially with respect to the impact of medications no clear conclusions can be drawn.

Are there Other Therapeutic Options then Antipsychotic Drugs to Stop Brain Volume Loss?

Given the numerous reports of structural abnormalities and potential relevance of progressive changes in the pathophysiology of schizophrenia it seems important to have therapeutic options to stop the brain volume loss. There are already first ideas how a progressive brain volume loss in schizophrenia could be treated or prevented: In a sample of chronic patients with schizophrenia it was shown that recombinant human erythropoietin was able to stop the loss of gray matter brain volume. Wustenberg et al. investigated 32 men who suffered from chronic schizophrenia and received weekly intravenous infusions of high-dose erythropoietin versus placebo over a twelve week course of treatment. Erythropoietin showed neuroprotective effects in schizophrenic patients compared to placebo: Over the course of the study erythropoietin prevented gray matter loss in brain areas that have typically been associated with volume loss in schizophrenia like the right ventral frontal cortex [34].

It has also been proposed that exercise therapy could be a strategy against brain volume loss: Malchow et al. reported that a three month endurance training lead to an increased volume of the left superior, middle and inferior anterior temporal gyri compared to baseline in patients with schizophrenia [35]. Others have found that the hippocampal volume increases in response to aerobic fitness in patients with schizophrenia as well as in controls [36].

Another approach to stop gray matter loss in schizophrenia is cognitive enhancement therapy. A study by Eack et al. investigated over a two year period whether cognitive enhancement therapy is more effective in reducing gray matter loss in early course patients with schizophrenia than enriched supportive therapy used as a control group setting. The group of patients under cognitive enhancement therapy had significantly less loss of gray matter volume in the left hippocampus, fusiform gyrus, parahippocampal gyrus and increases were found in the left amygdala [37].

However, these findings originate from a rather small sample size and should be interpreted with caution. Furthermore, it would be

interesting to see studies that combine treatment with erythropoietin, exercise therapy, enhanced cognitive therapy and atypical antipsychotics in patients with schizophrenia and measure their impact on brain volume changes.

Conclusion

The precise impact of antipsychotics on brain volume and its relevance on the clinical course in schizophrenia is not overall clear and cannot be explained with complete certainty. However, there is convincing evidence that changes in brain volumes in schizophrenia are already present before the onset of clinical relevant symptoms and that these brain volumes changes, especially in gray matter and basal ganglia can be influenced by antipsychotic medication. To date several studies point at different effects of treatment with typical or atypical antipsychotic drugs: According to the data, this difference seems to be in favor of the use of atypical antipsychotic medication, as several of these drugs have been identified to have augmentative effects on brain volumes instead of further reductions. However, brain volume changes are probably not the main cause of disease progression, as not all patients with schizophrenia have a reduced gray matter volume. In this respect a recent study showed that over the course of nine years 21% of patients with schizophrenia had the same levels of gray matter as the healthy control cohort [38].

Nevertheless brain volume changes in schizophrenia might be a relevant disease pathology that is worth the effort to try to prevent it. Future studies need to address whether a combination therapy of atypical antipsychotic medication and other alternative treatment methods that have been identified to prevent brain volume loss (e.g. physical exercising) could be helpful. Currently the diagnosis of schizophrenia is based on the presentation of clinical symptoms. However, damage to neurons and glia cells might have occurred already many years earlier reflected by the measured brain volume changes in prodromal states of prospect schizophrenic patients. In the future, early interventions strategies are needed that prevent this early, partly irreversible brain volume loss in schizophrenia.

References

1. Bogerts B, Meertz E, Schonfeldt-Bausch R. (1985) Basal ganglia and limbic system pathology in schizophrenia. A morphometric study of brain volume and shrinkage. Arch Gen Psychiatry. 42: 784-791.
2. van Haren NE, Hulshoff Pol HE, Schnack HG, Cahn W, Brans R, et al. (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.
3. Huang P, Xi Y, Lu ZL, Chen Y, Li X, et al. (2015) Decreased bilateral thalamic gray matter volume in first-episode schizophrenia with prominent hallucinatory symptoms: A volumetric MRI study. Sci Rep. 5: 14505.
4. Kalmady SV, Venkatasubramanian G, Shivakumar V, Gautham S, Subramaniam A, et al. (2014) Relationship between Interleukin-6 gene polymorphism and hippocampal volume in antipsychotic-naive schizophrenia: evidence for differential susceptibility? PLoS One. 9: e96021.
5. van Erp TG, Hibar DP, Rasmussen JM, Glahn DC, Pearlson GD, et al. (2016) Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Mol Psychiatry. 21: 547-553.
6. Lui S, Deng W, Huang X, Jiang L, Ma X, et al. (2009) Association of cerebral deficits with clinical symptoms in antipsychotic-naive first-episode schizophrenia: an optimized voxel-based morphometry and resting state functional connectivity study. Am J Psychiatry. 166: 196-205.
7. Kambeitz-Ilankovic L, Meisenzahl EM, Cabral C, von Saldern S, Kambeitz J, et al. (2016) Prediction of outcome in the psychosis prodrome using neuroanatomical pattern classification. Schizophr Res. 173: 159-165.
8. Takahashi T, Wood SJ, Yung AR, Soulsby B, McGorry PD, et al. (2009) Progressive gray matter reduction of the superior temporal gyrus during transition to psychosis. Arch Gen Psychiatry. 66: 366-376.
9. Pina-Camacho L, Del Rey-Mejías Á, Janssen J, Bioque M, González-Pinto A, et al. (2016) Age at First Episode Modulates Diagnosis-Related Structural Brain Abnormalities in Psychosis. Schizophr Bull. 42: 344-357.
10. Haijma SV, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE, et al. (2013) Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. Schizophr Bull. 39: 1129-1138.
11. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, et al. (2013) Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. Neurosci Biobehav Rev. 37: 1680-1691.
12. Molina V, Reig S, Sanz J, Palomo T, Benito C, et al. (2005) Increase in gray matter and decrease in white matter volumes in the cortex during treatment with atypical neuroleptics in schizophrenia. Schizophr Res. 80: 61-71.
13. Garver DL, Holcomb JA, Christensen JD. (2005) Cerebral cortical gray expansion associated with two second-generation antipsychotics. Biol Psychiatry. 58: 62-66.
14. van Haren NE, Schnack HG, Cahn W, van den Heuvel MP, Lepage C, et al. (2011) Changes in cortical thickness during the course of illness in schizophrenia. Arch Gen Psychiatry. 68: 871-880.
15. Lieberman JA, Tollefson GD, Charles C, Zipursky R, Sharma T, et al. (2005) Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry. 62: 361-370.
16. Ahmed M, Cannon DM, Scanlon C, Holleran L, Schmidt H, et al. (2015) Progressive Brain Atrophy and Cortical Thinning in Schizophrenia after Commencing Clozapine Treatment. Neuropsychopharmacology. 40: 2409-2417.
17. Gur RE, Maany V, Mozley PD, Swanson C, Bilker W, et al. (1998) Subcortical MRI volumes in neuroleptic-naive and treated patients with schizophrenia. Am J Psychiatry. 155: 1711-1717.
18. Li M, Chen Z, Deng W, He Z, Wang Q, et al. (2012) Volume increases in putamen associated with positive symptom reduction in previously drug-naive schizophrenia after 6 weeks antipsychotic treatment. Psychol Med. 42: 1475-1483.
19. Glenthoj A, Glenthoj BY, Mackeprang T, Pagsberg AK, Hemmingsen RP, et al. (2007) Basal ganglia volumes in drug-naive first-episode schizophrenia patients before and after short-term treatment with either a typical or an atypical antipsychotic drug. Psychiatry Res. 154: 199-208.
20. Boonstra G, van Haren NE, Schnack HG, Cahn W, Burger H, et al. (2011) Brain volume changes after withdrawal of atypical antipsychotics in patients with first-episode schizophrenia. J Clin Psychopharmacol. 31: 146-153.
21. Konradi C, Heckers S. (2001) Antipsychotic drugs and neuroplasticity: insights into the treatment and neurobiology of schizophrenia. Biol Psychiatry. 50: 729-742.
22. Koolschijn PC, van Haren NE, Cahn W, Schnack HG, Janssen J, et al. (2010) Hippocampal volume change in schizophrenia. J Clin Psychiatry. 71: 737-744.

Citation: Krause D, Pogarell O. Shrinking Brain and Schizophrenia: A Review of Current Studies on the Effect of Antipsychotic Medication on Gray Matter Volume. Psych Mental Disord. 2017; 1:102.

23. Kubota M, van Haren NE, Haijma SV, Schnack HG, Cahn W, et al. (2015) Association of IQ Changes and Progressive Brain Changes in Patients with Schizophrenia. JAMA Psychiatry. 72: 803-812.

24. Rais M, Cahn W, Schnack HG, Hulshoff Pol HE, Kahn RS, et al. (2012) Brain volume reductions in medication-naive patients with schizophrenia in relation to intelligence quotient. Psychol Med. 42: 1847-1856.

25. Cotel MC, Lenartowicz EM, Natesan S, Modo MM, Cooper JD, et al. (2015) Microglial activation in the rat brain following chronic antipsychotic treatment at clinically relevant doses. Eur Neuropsychopharmacol. 25: 2098-2107.

26. Wu JQ, Kosten TR, Zhang XY. (2013) Free radicals, antioxidant defense systems, and schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 46: 200-206.

27. Parikh V, Khan MM, Mahadik SP. (2003) Differential effects of antipsychotics on expression of antioxidant enzymes and membrane lipid peroxidation in rat brain. J Psychiatr Res. 37: 43-51.

28. Pillai A, Parikh V, Terry AV Jr, Mahadik SP. (2007) Long-term antipsychotic treatments and crossover studies in rats: differential effects of typical and atypical agents on the expression of antioxidant enzymes and membrane lipid peroxidation in rat brain. J Psychiatr Res. 41: 372-386.

29. Nel A, Harvey BH. (2003) Haloperidol-induced dyskinesia is associated with striatal NO synthase suppression: reversal with olanzapine. Behav Pharmacol. 14: 251-255.

30. Tarazi FI, Zhang K, Baldessarini RJ. Long-term effects of newer antipsychotic drugs on neuronal nitric oxide synthase in rat brain. Nitric Oxide. 7: 297-300.

31. Anderson VM, Goldstein ME, Kydd RR, Russell BR. (2015) Extensive gray matter volume reduction in treatment-resistant schizophrenia. Int J Neuropsychopharmacol. 18: pyv016.

32. Collin G, Derks EM, van Haren NE, Schnack HG, Hulshoff Pol HE, et al. (2012) Symptom dimensions are associated with progressive brain volume changes in schizophrenia. Schizophr Res. 138: 171-176.

33. Neckelmann G, Specht K, Lund A, Ersland L, Smievoll AI, et al. (2006) Mr morphometry analysis of grey matter volume reduction in schizophrenia: association with hallucinations. Int J Neurosci. 116: 9-23.

34. Wüstenberg T, Begemann M, Bartels C, Gefeller O, Stawicki S, et al. (2011) Recombinant human erythropoietin delays loss of gray matter in chronic schizophrenia. Mol Psychiatry. 16: 26-36, 1.

35. Malchow B, Keeser D, Keller K, Hasan A, Rauchmann BS, et al. (2016) Effects of endurance training on brain structures in chronic schizophrenia patients and healthy controls. Schizophr Res. 173: 182-191.

36. Pajonk FG, Wobrock T, Gruber O, Scherk H, Berner D, et al. (2010) Hippocampal plasticity in response to exercise in schizophrenia. Arch Gen Psychiatry. 67: 133-143.

37. Eack SM, Hogarty GE, Cho RY, Prasad KM, Greenwald DP, et al. (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.

38. Veijola J, Guo JY, Moilanen JS, Jääskeläinen E, Miettunen J, et al. (2014) Longitudinal changes in total brain volume in schizophrenia: relation to symptom severity, cognition and antipsychotic medication. PLoS One. 9: e101689.

Citation: Krause D, Pogarell O. Shrinking Brain and Schizophrenia: A Review of Current Studies on the Effect of Antipsychotic Medication on Gray Matter Volume. Psych Mental Disord. 2017; 1:102.