The Effects of Antipsychotics on Brain Structure

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Abstract

Schizophrenia, defined by the presence of delusions, hallucinations, and flat affect, is more commonly seen alongside depression, anxiety, and substance misuse in patients. Antipsychotics, including second-generation antipsychotics olanzapine, clozapine, and risperidone, are prescribed to control symptoms of schizophrenia, and function through the antagonism and agonism of various receptors including D2, 5-HT2C, 5-HT2A, and 5-HT1A. The effects of antipsychotics are widespread and often include varying impacts to multiple cerebral areas and functions such as measured cortical thickness, regional homogeneity, and volume of numerous brain components like the caudate, putamen, and gray matter. This study aimed to analyze the widespread effects of antipsychotic use on various brain structures based on a review of current scientific literature. Our review revealed that impacts to brain function were widely varied, showing a need for more robust clinical research. A comprehensive understanding of the effects on brain structures of antipsychotics will help to guide medical professionals in the treatment and management of psychosis-related syndromes.

Introduction

Antipsychotics were first used in anesthesia in the 1950s but are now utilized for their antipsychotic properties (1). These drugs are classified as either typical or atypical based on differences in their adverse effects and mechanism of action (1). The mechanism of action of antipsychotics are similar overall, but with some key differences. Typical antipsychotics work by inhibiting D_2 dopamine, cholinergic, and histaminergic receptors while atypical antipsychotics work by also inhibiting D_2 dopamine receptors as well as sub-type 5-$HT2_A$ serotonin receptors (2). Some research shows that antipsychotics block the D_1, D_2, and D_3 dopamine receptors in the forebrain, affecting the basal ganglia as well as other areas of the brain (3, 4). Prescribed more frequently than typical antipsychotics, atypical antipsychotics work on a wider range of symptoms in mood disorders (5). Typical antipsychotics work mainly on reducing the positive symptoms of mood disorders, while atypical antipsychotics are effective on negative and cognitive symptoms (2). Positive symptoms are usually defined as symptoms that distort daily life through a surplus of symptoms such as delusions or hallucinations, while negative symptoms are usually defined as an absence of certain behaviors that are deemed normal (6). Another way to define typical and atypical antipsychotics is using the nomenclature of first-generation (FGA) or second-generation antipsychotics (SGA), respectively (7).

Antipsychotics affect the brain in a regional manner, rather than a global manner (8). There is an association of greater changes in brain activity and gray matter volumes (GMV) with typical antipsychotics when compared to atypical antipsychotics (8). The areas of the brain that these medications work on were shown to be centered around the frontal and temporal lobes, limbic system, and basal ganglia (9). However, the changes in brain activity and volume are dependent on the type of antipsychotic administered (9). The frontal lobe is essential for memory and speech production (10). The temporal lobe is divided into the superior temporal sulcus and lateral temporal sulcus, with the main functioning areas being the superior temporal gyrus (STG) and the middle temporal gyrus (MTG). These areas are involved in memory, but it also has a defining role in speech comprehension (10). Lesions in the frontal lobe can lead to adverse effects such as personality disorders, aphasia, and apraxia while lesions in the temporal lobe can lead to auditory or visual hallucinations (10). The basal ganglia are responsible for the initiation of motor movement as well as sending signals to the limbic system, cortex, and thalamus. This allows the basal ganglia to also play a role in emotion and executive function (11). Although there is no universal consensus on the identity of the structures that compose the limbic system, the structures that are normally thought of as being part of the system are the limbic cortex, hippocampus, hypothalamus, amygdala, and septal area. This system

is thought to be responsible for many functions but is mainly known for being responsible for emotions (12).

Psychosis is a very common symptom of many different psychiatric and neurological disorders, especially those on the schizophrenia spectrum (13). Psychosis is defined as any symptoms that cause a detachment from reality as well as a loss of functioning in daily life (13). Psychosis is usually diagnosed through a collection of symptoms, rather than a single symptom (14). However, there is no precise definition of the mechanisms in place that cause psychosis or clinical symptoms of psychotic disorders (14). Although the use of SGA is prevalent in treating psychosis, there are also many researched adverse effects of SGAs that are metabolic, such as obesity and Type 2 diabetes (2, 15). Some of the medications relevant to the suppression of negative symptoms and cognitive deficits are clozapine, risperidone, and olanzapine (15). The focus of this review is to examine the changes to brain structure associated with the use of antipsychotic medications.

Methods

To examine the role of antipsychotics and their effects on brain structure, we conducted a literature search using PubMed, Google Scholar, and Science Direct databases. Screened keywords included: amplitude of low-frequency fluctuations, antipsychotics, aripiprazole, brain structure, caudate, changes in brain structure, clozapine, gray matter volume, olanzapine, putamen, regional homogeneity, risperidone. We obtained 62 total articles. References used were peer-reviewed and determined to be acceptable and reliable. References were evaluated by the number of citations used within the paper, the impact on the scientific community as determined by the number of times the paper was cited, and the impact factor of the journals in which the paper was published. Papers from journals with an impact factor of 2 or less were excluded from this review. There was no date range applied. Articles from journals not written in English were excluded from the analysis.

Discussion

Effects of Antipsychotic Use on Cortical Thickness

Cortical thickness is defined as the width of gray matter of the cortex (16) and is positively correlated with intellectual ability (17). In patients with schizophrenia, cortical thinning is demonstrated in the fronto-temporo-parietal region (18). Without treatment, schizophrenia patients exhibit a gradual cortical thinning and flattening, which is associated with negative clinical outcomes (19). Two antipsychotics, olanzapine and clozapine, have been shown to impact cortical thickness.

Olanzapine, an antagonist of dopamine D2 receptors, has been shown to decrease cortical thickness, with the greatest decreases seen in patients who had sustained remission of schizophrenia compared to placebo patients (20). A key limitation of this finding was that in this investigation, patients were also using sertraline which has been previously proven to protect brain structure (21), complicating the results and not allowing for a complete understanding of olanzapine's singular effects on cortical thickness. Animal studies using rats have demonstrated that antipsychotics themselves may directly cause a decrease in volume and thickness of the anterior cingulate cortex and cortex after chronic use of antipsychotics, illustrating that the changes seen in these studies may be attributable to the antipsychotics and not the underlying mechanisms of schizophrenia (22). Moreover, additional research showed that mid- to long-term use of atypical antipsychotics such as olanzapine led to significant decreases in cortical thickness in the frontal, temporal, and parietal areas (23). Decreases in cortical thickness were also correlated to worsened symptoms and cognitive deficits in these patients (23). A possible mechanism in humans involves the loss of synapses, which contributes to cortical thinning in patients with long-term use of atypical antipsychotics (24).

Lastly, clozapine, an antipsychotic used for treatment-resistant schizophrenia, has also been linked to cortical thinning in patients. Significant cortical thinning was noted after just 12 weeks of treatment with clozapine (25), while longer periods of clozapine administration resulted in further cortical thinning (26), indicating a progression of cortical thinning related to the duration spent using clozapine. Although the cortical thinning exhibited by antipsychotics has been correlated to decreases in cognitive function and overall worse outcomes for patients, the mechanism behind cortical thinning may be the brain's attempt at self-preservation, possibly as a response to increased metabolic stress or with the pruning of malfunctioning neurons (27). All in all, atypical antipsychotics have been shown to cause accelerated cortical thinning

in schizophrenia patients with a noted correlation between cortical thinning and the time spent using these medications. Research involving animals demonstrates that chronic use of antipsychotic drugs causes decreases in volume and thickness of the cortex (22), but more research must be done to confirm the mechanisms behind antipsychotic medication-induced cortical thinning in human models. An important limitation of these studies is the inherent difficulty of formulating *in vivo* studies that account for the reality of schizophrenia. For example, the disease process of schizophrenia, including age of diagnosis, severity of disease, and effectiveness of treatment plan, have been shown to cause varying effects on brain structures in human patients (18), leading to an inconsistent baseline between patients with schizophrenia for study. Moreover, the high rates of comorbidity of other mental illnesses including depression and anxiety (21) may confound the results and make studying solely schizophrenia and the impact of these medications difficult.

Effects of Antipsychotic Use on Gray Matter Volume, Regional Homogeneity, and Amplitude of Low-Frequency Fluctuations

Frequently prescribed antipsychotics, such as olanzapine, aripiprazole, and risperidone, share similar MOA. Defined as atypical antipsychotics (28), these drugs are SGAs which produce significantly fewer extrapyramidal symptoms than first-generation antipsychotics (FGA) (29), including restlessness, muscle contractions, tremors, and involuntary movements (30). However, SGAs promote the development of metabolic conditions such as insulin resistance, clinically significant weight gain, Type 2 diabetes mellitus, and dyslipidemia at much higher rates than FGAs (31). Mechanistically, SGAs target monoaminergic GPCRs and interfere with hypothalamic center activity. In doing so, SGAs modulate hypothalamic arcuate and paraventricular nuclei activity, leading to interactions at histamine (H_1) receptors that favor weight gain and metabolic dysregulation (31). Additionally, SGAs blockade of serotonin (5-HT2$_C$) receptors may be key in causing substantial weight gain (32). As SGAs, olanzapine, aripiprazole, and risperidone interact non-specifically with serotonin-dopamine receptors such as dopamine D_2 and serotonin 5-HT2$_A$/5-HT1$_A$/5-HT2$_C$ receptors (33). Specifically, olanzapine is an antagonist of dopamine D_2 receptors and works to decrease positive symptoms of schizophrenia (34). Aripiprazole can be defined as a partial agonist of dopamine D_2 and 5-HT2$_A$ receptors in the mesolimbic and mesocortical pathways (35). Lastly, risperidone functions again at the dopamine D_2 but acts strongly on the 5-HT2$_A$ and 5-HT1$_A$ receptors as an antagonist (36).

When used as part of psychosis treatment, these antipsychotics have been shown to cause changes in brain structure, including gray matter volume (GMV), regional homogeneity (ReHo), and amplitude of low-frequency fluctuation (ALFF) in humans (37), measured with structural magnetic resonance imaging. GMV can be used as a measure of an individual's gray matter, which is involved in movement control, memory, and emotions (38). Studies have shown patients with schizophrenia have lower measures of cortical gray matter volume at presentation compared to patients with no diagnosed schizophrenia (39, 40), contributing to the lower quality of life and neurocognitive deficits (39). ALFF measures fluctuations in the blood-oxygen-level-dependent signal. This shows spontaneous neural activity of specific regions in the brain (41). The reduction in measurement of ALFF is correlated to cognitive impairment in schizophrenia patients (41). Lastly, ReHo measures brain activity and evaluates the similarity of a given voxel and its nearest neighbors (42) to show the degree of brain damage in patients (43) and the ability of the brain to coordinate neuron activity (37).

After a course of treatment with antipsychotics such as olanzapine, aripiprazole, and risperidone, GMV is shown to increase across various brain areas including the right cerebellum, right inferior temporal gyrus, and left middle frontal gyrus (37). Importantly, these increases in GMV after antipsychotic treatment were correlated with abating clinical symptoms, indicating that these drugs can reduce the strength of schizophrenia symptoms (37). Contrarily, these antipsychotics also caused a reduced GMV after treatment in the left occipital lobe, gyrus rectus, and right orbital frontal cortex (37). The gyrus rectus and right orbital frontal cortex are found within the prefrontal cortex and contribute to working memory and social cognition (44). The noted decreases of gray matter within these areas contribute to the positive and negative symptoms exhibited by patients with schizophrenia. ALFF was shown to increase in the medial superior frontal gyrus, bilateral prefrontal and parietal cortex and right caudate nucleus with

respective p-values of 0.042, 0.043, and 0.002 (45). Additionally, increases were shown after short-term use of these antipsychotics in the anterior cerebellum, although no correlation was found between ALFF volumes and psychiatric symptoms, indicating a lack of clinical significance (46). Lastly, ReHo was shown to increase in the caudate with a p-value of 0.003 (47), showing an increase in coordinated activity after treatment with risperidone. The lack of clinical significance found could be attributed to small sample size (37, 40, 43, 44), the thickness of examined brain slices (39), not separating the data for specific subgroups (40), participants not being in the ideal resting-state (41), or to the previously mentioned limitations of human, in-vivo schizophrenia studies. Overall, treatment with SGAs such as olanzapine, aripiprazole, or risperidone has been shown to result in changes to GMV, ALFF, and ReHo, although future research is required to assess the clinical significance of the changes seen in ALFF and ReHo.

Effects of Antipsychotic Use on Caudate and Putamen Volume

The caudate and putamen, also known as the corpus striatum, are one of the main components of the basal ganglia and integrate information for motor control, cognition, and emotion (48). Schizophrenia causes abnormalities within these structures (49). Enlarged volumes of the caudate, +9.5%, and putamen, +15.9%, were seen across 15 human male patients with diagnosed schizophrenia (49). Similarly, in a study comparing 37 patients with schizophrenia and 37 patients without schizophrenia, MRI and traces on axial slices showed marked enlargements on the dorsal putamen (50). Although larger caudate and putamen volumes were observed, postmortem studies showed that there was nearly a 40% decrease in the number of mitochondria per synapse within these structures despite their greater volumes (51).

Abnormal function in the hyperconnectivity between the putamen and prefrontal cortex may cause auditory verbal hallucinations, as well as putamen regional and network functional deficits may be associated with the imbalance in neuromodulation of auditory verbal hallucinations in schizophrenia (52). Individuals with schizophrenia that are antipsychotic-naive showed larger bilateral putamen size overall, but the ventrally located putamen was associated with less severe symptoms (53). A mutation in the gene SLC39A8 increases GMV in the putamen, but this association is greatly reduced in those with schizophrenia (54). Putamen volume is seen to increase when neurological and psychiatric disorders are present, but it is seen to decrease in males and females who are not affected by a disorder as they age (55). Overall, putamen volumes may be a longitudinal marker of treatment responsiveness and outcomes in individuals with schizophrenia (56).

Schizophrenia patients have altered spatial activity patterns and decreased intra-network functional connectivity in the caudate (57). The differences seen between gene expressions based on antipsychotic toxicology are different between different brain regions, which could be because of the different cell types affected (58). Antipsychotic medication was seen to influence caudate gene expression, and the caudate gene expression networks highlight interactions involving schizophrenia risk (59). Typical antipsychotics induced striatal enlargement in schizophrenia patients (60). Schizophrenia patients who have switched from typical antipsychotics to clozapine have shown decreased caudate volume (60). Clozapine displays a lower affinity to dopamine receptors compared to other antipsychotics (61), which may contribute to the neural changes seen when a patient switches from a typical antipsychotic to clozapine. All in all, antipsychotic use related to enlarged striata, while switching from typical antipsychotics to clozapine led to a decrease in caudate volume, showing the effects that different antipsychotics have on brain structures.

Conclusion

The changes seen in brain structure and volume after the use of antipsychotics are of particular concern to medication-prescribing providers and the patients using these medications. This is because the decreases in a patient's measured cortical thickness after the use of antipsychotics are correlated to poor patient outcomes and must be better understood to help mitigate these changes in patients. Antipsychotic use was shown to decrease cortical thickness and the number of mitochondria per synapse despite the larger volume seen overall in the caudate and putamen. Antipsychotic use also caused decreased GMV and ALFF values while contributing to an increase in ReHo. Overall, the increase and decrease in GMV, ALFF, and ReHo across the putamen and other brain structures are of key importance and must be further understood,

as these changes impact patients in ways yet to be realized. A key limitation to the data presented are the issues associated with functional MRI data, as the results may be gratuitous and show false positive activations (62). Moreover, the studies referred to in this review are limited by small sample sizes, which limits the generalizability of the results. Utilizing larger sample sizes, with patients taking only the designated antipsychotic, would help fill the knowledge gaps and aid medical professionals in understanding more precisely how antipsychotics will impact their patients' brain structure, leading to better patient outcomes.

Disclosures

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