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Review

Antipsychotics and structural brain changes: could treatment adherence explain the discrepant findings?

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Abstract: Progressive structural brain changes are well documented in schizophrenia and have been linked to both illness progression and the extent of antipsychotic treatment exposure. Literature reporting longitudinal changes in brain structure in individuals with schizophrenia is selectively reviewed to assess the roles of illness, antipsychotic treatment, adherence and other factors in the genesis of these changes. This narrative review considers literature investigating longitudinal changes in brain structure in individuals with schizophrenia. The review focusses on structural changes in the cortex, basal ganglia and white matter. It also examines effects of medication non-adherence and relapse on the clinical course of the illness and on structural brain changes. Studies investigating structural magnetic resonance imaging changes in patients treated with long-acting injectable antipsychotics are reviewed. Temporal changes in brain structure in schizophrenia can be divided into those that are associated with antipsychotic treatment and those that are not. Changes associated with treatment include increases in basal ganglia and white matter volumes. Relapse episodes may be a critical factor in illness progression and brain volume reductions. Medication adherence may be an important factor that could explain the findings that brain volume reductions are associated with poor treatment response, higher intensity of antipsychotic treatment exposure and more time spent in relapse. Improved adherence *via* long-acting injectable antipsychotics and adherence focussed psychosocial interventions could maximize protective effects of antipsychotics against illness progression.

Keywords: antipsychotics, brain structure, long-acting injectable, schizophrenia

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Introduction

Numerous studies have demonstrated that schizophrenia is associated with structural brain differences when compared with healthy controls. These differences are both general and regional, mostly comprising smaller grey matter volumes, and are present to some extent at, and even prior to, the first onset of psychosis.[1] In addition, both larger and smaller grey matter volumes in basal ganglia[2] and white matter[3] have been reported. While these differences have been linked to neurodevelopmental factors[4] and as such considered trait related and relatively stable, there is also evidence of structural brain changes over time. Longitudinal studies indicate progressive reductions in both grey and white matter volumes in some patients, particularly in the early years of illness.[5–7] Questions arise as to the origins and implications of these progressive changes. Selected literature is reviewed of magnetic resonance imaging (MRI) studies investigating structural brain differences in schizophrenia and their relationships to the illness, its outcome and to antipsychotic treatment. The brain regions of particular interest here are the cortex (thickness and volume), basal ganglia and white matter volumes. Evidence suggests that structural brain changes in

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schizophrenia can be broadly divided into those that are responsive to antipsychotic treatment and those that are not. This paper argues that non-adherence could explain many of the apparent discrepancies in the literature. Relapses could explain the reported associations between brain volume reductions and both higher antipsychotic dose and greater symptom severity rather than direct effects of antipsychotics and illness severity, respectively. Finally, it is suggested that antipsychotics do indeed protect against the neuroprogressive effects of unmitigated illness when treatment is continuous by way of long-acting injectable (LAI) formulation.

Cortical thickness and volume reductions

Reduced cortical thickness and volumes compared to matched healthy controls are among the most frequently reported findings in schizophrenia. An Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) consortium meta-analysis conducted in 4474 individuals with schizophrenia and 5098 healthy volunteers reported widespread thinner cortex in schizophrenia with the largest effect sizes in frontal and temporal regions. Regional cortical thickness was negatively correlated with estimated antipsychotic dose, symptom severity and duration of illness, and positively correlated with age at illness onset.[8] There is also evidence of accelerated cortical volume loss over time. A systematic review and meta-analysis of cortical thickness differences at different stages of illness found no differences between clinical high-risk individuals and those with a first episode of schizophrenia although patients with long-term illness had greater cortical thinning than those with first-episode schizophrenia suggesting progressive reductions following illness onset.[9] A meta-analysis of longitudinal MRI studies in schizophrenia comparing cortical grey matter volume over time between patients and healthy controls reported progressive reductions in the patients. In a sub-analysis of the first-episode patients, reductions were most pronounced in frontal, temporal and parietal lobes, were particularly active in the early stages of illness and were most prominent in patients treated with first-generation antipsychotics.[10]

Basal ganglia volume

Basal ganglia volume differences in schizophrenia have been extensively reported and have consistently been associated with antipsychotic treatment. Treatment-related changes occur soon after initiation of treatment and are correlated with positive symptom reductions.[11] However, findings have not been consistent, with reports of both larger and smaller basal ganglia volumes in different patient samples. A meta-analysis by the ENIGMA consortium found larger pallidum volumes but no differences in caudate and putamen volumes among individuals with schizophrenia on antipsychotic medications.[12] While first-generation antipsychotics specifically were associated with basal ganglia volume increases,[13] a later review of 13 longitudinal studies found both increases and decreases, and contrary to previous findings, the effects were not specific to first- or second-generation antipsychotics.[14]

White matter volumes

Disrupted connectivity has been implicated as a core abnormality in schizophrenia,[15] and consequently, white matter abnormalities have been a focus of interest in MRI studies. Smaller global white matter volumes were reported in medicated and unmedicated individuals with schizophrenia,[16,17] and regional reductions in prefrontal cortical white matter have been associated with negative symptoms.[18] In a small longitudinal study in antipsychotic-naïve patients and treatment resistant patients, both groups of patients displayed grey matter volume increases and white matter decreases after 2 years of treatment.[19] The Iowa Longitudinal Study followed 202 first-episode schizophrenia patients in a naturalistic setting for up to 18 years. They found progressive volume reductions in a subset of patients that were most severe in the early stages of illness and affected white matter even more pervasively than grey matter.[20] Regional differences in white matter volumes have been linked to different symptoms. Superficial white matter underlying the occipital and paralimbic regions was smaller in patients than controls and correlated significantly with positive symptoms, whereas white matter within the cingulate gyrus and core of the temporal lobe was significantly larger and correlated negatively with negative symptoms.[3]

The following sections consider evidence suggesting that active psychosis is associated with illness progression and brain volume reductions, that antipsychotics mitigate against this progression, and that assured adherence *via* LAI

provides optimal protection against brain volume reductions and is even associated with volume increases that are linked to the beneficial effects of these agents.

Possible causes of structural brain changes over time

The cause of brain volume reductions in schizophrenia is the subject of ongoing debate.[21] Initially, volume reductions were ascribed to 'neuroprogression', as an intrinsic aspect of the illness, based on studies showing that greater volume reductions were related to more severe illness and poorer clinical outcome.[7,22] Furthermore, consistent with earlier studies suggesting that antipsychotics mitigate against the 'toxic' effects of active illness,[23] it has been argued that antipsychotics, particularly the newer generation agents, provide measurable neuroprotective effects mediated *via* multiple molecular mechanisms ranging from preventative to restorative.[22,24] On the other hand, antipsychotics have themselves been implicated in brain volume reductions. In a landmark study in which macaque monkeys received chronic antipsychotic exposure to haloperidol, olanzapine or sham, 8–11% reduction in brain weight was observed in both antipsychotic-treated groups, involving both grey and white matter.[25] A subsequent study in the Iowa Longitudinal Cohort provided further evidence of an association between antipsychotic exposure and brain volume loss. Greater intensity of antipsychotic treatment was associated with progressive reductions in grey and white matter volumes, leading the authors to conclude that antipsychotics have a subtle but measurable influence on brain tissue loss over time.[6] Veijola *et al.*[26] studied longitudinal changes in total brain volume over almost a decade from a population-based sample. The mean annual whole brain volume reduction was 0.69% in schizophrenia and 0.49% in controls. The volume reduction was significantly predicted by the estimated amount of antipsychotic medication received over the follow-up period, but not by symptom severity, level of functioning or cognitive decline. Several other studies suggested an association between antipsychotic exposure and brain volume reductions, although results have been inconsistent. A meta-analysis of longitudinal MRI studies reported progressive grey matter volume decreases that were inversely correlated with estimated cumulative antipsychotic exposure, while no effects were observed for duration of illness or illness severity.[27] While these findings could point to antipsychotic treatment *per se* resulting in brain volume reductions, cautious interpretation is indicated. Most studies were *post hoc* analyses of existing datasets derived from naturalistic settings, with retrospective estimates of cumulative antipsychotic exposure and rudimentary assessment of medication adherence. They were not designed to assess the directionality of an association between antipsychotic exposure and brain volume changes. An alternative explanation is that people with more severe illness are prescribed a higher dose of antipsychotic medication and are also likely to exhibit greater structural brain differences.[8] Additionally, factors other than the direct effects of illness or antipsychotic treatment have been proposed, including substance use and comorbid medical conditions – both of which are highly prevalent in individuals with schizophrenia.[28]

A recent study with a novel design was able to address several of the methodological shortcomings of previous studies and provides new insights into the effects of illness and treatment on brain volume changes. Chopra *et al.*[29] examined illness *versus* antipsychotic medication related brain volume changes in first-episode psychosis over 3 months of treatment. All participants received intensive psychosocial therapy and were randomized to either supplemental antipsychotic treatment ($n = 30$) or placebo ($n = 32$). After 3 months of treatment, pallidal volume increased in those receiving antipsychotics, while it decreased in those on placebo and remained unchanged in a group of healthy controls ($n = 27$). Increased pallidal volume was associated with greater symptom reduction. The authors concluded that antipsychotic medication appears to prevent and possibly even reverse illness-related volume loss in the pallidum. They also found small effect size volume reductions in the visual and prefrontal cortices in both patient groups that were unrelated to symptom reduction and which they ascribed to an unmodified effect of illness, independent of treatment. In this study, even though oral medications were prescribed, treatment adherence was likely to have been good given that all patients received concomitant intensive social therapy and the period between scans was relatively brief.

Time spent in relapse and illness progression

Original support for the possibility of active psychosis being 'toxic' and associated with 'neuroprogression' was based on the well-established association between a longer duration of untreated first psychotic episode and poorer outcome.[30] Active psychosis also occurs during relapse episodes, and over the course of illness, relapse rates are very high. In the much-cited New York Hillside Hospital longitudinal study of individuals with first-episode schizophrenia, 82% relapsed within the first 5 years after recovery, the majority of whom went on to experience multiple relapses. The strongest predictor of relapse by far was non-adherence.[31] Indeed, a review of studies assessing relapse rates after antipsychotic discontinuation indicated that even after a single episode of psychosis, the vast majority of individuals will experience relapse if followed up long enough.[32] In addition to the considerable negative psychosocial consequences associated with relapse, there is a risk of biological harm insofar as responsiveness to treatment diminishes and morbidity accrues. Back in 1991, Dr Richard J. Wyatt published a seminal paper in which he reviewed studies of patients with schizophrenia who were or were not given antipsychotics during the course of their illness. He found that in some patients, early intervention with antipsychotics reduced long-term morbidity including decreasing the number of relapses. He observed that 'some patients are left with a damaging residual if a psychosis is allowed to proceed unmitigated' and suggested that in addition to being demoralizing and stigmatizing, psychosis may also be biologically toxic.[23] A subsequent important study implicated relapse events as a critical factor in determining the outcome of illness. A 15-year follow-up in a Dutch incidence cohort of 82 first-contact cases revealed a pattern of chronicity and high relapse rates. The authors reported two 'striking' findings. First, on average, one in six (17%) did not remit from a psychotic episode, irrespective of whether it was the first or a subsequent episode. Second, about 21% experienced persistence of negative symptoms after relapse. Thus, both positive and negative symptoms persisted in a subset of patients after each relapse.[33]

Several longitudinal studies have provided empirical evidence of post-relapse attenuated treatment response in both first-episode and multi-episode samples. A preliminary study compared treatment response times of first and subsequent psychotic episodes, and found a significantly longer time to remission for the second and third episodes compared to the first episode[34]; in a study comparing the treatment response in the first psychotic episode with that of the second episode in patients receiving the same antipsychotic treatment for each episode, emergent treatment failure was observed in 16% of patients[35]; in a sample of multi-episode patients who relapsed while receiving placebo in a randomized controlled maintenance treatment trial, 14.4% of patients who had initially responded favourably to treatment met predefined nonresponse criteria in the post-relapse treatment phase[36]; and in another study comparing treatment response in the first *versus* the second psychotic episode of schizophrenia in patients who received the same antipsychotic in both episodes, the outcome was more favourable in the first episode and antipsychotic doses were significantly higher in the second episode.[37]

Relapse and brain volume changes

In a separate analysis of the 202 patients with MRI data drawn from the Iowa Longitudinal Study of first-episode schizophrenia, measures of relapse number and duration were computed and related to the MRI findings. It was found that relapse duration (but not number of relapses) was associated with significant reductions in brain volume measures. Significant effects were also observed for treatment intensity. The authors concluded that extended periods of relapse may have a negative effect on brain integrity in schizophrenia, thereby emphasizing the importance of improving adherence and preventing relapse. At the same time, they highlight the clinical dilemma facing clinicians and consideration of the relative balance of effects, that is, relapse duration *versus* antipsychotic treatment intensity. They cautioned that, while relapse prevention is important, it should be attained using the lowest possible medication dosages.[38] In an analysis of 33 individuals with schizophrenia and 71 controls drawn from the Northern Finland Birth Cohort who underwent MRI scans at mean age 34.7 years and at follow-up 10 years later, it was found that individuals with schizophrenia exhibited greater progressive brain volume reductions than controls, mainly in the frontal and temporal lobes. The degree of reduction was predicted by antipsychotic medication exposure and by the number of days spent in hospital between the scans (used as a proxy measure of relapse duration). These

findings again suggest that both antipsychotic medication exposure and time spent in relapse contribute to progressive brain volume reductions in schizophrenia.[39] Another study investigated the relationship between brain volume changes and relapse, again using hospitalization as a proxy for relapse. This was a 5-year longitudinal study in 96 patients with schizophrenia and 113 matched healthy controls. Excessive reductions in grey matter density were found in patients in several regions. Reduced density in the superior frontal grey matter was related to increased number of hospitalizations, whereas a higher cumulative dose of clozapine and olanzapine during the scan interval was related to lesser reductions in this area. The authors concluded that the progression observed in left frontal density appears to be related to an increased number of psychotic episodes, with atypical antipsychotic medication attenuating these changes.[40]

Long-acting injectable antipsychotics and brain structural changes

Relatively few studies have investigated structural brain changes in individuals treated with LAI antipsychotics. Those few studies suggest that LAIs are associated with structural brain changes that are linked to beneficial treatment response. A randomized trial of long-acting LAI risperidone ($n=11$) *versus* oral risperidone ($n=13$) and healthy controls ($n=14$) was conducted over 6 months in individuals with first-episode schizophrenia to investigate the effect of antipsychotic formulation on frontal lobe white matter volume. White matter volume remained stable in the LAI group and decreased significantly in the oral risperidone group, while the healthy controls did not differ significantly from the two patient groups. White matter increase was associated with cognitive improvement insofar as reaction times were faster in tests involving frontal lobe function. The authors proposed that better adherence provided by LAI may explain the modified trajectory of myelin development.[41]

In a pilot study, seven patients with acute psychosis underwent MRI at baseline and were treated with once monthly paliperidone palmitate LAI 24 for weeks. Subjects with larger baseline total grey matter volumes had significantly greater symptom reduction at end point.[42] In a small longitudinal study with a carefully selected sample, our group compared changes in grey and white matter volume over the first 12 months of treatment. Twenty-three antipsychotic-naïve individuals with a first episode of schizophrenia were treated with the lowest effective dose of LAI flupenthixol decanoate, and MRI scans were compared with 53 matched healthy individuals. The precise total antipsychotic dose was calculated and its relationship with brain volume changes investigated. Excessive cortical volume reductions were found in patients [−4.6 (6.6)%] *versus* controls [−1.12 (4.0)%] ($p=0.009$), but there were no significant changes in subcortical grey matter and white matter volumes. The only significant predictor of cortical volume change was total antipsychotic dose received ($p=0.04$). Cortical volume change was not significantly associated with the changes in psychopathology or adverse effects of medication. Overall, patients responded very well to treatment. This study indicated that cortical volume reductions during antipsychotic treatment are not restricted to poor outcome patients and may occur even with the lowest effective dose of antipsychotic.[43]

A recent open-label randomized controlled trial compared the effects of treatment with paliperidone palmitate LAI ($n=23$) with oral antipsychotics ($n=48$) on MRI attained frontal lobe intracortical myelin volume in recent-onset schizophrenia and 64 healthy controls over 9 months. The intracortical myelin volume at end point was significantly reduced from baseline in the oral antipsychotic group ($p=0.004$) but not in the paliperidone palmitate group ($p=0.728$), although the difference between groups was not significant ($p=0.147$). The authors concluded that treatment with LAI antipsychotics might slow the progression of frontal myelination abnormalities in individuals with recent-onset schizophrenia.[44]

In a longitudinal cohort, we treated 99 treatment-naïve or previously minimally treated individuals with schizophrenia over 24 months according to a fixed protocol with LAI flupenthixol decanoate, and 98 matched healthy controls. Clinical, cognitive and MRI assessments were performed at months 0, 12 and 24, respectively. Global cortical thickness, white matter volume and basal ganglia volume were selected as the regions of interest. Compared to baseline, patients but not controls displayed small but significant cortical thickness reductions, although the group × time effect was not significant. Changes in cortical thickness were unrelated to treatment. In the patients, white matter volumes increased significantly from baseline, while there were no significant changes in

the controls. The white matter volume increases in patients were associated with lower cumulative antipsychotic dose, greater improvements in psychopathology and cognitive function, and more extrapyramidal symptoms. Basal ganglia volumes increased significantly in patients but not in controls, and the group × time effect was significant. Basal ganglia increases were associated with greater improvements in psychopathology, greater increases in BMI and more extrapyramidal symptoms. These findings provide further evidence for brain plasticity in response to antipsychotic treatment, most likely linked to their dopamine antagonistic effects. The associations between white matter and basal ganglia volume increases and better outcome suggest a beneficial effect for these brain changes. On the other hand, the finding that cortical thickness reductions were independent of treatment effects suggests that they may be more closely related to neurodevelopmental, non-dopaminergic aspects of the illness.[45]

Recent neuroimaging developments provide a new avenue for considering brain regions in schizophrenia according to whether they are or are not responsive to antipsychotic treatment. Using novel machine learning methods on regional brain volumetric measures, two distinct neuroanatomical signatures of schizophrenia were recently identified.[46,47] Signature 1 is characterized by widespread reduction of mainly cortical grey matter volume, and signature 2 with increased basal ganglia and internal capsule volume but normal cortical anatomy. The authors proposed that signature 1 is related to neurodevelopmental components of the illness and signature 2 to functional abnormalities, possibly in dopamine systems, leading to secondary basal ganglia enlargement. In a collaboration with that group, we applied these neuroanatomical signatures to our longitudinal patient cohort of individuals with first-episode schizophrenia and matched healthy controls to assess their associations with treatment effects over the first 2 years of treatment with a LAI antipsychotic.[48] Signature 2 expression showed several interesting associations with treatment. Signature strength increased significantly with treatment in the patients, and greater expression was strongly associated with both efficacy and adverse effects in that larger reductions in positive symptoms and increases in BMI were observed. On the other hand, signature 1 expression remained stable over time, showed trend associations with indicators of neurodevelopmental compromise and was not related to treatment effects. These findings suggest that basal ganglia and internal capsule white matter represent the treatment responsive brain structures in schizophrenia. The increase in signature 2 expression together with our previously reported basal ganglia and white matter volume increases accompanying antipsychotic treatment is unlikely to represent neurogenesis and restoration of underlying illness-related neurodegeneration[24] however, as they did not differ from controls at baseline, and the increases went beyond those of the controls during treatment. Rather, this suggests an adaptive or compensatory response accompanying the therapeutic effect of antipsychotics, possibly involving structural remodelling,[49] microglial proliferation,[50] increased water content or even augmented blood flow.[51]

A proposal and conclusions

Available evidence indicates that structural brain abnormalities in schizophrenia are not static, and both reductions and increases occur over time. Most attention has focussed on the volume reductions that are consistent with accelerated grey and white matter loss and occur even in patients with low antipsychotic dose and overall favourable response.[43] The most likely explanation is that these changes are related to the illness itself, probably reflecting neuroprogression and independent of treatment effects. On the other hand, volume increases in basal ganglia and some white matter appear to be directly related to treatment and may be linked to mechanisms responsible for antipsychotic efficacy and adverse effects. This makes the reported association between greater antipsychotic exposure and brain volume reductions more difficult to explain. A possibility to consider is that poor medication adherence could play a role. Non-adherence is a major impediment to effective treatment and rates of non- and partial adherence are very high in clinical settings.[52] Non-adherence affects more than one-third of patients with schizophrenia per annum, is often covert and is underestimated by clinicians. It increases the risk of relapse, rehospitalisation and poorer overall outcome.[53] Patients not taking medication as prescribed respond poorly and clinicians who may be unaware of the non-adherence may increase the dose in an attempt to achieve a better response. Therefore, rather than illness severity, suboptimal treatment adherence could explain the reported association between higher antipsychotic dose and poorer treatment outcome. Similarly, poor treatment adherence

could account for some of the progressive structural brain reductions observed over time. Indeed, as outlined above, there is evidence to suggest that relapse episodes may be a critical factor in illness progression, and time spent in relapse is associated with brain volume reductions.

At the same time, the reported basal ganglia and white matter volumetric increases associated with antipsychotic treatment and their association with better efficacy raise the possibility that they reflect neuroprotective effects of antipsychotics. The increasing number of MRI studies in populations treated with LAIs suggests that the neuroprotective effects of antipsychotics are optimized with assured adherence. Together with the clinical evidence of relapse events being a critical factor in illness progression, this would argue for greater use of LAI antipsychotics and adherence-focused psychosocial interventions to address the non-adherence problem, particularly in the early years when the illness is at its most aggressive. Some cautions are indicated. First, reference to previous studies was selective, and it is important to recognize that much of the literature on brain structural changes and their associations in schizophrenia is inconsistent. For example, not all longitudinal studies report brain volume reductions over time,[54] and one systematic review did not find a consistent relationship to antipsychotic treatment exposure.[55] Second, there are likely multiple factors other than non-adherence contributing to structural brain changes in schizophrenia. Factors such as genetic susceptibility, childhood adversity, substance use and social adversity on their own may contribute to progressive brain structural changes and explain poor outcomes.[21,28] Third, the causes and implications of MRI-derived brain volume changes are not clear. Structural MRI is not a direct measure of brain structure and may be confounded by many epiphenomena and artefacts.[56] Volume reductions, therefore, do not necessarily imply tissue loss, and volume increases are not necessarily beneficial. Future longitudinal studies would do well to focus on the role of adherence and to further investigate structural brain changes in patients treated with LAI *versus* oral antipsychotics and their relationships to clinical outcome in schizophrenia.

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