Antipsychotics and Their Impact on Cerebral White Matter: Part of the Problem or Part of the Solution?

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The dysmyelination hypothesis of schizophrenia proposes that dysfunctional oligodendrocytes, the class of glial cells responsible for producing and maintaining myelin within the central nervous system, may lead to a disruption in short- and long-distance communication between neural cells. Miscommunication between individual neurons and, on a larger scale, distant cortical areas is posited to be the origin of clinical symptoms, such as hallucinations, delusions, or thought disorder. The myelin sheath formed by the oligodendrocytes provides structural stabilization and protection, and at the same time it plays a major role in modulating the rate of axonal conductivity. Support for the dysmyelination hypothesis comes from several postmortem studies, which report decreased density, number, and size of oligodendrocytes (1) and a reduction of myelin basic protein within the myelin sheath (1), as well as from neuroimaging studies that report both reductions in white matter volume and decreased diffusion fractional anisotropy, an indirect measure of axonal integrity and/or myelination (1). Yet despite the increasing evidence for a central role of white matter pathologies in schizophrenia (1), two major questions related to the dysmyelination hypothesis are still largely unanswered: 1. Are changes in white matter progressive in nature? 2. Is this progression modulated by antipsychotic medication? In the context of a chronic disorder such as schizophrenia, both questions are closely related and difficult to disentangle.

The general consensus of longitudinal neuroimaging studies is that both cortical and subcortical gray matter show progressive changes during the first few years after the onset of psychotic symptoms. These reductions have been explained mostly as a loss of neuropil and are believed to be nonreversible (2). These reductions in overall gray matter volume have been shown to be positively correlated with cumulative medication exposure (2, 3) despite not being functionally debilitating (4).

However, the trajectory of white matter alterations in schizophrenia, and more importantly, the impact of antipsychotic medication on white matter, are still areas of open discussion. Several studies in animal models have suggested that there may be a phase of white matter loss subsequent to the loss of gray matter that may be predominantly mediated by medication. In fact, preclinical studies have shown that long-term antipsychotic use may lead to the loss of both oligodendrocytes and astrocytes, which can negatively affect brain communication and connectivity (5). Conversely, other studies in mice show that some atypical antipsychotic medications, particularly quetiapine (6, 7), may actually improve oligodendrocyte function and assist in rebuilding the myelin sheath. There are also reports that administration of antipsychotics reduces levels of cortisol and proinflammatory cytokines in psychotic patients, providing evidence that antipsychotic treatments may hold potential anti-inflammatory properties as well, which may help mitigate damage to myelin (8). Ultimately, it is of paramount importance to understand better the impact that antipsychotic medication may have on white matter. This knowledge could not only lead to the development of better, more targeted drugs for treating schizophrenia symptoms, but it also could contribute to the still controversial issue of whether to treat individuals with prodromal symptoms.

The current issue of the *Journal* brings an interesting article by Xiao and colleagues (9) from the West China Hospital of Sichuan University that sheds more light on the relationship between

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white matter microstructure and long-term medication exposure. Their study reports the results of a cross-sectional neuroimaging investigation performed on 134 subjects from three age- and sex-matched groups: healthy comparison subjects, chronic schizophrenia patients treated with atypical antipsychotic medication, and another group of chronic patients who have never been treated. The uniqueness of the latter group makes this article particularly noteworthy because it provides an avenue to assess whether chronic antipsychotic medication exposure can have adverse or beneficial effects on white matter in patients with schizophrenia. All subjects included in this study were scanned using a state-of-the-art 3-T clinical scanner, and the research group employed a suite of image processing methods that allowed for the direct assessments of white matter microstructure across groups. The primary outcome measure was fractional anisotropy, a well-established neuroimaging index thought to be sensitive (but, perhaps, not specific) to

myelin health. The three groups were contrasted to investigate whether there were progressive white matter changes in patients overall and whether this progression was further exacerbated or attenuated within the treated patient group. The authors report an overall reduction in fractional anisotropy in patients relative to comparison subjects, aligning with previous studies on the presence of white matter pathology. More importantly, the degree of changes in the white matter of never-treated chronic patients was more severe than in treated patients. Furthermore, the fractional anisotropy in the never-treated group exhibited a faster decline with age when compared with the other two groups, particularly in the corpus callosum, the largest white matter structure.

These results lend support to previous studies that argue antipsychotic medication may have long-term beneficial effects on white matter health. Because of the unique nature of a never-treated chronic schizophrenia sample, this study offers valuable information that is presently missing in the field. However, previous diffusion imaging studies performed in never-treated first-episode patients suggest that antipsychotic medication may lead to reductions in fractional anisotropy (10). Whether these discordant findings can be explained by environmental, cultural, or clinical differences between the samples is not yet clear. However, it is important to note that within the present sample, younger, treated patients show more white matter pathology (reduced fractional anisotropy compared with age-matched controls) than the older, longer-treated patients. This suggests that both types of medication effects, the potentially adverse short-term effects, as well as the protective long-term effects, might coexist. The authors suggest that the "longer-term treatment effects may be positive via cumulative pharmacologic effects, which may reduce adverse effects of persistent acute psychosis and improve multiple factors in general medical health over the illness course" (9). While very speculative, it is feasible that in the short term, antipsychotics may initially affect glial cells, but with increasing exposure, antipsychotics may ultimately exert anti-inflammatory or myelinpromoting functions to mitigate the progression of white matter pathologies.

While the results of this study present additional pieces of the larger puzzle, they still should be interpreted with caution. Despite responsible approaches to image analysis, there are many steps within an analysis pipeline that could introduce type I or type II errors (noise reduction, betweensubject registration, tract definition and extraction steps). In fact, a recent mega-analysis (11) demonstrated that the confidence of finding white matter pathology in schizophrenia populations increases significantly after at least 60 subjects per group are used. Given the limited number of subjects studied in the present analysis, as well as the large variance in the data points (see Figure 2 in the article), it is important that these results be replicated in a large, independent sample before definitive conclusions are drawn. Similarly, it is necessary to consider that the nevertreated population is likely significantly different from the group treated with antipsychotics in multiple ways. As an example, drug-naive patients are more likely (although not explicitly measured) to have lower socioeconomic status, less family support, lack of physical activity, and a possible substance abuse disorder, as well as a higher likelihood of malnutrition. Nonetheless, the findings are still very intriguing and will no doubt provide renewed energy to the debate about the impact of antipsychotic medications.

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