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Abnormal Trajectory of Intracortical Myelination in Schizophrenia Implicates White Matter in Disease Pathophysiology and the Therapeutic Mechanism of Action of Antipsychotics

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ABSTRACT

BACKGROUND: Postmortem and imaging studies provide converging evidence that the frontal lobe myelination trajectory is dysregulated in schizophrenia (SZ) and suggest that early in treatment, antipsychotic medications increase intracortical myelin (ICM). We used magnetic resonance imaging to examine whether the ICM trajectory in SZ is dysregulated and altered by antipsychotic treatment.

METHODS: We examined 93 subjects with SZ (64 men and 29 women) taking second-generation oral antipsychotics with medication exposures of 0–333 months in conjunction with 80 healthy control subjects (52 men and 28 women). Frontal lobe ICM volume was estimated using a novel dual contrast magnetic resonance imaging method that combines two images that track different tissue components.

RESULTS: When plotted against oral antipsychotic exposure duration, ICM of subjects with SZ was higher as a function of medication exposure during the first year of treatment but declined thereafter. In the age range examined, ICM of subjects with SZ was lower with increased age, while ICM of healthy control subjects was not.

CONCLUSIONS: In adults with SZ, the relationship between length of exposure to oral second-generation antipsychotics and ICM was positive during the first year of treatment but was negative after this initial period, consistent with suboptimal later adherence after initial adherence. This ICM trajectory resembles clinically observed antipsychotic response trajectory with high rates of remission in the first year followed by progressively lower response rates. The results support postmortem evidence that SZ pathophysiology involves ICM deficits and suggest that correcting these deficits may be an important mechanism of action for antipsychotics.

Keywords: Atypical antipsychotic, Medication, Myelin, Oligodendrocyte, Schizophrenia, White matter

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Antipsychotic medications have been shown to promote oligodendrocyte survival and recovery from insults (1,2), promote myelin repair (1–3), promote increases in the number of oligodendrocyte precursors (4,5), facilitate maturation of oligodendrocyte precursors (2), and increase the amount of intracortical myelin (ICM) (1,6) in a variety of rodent models (7). In nonhuman primates, short-term (6 months) exposure to typical and atypical oral antipsychotics seems to increase glia density in the lower layers of cortex (8), while long-term treatment (17–27 months) may eventually decrease their density (9). In subjects with schizophrenia (SZ) treated with antipsychotics, a pattern of changing gene expression for brain lipidation pathways also occurs primarily early in the disease course (10), consistent with imaging evidence of initial treatment-related increases in ICM (6) in subjects with first-episode SZ (11,12). Nevertheless, imaging studies that examined subcortical white matter (WM) reported disruptions (increased diffusivity) in WM integrity that are associated with initial treatment, although these changes were not associated with clinical improvements (13,14), which may be worse in individuals with poor outcome (15). Others report improved WM integrity (reduced diffusivity) (16), with best improvements seen in subjects who responded to medication (17). Consistent with these subcortical integrity changes, long-term studies report that intensity of antipsychotic treatment may be associated with subcortical WM volume losses (18,19), which might be exacerbated by length of relapses (20). Surprisingly, short-term treatment intervention studies have also reported WM volume losses (21,22) as well as gray matter increases (21,23,24) and losses (25). Gray matter losses appear to be more clearly associated with first-generation than with second-generation antipsychotic medications (26). Thus, it

appears that the brain is dynamically responsive to interventions with antipsychotics, albeit in complex and difficult-to-reconcile ways that may depend on factors such as outcomes and/or adherence (27–29).

Clinical response to antipsychotics follows a similar pattern with a striking initial benefit resulting in a 70% to 87% remission of psychotic symptoms in the first year of treatment (30–32). This exceptional initial response to antipsychotics is unfortunately followed by considerably reduced response to treatment (<30%) or treatment resistance and substantial and lasting clinical deterioration over subsequent years (33–38). A disruption in the developmental trajectory of myelination has been proposed as an etiologic component of SZ (39–41) as well as some other uniquely human neuropsychiatric disorders [reviewed in (42)].

Unlike our closest primate relative the chimpanzee (43), humans continue developing their ICM well past the late teens and into middle age (44,45). Myelin is a highly specialized lipid membrane wrapping of axons that markedly increases action potential transmission speed (up to 100-fold) and helps make possible the synchronous neural network oscillations on which normal human brain function is based. The human brain is proportionately more myelinated than other species (approximately 20% more than nonhuman primates) with WM and myelin making up approximately half and one-quarter of our brain volume, respectively [reviewed in (46)]. Especially underappreciated is the degree to which human cerebral cortex becomes myelinated, mostly in the lower cortical layers (Figure 1).

Cross-sectional imaging and postmortem studies have demonstrated that subjects with SZ have an abnormal myelination trajectory compared with healthy control (HC) cohorts (40,47–49). Human postmortem data suggest that the glial deficit in the cortex of SZ seems to be particularly prominent in the frontal lobes (48,50,51) [reviewed in (12,46)]. Prospective imaging studies of SZ and HC cohorts followed over several years confirmed an increasing divergence in WM volumes as the disease progressed into chronic stages (52–54). Myelination deficits have been consistently reported in postmortem cytology, myelin stain, and proteome/transcriptome studies of chronic SZ (50,51) [reviewed in (46)]. These postmortem observations are consistent with the clinical observation of

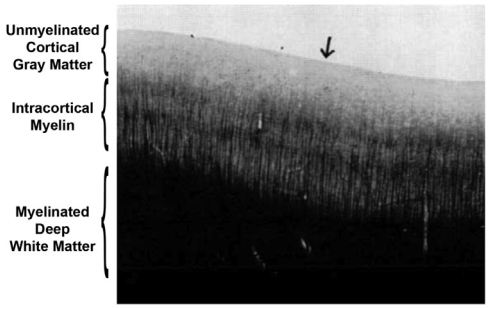

Figure 1. Histological visualization of intracortical myelin. Postmortem photomicrograph of myelination within frontal lobe cortical layers. Myelin stain (black) illustrates regions of highly myelinated deep white matter, unmyelinated cortical gray matter, and regions of intracortical myelin depicting cortical layers with varying levels of myelination. [Reproduced with permission from Braitenberg (90), copyright 2004 John Wiley and Sons, original copyright 1962 The Wistar Institute of Anatomy and Biology.]

treatment resistance (33–35), and the declines in response rates were hypothesized to be associated with worsening ICM deficits (55,56).

Recent studies support the possibility that a mechanism of action of antipsychotic medications may involve correction of disease-related ICM deficits [reviewed in (46)]. Promyelinating effects of antipsychotics have been detected in the early stages of SZ (11,27). Nevertheless, to date, no study has directly examined the hypothesis that the ICM trajectory follows the quadratic (inverted U) clinical trajectory of a positive response in the first year of treatment followed by declining response rates in chronic stages of SZ. The current study aimed to examine this possibility. A dual contrast magnetic resonance imaging (MRI) method was developed to estimate ICM in vivo and has been used to examine the effect of antipsychotic medications early in the disease course (11,27). The method uses the distinct tissue contrasts provided by inversion recovery (IR) and proton density (PD) MRI to delineate the extent of cortical myelination. Myelin has the highest cholesterol content of any brain tissue (57–59), and IR images are most sensitive to cholesterol concentrations (60). IR images thus provide optimal contrast for quantifying myelination (61–63) by best tracking myelin into the cortex. Conversely, PD images are not very sensitive to myelination (64) and can better delineate the border between gray matter and WM. Thus, the difference between IR and PD images can indirectly assess ICM (Figure 2) (11,27).

We used this dual contrast method to test the hypothesis that ICM is a key locus for the neurotransmitter-based mechanism of action for antipsychotic medications (46,56) resulting in an increase in myelination during the initial treatment with the antipsychotic medication (1,8,11,27). Based on postmortem data (9,48–51,65–67), we also hypothesized that during long-term treatment with oral antipsychotics, this initial ICM increase would be followed by an ICM decline that would be consistent with the clinical decline observed in chronic SZ (36,68). To test these hypotheses, we recruited a cohort of subjects with SZ with a large range of medication exposure to oral antipsychotic medication (0–333 months) and an age-matched HC cohort. There is evidence of differences in the impact on the brain of patients with SZ treated with first-generation (typical) antipsychotic versus second-generation (atypical) antipsychotic medications (11,26). For consistency, subjects were not included in the current study if they had previous exposure to any first-generation antipsychotic medications.

METHODS AND MATERIALS

Subjects

Study participants included 173 total subjects, of which 93 subjects between the ages of 18 and 51 had SZ. The subjects with SZ were recruited from longitudinal studies of SZ conducted at the Aftercare Research Program at the University of California, Los Angeles, Semel Institute for Neuroscience and Human Behavior (69,70) and had been prescribed oral second-generation antipsychotics except for one patient with SZ who did not receive medication before undergoing MRI because the patient and family refused. At time of MRI, most of the subjects with SZ (77 of 93, 83%) were taking oral