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Differential Effects of Typical and Atypical Antipsychotics on Brain Myelination in Schizophrenia

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Abstract

Context—Imaging and post-mortem studies provide converging evidence that patients with schizophrenia have a dysregulated developmental trajectory of frontal lobe myelination even in adulthood. Atypical antipsychotics have been shown to have a wide spectrum of efficacy across multiple psychiatric diseases and to be particularly efficacious in treatment resistant cases of disorders such as schizophrenia.

Objective—To test the a priori hypothesis that antipsychotic medications may differentially impact frontal lobe myelination in patients with schizophrenia.

Design, setting, and participants—Participants ranged in age from 18–35 years, were all male, and were recruited by a single group of investigators using the same criteria. Two cohorts of subjects with schizophrenia early in their disease who were treated either with oral risperidone (Ris) or fluphenazine decanoate (Fd) were imaged in conjunction with cohorts of healthy controls. Each cohort was imaged using a different MRI instrument using identical imaging sequences.

Main outcome measure—MRI measures of frontal lobe white matter volume.

Results—We estimated differences due to differences in the MRI instruments used in the two studies in the two healthy control groups matched to the patient samples, adjusting for age and other covariates. We then statistically removed those differences (which we assumed were instrument artifacts) from the data in the schizophrenia samples by subtraction. Relative to the differences seen in controls, the two groups of schizophrenic patients differed in their pattern of frontal lobe structure with the Ris-treated group having significantly larger white matter volume than the Fd group.

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Conclusions— The results suggest that the choice of antipsychotic treatment may differentially impact brain myelination in adults with schizophrenia. Prospective studies are needed to confirm this finding. MRI can be used to dissect subtle differences in brain tissue characteristics and thus could help clarify the effect of pharmacologic treatments on neurodevelopmental and pathologic processes in vivo.

Keywords

Schizophrenia; antipsychotic; medication; typical; atypical; frontal lobe; myelin; white matter; gray matter; oligodendrocyte; trajectory; development; lipid; intracortical; age; treatment; prevention; human; primate

Introduction

The human brain is unique in its disproportionately high myelin content and long developmental (myelination) phase (Bartzokis, 2004a;Bartzokis, 2005). Imaging data confirm post-mortem evidence suggesting that the temporal extent of normal brain development extends until approximately age 50 when maximal white matter volumes and myelination are reached in frontal lobes and association areas (Allen et al, 2005;Bartzokis et al, 2001;Benes et al, 1994;Ge et al, 2002;Jernigan and Gamst, 2005;Kemper, 1994;Miller et al, 1980;Sowell et al, 2003;Walhovd et al, 2005;Yakovlev and Lecours, 1967). The age-related increase in myelinated white matter (WM) volume occurs in concert with a linear decrease in gray matter (GM) volumes measured with MRI (Allen et al, 2005;Bartzokis et al, 2001;Ge et al, 2002;Jernigan and Gamst, 2005;Sowell et al, 2003;Walhovd et al, 2005) while total brain volume remains stable (Miller et al, 1980). Thus in adulthood (18–50 years), the normal brain undergoes a continual change in the proportion of myelinated white matter while total brain volume remains stable (Bartzokis et al, 2001;Miller et al, 1980).

The extensive process of myelination increases our brain's capacity to process information distributed over multiple interconnected regions and underlies many of our unique capabilities such as language. The vulnerability of the myelination process likely also contributes to the unique susceptibility of the human brain to highly prevalent disorders of development (e.g., schizophrenia, autism, ADHD, bipolar disorder) (Bartzokis, 2002;Bartzokis, 2004b;Bartzokis, 2005). A dysregulation in this developmental process is hypothesized to result in an insufficient capacity to maintain temporal synchrony of the brain's widely distributed functional neural networks and manifests in the heterogeneity of symptoms and cognitive impairments that characterize disorders such as schizophrenia (Bartzokis, 2002;Bartzokis, 2005;Spencer et al, 2004;van der Stelt et al, 2004).

The possibility that such a dysregulation of the myelination process may contribute to the syndrome of schizophrenia is supported by both in vivo and post-mortem studies. Both cross-sectional and prospective volumetric MRI studies (Bartzokis et al, 2003;Ho et al, 2003;McDonald et al, 2004) as well as diffusion tensor imaging studies (Ardekani et al, 2005;Ardekani et al, 2003;Kubicki et al, 2005;Szeszko et al, 2005; for review see Kanaan et al, 2005) suggest abnormal developmental trajectories with abnormal myelination. Post mortem data revealed decreased numbers of intracortical oligodendrocytes, decreased expression of myelin-related genes, and decreased levels of myelin markers (Chambers and Perrone-Bizzozero, 2004;Flynn et al, 2003;Hakak et al, 2001;Hof et al, 2002;Peirce et al, 2006;Schmitt et al, 2004;Tkachev et al, 2003;Uranova et al, 2005;Uranova et al, 2004). In adults with schizophrenia atypical antipsychotics could be differentially impacting this dysregulated developmental process when compared to typical antipsychotics (Cahir et al, 2005;Garver et al, 2005;Kodama et al, 2004;Lieberman et al, 2005;Molina et al, 2005;Selemon et al, 1999;Wang et al, 2004a).

Myelin has the highest cholesterol content of any tissue (Bartzokis, 2004a; O'Brien and Sampson, 1965; Rouser et al, 1972). Inversion-recovery (IR) MRI images are most sensitive to the high cholesterol concentrations in myelin (Koenig, 1991), and are optimal for quantifying myelination (Barkovich et al, 1992; Valk and van der Knaap, 1989; van der Knaap and Valk, 1990). There is excellent agreement between the lifetime myelination trajectory of normal individuals observed in vivo with IR sequences and published post mortem data (Bartzokis, 2005; Bartzokis et al, 2001). In frontal lobes peak myelination is reached at age 45 as measured by both this in vivo and post mortem myelin stain data (Bartzokis et al, 2001; Kemper, 1994) (Figure 1). This close agreement with post mortem data validates in vivo IR volume measures and suggests that IR sequences likely track what may be better referred to as "myelinated WM volume" which includes highly myelinated portions of the lower cortical layers (see Figure 1). For simplicity this measure will be referred to herein as WM.

Atypical antipsychotics have been shown to be particularly efficacious in some treatment resistant cases of schizophrenia and show a wide spectrum of efficacy across multiple psychiatric diseases. We hypothesized that in adults with schizophrenia, exposure to atypical antipsychotics may differentially promote brain myelination compared to exposure to typical antipsychotics (Bartzokis, 2002; Bartzokis, 2005; Bartzokis and Altshuler, 2003; Bartzokis et al, 2003). We tested this possibility using available MRI data acquired with identical IR sequences. Specifically, we hypothesized that when compared to Fd, treatment with Ris will be associated with increased intracortical myelination that on MRI will manifest as a shift in the gray/white matter boundary and manifest as an increased WM volume and decreased GM volume.

METHODS

Subjects

Two male cohorts between age 18 and 35 were recruited from longitudinal studies of schizophrenia conducted at the UCLA Aftercare Research Program (Nuechterlein et al, 1994). All subjects received written and oral information about the study and signed written informed consents approved by the local institutional review board prior to study participation.

The first cohort of schizophrenic and healthy control subjects was originally imaged before the introduction of atypical antipsychotics. This sample consisted of 51 schizophrenic subjects treated only with Fd and 23 healthy controls. The second cohort of similarly recruited groups was imaged after the introduction of Ris. This second sample consisted of 20 schizophrenic subjects treated with Ris and 38 healthy controls. Characteristics of all four groups are summarized in Table 1.

Even though an ANOVA revealed an overall group difference in age, post-hoc analysis using the Scheffe test did not detect any significant differences between groups. However, post-hoc analysis did indicate that the healthy control group from the second cohort had a significantly greater mean number of years of education than the control group for the first cohort and the schizophrenic cohorts. The second cohort of schizophrenia patients also had significantly fewer years of medication exposure than the first cohort.

All subjects with schizophrenia had a DSM-III-R diagnosis of schizophrenia or schizoaffective (depressed type) disorder, which was established using structured diagnostic interviews by diagnosticians with demonstrated inter-rater reliability (Nuechterlein et al, 1994; Nuechterlein et al, 2001). The vast majority (over 90%) had a DSM-III-R diagnosis of schizophrenia. Patients with significant substance abuse or history of neurological disorders or significant head trauma were excluded (see Nuechterlein et al, 1994).

At a minimum, each healthy subject completed a clinical interview based on written standardized questions and administered by an experienced clinician-investigator (GB) to assess the history of medical, psychiatric, and substance dependence disorders. Selection criteria were as follows: no evidence of significant current or past psychiatric diagnosis or substance dependence based on DSM-IV criteria; no significant use of drugs or alcohol in the past year (amount of use did not meet DSM-IV criteria for alcohol/substance dependence or abuse); no history or gross evidence of central nervous system impairment or any history of neurological disorder (head trauma with loss of consciousness for greater than 15 minutes), no history of chronic medical conditions that are likely to result in structural brain abnormalities (i.e. stroke, transient ischemic attack, seizures, hypertension, diabetes, etc.); and self-report that no first-degree relatives have been treated for a major psychiatric disorder.

Imaging

The two cohorts were scanned using the same MRI techniques, MRI instrument type, and field strength (1.5 Tesla) but each cohort was scanned with a different instrument.

MRI Protocol—The MRI examination used our previously published methods (Bartzokis et al, 2001; Bartzokis et al, 1993). In brief, a coronal pilot sequence was used to align a sagittal MRI pilot sequence. The sagittal pilot sequence was then used to specify the position of the coronal image acquisition grid. The sagittal image containing the left hippocampus was used to define an oblique coronal acquisition plane perpendicular to the hippocampus. Two coronal sequences of the same brain slices were acquired: a transverse asymmetric dual spin-echo Carr-Purcell-Meiboom-Gill sequence (TR=2500, TE=30,90) and an inversion-recovery (IR) sequence (TR=2500, TI=600, TE=30). Both sequences have 256×192 view matrix, 25 cm field of view, 2 repetitions, and produce co-registered 3 mm thick contiguous slices. Inversion recovery sequences provide the maximum gray/white contrast available with MRI (see Figure 2).

Image Analysis—The scans were rated in random order by a single individual who was blind to clinical and demographic characteristics of subjects. A contiguous seven-slice volume centered on the anterior commissure is used for data quantification (Bartzokis et al, 1993). Volumes are computed by multiplying each cross-sectional area by the slice thickness and summing these products. Previously published test-retest reliabilities for the regions of interest had an intraclass reliability coefficient (r_{xx}) of .86 for total frontal lobe volume and .90 for WM (Bartzokis et al, 1993).

Data analyses

All analyses were restricted to subjects age 35 or younger as there was only one schizophrenic subject above that age (age 40). His age was 2.3 SD above the mean age of the rest of the participants, so he was excluded because his data might unduly influence the regression analyses.

It is known that age has a nonlinear (quadratic) relationship with white matter of healthy males in variables spanning a wider age range (Bartzokis et al, 2001) (Figure 1), but this age restriction made a linear aging model appropriate for all the variables studied as the peaks are well above age 35 (by a decade). Two different instruments were used (one for each cohort) in the study and therefore it is possible that group differences could have been generated by the difference in the instruments. Our analyses rest on the assumption that differences between the control groups estimate machine-generated differences rather than real differences between the cohorts (a necessary assumption given our non-experimental design), and we statistically adjusted for what we took to be instrument differences by using the covariate and age-adjusted results from the two healthy control groups that were scanned with each patient cohort. MRI instrument

effects were estimated by regressing the variables of interest on Study (a dummy coded dichotomous variable) in the samples of healthy subjects in the two projects (N=23 and 38). The model assumed parallel age slopes of the healthy cohorts on the two instruments. Age, education, and ethnicity (white versus non-white) were also included as covariates in the regression models to control for possible differences in the samples due to confounding with those variables. The covariate-adjusted instrument means were then subtracted from the respective raw scores. Finally, the scores were divided by the within-study standard deviation, again calculated using the healthy controls. The procedure yielded standard scores in the healthy control samples with mean equal zero for all variables and standard deviation equal one. We then evaluated differences between the two Study samples of schizophrenia patients (Study 1: fluphenazine, N=51; Study 2: risperidone, N=20) in separate analyses of covariance on the three residual scores (total frontal, white matter, gray matter). The analysis used Study as the independent variable, and controlled for age, ethnicity (coded as above), education and years of medication exposure, using a square root transformation on years of medication exposure to correct positive skew. In addition to comparing the two Study groups (the notable difference of interest between studies was the typical versus atypical antipsychotic medication used), we also tested the group mean scores against zero (the value in the study normal controls).

Results

The results are summarized in Table 2 and Figure 3. The table presents unadjusted means and standard deviations (SD), and the covariate-adjusted means on which the statistical tests are based. Note that a similar table for healthy controls would have mean=0 and SD=1 in each cell.

The overall size of the frontal lobe did not differ between the Ris- and Fd-treated groups although the total frontal lobe measure of the Fd group was significantly smaller than the normal controls. Both groups of subjects with schizophrenia had significantly lower GM volumes than the healthy control group with the Ris group having a lower level of GM than the Fd group at a trend level ($p=0.09$).

Raw volumes of WM were significantly different between the two medication groups with the Ris group having significantly more WM than the Fd group. The two groups of patients differed significantly from the healthy controls in opposite directions: the Ris group had an increase in WM volume while the Fd group had a decrease in WM volume compared to the control group.

Discussion

Post mortem (Benes et al, 1994; Kemper, 1994; Yakovlev and Lecours, 1967) and in vivo cross-sectional studies (Allen et al, 2005; Bartzokis et al, 2001; Ge et al, 2002; Jernigan and Gamst, 2005; Sowell et al, 2003; Walhovd et al, 2005) have demonstrated that healthy controls continue myelinating and increasing their WM until the fifth decade of life (Figure 1). Adult schizophrenia subjects do not follow this normal trajectory of increasing WM but rather have a flat WM trajectory with increasing age. In treated subjects with schizophrenia, their flat WM trajectory crosses the upward trajectory of healthy individuals at approximately age 30. Before that age subjects with schizophrenia have higher WM while after 30 and beyond they have significantly lower WM compared to controls (Bartzokis, 2002; Bartzokis et al, 2003). This pattern of divergence from the normal brain developmental trajectory is consistent with the observation that treatment success is excellent early in the disease process but treatment refractoriness and functional decline increase over time (Bartzokis and Altshuler, 2003). Three prospective studies of chronic treatment (greater than 1 year) confirm these divergent trajectories and reported significant declines in WM volumes of patients with schizophrenia

when compared to controls whose WM increased over the follow-up interval (Ho et al, 2003;Lu et al, 2006;Molina et al, 2005).

To our knowledge the current study is the first to report a differential effect of typical and atypical medications on WM. Strengths of the study were the use of IR imaging sequences that optimally track the process of myelination (Figure 1), excellent reliability, and young cohorts of ill subjects treated with one or the other medication. We observed that in the frontal lobe of schizophrenic subjects the atypical antipsychotic Ris is associated with greater WM volume compared to treatment with the typical antipsychotic Fd. The abnormally low GM volume we observed in both schizophrenic groups is consistent with prior studies that examined schizophrenia in the first few years of the disease process (Lieberman et al, 2005;Molina et al, 2005). In our data at least part of the observed larger WM volume in Ris-treated patients represents a shift of the GM/WM boundary *into* the cortex. This is suggested by the fact that both the Ris and Fd groups had a smaller GM volume than controls but the total frontal lobe volume (composed of WM plus GM) was significantly lower than controls only in the Fd group (Figure 2).

Multiple studies have reported significant but inconsistent effects of antipsychotic medication on brain GM volumes of patients with schizophrenia (Garver et al, 2005;Lieberman et al, 2005;McCormick et al, 2005;Molina et al, 2005). Chronic atypical antipsychotic treatments have been associated with increased (Molina et al, 2005) as well as decreased (McCormick et al, 2005) cortical volumes. Similarly, chronic typical medications have been associated with increased (McCormick et al, 2005) as well as decreased (Lieberman et al, 2005) cortical volumes. The inconsistent results could be due to effects on myelination that shift the gray/white border depicted by different MRI imaging sequences with differing sensitivities to the intracortical myelination process (Figure 1) (Bartzokis et al, 2001). The use of IR sequences may have improved our ability to track intracortical myelination but also made it difficult to directly compare the results with prior studies examining differential effects of treatments on brain structure (Garver et al, 2005;Ho et al, 2003;Lieberman et al, 2001;Lieberman et al, 2005;McCormick et al, 2005;Molina et al, 2005).

In view of the inconsistent imaging literature, it is important to also examine the post-mortem and animal model literature. Human post mortem data suggests that a glial deficit exists in the frontal cortex of patients with schizophrenia (Cotter et al, 2002;Stark et al, 2004) and that this deficit is primarily due to lower oligodendrocyte numbers (Hamidi et al, 2004;Hof et al, 2003;Uranova et al, 2005;Uranova et al, 2004). This is likely accompanied by a deficit in intracortical myelination as suggested by decreased expression of myelin genes (Aston et al, 2004;Hakak et al, 2001;Peirce et al, 2006;Tkachev et al, 2003), and decreased intracortical myelin markers (Chambers and Perrone-Bizzozero, 2004;Flynn et al, 2003). We (Bartzokis and Altshuler, 2005) have previously suggested that reduced levels of intracortical oligodendrocytes and myelin may underlie the reduced intracortical neuropil that results in increased neuronal density observed in many post-mortem studies (Selemon and Goldman-Rakic, 1999;Selemon et al, 2003;Selemon et al, 1995). Intracortical myelin reduces the amount of fixation-associated cortical shrinkage and thus reduced intracortical myelin could account at least in part for the observed reduction of neuropil in frontal cortex (Bartzokis and Altshuler, 2005).

Atypical but not typical antipsychotics have been shown to increase the genesis of glia (gliogenesis) in the frontal cortex of primates and rodents (Kodama et al, 2004;Selemon et al, 1999;Wang et al, 2004a). A similar effect is evident with electroconvulsive treatment (ECT), a highly effective intervention for severe psychiatric disorders such as psychotic depressions that are often treatment resistant (Madsen et al, 2005). It is possible that like ECT (Madsen et al, 2005), atypical medications may mitigate such deficits in intracortical oligodendrocytes

(Wang et al, 2004a) and/or myelin (Bartzokis and Altshuler, 2005;Bartzokis and Altshuler, 2003;Braga and Petrides, 2005). The reported absence of a myelin deficit in *deep* white matter (Marner and Pakkenberg, 2003) suggests that this deficit may be limited to late-myelinating structures such as the cortex and adjacent WM (Bartzokis, 2005;Uranova et al, 2005). This intracortical myelin signal is likely best detected using IR images (Koenig, 1991) (Figure 1) and the use of this imaging sequence and the long gray/white matter border of the human frontal lobe (Figure 2) may have contributed to the robustness of the results.

The possibility of treatment-related increased intracortical myelination is supported by a primate model that showed increased glial (but not neuron) density in the frontal cortex of animals chronically treated with either typical or atypical antipsychotic medications (Selemon et al, 1999). Unfortunately this study did not assess differential effect on glial cell subtypes (e.g., astrocytes versus oligodendrocytes) and myelin stains were not used to assess the impact of medications on intracortical myelination. If the same treatment-associated effect occurs in humans, then the glial deficit observed in patients with schizophrenia may in part be corrected by antipsychotics through restoration of adequate numbers of intracortical oligodendrocytes (Wang et al, 2004a) and/or promoting myelination (Bartzokis and Altshuler, 2003). In the same study (Selemon et al, 1999), only Ris treatment was associated with a decline in neuronal density. The greater intracortical myelination in the Ris group suggested by the current study (Figure 3) could reduce fixation-associated cortical shrinkage (Bartzokis and Altshuler, 2005;Bartzokis and Altshuler, 2003) and thus explain the Ris-associated decline in neuronal density in the primate model (Selemon et al, 1999).

In the current cross-sectional study it is not possible to determine if the greater WM of the Ris-treated group, compared to the Fd-treated group, represents maintenance of preexisting higher WM that preceded treatment or was induced by the treatment itself. Similarly this study cannot determine whether the lower WM of the Fd group was related to a decline from higher levels or a lack of a treatment-related increase. Prospective studies of first episode subjects are needed to address such questions. Several additional limitations must also be acknowledged before further interpretation of the data. First, the sample was composed of males of a restricted age-range (18–35 years of age), thus limiting the generalizability of the results to females and older or younger cohorts. Second, the two cohorts of schizophrenia subjects were not randomly assigned to the treatment arms. Although this could result in a biased group assignment or cohort effects, the cohorts were selected with parallel criteria from the same psychiatric facilities by the same research team. Finally, the groups were not matched in age, race, education, or medication exposure. Statistically controlling for these variables strengthened the results. However, replication of these findings with samples that are matched on these variables would be very helpful in ruling out these variables as contributing factors.

It is unclear what the underlying molecular mechanism for a promyelinating effect of atypical antipsychotic medications may be. Multiple non-exclusive mechanisms are possible. Recent data suggests that atypical antipsychotic medications change lipid metabolism (Ferno et al, 2005), an effect that may also be related to the weight gain associated with many atypical antipsychotics (Bartzokis, 2002). Other mechanisms are consistent with neurochemically-based models that suggest increased prefrontal cortex dopaminergic neurotransmission underlies some of the beneficial effects of atypical antipsychotics (Barch and Carter, 2005;Eltayb et al, 2005;Li et al, 2005). Consistent with the possibility that this effect could be mitigated by oligodendrocytes, in vitro models have suggested that dopamine stimulation may be protective of oligodendrocytes (Belachew et al, 1999;Rosin et al, 2005) and/or promote the genesis of new cells (Van Kampen et al, 2004). Finally, recent studies suggest that the Neuregulin 1 gene, one of the genetic loci most strongly linked to schizophrenia (Li et al, 2004;Liu et al, 2005;Stefansson et al, 2003; for review see Tosato et al, 2005), may be particularly important for adequate myelination of smaller diameter axons (Michailov et al,

2004). In late-myelinating regions such as the frontal cortex (Figure 1), these *smaller* diameter axons with thinner sheaths are being myelinated during the teens and early twenties when onset prevalence of schizophrenia and bipolar disorder reach their highest levels. This gene may therefore contribute to the pathophysiology of these diseases by disrupting the later stages of brain myelination and could help explain the observed comorbidity of many psychiatric disorders (Bartzokis, 2005).

Severe depression, bipolar disorder, and other neuropsychiatric disorders have also been associated with myelination deficits (Aston et al, 2005;Bartzokis, 2005;Beasley et al, 2005;Hamidi et al, 2004;McDonald et al, 2004;Tkachev et al, 2003;Uranova et al, 2005;Uranova et al, 2004;Wang et al, 2004b;Zai et al, 2004). If, as we suggest, treatment with atypical antipsychotics can mitigate myelination deficits, then such treatment could also mitigate similar deficits in these other psychiatric conditions. The shared deficit in myelination could thus offer an explanation for the wide spectrum of efficacy of atypical antipsychotic medications such as Risperidone on multiple diseases such as schizophrenia, autism, bipolar disorder, severe depression, post traumatic stress disorder, as well as their associated cognitive deficits (Bartzokis, 2002;Bartzokis, 2005;Bartzokis et al, 2005;Harvey et al, 2003;Mori et al, 2004).

The importance of human brain myelination has been generally underappreciated, but recently a conceptual “myelin model” has served to correct this gap in our knowledge and provide novel and testable approaches to treatment and prevention efforts (Bartzokis, 2002;Bartzokis, 2004b;Bartzokis, 2005;Walterfang et al, 2005;Woo and Crowell, 2005). The advent of in vivo neuroimaging methods that can assess myelination on a regional basis may have direct applications in medication development (Bartzokis, 2004a;Bartzokis et al, 2004). This study demonstrates that it is currently feasible to detect pharmacologic and therefore other (dietary, psychosocial, ECT-related) myelin-centered interventions in vivo through imaging markers (Bartzokis, 2004a;Woo and Crowell, 2005). The “myelin model” suggests that interceding early in dysregulated developmental trajectories may increase the effectiveness of treatments and decrease the need for later more aggressive interventions (Bartzokis, 2002;Bartzokis, 2004a).

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Figure 1. Quadratic (inverted U) trajectories of human brain myelination over the lifespan
 Myelination (Y axis) versus age (X axis) in frontal lobes of normal individuals. Left figure is in vivo data from Bartzokis et al (2001) where an inversion recovery sequence was used to assess white matter volume. Right figure shows post-mortem *intracortical myelin* stain data from Kaes (1907), [adapted and reproduced in Kemper (1994)]. Used with permission. The data were acquired 100 years apart yet the two samples of normal individuals show remarkably similar frontal lobe myelination trajectories, both reaching a peak at age 45.

Figure 2. Inversion recovery (IR) image used to measure myelinated volume in the frontal lobe. The outer border of the brain and “islands” of lighter material seen in the frontal gray matter are CSF areas that are eliminated from computation using a co-registered T_2 image (not shown here – see Bartzokis et al, 1993).

Figure 3. Frontal Lobe Volume Residual z-scores in Male Subjects with Schizophrenia Receiving a Typical or Atypical Antipsychotic Medication

WM = Frontal lobe white matter; GM = Frontal lobe gray matter.

Between Group Tests (risperidone vs. fluphenazine): † $P < 0.05$.

Within Group Tests (schizophrenic vs. healthy controls, standardized to mean = 0 and SD = 1):

* $P < 0.05$,

** $P < .05$,

*** $P < .001$.

Table 1

Characteristics for Schizophrenic and Healthy Control Cohorts

	Schizophrenia		Controls		F or χ^2	p
	First Cohort (N=51)	Second Cohort (N=20)	First Cohort (N=23)	Second Cohort (N=38)		
Demographics	M (sd)	M (sd)	M (sd)	M (sd)		
Age	27.3 (4.9)	24.2 (4.6)	25.5 (4.3)	27.2 (4.1)	2.97	.034
Education	12.9 (1.6)	13.7 (1.7)	14.1 (2.2)	16.4 (2.3)	23.28	<.0001
Race, white/non-white	36/15	9/11	21/2	25/13	10.97	.012
Illness Information					t	p
Age at onset (yrs.)	23.9 (4.2)	23.4 (4.4)			0.39	.70
Medication exposure (yrs.)	3.3 (3.3)	1.3 (0.8)			4.09	.0001

Table 2Raw mean (SD)/covariate-adjusted mean scores in subjects with schizophrenia^a

Region	Study 1 (Fluphenazine)	Study 2 (Risperidone)	t	p
Frontal lobe	-0.78 (1.09)***	-0.42 (0.92)	-1.41	0.16
Frontal white volume	-0.39 (1.23)**	0.52 (0.99)*	-3.45	0.001
Frontal gray volume	-0.71 (0.88)***	-1.19 (1.04)***	1.74	0.09

^aThe t-test results are between-group comparisons; all df = 65. Within-cell t-tests were based on the covariance adjusted means (not shown).

*
p<.05;

**
p<.01;

p<.001