



In vivo evidence of differential impact of typical and atypical antipsychotics on intracortical myelin in adults with schizophrenia ☆

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ARTICLE INFO

Article history:

Received 18 March 2009

Received in revised form 13 June 2009

Accepted 16 June 2009

Available online 17 July 2009

Keywords:

Schizophrenia

Second generation antipsychotic medication

Atypical

Intracortical myelin

White matter

Gray matter

Oligodendrocyte

Trajectory

Development

Lipid

Age

Prevention

ABSTRACT

Context: Imaging and post-mortem studies provide converging evidence that patients with schizophrenia have a dysregulated developmental trajectory of frontal lobe myelination. The hypothesis that typical and atypical medications may differentially impact brain myelination in adults with schizophrenia was previously assessed with inversion recovery (IR) images. Increased white matter (WM) volume suggestive of increased myelination was detected in the patient group treated with an atypical antipsychotic compared to a typical one.

Objective: In a follow-up reanalysis of MRI images from the original study, we used a novel method to assess whether the difference in WM volumes could be caused by a differential effect of medications on the *intracortical* myelination process.

Design, setting, and participants: Two different male cohorts of healthy controls ranging in age from 18–35 years were compared to cohorts of subjects with schizophrenia who were treated with either oral risperidone (Ris) or fluphenazine decanoate (Fd).

Main outcome measure: A novel MRI method that combines the distinct tissue contrasts provided by IR and proton density (PD) images was used to estimate intracortical myelin (ICM) volume.

Results: When compared with their pooled healthy control comparison group, the two groups of schizophrenic patients differed in the frontal lobe ICM measure with the Ris group having significantly higher volume.

Conclusions: The data suggest that in adults with schizophrenia antipsychotic treatment choice may be specifically and differentially impacting later-myelinating intracortical circuitry. In vivo MRI can be used to dissect subtle differences in brain tissue characteristics and thus help clarify the effect of pharmacologic treatments on developmental and pathologic processes.

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☆ Presented in part at the 47th ACNP Annual Meeting in Scottsdale, Arizona, December 10, 2008.

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1. Introduction

The extensive process of myelination increases the human brain's capacity to process information and underlies many of our unique behavioral and cognitive capabilities such as language (Bartzokis, 2004a, 2005). The human brain is

unique in its disproportionately high myelin content and long developmental (myelination) phase that extends until middle age when maximal myelinated white matter (WM) volumes 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; reviewed in Bartzokis, 2009) (Fig. 1).

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, 2004b, 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, 2005; Dwork et al., 2007; Spencer et al., 2004; van der Stelt et al., 2004).

Myelin has the highest cholesterol content of any brain tissue (O'Brien and Sampson, 1965; Rouser et al., 1972; Saher et al., 2005). 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, 2009; 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) (Fig. 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" that includes the heavily myelinated lower layers of cortex (Bartzokis et al., 2001, 2007, 2003b) (Fig. 1). For simplicity this measure will herein be referred to as WM.

Atypical (also referred to as second generation) 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, 2005; Bartzokis and Altshuler, 2003; Bartzokis et al., 2003b). Using available data, we previously tested and reported on the possibility that when compared to Fd, treatment with Ris was associated with increased myelination that on IR images manifests as increased WM and decreased gray matter (GM) volumes (Bartzokis et al., 2007).

As depicted in Fig. 1 (left panel), the human frontal lobe undergoes extensive intracortical myelination that does not peak until middle age. In the current study we used the different contrasts available from our imaging protocol to measure whether the medication effect on WM observed in our prior study (Bartzokis et al., 2007) was driven by an effect on this later-developing intracortical myelination process.

2. Methods

2.1. 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., 1992). 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.

All subjects with schizophrenia had a DSM-IV diagnosis of schizophrenia and 13% of each cohort had a diagnosis of schizoaffective (depressed type) disorder, which was established using structured diagnostic interviews by diagnosticians with demonstrated inter-rater reliability (Nuechterlein et al., 1994, 2001). 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 (all males) completed a clinical interview based on written standardized questions and administered by an experienced clinician-investigator

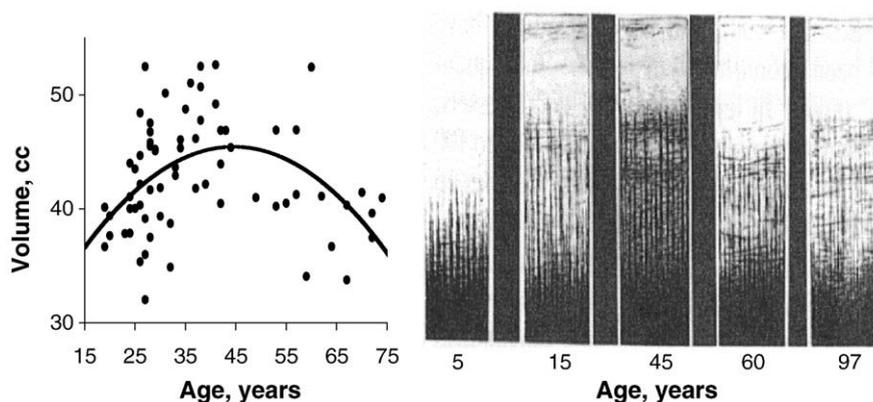


Fig. 1. Quadratic (inverted U) trajectories of human brain myelination over the lifespan. Myelination (Y axis) versus age (X axis) in frontal lobes of normal individuals. Left panel is in vivo data from Bartzokis et al. (2001). Right panel shows post-mortem intracortical myelin stain data from Kaes (1907) adapted and reproduced in Kemper (1994) depicting the heavy myelination of the lower cortical layers. 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.

(GB) to assess the history of medical, psychiatric, and substance dependence disorders. The MRI scans were obtained after diagnosis, early in the course of treatment (Table 1), and at variable times in relation to clinical assessments. 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 min), 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.

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 fluphenazine decanoate (Fd) (Nuechterlein et al., 1992) and 23 healthy controls. The dosage was adjusted based on clinical need with the target dose of 12.5 mg IM every two weeks; this was achieved by over 50% of subjects with the vast majority of the remainder receiving half that dose. The second cohort of similarly recruited groups was imaged after the introduction of risperidone (Ris), which then became the first line antipsychotic in the Aftercare Research Program protocol. This second sample consisted of 20 schizophrenic subjects treated with Ris and 38 healthy controls. Their dosage was also adjusted based on clinical need with the 3–6 mg per day target range achieved by the vast majority. Of these 132 subjects, 38 did not show a sufficiently bimodal histogram on the PD image to reliably use the histogram-based gray/white matter separation protocol and were eliminated from further analysis. Another subject had marked movement on MRI and was also removed from analysis. Demographics and clinical information for the remaining evaluable subjects are presented 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 from the first cohort and the schizophrenic cohorts. The second cohort of schizophrenia patients also had significantly fewer years of medication exposure at the time of the MRI scan than the first cohort.

2.2. 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 (Bartzokis et al., 2007).

2.2.1. MRI Protocol

The MRI examination used our previously published methods (Bartzokis et al., 2001, 2007, 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 best gray/white contrast available with MRI, especially compared to proton density (PD) sequences (see Fig. 2).

2.2.2. Image analysis

All images were initially assessed and blindly rated for whether the protocol could be carried out using both the IR and PD contrast. The 93 scans that qualified were analyzed in random order by a single rater who was blind to clinical and demographic characteristics of subjects. The brain/CSF boundary in the frontal lobe was traced using the contrast of a calculated T2 image (Bartzokis et al., 1993). The resultant brain ROI was pasted onto both the inversion recovery (IR) image and PD image. Using the IR image, myelinated WM volume in the frontal lobe was measured using a histogram-based separation of the bimodal distribution of pixel intensities of white and gray matter (Bartzokis et al., 2007, 1993). On the PD image, the gray matter histogram peak was eliminated using the shrink function to produce an ROI containing only WM intensity pixels. The resulting PD ROI was pasted onto the co-registered TE = 90 image to better visualize the boundary of the brain's gyri and sulci. The PD ROI was then manually corrected so that the only permitted difference between the IR and PD ROIs was along the cortical white/gray matter boundary (Fig. 2).

A contiguous seven-slice volume centered on the anterior commissure was used for data quantification (Bartzokis et al., 1993). Volumes were 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})

Table 1
Characteristics for schizophrenic and healthy control cohorts.

	Schizophrenia		Controls		F or χ^2	p
	First cohort (N = 34)	Second cohort (N = 16)	First cohort (N = 17)	Second cohort (N = 26)		
<i>Demographics</i>	M (sd)	M (sd)	M (sd)	M (sd)		
Age	27.1 (5.1)	23.6 (4.3)	24.9 (4.1)	27.2 (4.5)	2.97	0.036
Education	12.6 (1.5)	13.3 (1.7)	14.2 (2.4)	15.9 (2.1)	15.55	<0.0001
Race, white/non-white	26/8	7/9	15/2	17/9	8.86	0.031
<i>Illness information</i>					t	p
Age at onset (years)	23.3 (4.1)	22.7 (4.3)			0.44	0.66
Medication exposure (years)	3.5 (3.6)	1.1 (0.8)			3.64	0.0008

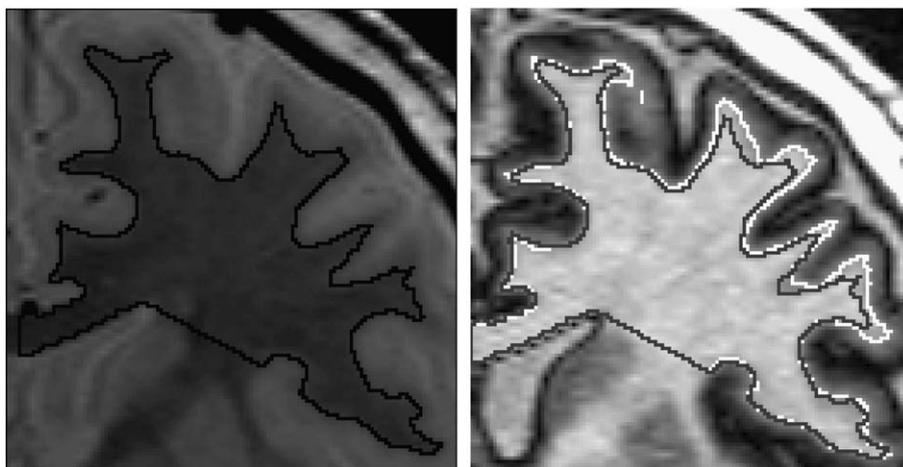


Fig. 2. In vivo measure of frontal lobe intracortical myelin volume. Left: Proton density (PD) image that is *not* sensitive to the cholesterol in myelin. The black region of interest (ROI) line depicts the border between the gray and white matter (WM). This *same* gray/white separation line is depicted in the image on the right as the gray line *inside* the white line. Right: Inversion recovery (IR) image of the *same* slice of brain as in the PD image on the left (both images obtained sequentially in the same imaging session). The IR image optimally detects the high cholesterol in myelin and is used to obtain the “myelinated WM volume” that includes heavily myelinated parts of the deeper portions of gray matter (see Fig. 1). The white ROI line separates myelinated WM and unmyelinated portion of gray matter. The difference between the gray and white lines is the measure of *intracortical* myelination.

of 0.86 for total frontal lobe volume and 0.90 for WM (Bartzokis et al., 1993).

2.3. Data analyses

It is known that age has a nonlinear (quadratic) relationship with WM of healthy males in variables spanning a wider age range (Bartzokis et al., 2001) (Fig. 1), but the age range of our sample made a linear aging model appropriate for all the variables studied as the peak of WM development in males are well above (by a decade) the maximum 35 years of age of our study samples. Different MRI instruments were used (one for each cohort) in the study and therefore it is possible that group differences can be generated by the difference in the instruments. We statistically adjusted for any such global instrument differences by using the respective healthy control group that was scanned with that 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 ($N=17$ and 26). 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 attributable to 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 of zero and standard deviation of one for all variables. We then evaluated differences between the two Study samples of schizophrenia patients (Study 1: fluphenazine, $N=34$; Study 2: risperidone, $N=16$) in separate analyses of covariance on the four residual scores (total frontal, WM, gray matter, and intracortical myelination (ICM), defined as the volume difference between IR and PD images). 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).

3. Results

The results are summarized in Table 2 and Fig. 3. The table presents covariate-adjusted means and standard deviations (SD) on which the statistical tests are based. Note that a

Table 2
Covariate-adjusted mean (SD) scores in subjects with schizophrenia.

Region	Study 1 (fluphenazine) $N=34$	Study 2 (risperidone) $N=16$	t	p
Frontal lobe	−0.49 (0.89)**	−0.17 (1.11)	−1.03	0.308
Frontal white volume	−0.07 (1.19)	0.76 (1.15)	−2.40	0.021
IR				
Frontal gray volume	−0.70 (0.80)***	−0.90 (1.07)**	0.64	0.526
IR				
Frontal white volume	−0.23 (1.13)	0.09 (1.04)	−0.96	0.342
PD				
Frontal gray volume	−0.54 (0.92)**	−0.34 (0.97)	−0.55	0.584
PD				
Frontal ICM	0.26 (0.96)*	0.92 (0.84)*	−2.14	0.038

The t -test results are between-group comparisons; all $df=44$. Within-cell t -tests to contrast with healthy controls were based on the covariance-adjusted means.

* $p<0.05$.

** $p<0.01$.

*** $p<0.001$.

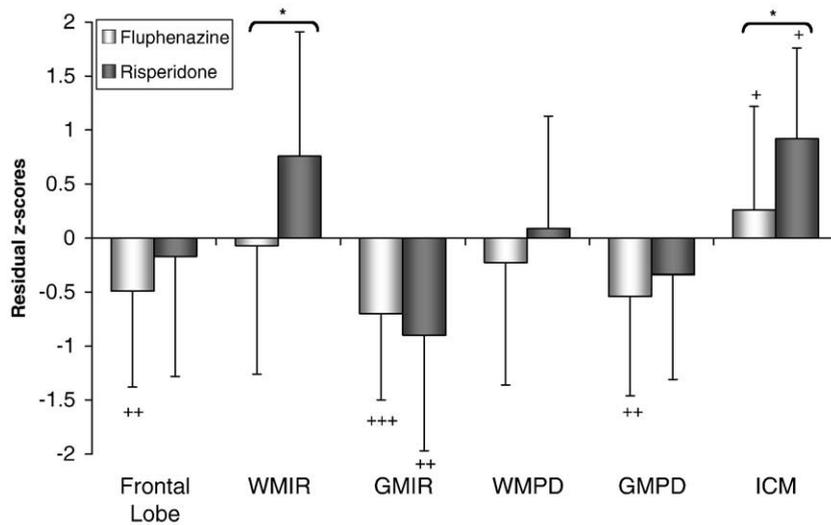


Fig. 3. Frontal lobe volume residual z-scores in male subjects with schizophrenia receiving either a typical or atypical antipsychotic medication. Frontal lobe = total frontal lobe (white plus gray matter), WMIR = frontal lobe white matter volume measured on IR images, GMIR = frontal lobe gray matter volume measured on IR images, WMPD = frontal lobe white matter volume measured on PD images, GMPD = frontal lobe gray matter volume measured on PD images; ICM = intracortical myelination. Between group tests (risperidone vs. fluphenazine): * $p < 0.05$. Within group tests (schizophrenic vs. healthy controls, standardized to mean = 0 and SD = 1): + $p < 0.05$, ++ $p < 0.01$, +++ $p < 0.001$.

similar table for healthy controls would have mean = 0 and SD = 1 in each cell.

The data resulting from the IR images are essentially the same as those published in our prior study (Bartzokis et al., 2007) despite the reduced samples of the current analysis. The IR-derived myelinated WM volume was 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 from healthy controls in opposite directions: the Ris group had increased WM volume while the Fd group had decreased WM volume relative to the control group, although the differences did not reach statistical significance (Fig. 3). The overall size of the frontal lobes 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.

The PD image analysis could not differentiate between the two medication groups in either white or gray matter volume. The GM volume of the Fd-treated schizophrenic group was significantly smaller when compared to normal controls (Fig. 3).

The ICM measure differentiated the two treatment groups with the Ris-treated group having significantly more ICM than the Fd group, and both patient groups had higher ICM volume compared to the control group (Fig. 3).

4. Discussion

To our knowledge this is the first study to report a differential effect of type of medication on ICM volume. We observed that in the frontal lobe of schizophrenic subjects the atypical antipsychotic Ris is associated with greater ICM volume compared to treatment with the typical antipsychotic

Fd (Table 2 and Fig. 3). Furthermore, the ICM data (Fig. 3) suggest that, as hypothesized (Bartzokis et al., 2007), the medication effect may primarily impact later-developing intracortical myelin.

The data also demonstrate that different image acquisition protocols produce different image contrasts (Fig. 2), track different underlying cellular substrates, and thus detect different aspects of underlying physiology (Fig. 3). We previously proposed that the high sensitivity of IR sequences to cholesterol levels (Koenig, 1991) and the very high concentration of cholesterol in myelin (O'Brien and Sampson, 1965; Rouser et al., 1972; Saher et al., 2005) make IR sequences optimal for assessing myelinated WM volume, a measure which includes the heavily myelinated lower layers of cortex (Bartzokis et al., 2001, 2007, 2003b) (Figs. 1 and 2). The data support this assertion and show that unlike IR images, PD images do not detect a significant treatment effect.

Depending on the contrast produced by different imaging sequences the white/gray matter boundary shifts (Bartzokis et al., 2007) (Fig. 2) changing gray/white matter segmentation characteristics. The GMPD data best exemplify how such differences could help explain some of the inconsistencies in the literature (Walterfang et al., 2008; Witthaus et al., 2008). Unlike IR, PD images are less impacted by the myelination process and thus produce data that may more closely reflect gray matter volume. The GMPD measure shows that when compared to the control sample, the Fd-treated group has significant smaller gray matter (Fig. 3) while the Ris-treated subjects do not differ significantly from the healthy controls. Both the GMPD measures and total frontal lobe (left column Fig. 3) follow the same diagnosis and non-significant medication effect pattern. Studies that acquire images whose contrast characteristics are influenced by similar underlying physiology as our PD images, could be interpreted to suggest that the "gray matter" is driving frontal lobe

volume differences. On the other hand, the IR and ICM measures suggest that, as depicted in Fig. 1 and predicted by our initial analysis (Bartzokis et al., 2007), the principal medication effect may be on myelination (Table 2 and Fig. 3).

The differential sensitivity of imaging sequences to underlying physiology may help explain inconsistent antipsychotic medication effects on brain volumes of patients with schizophrenia (Garver et al., 2005; Lieberman et al., 2005; McCormick et al., 2005; Molina et al., 2005; Thompson et al., 2009). 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; Thompson et al., 2009) cortical volumes.

Human post-mortem data suggest 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, 2004). A deficit in intracortical myelination is also 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) in post-mortem samples. The reported absence of a myelin deficit in subcortical WM (Marner and Pakkenberg, 2003) suggests that a myelination deficit may be limited to late-myelinating structures such as the cortex and adjacent WM (Bartzokis, 2005; Uranova et al., 2005). We have previously suggested (Bartzokis and Altshuler, 2005) that reduced levels of intracortical oligodendrocytes and myelin may underlie the reduced intracortical neuropil that results in increased neuronal density observed in post-mortem studies (Selemon and Goldman-Rakic, 1999; Selemon et al., 2003, 1995).

By their very nature however, most post-mortem data are limited to samples from subjects that were chronically treated and/or in later stages of life when degenerative processes may predominate especially in vulnerable late-myelinating regions such as the frontal lobes (Bartzokis et al., 2003a; Salat et al., 2005). Myelination trajectories over the lifespan suggest that great changes occur during normal aging (Fig. 1) and between early- and late-disease stages (Bartzokis, 2002; Bartzokis et al., 2003b). This wider lifespan perspective has been developed into a “myelin model” of the human brain which suggests that deviations from the normal trajectory of myelination (Fig. 1) are key contributors to the derangements observed in schizophrenia as well as other neuropsychiatric disorders (Bartzokis, 2002, 2004b, 2005, 2009).

In treated subjects with schizophrenia, their WM trajectory is flat and crosses the upward trajectory of healthy individuals (Fig. 1) in the third decade. Before that age, treated subjects with schizophrenia have higher WM while afterwards and beyond they have significantly lower WM compared to controls (Bartzokis et al., 2003b; Okugawa et al., 2007; Tanskanen et al., 2008; reviewed in Bartzokis, 2002). In samples such as the one in this study that are early in their illness (Table 1), compensatory processes may predominate, resulting in increased myelination that, later in the disease process, can turn into deficits (Bartzokis et al., 2003b; Ho et al., 2003; Molina et al., 2005; Whitford et al., 2007) and

may contribute to the common occurrence of treatment resistance (Bartzokis and Altshuler, 2003). Brain changes associated with different disease and treatment stages have been observed in gene expression studies (Narayan et al., 2008), primate models with different levels of medication exposure (Konopaske et al., 2008; Selemon et al., 1999), and imaging studies demonstrating progressive changes (Garver et al., 2005; Ho et al., 2003; Lappin et al., 2007; Lieberman et al., 2005; Thompson et al., 2009; Whitford et al., 2007).

It is possible that early in treatment atypical antipsychotics have a greater “promyelinating” effect than typical antipsychotics (Fig. 3). Evidence of initial promyelinating effects of treatments has emerged from animal models. Electroconvulsive (ECT) (Madsen et al., 2005) and atypical antipsychotics treatments have been shown to increase the genesis of glia (gliogenesis) (Kodama et al., 2004; Selemon et al., 1999; Wang et al., 2004a; Xiao et al., 2008). A primate model that compared multiple typical and atypical antipsychotics showed increased glial (but not neuron) density in the frontal cortex of chronically treated animals; however, only Ris treatment was associated with a decline in neuronal density (Selemon et al., 1999). The greater intracortical myelination in the Ris group suggested by our data (Fig. 3) could reduce fixation-associated cortical shrinkage (Bartzokis and Altshuler, 2005; 2003) and thus explain the Ris-associated decline in neuronal density observed in this primate model (Selemon et al., 1999). Unfortunately this primate study did not provide direct evidence of a medication effect on intracortical myelination because glial cell subtypes (e.g., astrocytes versus oligodendrocytes) and myelin stains were not assessed (Selemon et al., 1999).

The current cross-sectional study cannot determine if the greater WM of the Ris-treated group, compared to the Fd-treated group was induced by the treatments themselves or represents maintenance of preexisting higher WM that preceded treatment (Molina et al., 2005). Similarly this study cannot determine whether the lower ICM of the Fd group was related to smaller treatment-related increase or a larger decline from higher pretreatment levels. Prospective studies of unmedicated first episode subjects are needed to address such questions. Several additional important limitations must also be acknowledged before further discussion. 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 (Chambers and Perrone-Bizzozero, 2004). 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 and were treated with either typical or atypical medications. Finally, the groups were not matched in age, race, education, medication exposure, or duration of illness; however, statistically controlling for these variables did not meaningfully alter the results. Replication of these findings using randomized matched samples is necessary to fully rule out these variables as contributing factors and prospective design that includes healthy controls is needed to definitively define treatment effect on disease course.

Multiple non-exclusive molecular mechanisms could underlie promyelinating effects of atypical antipsychotic

medications. Recent data suggests that atypical antipsychotic medications change lipid metabolism (Ferno et al., 2005; La et al., 2007; Le Hellard et al., 2008; Raeder et al., 2006; Smith et al., 2008), an effect that may also be related to the weight gain and peripheral lipid abnormalities associated with their use (Bartzokis, 2002; Le Hellard et al., 2008; Meyer et al., 2008). Similarly, elevation in prolactin is associated with both typical antipsychotic and Ris treatment (Baptista et al., 2001; Friberg et al., 2009), and prolactin has been shown to have substantial promyelinating effects (Gregg et al., 2007). Other mechanisms could involve neurotransmitters that may act on glia and serve as a mode of neuron–glial communication and coordination (Bartzokis, 2007). Many key neurotransmitters such as dopamine, acetylcholine, and serotonin are released non-synaptically (Aznavour et al., 2005; Descarries and Mechawar, 2000; Umbriaco et al., 1995) and could fulfill such a role. 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; Roy et al., 2007). Consistent with these possibilities *in vitro* and *in vivo* models have suggested that dopamine and cholinergic stimulation may be protective of oligodendrocytes (Altar et al., 2008; Belachew et al., 1999; Rosin et al., 2005; Roy et al., 2007) and promote the genesis of new cells (Van Kampen et al., 2004) and/or myelination (Bartzokis, 2007). 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 (Fig. 1), these *smaller* diameter axons with thinner sheaths are being myelinated during the teens and early adulthood when onset prevalence of schizophrenia and bipolar disorder reach their highest levels. By disrupting the later stages of brain myelination, abnormalities in myelination signaling and repair processes may therefore contribute to the pathophysiology of these diseases and could help explain the high comorbidity of several neuropsychiatric disorders (Bartzokis, 2005).

In addition to schizophrenia, severe depression, bipolar disorder, and other neuropsychiatric disorders have also been associated with abnormal myelination (Aston et al., 2005; Bartzokis, 2005; Hamidi et al., 2004; Jones et al., 2009; Le-Niculescu et al., 2009; McDonald et al., 2004; Regenold et al., 2007; Tkachev et al., 2003; Uranova et al., 2005, 2004; Wang et al., 2004b; Zai et al., 2004). If treatment with atypical antipsychotics alters myelination, then such treatment could be effective in these other psychiatric conditions (Jones et al., 2009). Shared abnormalities in the myelination process could thus offer a parsimonious explanation for the wide spectrum of efficacy of atypical antipsychotic medications such as Ris on multiple diseases such as schizophrenia, autism, bipolar disorder, severe depression, and post traumatic stress disorder, as well as their associated cognitive deficits (Bartzokis, 2002, 2005; Bartzokis et al., 2005; Harvey et al., 2003; McDougle et al., 2008; Mori et al., 2004; Sachs and Gardner-Schuster, 2007).

In vivo MRI can be used to dissect subtle differences in brain tissue characteristics and thus help clarify the effect of pharmacologic treatments on developmental and pathologic

processes (Bartzokis, 2004a; Woo and Crowell, 2005) and may have applications in medication development (Bartzokis, 2004a; Bartzokis et al., 2007, 2004; Garver et al., 2008; Molina et al., 2005; Thompson et al., 2009). The myelin model of the human brain suggests that interceding early in dysregulated developmental trajectories may increase the effectiveness of treatments and decrease the need for more aggressive later interventions (Bartzokis, 2002; Bartzokis, 2004a). Improved long-term outcome however, will likely depend on targeting treatments to specific disease stages, genetic markers, and environmental circumstances that likely impact the continual process of brain development and repair across the human lifespan (Bartzokis, 2009).

Role of funding source

Funding for this study was supported in part by NIH grants (MH 0266029; AG027342; MH51928; MH6357; MH37705; P50 MH066286); an investigator-initiated grant from Janssen Pharmaceutical Inc.; and the Department of Veterans Affairs. The NIH, Janssen Pharmaceutical Inc., and the Department of Veterans Affairs had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

George Bartzokis and Keith Nuechterlein designed the study and wrote the protocol. Jim Mintz, Po Lu, and Stephanie Stewart undertook the statistical analysis. George Bartzokis, Keith Nuechterlein, Michael Gitlin, and Kenneth Subotnik recruited and supervised the assessments of the subjects. Stephanie Stewart, Bolanle Oluwadara, Andrew Lucas, Joanna Pantages, and Erika Pratt performed and managed the image analyses. George Bartzokis, Po Lu, Jim Mintz, Stephanie Stewart, and Bolanle Oluwadara wrote the first draft of the manuscript. George Bartzokis, Keith Nuechterlein, Michael Gitlin, Lori Altshuler, Jonathan Sherin, and Kenneth Subotnik edited and revised the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

George Bartzokis and Keith Nuechterlein have received funding from Janssen Pharmaceutical Inc. George Bartzokis has consulted for Janssen Pharmaceutical Inc. All other authors declare that they have no conflicts of interest.

Acknowledgements

This work was supported in part by NIH grants (MH 0266029; AG027342; MH51928; MH6357; MH37705; P50 MH066286); an investigator-initiated grant from Janssen Pharmaceutical Inc.; and the Department of Veterans Affairs.

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