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Long Acting Injection Versus Oral Risperidone in First-Episode Schizophrenia: Differential Impact on White Matter Myelination Trajectory

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Abstract

Context—Imaging and post-mortem studies provide converging evidence that subjects with schizophrenia (SZ) have a dysregulated trajectory of frontal lobe myelination. Prior MRI studies suggested that early in treatment of SZ, antipsychotic medications initially increase frontal lobe white matter (WM) volume, which subsequently declines prematurely in chronic stages of the

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Author Disclosure - Contributors

George Bartzokis and Keith Nuechterlein designed the study and wrote the protocol. Jim Mintz and Po Lu undertook the statistical analysis.

Keith Nuechterlein, Joseph Ventura, Nicole Detore, Laurie Casaus, John Luo, and Kenneth Subotnik recruited and supervised the assessments of the subjects.

Erika Raven and Chetan Amar performed and managed the image analyses.

George Bartzokis, Po Lu, and Jim Mintz wrote the first draft of the manuscript.

George Bartzokis, Keith Nuechterlein, Lori Altshuler, and Kenneth Subotnik edited and revised the manuscript.

All authors contributed to and have approved the final manuscript.

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Author Disclosure - Conflict of Interest

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disease. Insofar as the trajectory of WM decline associated with chronic disease may be due to medication non-adherence, it may be modifiable by long acting injection (LAI) formulations.

Objectives—Examine the impact of antipsychotic formulation on the myelination trajectory during a randomized six-month trial of LAI risperidone (RLAI) versus oral risperidone (RisO) in first-episode SZ subjects.

Design—Two groups of SZ subjects (RLAI, N=11; and RisO, N=13) that were matched in pre-randomization oral medication exposure and 14 healthy controls (HCs) were prospectively examined. Frontal lobe WM volume was estimated using inversion recovery (IR) MRI images. A brief neuropsychological battery that focused on reaction times was performed at the end of the study.

Main outcome measure—WM volume change scores.

Results—WM volume remained stable in the RLAI and decreased significantly in the RisO groups resulting in a significant differential treatment effect, while the HC had a WM change intermediate and not significantly different from the two SZ groups. WM increase was associated with faster reaction times in tests involving frontal lobe function.

Conclusions—The results suggest that RLAI may improve the trajectory of myelination in first-episode patients and have a beneficial impact on cognitive performance. Better adherence provided by LAI may underlie the modified trajectory of myelin development. In vivo MRI biomarkers of myelination can help clarify mechanisms of action of treatment interventions.

Keywords

antipsychotic; medication; dopamine; second generation; atypical; myelin; white matter; gray matter; oligodendrocyte; development; aging

INTRODUCTION

Many patients treated in their first-episode of schizophrenia (SZ) respond very well to antipsychotics and can achieve high levels of symptom remission within the first year, ranging from 70 to 87% (Boter et al, 2009; Emsley et al, 2007; Lieberman et al, 1993; Nuechterlein et al, 2006; Robinson et al, 1999; Robinson et al, 2004; Saravanan et al, 2010). Over subsequent years, recurrent episodes, often brought on by poor adherence or insufficient treatment, often lead to substantial chronic deterioration (Lieberman, 2006) and reduced responsiveness to antipsychotics or “treatment resistance” (Kane et al, 1988; Lieberman et al, 2001a; Lieberman et al, 2001b). The use of long-acting injection (LAI) formulations of antipsychotics result in improved outcomes, suggesting that worse outcomes with oral medications may be due to reduced adherence (reviewed in Keith, 2009).

The mechanism through which LAI medications may improve outcomes remains unknown. It has been proposed that the biological underpinnings of functional deterioration and “treatment resistance” observed in chronic SZ may involve deficient myelination (Bartzokis and Altshuler, 2005; Bartzokis and Altshuler, 2003; Bartzokis et al, 2011) and that dysregulation of the myelination trajectory may contribute to the etiology of schizophrenia (Bartzokis, 2002). A deficiency in the myelination trajectory was initially observed in cross sectional imaging and postmortem studies (Bartzokis, 2002; Bartzokis et al, 2003; Uranova et al, 2004) and confirmed in prospective imaging studies of SZ and healthy control cohorts followed over several years (Cocchi et al, 2009; Ho et al, 2003; Whitford et al, 2007). We suggested that antipsychotic medications promote WM development and specifically promote myelination of the lower layers of cortex as one of their mechanisms of action (Bartzokis, 2002; Bartzokis, 2011; Bartzokis et al, 2009). In a prior cross-sectional study we

observed that, very early in treatment, both typical and atypical antipsychotics increased WM volume above that of healthy controls (Bartzokis et al, 2007) primarily due to increased myelin in the lower cortical layers (Bartzokis et al, 2009). The current prospective study examined whether improved medication adherence made possible by LAI could influence this myelination process in patients with first-episode SZ.

In healthy individuals, the developmental trajectory of brain myelination continues well into middle age, when WM makes up approximately half the brain volume, with approximately half the WM volume consisting of myelin (Figure 1) (Bartzokis et al, 2001; Kemper, 1994) (reviewed in Bartzokis and Lu, 2009). Myelin is a highly specialized lipid membrane wrapping of axons that has the highest cholesterol content of any brain tissue and increases action potential transmission speed over 100 fold (O'Brien and Sampson, 1965; Rouser et al, 1972; Saher et al, 2005). Inversion-recovery (IR) MRI images are optimal for quantifying myelination (Barkovich et al, 1992; Valk and van der Knaap, 1989; van der Knaap and Valk, 1990) because they are most sensitive to the high cholesterol concentrations in myelin (Koenig, 1991). There is excellent agreement between the lifetime myelination trajectory of normal individuals observed in vivo with IR sequences and published postmortem data (Bartzokis et al, 2001; Bartzokis and Lu, 2009). In the frontal lobe, peak myelination is reached at age 45 as measured by both in vivo MRI 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" that includes the heavily myelinated lower layers of cortex (Bartzokis et al, 2001; Bartzokis et al, 2007; Bartzokis et al, 2003) (Figure 1). For simplicity this IR-based measure will herein be referred to as WM.

Long-acting injectable (LAI) delivery of typical antipsychotic medications has been available for several decades. However, an atypical (also referred to as second generation) LAI antipsychotic medication, Risperdal® CONSTA® (RLAI) has only been available recently. Treatment with RLAI has been associated with substantially improved clinical outcomes, decreased hospitalizations, and significant healthcare cost savings (Lindenmayer et al, 2009; Olivares et al, 2009b; Velligan et al, 2009; Willis et al, 2010) (reviewed in Keith, 2009). In a recent study, greater improvements in clinical parameters such as number and duration of hospitalizations were observed in RLAI-treated patients who were *recently* diagnosed with schizophrenia than for those with chronic schizophrenia (Olivares et al, 2009a) suggesting that improving adherence may be particularly important early in the disease.

Poor adherence to medications may be a modifiable risk factor for suboptimal outcomes in SZ antipsychotic treatment (reviewed in Keith, 2009). We examined treatment with risperidone, which is available in both RLAI as well as oral risperidone (RisO) formulations. We performed a randomized clinical trial comparing these two formulations in first-episode subjects to test the hypothesis that improved adherence can positively impact frontal lobe myelination and cognitive functions dependent on the frontal lobe.

METHODS

Subjects

Schizophrenic subjects were recruited from the fourth cohort of the Developmental Processes in Schizophrenia Disorders Project, conducted at the UCLA Aftercare Research Program (Nuechterlein et al, 1992; Nuechterlein et al, 2008). The first psychotic episode for the SZ subjects (18 males and 6 females, aged from 18 to 33 years old) began within the last two years (median duration since onset of first episode was 6 months (SD=5.9)) and a DSM-IV diagnosis of schizophrenia or schizoaffective (depressed type) disorder was established

using the Structured Clinical Interview for DSM-IV by diagnosticians with demonstrated inter-rater reliability (Nuechterlein et al, 2008). Patients with significant substance abuse or history of neurological disorders or significant head trauma were excluded (Nuechterlein et al, 2008).

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. 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, including 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, seizure disorder, etc.).

Forty-five patients were recruited for this MRI study component and entered the randomized trial in the Developmental Processes in Schizophrenia Disorders Project. All subjects were taking oral antipsychotic medications prior to randomization: risperidone 52%, olanzapine 24%, quetiapine 20%, and ziprasidone 4%. To establish a common baseline assessment point, the 48% of subjects whose antipsychotic medication was not already RisO were cross-tapered from their initial antipsychotic medication to RisO. All subjects were on RisO as the sole antipsychotic medication for a minimum of 10 weeks prior to baseline MRI assessment. When participants reached the randomization point, treatment arm assignment was done using a random number table. All treatment was open-label and not blinded. The RisO or RisC dose was optimized by the treating psychiatrists based on the clinical response of each patient. This resulted in a mean dose of 2.9 mg (SD=1.8, range 1 to 7.5 mg) for the RisO group and 26.4 mg (SD=4.2, range 12.5 to 37.5 mg) (modal dose 25 mg) for RisC group. These average doses are in line with the equivalent doses for switching from RisO to RisC (3 mg RisO and 25 mg RisC) (Bai et al, 2007). This MRI study component had an attrition rate of 33% between the baseline and the 6-month point (9 lost to follow-up and 6 were switched to a different medication before study end point). There was no difference in MRI study attrition rate between RLAI and RisO groups ($\chi^2=.19$, $p=.66$), or in the diagnosis of schizoaffective disorder (two in each group; 18% and 15%, respectively; $\chi^2=.034$, $p=.86$). Similarly, there were no significant differences in the demographics (age, gender, race) of the dropouts compared to the subjects who completed both MRIs on assigned medication (χ^2 and t-statistics, $p>.24$).

Our prior cross sectional data that examined white matter volume versus medication exposure showed a non-linear (quadratic – “inverted U”) trajectory that peaked at 12 months after the initiation of treatment, followed by a premature decline compared to normal controls (Bartzokis et al, 2011). This non-linear trajectory made it imperative that the RisO and RLAI groups were closely matched for pre-randomization medication exposure. We therefore set an a priori limit on the maximum difference in pre-randomization exposure to antipsychotic medications between the RisO and RLAI groups of one month. This set a minimum pre-baseline medication exposure of 4.3 months and excluded three RisO subjects with shorter exposures. On the upper end of exposures one subject was excluded because of pre-randomization medication exposure, almost 4 SDs longer than the entire sample. Excessive motion artifact excluded one subject and the discovery of exposure to LAI antipsychotic of a subject randomized to RisO excluded one additional subject. The average exposure to antipsychotic medications at the baseline scan for the twenty-four subjects included in the analysis was 7.2 months (range 4.3 to 14.2 months) and the two treatment groups did not differ on this parameter ($p=.17$) (Table 1). The two groups were not

statistically different in demographic variables except for racial/ethnic composition which differed between the groups ($\chi^2=10.2$, $df=3$, $p=.017$). The RisO group was comprised of 4 (31%) African Americans, 5 (38%) Hispanics, and 4 (31%) Caucasians while the RLAI group was comprised of 4 (36.4%) African Americans, 2 (18.2%) Hispanics, 5 (45.4%) Asians, and no Caucasians.

Our comparison group consisted of 14 healthy control (HC) subjects. 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 or head trauma with loss of consciousness for greater than 15 minutes; no history of chronic medical conditions likely to result in structural brain abnormalities (i.e., stroke, transient ischemic attack, seizures, hypertension, diabetes, etc.); and self-report that no first-degree relative has been treated for a major psychiatric disorder. These subjects were matched for demographic characteristics to the SZ cohort (age 24.4 vs. 24.6, $p=.88$; race, $p=.10$; and gender 18m/6f vs. 8m/6f, $p=.25$) with the exception of education (12.6 vs. 15.4 years, $p<.0001$).

Imaging

The two cohorts were scanned using the same MRI techniques, MRI instrument type, and field strength (1.5 Tesla).

MRI Protocol—The MRI examination used our previously published methods (Bartzokis et al, 2001; Bartzokis et al, 2007; Bartzokis et al, 1993). In brief, a coronal pilot sequence was used to align a sagittal MRI pilot sequence that 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 concomitant coronal sequences of the same brain slices were acquired. An inversion-recovery (IR) turbo sequence (TR=2500, TI=625, TE=11, 1 repetition) was used in subsequent analyses as the “myelinated white matter” measure (Figure 1 and 2). A transverse asymmetric dual spin-echo turbo sequence (TR=2500, 2 repetitions, TE=22,90) was used to produce the calculated T₂ image, which served to delineate the brain/CSF border in subsequent analyses (Figure 2). Both IR and spin-echo sequences have 256 × 192 view matrix, 24 cm field of view, to produce co-registered 3 mm thick contiguous slices.

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 three-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 data for the regions of interest showed an intraclass reliability coefficient (r_{xx}) of .86 for total frontal lobe volume and .90 for WM (Bartzokis et al, 1993).

Cognitive testing

The CogState computerized cognitive battery (Westerman R, 2001) was administered and available on all participants at the end of study. These tests include measures of *Simple Reaction Time*, *Choice Reaction Time*, *One-back Working Memory*, *Two-back Working*

Memory, and *Set-Shifting* (assesses mental flexibility, concept formation, and capacity to benefit from feedback).

Data analyses

We performed the Kolmogorov-Smirnov test of normality on the volume change measures for the frontal lobes, frontal WM, and frontal GM, which indicated that the data were normally distributed for the entire SZ sample and for each medication group separately ($p > .05$); therefore, we used parametric tests for all statistical analyses. Data analyses were performed using a one-way analysis of covariance. The dependent variable was change in WM volume from baseline. Because the racial distribution differed by medication group, the covariance analyses were adjusted for race. The analysis also included pairwise t-tests on the significance of within-group change.

To better understand the functional implication of brain changes, the association between WM volume change and cognitive outcome was examined for the entire SZ cohort regardless of treatment arm. Associations between change in WM volume from baseline to 6 months and cognitive performance of the SZ cohorts at the end of study were assessed with Pearson correlational analyses. All tests were 2-tailed with the level of significance set as $\alpha = .05$.

RESULTS

The volumetric change/month for each subject was the principal dependent variable of interest. These data are depicted in Table 2 and Figure 3.

The change in overall size of the frontal lobe did not differ between the RLAI- and RisO-treated groups. The change in WM volume was significantly different between the two medication groups with the RLAI group demonstrating non-significant increase in WM volume while the RisO group showed a reduction in WM volume across the study period. Conversely, the GM volume was increased in the RisO group while the RLAI-treated group showed a non-significant decrease in GM volume.

The corresponding volume changes for the HC subjects are included in Table 3. As expected, the interval change in WM for the healthy controls ($N=14$) was non-significant, intermediate between the RLAI and RisO groups, and not different from either treatment group.

For CogState performance at study end point, increased WM volume was significantly associated with faster reaction time on the two higher-order executive tasks involving working memory (two-back task: $r = -.431$, $p = .045$) and mental flexibility (set shifting task: $r = -.465$, $p = .029$) (Figure 4), which are associated with frontal-systems functioning. Statistically adjusting for intracranial volume tended to improve the strength of the relationships between change in WM volume with Two-Back Task ($r = -.527$, $p = .014$) and Set-Shifting response time ($r = -.618$, $p = .003$). In contrast, change in gray matter volume was marginally associated with slower response times on the same Two-Back Task ($r = .404$, $p = .062$) and on One-Back performance ($r = .324$, $p = .141$). Controlling for intracranial volume also tended to increase the strength of these relationships (Two-Back: $r = .455$, $p = .038$; One-Back: $r = .385$, $p = .085$). The other three measures from the Cogstate battery capture simple reaction time involving response to stimuli or choosing between two stimuli and are not cognitively demanding. These measures were not associated with change in WM volume ($p > .39$).

The subjects in this study had been treated for an average of 7.2 months before randomization and achieved substantial improvements in symptom severity by the time baseline assessment was done. Significant associations with symptom severity were therefore not hypothesized. For completeness, associations between brain volume changes and two measures of psychiatric symptom severity - the Brief Psychiatric Rating Scale (BPRS) (Ventura et al, 1993) and the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1984) - were performed. As expected, neither WM nor GM volume changes were associated with the BPRS total score or the global rating scores for any of the SANS subscales ($p>.05$).

DISCUSSION

To our knowledge this is the first study to report that medication delivery mode (LAI versus oral) has a significant differential effect on any brain volume variable. During this treatment trial, RLAI seems to promote myelination and stabilize frontal lobe WM volume compared to the decrease observed with RisO (Table 2 and Figure 3). A considerable part of the observed changes in WM represent a myelination-driven shift of the GM/WM boundary into or out of the cortex. This is most clearly demonstrated by examining the RisO data that show the *decrease* in WM volume to be accompanied by an *increase* in GM volume (Figure 3). Given that frontal lobe volume did not show a meaningful volume change, the most plausible explanation is that the changes in WM and GM detected by the myelin-sensitive IR images represent a shift of the GM/WM boundary (see Figures 1 and 2).

The antipsychotic medication exposure at the time of the baseline and end point assessments likely influenced the absolute values of WM change. In a recent cross-sectional study of SZ (Bartzokis et al, 2011), we examined a wide range of medication exposure durations to *oral* antipsychotics (2.3 to 273 months) and observed that frontal lobe myelination was affected by treatment duration. The myelination trajectory was significantly quadratic, reaching a peak at one year of antipsychotic treatment followed by a decline that was markedly accelerated compared to healthy subjects who do not decline until after the fifth decade of life (Figure 1) (Bartzokis et al, 2001; Bartzokis et al, 2011). In the current study our assessment points spanned this peak in antipsychotic treatment-associated myelination (baseline assessment at 7.2 months with the follow up at 14.9 months). The decline in WM volume observed in the RisO group (Table 2 and Figure 3) is therefore consistent with the trajectory of decline that occurs after the first year of treatment. Furthermore, the non-significant increase in WM volume observed with RLAI suggests that the trajectory defined by oral antipsychotic treatment may be modifiable with RLAI. This modification in the trajectory seems to be primarily driven by the superior adherence to medication achieved with RLAI since both treatment arms received the same antipsychotic medication and only differed in delivery mode.

The *change* in frontal lobe WM volume was positively associated with reaction time performance specifically on subtests involving higher-order executive functioning of working memory and mental flexibility functions (Figure 4). These functions are mediated by frontal lobe systems. This suggests that increased frontal lobe WM volume is associated with improved performance on cognitive measures. This relationship may be domain specific, as other measures from the Cogstate battery that capture simple reaction time involving response to stimuli or choosing between two stimuli without higher-level working memory demands were not associated with WM change. As explained above, the WM increase seems to be primarily due to an increase in myelination of the lower layers of the cortex that shifts the GM/WM border into the cortex, and therefore we observed essentially opposite and counterintuitive associations (better performance with decreased GM volumes).

An antipsychotic-induced increase in WM is also supported by our prior cross-sectional study which showed that, very early in treatment, both typical and atypical antipsychotics increase WM above that of healthy controls (Bartzokis et al, 2007). This was recently confirmed by our second cross-sectional study, showing the antipsychotic medication exposure-related quadratic trajectory of WM volume described above (Bartzokis et al, 2011). Although the WM increase may be greater with atypicals, this *common* effect of typical and atypical antipsychotics on myelination is consistent with the shared ability of all known antipsychotics to block dopamine 2 receptors and the striking correlation between their affinity to this receptor and the clinically effective dose (Seeman, 2010). The mechanism underlying an antipsychotic-induced myelination is likely indirect and may involve dopamine receptor blockade promoting increased intracortical myelination (reviewed in Bartzokis, 2011). The current data suggests that consistent medication levels achievable with LAI may have an advantage in achieving and maintaining a higher WM volume.

The increased intracortical myelin early in treatment is also consistent with the observation from a non-human primate study where adherence to antipsychotic treatment was experimentally controlled. The study revealed that non-human primates exposed to either typical or atypical antipsychotics for six months had an *increased* glial density (with unchanged neuronal density) (Selemon et al, 1999). In that same study, risperidone was the only antipsychotic associated with a decline in cortical neuron density. Greater intracortical myelination reduces fixation-associated cortical shrinkage, and could thus account for this risperidone-associated decline in neuronal density (Bartzokis and Altshuler, 2005; Bartzokis and Altshuler, 2003). In addition, several rodent models suggest that exposure to antipsychotics may promote oligodendrocyte differentiation and myelin repair (Wang et al, 2010; Xu et al, 2010). On the other hand, another study using non-human primates showed that a *loss* of glia may occur with oral antipsychotics when administered over much longer exposure times (17–27 months) (Konopaske et al, 2008). Loss of oligodendrocytes and myelin is also observed at post mortem of older chronic SZ subjects after many years of treatment with oral antipsychotics (reviewed in Bartzokis, 2011).

Adherence to medication treatment has been a chronic problem in the treatment of psychiatric disorders such as schizophrenia. Atypical antipsychotics are associated with lower risk of acute and chronic extrapyramidal side-effects, which may contribute to the better acceptance of both oral and LAI formulations (reviewed in Keith, 2009). The improved clinical outcomes, decreased hospitalizations, and significant healthcare cost savings associated with RLAI (Lindenmayer et al, 2009; Olivares et al, 2009b; Velligan et al, 2009; Willis et al) (reviewed in Keith, 2009) have spurred efforts to develop additional LAI treatments. However, these treatments remain underutilized, in part because of lack of clear biological evidence for benefits on disease progression and concerns about metabolic side-effects (reviewed in Keith, 2009; Lindenmayer et al, 2009). The current study suggests that the improved outcomes may be due to superior ability of RLAI to maintain frontal lobe myelination and supports the hypothesis that a promyelination effect may be a mechanism of action of antipsychotics (Bartzokis, 2002; Bartzokis et al, 2011) (reviewed in Bartzokis, 2011).

Strengths of this study included the use of imaging sequences that optimally track the process of myelination (Figure 1), excellent scoring reliability, prospective design, and a young cohort of first-episode SZ subjects randomly assigned to the two treatment arms. The study has several important limitations. The sample sizes of the treatment groups were small and not matched for race. Despite this limitation, treatment differences were apparent and remained significant when race was covaried (Table 2 and Figure 3). Complete cognitive data were available only at the follow-up time point, precluding the examination of change

in cognitive scores against change in WM volume. The absence of matched subjects with very minimal pre-randomization antipsychotic exposure precluded assessment of very early medication-related changes in WM and, although all subjects were placed on RisO for at least 10 weeks before randomization, treatment occurring prior to study entry was not standardized. The availability of only two time-points limits our ability to define trajectories of change that our cross-sectional oral treatment data suggest is quadratic and peaks at approximately one year of antipsychotic treatment (Bartzokis et al, 2011). Finally, our data suggest that antipsychotics may primarily change intracortical myelination (Figure 3) (Bartzokis et al, 2009) (reviewed in Bartzokis, 2011). To more fully define how LAI medications change the myelination trajectory beyond the first year of treatment, prospective randomized studies, over longer durations, and with multiple time points that also include measures of intracortical myelin are needed.

The advent of *in vivo* neuroimaging methods that can dissect subtle differences in brain tissue characteristics may help clarify disease pathophysiology as well as the mechanisms of action of antipsychotic treatments. These methods can examine clinical as well as treatment response endophenotypes and thus improve targeting of treatment interventions. By modifying adherence, RLAI may differentially impact myelination and account for the better long-term outcomes of RLAI compared to the oral treatments. Improved treatment decisions and early intervention may make it possible to increase effectiveness of antipsychotic treatments and thus provide an opportunity to mitigate the biologic and clinical trajectories of decline into chronic/refractory states of disease (Bartzokis et al, 2011; Lieberman, 2006).

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G. Bartzokis and Po H. Lu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. K. Nuechterlein directs the schizophrenia research program that provided the diagnosis and research treatment conditions for this study.

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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 panel is in vivo data from Bartzokis et al (2001). Right panel shows postmortem *intracortical* myelin (ICM) 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 in the middle of the fifth decade.

Figure 2.

Coronal inversion recovery (IR) image of the frontal lobe used to measure myelinated volume. 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 T₂ image (not shown here – see Bartzokis et al, 1993).

Figure 3. Covariate adjusted[†] mean change scores (SD) of randomized long-acting injectable risperidone consta (RLAI) versus oral risperidone (RisO) treatment in subjects with first-episode schizophrenia

WM = White Matter; GM = Gray Matter

Within-Group Test: ** $p < .05$

Between Group Tests (risperidone long-acting injection (RLAI) vs. oral risperidone (RisO)):

* $p < .05$.

[†]Results are based on covariance analyses adjusting for race.

Figure 4. Correlations between medication-related change in white matter (WM) volume and reaction time performance on higher-order executive tasks involving working memory
 Figure 4A (left): the relationship between change in WM volume and reaction time on the Two-Back task (a working memory task),
 Figure 4B (right): the relationship between change in WM volume and reaction time on a Set-Shifting task (a measure of mental flexibility).

Table 1

Characteristics of schizophrenia subjects matched in baseline medication exposure and randomized to a trial of long-acting injectable risperidone consta (RLAI) versus oral risperidone (RisO)

	RLAI (n=11)	RisO (n=13)		
	Mean (SD)	Mean (SD)	t	p
Age, years	25.4 (4.8)	23.5 (4.6)	1.00	.33
Education, years	13.3 (2.2)	12.0 (0.8)	1.79	.10
Medication exposure prior to baseline scan (months)	8.0 (2.9)	6.6 (2.1)	1.41	.17
Age at psychosis onset, years	24.9 (4.8)	23.0 (4.5)	1.02	.32
Time between Scans, months	8.1 (1.8)	7.4 (1.2)	1.04	.31
	Male/female	Male/female	χ^2	p
Gender	9/2	9/4	0.50	.48

Table 2

Covariate adjusted* mean change scores (SD) of frontal lobe white matter (WM) and gray matter (GM) in patients with first-episode schizophrenia randomized to treatment with long-acting injectable risperidone consta (RLAI) versus oral risperidone (RisO)

	MED	N	Baseline		Follow-up		Within-Group		Between-Group		
			Mean (SD)		Mean (SD)	Change	t	p	F	p	d'
Frontal Lobe	RLAI	11	31.59 (2.84)		31.48 (3.03)	-.116 (.913)	-0.47	.64	0.04	.84	.09
	RisO	13	34.43 (1.82)		34.39 (1.80)	-.040 (.656)	-0.18	.86			
Frontal WM	RLAI	11	11.57 (1.94)		11.74 (1.93)	+.164 (.671)	0.74	.47	4.80	.04	.96
	RisO	13	12.49 (1.09)		11.93 (1.09)	-.567 (.593)	-2.84	.01			
Frontal GM	RLAI	11	20.02 (1.72)		19.74 (1.42)	-.280 (.976)	-1.07	.30	4.18	.05	.89
	RisO	13	21.93 (1.06)		22.46 (1.15)	+.527 (.814)	2.23	.04			

* Results are based on covariance analyses adjusting for race.

d' denotes effect size (Cohen's d) (Cohen, 1988).

Table 3

Mean baseline, follow-up, and change scores (SD) of frontal lobe, white matter (WM) and gray matter (GM) for 14 age-matched healthy subjects

	Baseline	Follow-up	Change	Within-Group	
	Mean (SD)	Mean (SD)		F	p
Frontal Lobe	34.17 (2.49)	34.18 (2.60)	+.014 (.706)	0.33	.75
Frontal WM	12.67 (1.66)	12.40 (1.56)	−.267 (.442)	−1.63	.13
Frontal GM	21.50 (1.69)	21.78 (1.79)	+.281 (.890)	0.54	.60

* Results are based on covariance analyses adjusting for race.