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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 due to instrument effects) 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.
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

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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

1. Introduction

The human brain is unique in its disproportionately high myelin content and long developmental (myelination) phase (Bartzokis, 2004a, 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, 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; 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, 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, 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 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" which includes highly myelinated portions of the lower cortical layers (see Fig. 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