



Full length article

Differential susceptibility of white matter tracts to inflammatory mediators in schizophrenia: An integrated DTI study



Konasale M. Prasad ^{a,*}, Catherine H. Upton ^{a,1}, Vishwajit L. Nimgaonkar ^a, Matcheri S. Keshavan ^b

^a Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, United States

^b Department of Psychiatry and Behavioral Neuroscience, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States

ARTICLE INFO

Article history:

Received 26 January 2014

Received in revised form 23 September 2014

Accepted 25 September 2014

Available online 22 October 2014

Keywords:

Schizophrenia
Inflammation
Immune mediators
Cytokines
White matter
Connectivity

ABSTRACT

Background: The pathophysiological underpinnings of impaired anatomical and functional connectivity are not precisely known. Emerging data suggest that immune mediators may underlie such dysconnectivity. We examined anatomical brain connections using diffusion tensor imaging (DTI) data in relation to interleukin-6 (IL-6) and C-reactive protein (CRP) levels among early-course clinically stable schizophrenia subjects compared to healthy controls (HC).

Methods: DTI data were acquired in 30 directions with 2 averages. Fractional anisotropy (FA) and radial diffusivity (RD) maps were separately processed using FSL4.1.9 and Tract-Based Spatial Statistics (TBSS). Threshold free cluster enhancements (TFCE) were examined employing familywise error (FWE) corrections for multiple testing within linear regression models including age, sex and socioeconomic status as covariates. IL-6 and CRP were assayed using highly sensitive and specific sandwich immunosorbent assays.

Results: The groups did not differ in age and sex as well as in the IL-6 and CRP levels. IL-6 levels were negatively correlated with the FA and positively correlated with RD among schizophrenia subjects but not HC. The voxel clusters that showed significant correlations were localized to the forceps major, the inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus. CRP levels showed similar pattern except for lack of correlation with RD on any cluster that corresponded to the forceps major.

Discussion: Our results suggest that the IL-6 and CRP contribute to impaired anisotropy of water diffusion in selected pathways that have been previously associated with schizophrenia suggesting differential susceptibility of selected neural pathways to immune mediators.

© 2014 Elsevier B.V. All rights reserved.

1. Introduction

Impairments in both anatomical (Ellison-Wright and Bullmore, 2009) and functional (Fitzsimmons et al., 2013) connectivity suggest that schizophrenia may be a dysconnection syndrome. Elucidating the factors that contribute to the dysconnection is critical to identify novel targets for drug discovery.

Several lines of evidence strongly suggest the role of immune mediators in the pathophysiology of schizophrenia (Heath et al., 1967; Rothermundt et al., 2001; Saetre et al., 2007; Muller and Schwarz, 2010). Postmortem studies note activated microglia/macrophages (Bayer et al., 1999; Radewicz et al., 2000; Wierzba-Bobrowicz et al., 2005), elevated expression of inflammatory markers in the prefrontal cortex (PFC) neurons (Fillman et al., 2013) and vasculature (Harris et al., 2008), and autoantibodies against frontal (Henneberg et al., 1994), cingulate (Ganguli et al., 1987; Kelly et al., 1987; Henneberg et al., 1994), hippocampal cortices (Ganguli et al., 1987), and glutamate

receptors (Tsutsui et al., 2012) in schizophrenia. Autoimmune disorders may elevate the risk for schizophrenia both independently (Benros et al., 2011; Chen et al., 2012) and in combination with exposure to infectious agents (Benros et al., 2011). A meta-analysis noted elevated peripheral blood inflammatory cytokines in schizophrenia compared to healthy controls (HC) (Potvin et al., 2008). Genome-wide association studies replicate the association of Major Histocompatibility Complex (MHC) region variants (where a majority of immune genes are located) with schizophrenia (Purcell et al., 2009; Shi et al., 2009; Stefansson et al., 2009; Ripke et al., 2011). Non-steroidal anti-inflammatory drugs may reduce psychotic symptom severity (Muller et al., 2002, 2010; Sommer et al., 2012). However, the mechanisms through which immune mediators affect cognitive impairments and psychopathology are under active investigation.

Characterizing peripheral immune markers that are relevant to the pathophysiology of schizophrenia is critical for early diagnosis, novel drug discovery, monitoring treatment response and predicting risk. We examined the association of the C-reactive protein (CRP)—an acute phase reactant, and interleukin-6 (IL-6)—a predominantly pro-inflammatory cytokine with the anisotropy of water diffusion using diffusion tensor imaging (DTI). CRP is a pattern recognition molecule

* Corresponding author at: Rm 422, Ste 431, Western Psychiatric Institute and Clinic, 3811 O'Hara St, Pittsburgh, PA 15213, United States.

¹ Formerly of the Department of Psychiatry, University of Pittsburgh School of Medicine.

that is phylogenetically highly conserved and is primarily expressed in liver following induction by IL-6 (Black et al., 2004). Although extrahepatic expression of CRP in the neurons (Yasojima et al., 2000) and lymphocytes (Kuta and Baum, 1986) are described, plasma levels mainly reflect hepatic synthesis (Black et al., 2004). CRP may be either pro- or anti-inflammatory depending on the context (Eisenhardt et al., 2009). IL-6 is mainly a pro-inflammatory cytokine secreted by T cells and macrophages (Kato et al., 2009). Quantitative reviews have reported elevated levels of IL-6 (Potvin et al., 2008) and CRP (Miller et al., 2014) in schizophrenia with variations related to antipsychotic use, associated comorbidities and stage of illness.

Elevated CRP is associated with cognitive deficits in schizophrenia both independently (Dickerson et al., 2007) and through interaction with exposure to Herpes Simplex Virus 1—a neurotropic virus (Dickerson et al., 2012). Although quantitative reviews suggest elevated IL-6 in schizophrenia, few studies have examined the association of IL-6 with *in vivo* neurobiology of schizophrenia. Among middle-aged and elderly healthy subjects, elevated IL-6 was associated with cognitive impairments (Weaver et al., 2002; Marsland et al., 2006) and hippocampal volume reductions (Marsland et al., 2008). However, the association of CRP and IL-6 with brain connections in schizophrenia is not examined adequately.

DTI offers insights into axonal integrity by characterizing anisotropy of water diffusion. DTI is based on the principle that water tends to diffuse more freely along the longitudinal axis (λ_1) than along the transverse axes (λ_2, λ_3) of axons. The fractional anisotropy (FA)—diffusion along the λ_1 compared to λ_2 and λ_3 , and the radial diffusivity (RD)—the diffusion perpendicular to the axon orientation—index white matter integrity (Beaulieu, 2002). Factors affecting impaired anisotropy of water diffusion that could impact connectivity are unclear. DTI studies report altered diffusivity in the association (superior longitudinal fasciculus (SLF), uncinate fasciculus) (Friedman et al., 2008), commissural (corpus callosum, forceps minor) (Friedman et al., 2008) and projection (internal capsule and cingulum) (Kubicki et al., 2005; Cheung et al., 2008) fibers in schizophrenia compared to controls. A meta-analysis noted reduced anisotropy in the left frontal and left temporal deep white matter (Ellison-Wright and Bullmore, 2009) suggesting impaired prefrontal-thalamic and fronto-temporo-occipital connections. Our functional imaging study revealed increased activation in the PFC and thalamus among schizophrenia subjects compared to HC during episodic memory challenge (Stolz et al., 2012).

Our goal was to examine whether selected immune mediators (IL-6 and CRP) affected the anisotropy measures in these tracts. Specifically, we predicted that the IL-6 and CRP levels would be negatively correlated with FA and positively correlated with RD in the fronto-thalamic and fronto-temporo-occipital white matter tracts. Since FA and RD represent diffusion in orthogonal directions and may be negatively correlated with each other, we explored the correlation between the FA and RD extracted from the significant voxel clusters that show correlation with IL-6 and CRP within FSL.

2. Methods

2.1. Clinical evaluations

We enrolled 68 young adults (schizophrenia/schizoaffective disorder = 39, HC = 29). Of these participants, 64 subjects were included in the CRP analysis (SZ = 37; HC = 27) and 56 (SZ = 33, HC = 23) in the IL-6 analysis based on the availability of blood samples and assay qualities. The diagnosis of schizophrenia/schizoaffective disorder was obtained by administering the Structured Clinical Interview for DSM-IV (SCID) (First, 1997) and confirmed through consensus diagnosis by reviewing follow-up and medical chart data. The socioeconomic status (SES) was assessed using Hollingshead Index (Hollingshead, 1975). All patients were on stable doses of antipsychotics. The exclusion criteria were substance abuse in the previous month or dependence 6 months

prior to enrollment, mental retardation per the DSM-IV, and/or serious neurological or other medical illnesses. After fully explaining the experimental procedures, subjects provided informed consents. The University of Pittsburgh IRB approved the study.

2.2. Imaging procedures

The DTI data was acquired in 30 directions ($b = 1000 \text{ s/mm}^2$) with 2 averages on a 3T Siemens Tim Trio scanner. For each average, one $b = 0$ reference image was acquired. Scanning parameters were as follows: slices 48, thickness 3.2 mm, TE = 90 ms, TR = 6300 ms, flip angle = 90°, matrix 128×128 , FOV = 240 mm. Scans with motion artefacts were not included in the analysis. The diffusion data were processed using FSL 4.1 tools (Smith et al., 2006). The FA and RD maps were separately analyzed. Diffusion scans were skull-stripped using FSL's brain extraction tool and manually checked for optimum brain extraction. Eddy current and motion artefacts were then corrected before nonlinear registration of the skull-stripped FA maps to the MNI152 FA template. These co-registered images were processed using FSL's Tract-Based Spatial Statistics (TBSS) tool. Randomize 4.1.9 was used to compare study groups. Threshold free cluster enhancements (TFCE) were examined correcting for multiple comparisons using the familywise error (FWE) correction at $p \leq 0.05$ and 10000 permutations. The JHU White-Matter Tractography Atlas tool was used to identify significant regions-of-interest. The RD images were also processed using the same pipeline.

Using regression, CRP and IL-6 values were regressed to the FA and RD separately controlling for age, sex and SES. Fslmeans tool was used to extract FA values for each subject from the voxel clusters that showed significant differences in each model and identified using the JHU White-Matter Tractography Atlas.

2.3. Immunoassay

Highly specific singleplex quantitative ultrasensitive sandwich immunosorbent bead assay for IL-6 and CRP were conducted at the Luminex facility of the University of Pittsburgh Cancer Institute. Sandwich immunoassay uses the magnetic bead technology employing polystyrene microsphere beads that are internally dyed with red and infrared fluorospheres of differing intensities. After the sandwich immunoassay, beads are read for fluorescence signal intensity using Luminex detection systems.

2.4. Neuropsychological assessments

Sustained attention and executive functions were evaluated within a week of imaging using the Continuous Performance Test (CPT-IP) (Cornblatt and Keilp, 1994) and the Wisconsin Card Sorting Test (WCST) (Sharma, 2003), respectively. Verbal d' from the CPT-IP was used as a sensitivity measure of discrimination of signal from the false alarms. Within the WCST, we used percentage of perseverative errors to index executive functions.

2.5. Plan of analysis

After examining the group main effect on FA and RD controlling for age, sex and SES within FSL, we investigated the correlation of CRP and IL-6 levels with anisotropy of water diffusion. General linear model linear regressions were set up within the FSL to regress the CRP and IL-6 levels to the whole-brain FA and RD separately controlling for age, sex and SES. Statistical thresholds were applied as stated above. Next, we examined the correlation between the FA and RD extracted from the white matter regions with voxel clusters that showed significant correlation with IL-6 and CRP within FSL. The diagnostic groups were compared for differences in cognitive performances controlling for age and sex using ANCOVA models. We, then, examined the

متن کامل مقاله

دریافت فوری ←

ISIArticles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات