

White Matter Integrity and Antipsychotic Treatment in Schizophrenia

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Decreased white matter integrity was reported in schizophrenia, but little is known about the relationship with antipsychotic medications. We enrolled 42 unmedicated patients with schizophrenia in a longitudinal trial with risperidone. Symptom severity was assessed with the Brief Psychiatric Rating Scale (BPRS). We obtained diffusion weighted images before medication was started, and after six weeks of treatment. Matched healthy controls were also scanned twice six weeks apart. 30 diffusion sampling directions spanning the whole sphere were acquired twice and concatenated. To assess whole brain voxel-wise group differences and changes over time in scalar indices used AFNI's 3dttest++ (age, sex, and RMSrel as covariates) with clustsim, a bootstrapping method used to correct for multiple comparisons. Mean age of patients was 26.62 years, 62% of subjects were male. Of the 42 patients included here, 33 completed the study. BPRS total scores decreased significantly during 6 weeks treatment, average risperidone dose was 3.73+/-1.72mg. Fractional anisotropy (FA) was significantly decreased in a small area of the medial temporal lobe and mean diffusivity (MD) was significantly increased in the hippocampal part of the cingulum in unmedicated patients (n=40) compared to healthy controls (n=41). Longitudinal analyses showed no changes in FA, MD, RD or white matter macrostructure in healthy controls over time, and no changes in patients after six weeks of treatment with risperidone. We found only small areas of white matter integrity deficits in our predominantly medication-naïve patients. Our data suggests that a short-term course of antipsychotic medication may not alter white matter microstructure.

White matter integrity in bipolar disorder: effects of genes, stress, and immune factors.

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White matter (WM) microstructure and oligodendroglia have been associated with Bipolar Disorder (BD). In vivo, diffusion tensor imaging (DTI) studies consistently documented a pattern of higher mean diffusivity of water (MD), with higher diffusivity perpendicular to the main axis of brain WM tracts, although coated by myelin sheaths (radial diffusivity, RD), and lower diffusivity along the main axis of the WM fiber (axial diffusivity), altogether resulting in a lower preferential diffusivity along WM tracts, also reflected by decreased fractional anisotropy (FA). These measures reflect the myelination, orientational coherence, and microtubular axonal structure of fibers, and, in clinical settings, they associate with core clinical features of BD including impulsivity and suicide, cognitive performance, and response to antidepressant treatment. These differences have been associated both, with the genetic risk for BD, with specific gene polymorphisms influencing neurotransmission and the biological clock, and with environmental stressors increasing the risk for the disease, such as adverse childhood experiences. These differences are counteracted by lithium salts, the mainstay for the treatment of BD. They are worse in the presence of elevated biomarkers of cell-mediated immune activation and inflammation, and of elevated body mass index, both influencing, in turn, the outcome of the disorder. Altogether, DTI studies support the hypothesis that changes of WM microstructure in circuitries critical for emotional and cognitive processing could be linked with BD psychopathology, and that WM alterations in BD are a potential target both, for the development of new diagnostic techniques aiming at the definition of the biological underpinning of the disorder, and for drug discovery and development.

Developing big data neuroimaging approaches to understand the neurobiology of cognitive deficits in schizophrenia and other psychiatric disorders.

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Cognitive deficits in schizophrenia contribute to the functional and socioeconomic burden in the patients and may be related to functional and structural impairments of cerebral networks. We used Big Data approaches to clarify the functional and structural connectivity deficits and their independent and joint roles supporting two neurocognitive functions affected in schizophrenia: working memory and processing speed. A total of 261 patients (161M/100F; age=18-63 years) and 327 controls (146M/211F; age=18-65 years) were ascertained using ENIGMA rsfMRI and DTI analyses pipelines. ENIGMA mega-analytical aggregation was used to derive functional connectivity (FC) and structural fractional anisotropy (FA) measures. Canonical correlation analysis was used to study the association between cognitive deficits and functional and structural connectivity measures. Patients showed consistent cognitive, functional and structural deficits. Highest patient-control effect sizes were observed for cognitive deficits, followed by structural and functional connectivity measures (average Cohen's $d=0.72\pm 0.21$, 0.49 ± 0.14 and 0.31 ± 0.09). Functional and structural connectivity measures were uncorrelated and explained between 12 and 17% of individual variances in working memory and processing speed independently and up to 31% of the variance when combined, with relatively minimal overlaps. The regional functional and structural connectivity and their associations with neurocognitive deficits were proportional to the patient-control differences in regional connectivity. Functional and structural connectivity abnormalities both contribute to working memory and processing speed deficits in schizophrenia but largely independently, suggesting partially segregated mechanisms. The pattern of association suggested that schizophrenia specifically affected functional networks and white matter tracts that serve these cognitive domains. This association was replicated in normal controls and is likely independent of the diagnosis of schizophrenia.

Harmonization of Multi-Site diffusion MRI Schizophrenia Datasets

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Diffusion MRI (dMRI), the only non-invasive modality that can map the white matter (WM) connections of the brain, has been used extensively to investigate abnormalities in schizophrenia. Massive amounts of dMRI data have been acquired as part of many, usually small and underpowered, research experiments. Recent years have brought about attempts to pool such

datasets together to perform larger meta-analyses. Here, we present results of the first attempt to harmonize and analyze raw diffusion data across multiple schizophrenia datasets. DMRI data from 10 sites (ranging the spectrum of patients from early onset, first episode, early course and chronic schizophrenia, and as well as healthy controls) were pooled with a total of 509 healthy controls (234F, 274M: age 29.26+/-14.42) and 803 schizophrenia patients (363F, 439M: age 33.59+/-14.39). Pre-processing and data harmonization based on the rotation invariant spherical-harmonics (RISH) were used to remove the nonlinear scanner and sequence differences across sites. After all harmonized data was registered to the common template, global and regional WM integrity (FA and MD) across schizophrenia lifespan were computed using the tractography atlas, then statistically modeled across age. Significantly lower FA in patients were observed at all stages of schizophrenia, in majority of regions. The most significant differences in MD (predominantly higher in patients) were observed around the maturational peak. Differences between males and females were also observed in both groups. We will present the trajectories and quantitative parameters (peak age and effect sizes) of the whole-brain and specific regions for both genders in health and in schizophrenia.