BACKGROUND

There is consistent evidence that people with schizophrenia exhibit subnormal levels of Fractional Anisotropy (FA) in many regions of the brain, which may suggest demyelination or damage to the axon structure of white matter fibers (Kubicki et al., 2007). As shown in neurodegenerative diseases known to affect white matter integrity, reduced FA is correlated with neurophysiological functioning (Fink et al., 2010). It has also been demonstrated that proper cognitive functioning depends on efficient coordination of distinct brain regions, forming functional networks. Since these networks are interconnected by white matter tracts, we were interested in whether it is possible to delineate those networks by means of DTI, factor analysis, and cognitive domains.

The present study compared chronic schizophrenia patients and matched healthy controls on a recently developed automatic white matter clustering method to see: 1) if patients with schizophrenia have reductions in FA in anatomical bundles, 2) if factor analysis can group anatomical bundles into meaningful functional white matter networks, and 3) how functional white matter networks are associated with cognitive functioning in patients and controls.

METHODS

• A 3T GE magnet equipped with 8 channel coil was used to obtain scans from 50 male subjects (26 schizophrenia patients, 24 normal controls), who were group-matched on age, handedness, & parental socioeconomic status (Table 1).

• DTI Scan Parameters: Fifty-one directions, b=900s/mm², TR 17000 ms, TE 78 ms, FOV 24 cm, 144x144 encoding steps, 1.7 mm slice thickness, 85 axial slices.

• Deterministic (streamline) tractography was performed (Rosenberger et al., 2008), where tracts were seeded at every point in the brain where Linear Anisotropy (CL) was greater than 0.3 and truncated when CL fell below 0.15. Tracts shorter than 20mm were discarded (Fig. 1a).

• Fiber-clustering (O’Donnell et al., 2005) grouped fibers with similar shapes and spatial positions into clusters. This yielded 200 fiber clusters (FCs) (Fig. 1b) each consisting of a spatially similar subset of the fibers generated from the whole-brain tractography.

• The 200 FCs were grouped into 23 known anatomical white matter bundles by two raters (DT & MK) (Fig. 1c) to reduce the data for analysis. FA and Tract Diffusivity for each anatomical bundle was measured. Then, FA and Tract Diffusivity for each bundle was factor analyzed into one of 9 factors with a Varimax rotation with eigenvalues ranging from 10.0-5.0, which explained >85% of the variance (Table 2), (Fig. 1d). FA and diffusivity were calculated for each factor.

• Subject assignment also included neuropsychological tests on tasks relevant to cognition in schizophrenia, yielding over 300 cognitive variables. To reduce this data, Z scores were computed for each of the following variables based on this sample, and then grouped to form composite scores for four cognitive domains (Delawalla et al., 2006).

WORKING MEMORY: Wechsler Adult Intelligence Scale- 3rd Edition (WAIS-III) digit span (total forward and backward), Wechsler Memory Scale- 3rd Edition (WMS-III) spatial span (total forward and backward), WAIS-III letter-number sequencing, and the CPT-IP (overall d-prime).

EPIDEMIC MEMORY: WMS-III logical memory and WMS-III family pictures.

EXECUTIVE FUNCTION: Verbal Fluency (phonological for letters “F”, “K”, and “S” plus categorical for animals), WAIS-III matrix reasoning, and Wisconsin Card Sorting Test perseverative errors.

CRYSTALLIZED INTELLIGENCE: Standard scores from WAIS-III vocabulary subset.

RESULTS

GROUP DIFFERENCES: For the patients with schizophrenia, there was reduced cognitive functioning in Working Memory (t[38]=-4.86, p<.001), Episodic Memory (t[42]=3.85, p<.001), Executive Functioning (t[48]=3.30, p<.002), and Crystalized Intelligence (t[42]=-4.02, p<.001) [Fig. 3]. There were also reductions in FA for CC1 (t[48]=-2.18, p=.036), ILF (t[48]=-2.01, p=.05), and a trend toward reductions in the FA of White Matter Factor 1 (t[48]=1.87, p=.06) [Fig. 4]. There were no group differences in trace.

DTI/CORRELATIVE ANALYSIS: Correlations were run between cognitive domains and the 9 factors for both FA and Diffusivity, as well as between cognitive domains and anatomical bundles. For FA, there was a trend level correlation between Factor 8 (fonnis) and Episodic Memory for the schizophrenic group [r=.3517, NC, n=127; Fisher Z Transformation=1.99, p=0.05] (Fig. 5). There were no other correlations for FA. There were no correlations for Tract Diffusivity.

DISCUSSION

• Results show that people with schizophrenia have lower scores when compared to control subjects in these cognitive domains. The FA reduction in the genu of the corpus callosum and in the ILF in patients with schizophrenia suggests a loss of white matter integrity in these regions (Kubicki et al., 2007). The reductions of FA in frontal callosal and in ILF tracts attribute to the reduced ability of FA 1.

• Factor analysis had some success grouping functional networks of the brain, like the limbic system (Factors 4 and 8), Factor 8 (fonnis) was the only region of the brain that showed a correlation with cognitive measures. The difference between correlation coefficients for Factor 8 for Episodic Memory suggest impairment in this functional network in the patient group, as the fonnis has been associated with episodic memory in healthy populations (Squire et al. 1991).

• However, other anatomical tracts were grouped based on anatomy (e.g. Factor 1 included all callosal tracts), which may explain why most factors did not show meaningful cognitive correlations. Possible explanations for this type of grouping include low specificity of factor analysis run on already large anatomical bundles or low sensitivity of FA measures averaged over the entire bundles/factors. Future studies will focus on using factor analysis to group white matter more according to functional networks. This study demonstrates the potential of white matter functional analysis and the current limitations of this approach.

REFERENCES


