Tract-specific effects of schizophrenia demonstrated with quantitative MR diffusion tractography.

P. G. Nucifora[1], E. R. Melhem[1], J. W. Loughead[2], R. C. Gur[2], R. E. Gur[2], and R. Verma[3]

[1]Department of Radiology, Division of Neuroradiology, University of Pennsylvania, Philadelphia, PA, United States, [2]Department of Psychiatry, Section of Neuropsychiatry, University of Pennsylvania, Philadelphia, PA, United States, [3]Department of Radiology, Section of Biomedical Image Analysis, University of Pennsylvania, Philadelphia, PA, United States

INTRODUCTION

Several studies have demonstrated foci of abnormal white matter in schizophrenia, suggesting that schizophrenia may be a disorder of cerebral connectivity. However, the specific white matter tracts that are involved in this disease remain uncharacterized. Quantitative tractography can produce an index of the probability that a voxel lies on the diffusion pathway that connects the two regions in the brain (connection probability index), which allows the direct evaluation of entire white matter tracts in patients with schizophrenia.[1] In this study, we present quantitative tractography data supporting tract-specific relationships between connectivity and age in schizophrenia.

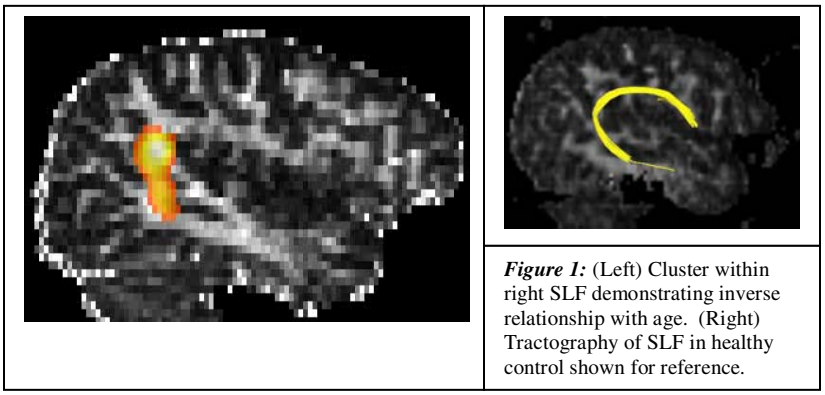

Figure 1: (Left) Cluster within right SLF demonstrating inverse relationship with age. (Right) Tractography of SLF in healthy control shown for reference.

METHODS

Diffusion tensor imaging (12-direction) was performed with a Siemens 3.0T scanner on 17 patients with schizophrenia (ranging in age from 23 to 52 years old) and 27 healthy controls (ranging in age from 21 to 52 years old). Datasets were registered using a combination of affine and nonlinear methods. Seed and target ROIs for individual white matter fiber tracts were defined using cortical and subcortical regions defined by the MNI atlas and coregistered across all subjects. Probabilistic tractography was performed for the major interlobar white matter tracts bilaterally. The probability maps generated for each tract were analyzed with cluster-level nonparametric testing using age as a covariate of interest. Both cerebral hemispheres were analyzed independently using this protocol.

RESULTS

Significant tract-specific correlations between connectivity and age were found in multiple white matter tracts in patients with schizophrenia. Specifically, the connection probability index of a cluster within the right superior longitudinal fasciculus (SLF) demonstrated a significant inverse relationship with age, as depicted in Figure 1. In addition, the connection probability index in a cluster comprising of nearly the entire left inferior longitudinal fasciculus (ILF) demonstrated a significant positive correlation with age, as depicted in Figure 2. Healthy controls did not demonstrate any significant relationships between age and connection probability index in either of these white matter tracts.

DISCUSSION

A decrease with age in the connection probability index of the right superior longitudinal fasciculus suggests an underlying abnormality in brain connectivity that may be specifically involved in schizophrenia. Decreased diffusion anisotropy in this region has previously been linked to auditory hallucinations,[2] and this work suggests a possible degenerative mechanism that is responsible for these symptoms.

An increase in the connection probability index of the left inferior longitudinal fasciculus with age may represent the effects of delayed maturation, as has been described in the left superior longitudinal fasciculus.[3] Taken together, these findings suggest that the effects of schizophrenia over time on white matter are dynamic and tract-specific.

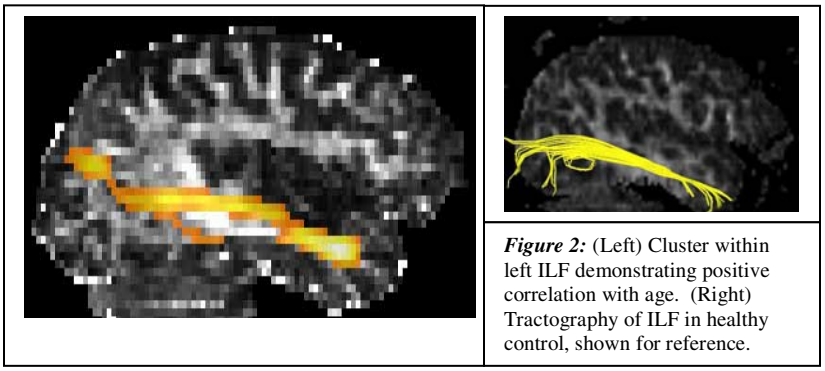

Figure 2: (Left) Cluster within left ILF demonstrating positive correlation with age. (Right) Tractography of ILF in healthy control, shown for reference.

References

1. Behrens, T. E. *et al.* Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nat. Neurosci.* **6**, 750-757 (2003).

2. Hubl, D. *et al.* Pathways that make voices: white matter changes in auditory hallucinations. *Arch. Gen. Psychiatry* **61**, 658-668 (2004).

3. Jones, D. K. *et al.* Age effects on diffusion tensor magnetic resonance imaging tractography measures of frontal cortex connections in schizophrenia. *Hum Brain Mapp* **27**, 230-238 (2006).