Motor Deficits Originating in the Extrapyramidal System in Chronic Schizophrenia: A Diffusion Tensor Imaging Study

Pelavin, P.E. (1), Alvarado, J.L. (1), Körte, I. (2), Saito, Y. (1), Schneiderman, J. (1), Niznikiewicz M.A. (3), McCarley, R.W. (3), Kubicki M. (1), Shenton, M.E. (1,3)

(1) Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts;

(2) Institute of Clinical Radiology Ludwig-Maximilians-University, Munich, Germany;

(3) Department of Psychiatry, VA Boston Healthcare System, Brockton Division, Harvard Medical School, Brockton, MA.

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Background

- The motor system is traditionally divided into pyramidal and extrapyramidal components; the pyramidal system contains the corticospinal tract (CST) and the corticobulbar tract while the extrapyramidal system includes virtually all other pathways which influence motor function including the basal ganglia and numerous projections from the brain stem.
- The CST originates in multiple cortical areas including the precentral gyrus (primary motor area) and the postcentral gyrus; it primarily controls the finer movements of distal muscles as well as the trunk, legs, and feet. For the extrapyramidal tract (EPT) we chose to look specifically at projections from the thalamus to the supplementary motor area; the EPT is responsible for reflexes, complex movements, and the initiation and inhibition for movement.
- Though these two tracts do differ in location and structure there is a great degree of overlap and crossing fibers. The distinction between these two motor systems is more for the distinction of their function which becomes apparent when damage is done to one system and not the other. The motor deficits in schizophrenia, for example, are attributed largely to the extrapyramidal side effects of neuroleptics.
- To look at the differences in these two motor systems we worked with Diffusion Tensor Imaging (DTI), which uses the patterns of water diffusion to determine the integrity and nature of white matter connections between different regions of the brain (**Figure 2**).

Methods

Subjects:

- Twenty-six male patients diagnosed with chronic schizophrenia (mean age=44.00) and twenty-six male healthy controls (mean age=41.85) matched for age (p=0.439), parental socio-economic status (p=0.311), and handedness (all right handed) **(Table 1)**.
- Within the patient group eighteen patients were taking atypical neuroleptics, two were taking typical neuroleptics, three were taking both, and three patients were not taking any at the time of the scan.

Image Acquisition and Processing:

- Diffusion tensor images were acquired on a GE 3T MRI scanner at a resolution of 1.7mm x 1.7mm x 1.7mm (51 diffusion directions, b=900, TR 17000 ms, TE 78 ms, FOV 24 cm, 144x144 matrix).

Tractography of the CST and EPT (Figure 1):

- Seven regions were extracted form the Freesurfer segmentation of each subject: precentral cortex, precentral white matter, postcentral cortex, postcentral white matter, and the thalamus of each hemisphere, in addition to the brain stem. The pons was traced manually in reference to a color-by-orientation map.
- Tractography of the CST was performed by seeding from both white matter regions and both cortical regions. The resulting fibers were then filtered through the anterior ipsilateral pons and any fibers passing through the thalamus were excluded; this was done separately for each hemisphere.
- Tractography of the EPT was performed by seeding from the thalamus and precentral white matter. These fibers were filtered through the precentral cortex and any fibers passing through the brainstem were excluded; this too was done for each hemisphere.
- Fractional Anisotropy (FA), mode and trace values were then calculated for all of the resulting tracts.

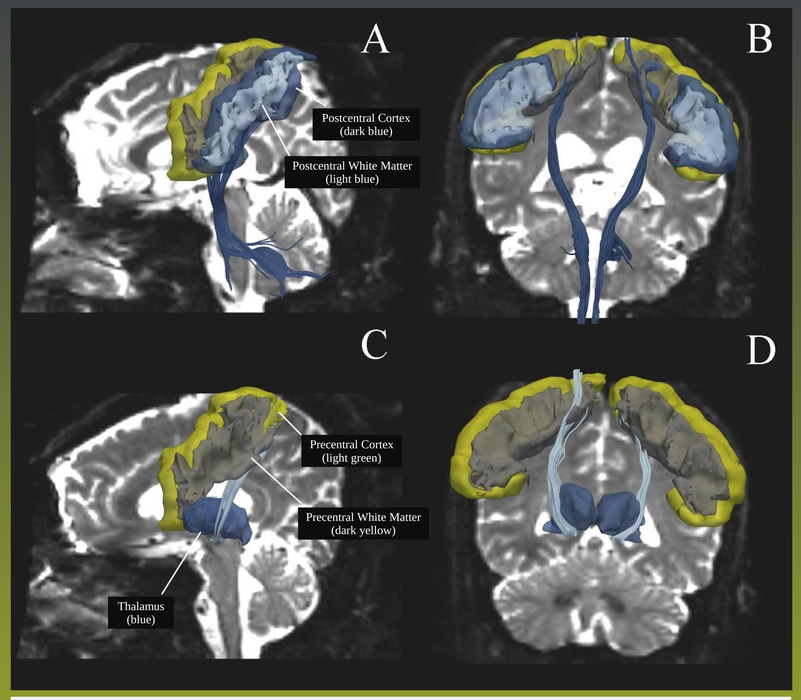

Figure 1: 3D rendering of the seeding regions used, the left hemisphere is labelled. (A) Sagittal view of the CST (B) Coronal view of the CST (C) Sagittal view of the EPT (D) Coronal view of the EPT.

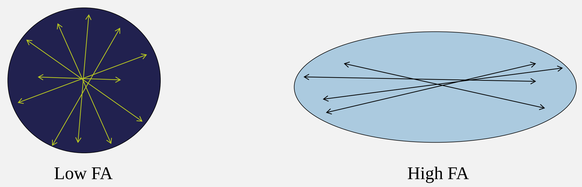

Figure 2: In areas with high FA water flow is very directional, often indicating dense white matter tracts with good myelination whereas a lower FA implies damage to the integrity and myelination of white matter.

Demographics for patients with chronic schizophrenia and matched healthy controls

	Mean (SD) [Range]		Independent Samples t-Test		
	Schizophrenic Patients n=26	Healthy Controls n=26	df[a]	t-test	P-value
Age (year)	44.00 (9.708) [22-55]	41.85 (10.177) [22-55]	1, 50	0.781	0.439
Gender (male/female)	26/0	26/0	1, 50		
Handedness[b]	0.72 (0.49)	0.71 (0.25)	1, 50	-0.291	0.773
Socioeconomic Status[c]					
subject's own (SES)	3.42 (1.07)	2.00 (0.80)	1, 50	5.45	0.0002**
parental (PSES)	2.60 (1.16)	2.27 (1.15)	1, 49	1.024	0.311
Education (school year)	13.13 (1.82)	14.94 (1.99)	1, 50	-3.417	0.001**
WAIS-III Overall IQ	95.81 (15.21)	110.0 (14.77)	1, 46	3.264	0.002**
Symptom Onset (years)	23 (4.99) [16-37] n=22	n/a			
Duration of Illness (years)	18.32 (10.31) n=22	n/a			
Antipsychotic Meds Dosage[d]	342.73 (268.67) n=24	n/a			
PANSS (total score)	81.4 (28.20) n=25	n/a			

WAIS-III = Wechsler Adult Intelligence Scale - 3rd Edition (Wechsler, 1997); n/a = data not applicable.

[a]The df differ due to unavailability of data in some cases. [b]Edinburgh inventory; right-handedness is above zero. [c]Higher scores indicated lower SES (Hollingshead, 1965). [d]Chlorpromazine equivalent (mg), three patients were not taking medicaiton at the time of the testing.

*P <0.05, **P<0.01

Table 1: T-tests were performed to match the subjects of the two groups.

Results

- No significant differences were found in FA, mode, or trace values when comparing the tracts of the two groups.
- There were a number of clinical correlations between the FA values of the right EPT and the clinical measures of the patients. Using Spearman correlations we looked primarily at clinical measures related to motor function from the Positive and Negative Syndrome Scale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS). We found that lower FA values of the EPT correlated with a greater severity of symptoms. The strongest relationship was seen between the FA value of the right EPT and the motor retardation subscore of the PANSS (p=.016, r=-.469) (**Figure 3**).
- While there were trends in the same direction for the FA values of the left EPT and many of the same measures, none of the correlations were significant.

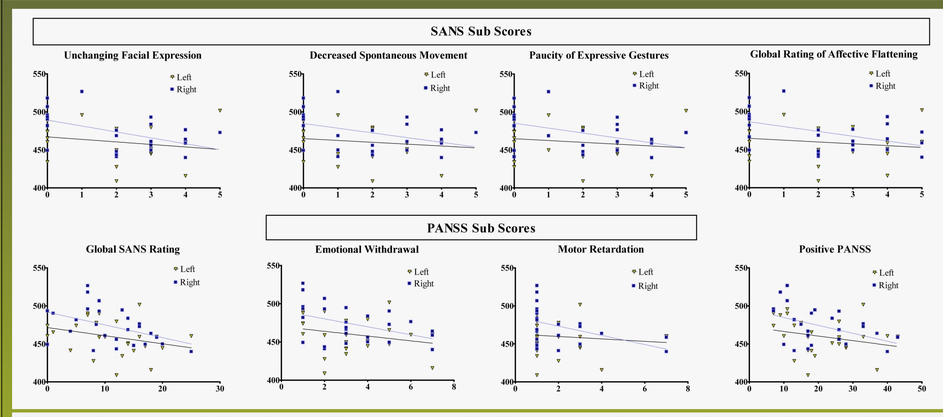

Figure 3: There were no findings for any of the CST measures but there were a number of correlations for the EPT. While there was only a positive trend (but no significant relationship) between some of the left EPT FA values and the clinical measures there were a number of significant negative correlations between the right EPT FA values and clinical measures (from top left to bottom right: p=.016, rho=-.477; p=.029, rho=-.437; p=.043, rho=-.408; p=.018, rho=-.460; p=.025, rho=-.439; p=.041, rho=-.403; p=.016, rho=-.469; p=.031, rho=-.424). [For all above graphs the y axis is the EPT FA value and the x axis is the clinical score, see graph title for clinical measure.]

Discussion

- We found that while there are motor deficits in the patients with chronic schizophrenia, as evidenced by the clinical scores pertaining to motor function, these deficits are not obvious from the DTI measures of the two groups which did not differ statistically.
- However, we observed a clear relationship between the EPT and motor function in the patients based on the negative correlations between white matter integrity, as measured by FA, and the various PANSS and SANS scores.
- The above findings support the division of these two motor systems based on their function. While the compromised integrity of the EPT appears to contribute to motor dysfunction in patients this relationship was not seen for the CST which suggests that it is, in some respects, independent of the EPT.
- For future studies it would be interesting to segment the motor system further and perform correlations with measures which encompass a wider variety of motor function. Further segmentation may also result in more pronounced differences in the motor systems of patients with chronic schizophrenia and healthy controls.

Selected References

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