schizophrenia compared with controls. We also predict decreased myelination (MTR) in the AL-IC, and increased diffusivity within the thalamus, prefrontal and cingulate white matter in patients with schizophrenia compared with controls, as the cortical regions connected by this fiber tract play important roles in cognitive functions, including executive functions such as working memory, which are reported to be abnormal in schizophrenia (see review in Shenton et al., 2001). Additionally, we predict that our exploratory measure of white matter tractography will reveal decreased numbers of fiber connections between prefrontal/anterior cingulate and thalamic nuclei traveling within the AL-IC in patients with schizophrenia. We also predict that thalamic and anterior cingulate volume will be reduced in patients with schizophrenia compared with controls. Further, we predict that these abnormal white matter fiber connections will be correlated with measures of positive and negative symptoms including hallucinations, delusions, and flat affect, as well as with measures of verbal (on the *left*) and spatial working memory (on the *right*). (See **Figure 3:1-1**). Finally, we predict that these working memory differences will be reflected in altered fMRI activation patterns that will be correlated with white matter and anatomic connectivity measurements.

Figure 3:1-1. Overall Model

Figure 1
Overview of Proposal

	Frontal and Temporal Connections			Left & Right Hemisphere	Cortical and Subcortical Regions
	AIM 1	**AIM 2**	**AIM 3**	**AIM 4**	**AIM 5**
	Uncinate Fasciculus	**Cingulate Fasciculus**	**Arcuate Fasciculus**	**Corpus Callosum**	**Internal Capsule (Anterior Limb)**
Function	•Connects anterior temporal region (including temporal pole) with ventral frontal regions. •Likely involved in decision making, autobiographical/episodic, verbal memory, visual attention.	•Connects cingulate gyrus with limbic structures including amygdala, nucleus accumbens, medial dorsal thalamus and dorsolateral prefrontal (anterior part) and temporal associative cortex, medial temporal cortex, parietal and orbitofrontal cortex (posterior portion). •Likely involved in the integration of error detection, decision making, self-monitoring, attention, emotional control, and memory.	•Connects Superior Temporal/Inferior parietal (on the left-Wernicke's area) with Inferior Frontal (on the left Broca's area). •Likely involved in the transfer of semantic and lexical information between inferior parietal/superior temporal and inferior frontal regions.	•Largest commissural fiber system topographically connecting the cerebral hemispheres. •Involved in the interhemispheric transfer of information and the integration of cerebral hemispheric processes.	•Reciprocally connects prefrontal and cingulate cortex with medial dorsal and anterior nuclei of the thalamus.
Predicted Symptoms*	•Paranoia •Auditory Hallucinations, Delusions	•Hallucinations •Psychomotor Poverty •Flat Affect	•Formal Thought Disorder •Hallucinations and Delusions	•Formal Thought Disorder •Hallucinations and Delusions	•Hallucinations and Delusions •Flat Affect
Predicted Cognitive and Neuropsycho-logical Deficits	•Impaired Verbal Memory (free recall) (Paired Associate Test-WMS-III) (*Left UF*). •Impaired Visual Attention (Trail Making Test-Part B) (*Right UF*).	•Impaired attention and error detection (Stroop Paradigm). •Impaired Self-Monitoring Performance (CPT Task). •Flattened Emotion (Emotional Stroop Paradigm).	•Abnormal Semantic Priming (Priming Paradigm). •Abnormal Semantic Encoding (Levels of Processing Paradigm).	•Abnormal Interhemispheric Communication (Reduced *Right* Ear, *Left* Hemisphere Advantage, on the Dichotic Listening Fused Rhymed Word Test).	•Impaired Verbal Working Memory (Alternative Semantic Categories) (*Left* Internal Capsule-Anterior Limb). •Impaired Spatial Working Memory (Spatial Span-WMS-III) (*Right* Internal Capsule-Anterior Limb).
ROI Associated with Fiber Tract Disruptions	•Temporal Pole *(Left TP Volume Reduction).*	•Amygdala-Hippocampal Complex *(Left Amygdala-Hippocampal Complex Volume Reduction).*	•Superior Temporal Gyrus *(Left STG Volume Reduction).* •Inferior Parietal Lobule *(Left IPL Volume Reduction).*	•Superior Temporal Gyrus *(Left STG Volume Reduction).*	•Thalamus (*Bilateral Medial Volume Reduction*). •Prefrontal Gray Matter (*Bilateral Volume Reduction*). •Anterior Cingulate Gray Matter (*Bilateral Volume Reduction*).
Predicted Findings	➢ ***Decreased Connectivity:*** •Decreased Anisotropy-*left* •Decreased Area- *left* •Increased Diffusivity within *left* TP WM •Decreased L>R Asymmetry •Decreased MTR- *left* •fMRI: Decreased Functional/Effective Connectivity of ROIs (Above) during Episodic Memory Processing; Related to Memory Task Performance	➢ ***Decreased Connectivity:*** •Decreased Anisotropy •Decreased Area •Increased Diffusivity within *left* Amygdala-Hippocampal Complex •Decreased MTR •fMRI: Decreased Functional/Effective Connectivity of ROIs During Episodic Memory Processing; Related to Error Pattern (Correct vs. Incorrect Responses)	➢ ***Decreased Connectivity:*** •Decreased Anisotropy-*left* •Decreased Area-*left* •Increased Diffusivity within *left* STG & *Left* IPL White Matter •Decreased L>R Asymmetry •Decreased MTR-*left* •fMRI: Decreased Functional/ Effective Connectivity of ROIs During Semantic Memory	➢ ***Decreased Connectivity:*** •Decreased Anisotropy in *Whole* CC but > Isthmus •Decreased Area •Increased Diffusivity within *left* STG White Matter •Decreased MTR •fMRI: Decreased Functional/ Effective Connectivity of Left vs. Right ROIs on fMRI Tasks	➢ ***Decreased Connectivity:*** •Decreased Anisotropy •Decreased Area •Increased Diffusivity within Thalamus, Prefrontal, & Cingulate White Matter •Decreased MTR •fMRI: Decreased Functional/ Effective Connectivity of ROIs on Working Memory Tasks

*Note: we include clinical symptoms though we will focus primarily upon neurocognitive deficits as these are less influenced by state variables and likely more reflective of deficits that are independent of clinical status.

Additional Exploratory Methods
1. Magnetization Transfer Ratio Imaging for Myelin Quantification
2. Analysis of Diffusivity within the White Matter Underlying Predefined ROIs
3. Analysis of Hemisphere Symmetry of Diffusion and Fiber Tract Directionality
4. White Matter Tractography
5. Functional & Effective Connectivity among above ROIs During Relevant fMRI Tasks

Figure 3:2-1 Overview of Proposal

	Role of DPFC and associated structures in schizophrenia			Endophenotypes	Endophenotypes
	AIM 1a	AIM 1b	AIM 1c	AIM 2	AIM 3
	DPFC and Dorsal Stream	**DPFC and STG**	**Dorsal / Ventral System Balance**	**Regional v Extended network**	**Genetic Contribution**
Function	•Mediates dorsal visual stream functions especially related to visuospatial tasks •Mediates visually directed smooth pursuit and some saccadic eye movement function •Mediates 'sense of self' and related spatial functions with environment and self •Mediates bilateral representation of body, planning of movements •Mediates "cold cognition", executive functions, short term memory, planning into the future, timing functions	•Major circuit for the integration of language functions between posterior "receptive " auditory (STG/BA22) and multimodal inferior parietal cortex(BA39/40), with prefrontal language processing cortices mediating semantic association and attention(BA47) and premotor language production (BA44/45) •High order auditory processing especially related to semantics, meaning, associative learning.	•Areas that connect both dorsal and ventral stream structures. •Cingulate functions include anterior and posterior attentional mechanisms, error detection •The basal ganglia integrates cortical information from dorsal and ventral stream •Integration of "cognitive" and" limbic" systems in forebrain •Involved in: balancing emotional and cognitive demands, switching between tasks, impulsivity restraint	•Executive function •Attention •Memory •Visuospatial processing •Language	•Executive function •Attention •Memory •Visuospatial processing •Language •Treatment efficacy •Risk of side effect development
Predicted Symptoms	•Negative symptoms •Flat affect •Psychomotor Poverty •Executive dysfunction	•Auditory hallucinations •Visual hallucinations •Language deficits	•Suicidality •Social indifference	•Thought disorder, Negative & Positive sx, Executive dysfunction, Social dysfunction, Suicidality, Memory & Attention deficits	•Thought disorder, Negative symptoms, Executive dysfunction, Social dysfunction, Suicidality, Memory and Attention deficits
Predicted Cognitive and Neuropsycho-logical Deficits	•Wisconsin Card Sorting Test •Tower of London •Mazes (NAB); •Letter-Number Sequencing (WAIS-III) •Spatial Span Test (WMS-III)	•Paired Associate Test-WMS-III) •Hopkins Verbal Learning Test (HVLT) Revised •(NAB)-Shape Learning •Category Fluency	•Stroop Paradigm. •Emotional Stroop Paradigm •Gambling Test (Bechara) •Fleming Emotional Word List	Impaired leaning (visual,verbal,shape) Impaired exececutive function Impaired attention & error detection Impaired semantic priming/encoding Flat affect, poor self monitoring Impaired emotion management	Impaired leaning (visual,verbal,shape) Impaired exececutive function Impaired attention & error detection Impaired semantic priming/encoding Flat affect, poor self monitoring Impaired emotion management
Associated ROI and Circuitry Abnoramlities	•Dorsal and ventral DPFC (BA 46 and BA 9) •Supramarginal and angular gyri of the inferior parietal lobule (BA 39, 40) •Dorsal occipital cortex (BA 18,19) •Superior parietal lobule (BA7);Precuneus (BA 31) •Intraparietal sulcus cortex (BA7) •Premotor SMA (BA6), Frontal eye fields (BA8)	•Dorsal and ventral DPFC (BA 46 and BA 9) •Superior temporal gyrus (BA22) •Inferior parietal cortex (BA40/39) •Posterior insula •Inferior frontal gyrus (BA47/44/45)	•Dorsal and ventral DPFC (BA 46 and BA 9) •Inferior frontal gyrus (BA 44/45/47) •Medial frontal gyrus (BA 32) •Amygdala/periamygdaloid cortex •Cingulate cortices (BA25/24/23/29/30) •Basal Ganglia (striato-pallidum, SN-VTA)	•Temporo-frontal •Parieto-frontal •Cerebello-thalamo-frontal •ATO •Prefrontal system circuitry.	•Temporo-frontal •Parieto-frontal •Cerebello-thalamo-frontal •ATO •Prefrontal system circuitry.
Algorithms	1) Segmentation of DPFC 2) Segmentation of the anterior cingulate and medial prefrontal cortex 3) Segmentation of superior and inferior parietal lobules, intraparietal sulcus cortex, and precuneus 4) Segmentation of premotor cortex and frontal eye fields	1) Segmentation of DPFC 2) Segmentation of the anterior cingulate and medial prefrontal cortex 3) Segmentation of the STG and surrounding areas 4) Segmentation of inferior frontal gyrus Automated segmentation and validation of the above areas	1) Segmentation of DPFC 2) Segmentation of the subgenual, anterior and posterior cingulate and medial prefrontal cortex 3) Segmentation of the inferior frontal gyrus 4) Segmentation of the subcommisural areas	•Structural equation modeling •Functional connectivity •Hierarchical models •Canonical variates •Supervised machine learning •Unsupervised clustering techniques	▪Individual genetic markers •Gene clustering approaches •Linkage-disequilibrium •Supervised machine learning •Unsupervised clustering techniques •Will refine the current Sz subtype definitions into endophenotypes that include genetic information which better enable diagnosis and treatment
Predicted Findings	➢Increased activation area with working memory load in DPFC and associated areas in Sz ➢Decreased activation in IPL and SPL in Sz compared to controls in working memory tasks ➢More pronounced functional abnormalities in predominately negative symptom than positive symptom schizophrenia	➢Flattened MMN response in the STG for Sz ➢Decreased MMN with increasing symptom duration ➢More pronounced activation abnormalities in Sz with auditory hallucinations ➢Correlations with decreased STG volume	➢Increased ventral activations for emotional processing in suicidal schizophrenics ➢Decreased dorsal activations for attentional processing in suicidal Sz ➢Anterior cingulate areas may show dysfunction in switching between emotional and attentional processing	➢Abnormal balance between dorsal and ventral circuitry in suicidal Sz ➢Positive and negative symptoms correlate with differential circuitry ➢Patterns of connectivity abnormalities with clinical/cognitive deficits ➢Will refine the current Sz subtype definitions into endophenotypes which better enable diagnosis and treatment	➢Reduced parietal lobe volume with gene dose (val66met BDNF) & lower efficiency ➢Greater ventral stream especially amygdala activation with gene dose (long/short 5HTTLTR) ➢Reduced myelination PFC connectivity by gene dose MOG (CA)n & (TAAA)n ➢TD risk related to gly9gly DRD3 & increased caudate and putamen activation ➢Reduced DLPFC efficiency during a working memory task; greater severity with gene dose (val158/108met COMT) ➢SNAP25 haplotypes will predict prefrontal activation and clinical response to clozapine