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.

Table: Overview of Overview of

<table>
<thead>
<tr>
<th>Frontal and Temporal Connections</th>
<th>AIM 1</th>
<th>AIM 2</th>
<th>AIM 3</th>
<th>AIM 4</th>
<th>Internal Capsule (Anterior Limb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim 1: Uncinate Fasciculus</td>
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<td>Aim 2: Cingulate Fasciculus</td>
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<td>Aim 3: Arcuate Fasciculus</td>
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<tr>
<td>Corpus Callosum</td>
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<tr>
<td>Cortical and Subcortical Regions</td>
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</tbody>
</table>

**Predicted Symptoms**:
- Paranoid
- Auditory Hallucinations, Delusions
- Formal Thought Disorder
- Hallucinations, Delusions
- Flat Affect

**Predicted Cognitive and Neuropsychological 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)
- Abnormal semantic priming (Priming Paradigm)
- Abnormal semantic encoding (Levels of Processing Paradigm)
- Abnormal interhemispheric communication (Radical Right Ear, Left Hemisphere Advantage, on the Dichotic Listening/Visual Rhythm 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)
- Temporal Pole (Left TP Volume Reduction)
- Amygdala-Hippocampal complex (Left Anterior 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 Grey Matter (Bilateral Volume Reduction)
- Anterior Cingulate Grey Matter (Bilateral Volume Reduction)

**Predicted Findings**
- Decreased Connectivity: Decreased Anisotropy-Left
- Decreased Area-Left
- Decreased Diffusivity within Left TP WM
- Decreased L>R Asymmetry
- Decreased MTR-Left
- AMR: Decreased Functional/Effective Connectivity of ROIs (Above) during Episodic Memory Processing: Reduced to Error Patterns (Correct vs. Incorrect Responses)

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

Note: we include clinical symptoms though we will focus primarily on neuropsychological deficits as these are less influenced by state variables and likely more reflective of deficits that are independent of clinical status.
### Figure 3:2-1 Overview of Proposal

<table>
<thead>
<tr>
<th>Role of DPFC and associated structures in schizophrenia</th>
<th>Endophenotypes</th>
<th>Endophenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AIM 1a</strong></td>
<td><strong>AIM 1b</strong></td>
<td><strong>AIM 1c</strong></td>
</tr>
<tr>
<td><strong>DPFC and Dorsal Stream</strong></td>
<td><strong>DPFC and STG</strong></td>
<td><strong>Dorsal / Ventral System Balance</strong></td>
</tr>
<tr>
<td>Mediates dorsolateral prefrontal cortex (DLPFC) function related to visuospatial tasks</td>
<td>Mediates superior temporal gyrus (STG) function related to auditory processing</td>
<td>Areas that connect dorsal and ventral stream structures</td>
</tr>
<tr>
<td>Mediates motor output</td>
<td>Mediates multimodal inferior parietal cortex (BA7/39) function related to somatosensory processing</td>
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<tr>
<td>Mediates executive function</td>
<td>Mediates anterior cingulate cortex (ACC) function related to attentional control</td>
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</tr>
<tr>
<td>Mediates reward processing</td>
<td>Mediates superior parietal lobe (SPL) function related to spatial cognition</td>
<td></td>
</tr>
<tr>
<td>Mediates working memory</td>
<td>Mediates inferior frontal gyrus (IFG) function related to language and executive function</td>
<td></td>
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<tr>
<td><strong>AIM 2</strong></td>
<td></td>
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<tr>
<td><strong>AIM 3</strong></td>
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</tr>
</tbody>
</table>

#### Function

- Mediates dorsal visual stream functions especially related to visuospatial tasks
- Mediates visual motion processing
- Mediates visuomotor processes

#### 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 defects

#### Predicted Cognitive and Neuropsychological Deficits

- Wisconsin Card Sorting Test
- Tower of London
- Maze (NAB)
- Letter-Number Sequencing (WAIS-III)
- Spatial Span Test (WMS-III)

- Pairs 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 learning (visual, verbal, shape) & increased sensitivity to emotion
- Impaired attention & error detection
- Impaired semantic priming/encoding
- Flat affect, poor self-monitoring

- Tempro-frontal
- Parieto-frontal
- Cerebello-thalamo-frontal
- Prefrontal system circuitry

- 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 DLPFC and associated areas in Sz
- Decreased activation in IPL and SPL in Sz compared to controls in working memory tasks
- Increased activation in DLPFC and associated areas in Sz with auditory hallucinations
- Correlations with increased STG volume

- Flattened MMN response in the STG for Sz
- Decreased MMN with increasing symptom duration
- Decreased activation in DLPFC and associated areas 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
- 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

- 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 SHMT1)
- Reduced myelination PFC connectivity by gene dose MDG (tau & ITA-AAt)
- TD risk related to ghrelin (DRD3 & increased caudate and putamen activation
- Reduced DLPFC efficiency during a working memory task; greater severity with gene dose (sall8/10/met COMT)
- SNAP25 haplotypes will predict prefrontal activation and clinical response to clonipramine