1. Specific Aims

Despite strong evidence that attention deficit-hyperactivity disorder (ADHD) is heritable (Faraone & Doyle, 2001), the complexity of the ADHD phenotype has complicated the identification of susceptibility genes. Given the heterogeneity of the ADHD phenotype, intermediate cognitive phenotypes may provide a closer link to the genetic pathway of the disorder than the clinical symptoms alone. ADHD is associated with established weaknesses in executive control (King et al., 2003). Often broadly defined, executive functions are processes mediated by prefrontal brain structures that maintain an appropriate problem solving set to attain a later goal (e.g., Pennington, 2002). Within the scope of executive deficits in ADHD, weaknesses in response inhibition (RI) and working memory (WM) are arguably the most robust (Willcutt et al., 2005). RI and WM deficits have also been shown to be moderately heritable and due to a subset of the same genes that influence ADHD (e.g., Ando et al., 2001; Chhabildas et al., submitted), and accumulating evidence suggests that both RI and WM are largely mediated by the prefrontal cortex (PFC). In contrast, the specific region of PFC that is most important may differ (Aron & Poldrack, 2005; Braver et al., 1997). Aron and Poldrack (2005) suggest that the right inferior frontal cortex (rIFC) and striatum may be especially important for RI (Aron & Poldrack, 2005), whereas the locus of control for WM is thought to be in the dorsolateral prefrontal cortex (DLPFC) (e.g. Braver et al., 1997).

Based on these results, the proposed project will examine the utility of RI and WM as intermediate phenotypes that may mediate the relation between specific candidate genes and neuroanatomical differences and the behavioral symptoms of ADHD.

The long-term objective of the proposed project is to characterize neurocognitive and neuroanatomic phenotypes that may enhance the power to detect susceptibility genes for ADHD. More specifically, this proposal tests the hypothesis that deficits in executive processing (in the domains of RI and WM) may be a more penetrant indicator of candidate genes than the ADHD phenotype alone. Further, by taking advantage of an ongoing neuroimaging study in Dr. Banich’s laboratory (co-sponsor), this proposal will test the hypothesis that these deficits and specific candidate genes for ADHD may be associated with structural abnormalities in PFC and striatum.

The specific objectives of this proposal are three-fold. The first objective is to quantify executive RI and WM deficits in ADHD and control participants using neuropsychological tasks. The second objective is to examine the associations between RI and WM task performance and prefrontal and striatal volume in ADHD and control participants. The third objective is to examine genetic contributions to RI and WM, prefrontal and striatal brain volumes, and ADHD symptoms. Specific aims are as follows:

Aim 1. The first aim is to replicate and extend previous research by comparing the performance of adults with and without ADHD on measures of RI and WM. Two non-executive cognitive measures (processing speed and simple vigilance) will be used to assess the discriminant validity of RI and WM deficits.

Hypothesis 1a. ADHD will perform significantly more poorly than controls on tasks of RI and WM. This difference between the groups will be independent of IQ and reading ability.

Hypothesis 1b. This group effect will be stronger for RI and WM tasks than for tasks of processing speed and simple vigilance.

Hypothesis 1c. Replicating previous research in children (e.g., Chhabildas et al., 2001), the group difference in RI and WM will be mediated by inattention rather than hyperactive symptoms.

Aim 2. The second aim is to use whole brain optimized voxel-based morphometry to quantify volume in a priori regions of interest in the PFC (5 sub-regions), striatum (3 sub-regions), and cerebellum, a control region that is implicated in ADHD but not in executive control, and to examine relations between volume of each of these brain regions, RI and WM performance, and ADHD symptomatology.

Hypothesis 2a. Replicating previous research, regional brain volume will be significantly smaller in ADHD than in control participants in the PFC, striatum, and cerebellum. The significance of these group differences will be maintained while controlling for whole brain volume.

Hypothesis 2b. PFC volume will be inversely correlated with performance on tasks of RI and WM.

Hypothesis 2b1. rIFC volume will correlate most strongly with RI performance.

Hypothesis 2b2. DLPFC volume will correlate most strongly with WM performance.

Hypothesis 2c. Striatal volume will be correlated with RI performance, but not WM performance.

Hypothesis 2d. Cerebellum volume will not be correlated with RI or WM performance in either group.
Aim 3. The third aim is to examine genetic influences on RI and WM, regional brain volumes, and ADHD. The relative influence of six candidate genes thought to contribute to ADHD (i.e. DAT1, DRD4, SNAP-25, DRD5, 5HT1B, and COMT), on task performance, volume of the PFC, striatum, and cerebellum, and the ADHD phenotype will be explored.

Hypothesis 3a. Risk alleles for all candidate genes except COMT will be associated with ADHD.

Hypothesis 3b. Risk alleles for DAT1 and DRD4 will be associated with RI deficits.

Hypothesis 3c. The COMT risk allele will be associated with WM deficits.

*Exploratory* Hypothesis 3d. DAT1 and DRD4 risk alleles will be associated with smaller PFC and striatal volume.

*Exploratory* Hypothesis 3e. The COMT risk allele will be associated with smaller prefrontal volume.