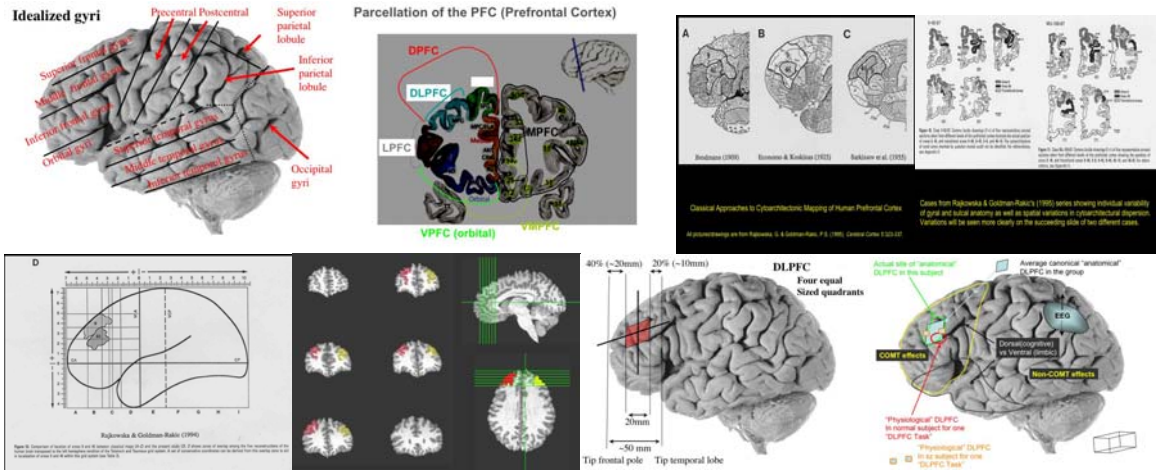
Core 3.2 Scientific Progress Report

Significant progress has been made in testing the hypotheses related to our specific aims during this early stage of the project. Due to the intensive interactions with other cores, some materials may overlap with other reports.

1. Creating custom brain segmentations using semi-automated techniques

The UCI Core 3.2 (Fallon) and Georgia Tech Core 1 (Tannenbaum) team has successfully developed a method for taking lengthy and complex neuroanatomical rules for defining a cortical area (Fallon) and creating a new semiautomated segmentor program that is anatomically accurate, but takes only a fraction of the time to carry out.

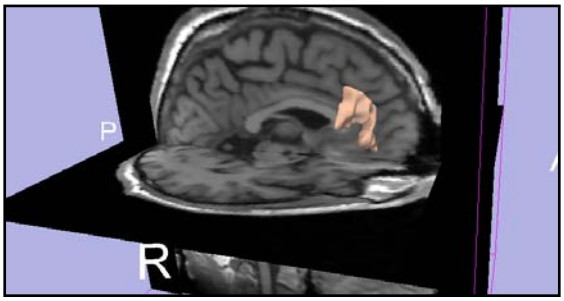
First, Fallon chose a highly variable and complex-shaped cortical area involved in executive brain functions and short term memory, the dorsolateral prefrontal cortex (DLPFC). We then created both quantitative and qualitative distance and shape 'rules' (based on neuroanatomical expertise and the literature) for defining its boundaries in different subjects. The rules for outlining the DLPFC were outlined in seven pages of text and twelve figures (a few examples are shown below):



This information was then tested in a series of subjects using manual segmentation techniques to create the most realistic 2-D and 3-D models of DLPFC. For each manual reconstruction carried out locally by a postdoctoral student (Dr. Sandy Kindermann) with some neuroanatomical expertise, then checked post hoc by Fallon for precision and accuracy. Each subject's manual reconstruction of DLPFC took about one full day. The rules were then sent to the Tannenbaum lab for adapting the neuroanatomical rules into a semiautomated algorithm program.

Ramsey Al-Hakim, an undergraduate research student working in Allen Tannenbaum's lab then developed a semi-automatic segmentation program based on domain specific (qualitative and quantitative neuroanatomy) rules formulated by the Core 3 researcher, James Fallon. The motivation of the DLPFC semi-automatic segmentor was to minimize segmentation time of the DLPFC by incorporating the Fallon rules into an algorithm, while still giving the user control of the segmentation process. The time to segment the DLPFC was reduced from over an hour or more to approximately 5 minutes. The algorithm requires a knowledge of Fallon's rules, and thus extensive knowledge of the entire human brain. The algorithm was originally developed in Matlab and returned a VTK file that is a 3D model of the DLPFC. Future work is to implement the algorithm into 3D Slicer of Brigham and Women's Hospital. Below are two

models of the DLPFC from the same MRI case. Figure1 shows a model that was created by the semi-automatic segmentor (in under 5 minutes) and figure 2 shows a model of the same case that was created by manual segmentation (over an hour). Both models are viewed in Slicer with the same right side-anterior-superior view.



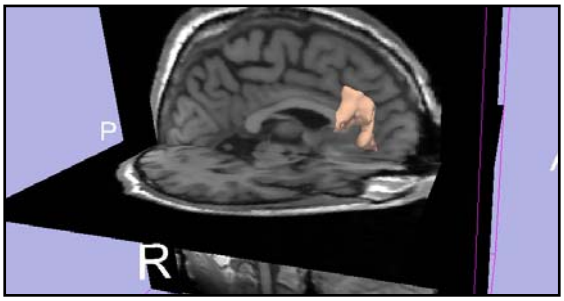


Figure 1. 3D model of the DLPFC created by the semi-automatic segmentor and viewed in SLICER. This is a right anterior- side- superior view.
Figure 2. 3D modelsof the DLPFC created by manual segmentation in SLICER. This is a right side-anterior- superior view (same view as Fig 1).

This NAMIC Core 1-Core 3 collaboration was completed through two face to face conversations and presentations at two NAMIC meetings, and through individual and conference calls, and email. In June of 2005, Allen Tannenbaum and Ramsey Al-Hakim will travel to Fallon's lab for four days to expand and deepen the Core 1- Core 3 interaction in order to determine how the neuroanatomical rules, i.e., both the quantitative definitions but importantly the more qualitative and intuitive features of the neuroanatomist's perceptions, estimations and determinations of location, shape, 'neighborhood' rules can be automated in such a way that retains the precision, accuracy, (and variability) of neuroanatomical expertise but which requires undergraduate level expertise at only a fraction of the time necessary for the manual segmentation.

2. Functional connectivity of the DLPFC investigated using partial least squares correlation

Drs. Lisa Kilpatrick and James Fallon investigated the functional connectivity of the DLPFC using partial least squares (PLS), PLS is a multivariate analytical technique used to summarize large neuroimaging datasets in such a way as to correlate patterns of activation with a variable(s) of interest (i.e. DLPFC activity). PLS works on the assumption that the focus of analysis is on which aspects of the signal in one dataset (neuroimaging data) are related directly to signals in another dataset (DLPFC activity). PLS computes a matrix that defines the relation between the two datasets then analyzes that "cross-block" matrix through singular value decomposition. PLS, as applied here, enables us to derive commonalties and differences among experimental conditions in DLPFC functional interactions with other brain regions. Drs. James Fallon and Lisa Kilpatrick hold weekly meetings (in person) to discuss the results and interpretation of the partial least squares analyses.

The functional connectivity of the DLPFC during performance of the Sternberg working memory task under a low memory load and a high memory load condition was examined. Areas displaying positive correlation with activity in the DLPFC during both low and high load conditions included other prefrontal areas such as the orbitofrontal cortex. Areas displaying a more positive correlation with activity in the DLPFC during the high load condition than during the low load condition included inferior parietal cortex.

An additional partial least squares analysis to investigate relationships between DLPFC functional connectivity and accuracy performance during the working memory task was performed. In this analysis, both DLPFC activity and accuracy were simultaneously entered as variables of interest. Prefrontal areas were positively correlated with DLPFC and negatively

correlated with accuracy during both low and ligh memory load conditions (Figure 1). Parietal areas were positively correlated with both DLPFC and accuracy during the high memory load condition (Figure 2). These results support the view that prefrontal dysfunction underlies working memory deficits in schizophrenic patients and suggest that there may be more dysfunctional and functional aspects of DLPFC networks in terms of supporting working memory performance. The dorsolateral prefrontal cortical networks will be further investigated using structural equation modeling. Structural equation modeling allows the examination of memory load-related changes in the direct influence of the DLPFC onto other brain regions, providing more specific information about the relationships between regions in the DLPFC network. This analysis complies with Specific Aims #1 and #2 by investigating the role of the DLPFC through interactions with other regions in prefrontal and extended networks. This analysis provides information about a general working memory network expressed in schizophrenic patients within which differences among subtypes of schizophrenia may exist.

Figure 1 **Figure 2**

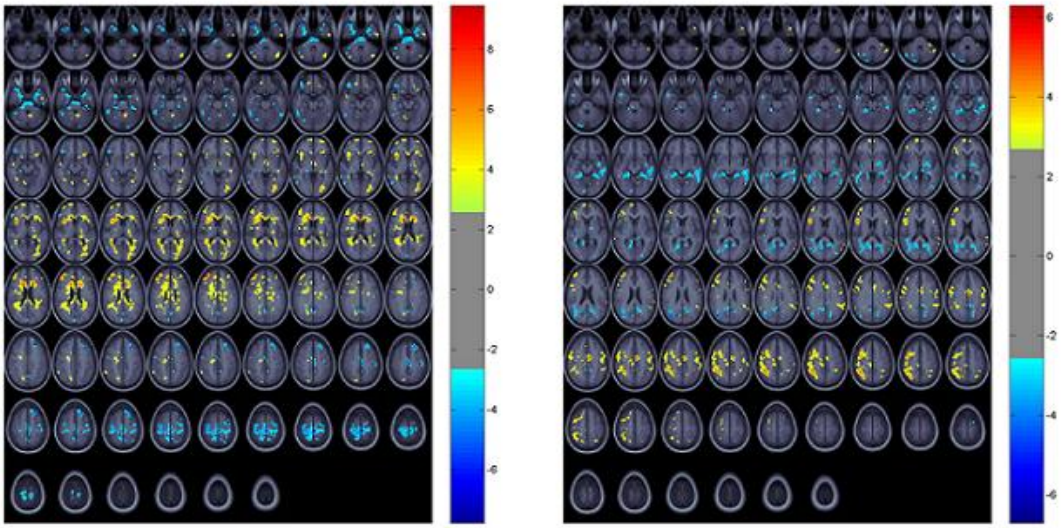


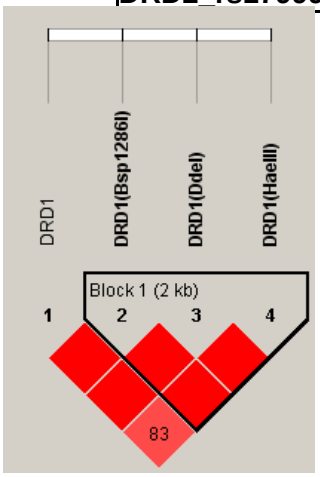
Fig.1. Hot areas are associated with a positive correlation with DLPFC activity and negative correlation with accuracy during low and high memory load conditions. Cool areas are associated with a negative correlation with DLPFC activity and positive correlation with accuracy during low and high memory load conditions. Fig. 2. Hot areas are associated with a positive correlation with both DLPFC activity and accuracy during the high load memory condition. Cool areas are associated with a negative correlation with both DLPFC activity and accuracy during the high load memory condition.

3. Preliminary analysis on genetic allelic variation of schizophrenia at UCI

We have genotyped 27 polymorphisms and tested for Hardy Weinberg Equilibrium across all the SNPs that had 2 alleles. We have also calculated the relative distance from consecutive polymorphisms (e.g., all the SNPs in the DRD2) and build their maps with the LD matrix. We have found that several SNPs show deviation from HWE, which may be informative when other imaging and clinical data have become available. It is difficult to interpret at the present time in absence of other information, but it is proof of concept of the general methods.

DRD1

Name	Position	ObsHET	PredHET	HWpval	%Geno	FamTrio	MendErr	MAF
DRD2		0.048	0.046	1.0	62.7	0	0	0.024
DRD2(BstNI)		0.212	0.236	0.661	98.5	0	0	0.136
DRD2(Taq1A)		0.431	0.386	0.597	97.0	0	0	0.262
DRD2_rs1800498	112796798	0.121	0.165	0.151	98.5	0	0	0.091
DRD2_rs4648317	112836742	0.515	0.498	1.0	98.5	0	0	0.47
DRD2_rs1799978	112851561	0.127	0.172	0.165	94.0	0	0	0.095



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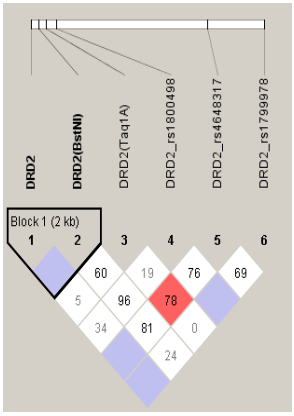

DRD2

DRD2_rs1799978	112851561	0.127	0.172	0.165	94.0	0	0	0.095

These graphs are Haploview output of LD structure and map for those genes where there are multiple SNPs. Due to the lengthy output, we are unable to show all allelic frequency tables in this report. Detailed information will be uploaded on the NAMIC Wiki website.

4. Imaging genetic article submitted for publication

A manuscript entitled "Imaging phenotypes and genotypes in schizophrenia" has been submitted for publication. In this paper we reviewed some of the key findings in imaging phenotyping and genotyping of schizophrenia, and the initial endeavors at their combination into more meaningful and predictive patterns, or endophenotypes identifying the relationships among clinical symptoms, course, genes and the underlying pathophysiology.

5. Brains / Slicer workshop, March 23, 2005

A collaborative effort between FBIRN and NAMIC led to UCI hosting a workshop on March 23 highlighting how to use two different analysis and visualization packages: BRAINS (University of Iowa/FBIRN) and Slicer (BWH/NAMIC). This Education and Dissemination event was publicized to the local UCI imaging community and was well-attended by BIRN, NAMIC, and UCI imaging researchers.

6. IRB permission for NAMIC community use of legacy data

UCI IRB approval was requested and obtained to share deidentified, defaced legacy data sets with NAMIC investigators. The resulting structural MRI, functional MRI, genetic and PET data for a particular legacy data set have been defaced when necessary, deidentified, and uploaded to a sharing area hosted by BIRN but made available to NAMIC investigators. The data collection and analysis methods were documented and made available on the NAMIC Wiki. These data have been downloaded for use by other NAMIC Cores.

Significance

All these activities and works comply with the project's specific aims of Core 3.2. We have demonstrated that the multilateral collaboration proposed in the NAMIC is feasible and fruitful in achieving our research goals. We have established the value of Core 3.2 as a driving biological project in shaping the tools of the other NAMIC cores. By increasing the sample size and continuing tool development, we are confident that we will be able to test all our hypotheses associated with the specific aims.

Future Plans

In the next project year, we will continue with our proposed timeline to (1) implement the DLPFC segmentation algorithm into 3D Slicer of Brigham and Women's Hospital, (2) apply the semi-automated techniques to other forebrain structures to determine the level of organization at which the circuitry produces different schizophrenic syndromes, and (3) use PLS analysis to explore the functional connectivity between DPFC structures and other variables, such as behavioral performance and genetic profile.