

A. SPECIFIC AIMS

The pathogenesis of schizophrenia remains unknown, and consequently our ability to treat or prevent this devastating illness effectively is limited. In light of the hypothesized neurodevelopmental basis of this brain disorder⁹ and of the accumulating evidence of progressive tissue loss after the first psychotic episode, some have spoken in favor of preventative interventions delivered before the onset of psychosis (during the “the prodrome”).^{8, 10} Prodromal individuals, usually adolescents or young adults, are identified as being at high clinical risk for psychosis based on either their clinical features or genetic risk. Although a portion of these prodromal persons will ultimately develop psychotic illness,^{10, 11} we cannot predict well who exactly will develop schizophrenia within this high-risk group based on clinical data alone. Thus, the identification of reliable biomarkers of the risk for illness is essential for developing preventative treatments and in advancing our understanding of the pathogenesis of schizophrenia. *In vivo* imaging offers a unique vantage point in that it allows us to follow, over time, the maturational events taking place in the brain of people with a vulnerability to psychosis as they move through adolescence. I propose to study longitudinally a cohort of healthy controls and adolescents and young adults prodromal for schizophrenia using MRI in order assess the presence and progression of anatomical brain abnormalities. I also propose to explore the association of these abnormalities with the development of psychotic symptoms and, ultimately, the conversion to psychosis. Our collection of longitudinal imaging data for more than one year after baseline assessment demonstrates the feasibility of this research. Further, through the execution of this K23 CDA research proposal and the supervision, coursework and tutorials detailed in the training plan, I will continue to learn advanced anatomical MRI techniques. I will also develop the skills to study adolescents prodromal for schizophrenia as well as deepen my knowledge of the pathophysiology of this devastating illness. Following are the specific Research Aims of this K23 application:

Aim 1 To delineate the trajectory of changes in cortical gray matter and cortical shape in a sample of healthy adolescents and young adults (ages 12-30 years) followed clinically over 4 years and scanned twice at a time interval of two years. We will obtain 1) measures of cortical thickness, and (2) morphometric measures describing the shape of the cortical surface, and we will compare these measures across time points.

Hypothesis 1 Normal brain development in adolescence will be characterized by a progressive decline in the thickness of the cortical mantle, starting in the parietal lobe and progressing in a back-to-front direction to engulf both temporal and frontal lobes by the end of adolescence. We expect that age will be associated with morphological features of the cortical surface, especially in the dorsal prefrontal and temporal cortices.

Aim 2 To evaluate changes in cortical gray matter and cortical shape prospectively in a prodromal sample and then compare these measures in prodromal persons who develop psychosis (“converters”) with those who do not (“non-converters”), as well as with measures in healthy, age-matched controls. As in Aim 1, we will collect measures of cortical thickness and shape across the entire cortical mantle at the same time interval.

Hypothesis 2 “Converters” will exhibit a more rapid decline in cortical thickness when compared to “non-converters” and to healthy controls. Based on our preliminary findings in a study of the shape of the cortical surface in adults with schizophrenia, we hypothesize that converters will exhibit progressive and focal indentations in the dorsolateral prefrontal cortex, the inferior parietal lobule, the superior and middle temporal gyrus, and the anterior and posterior cingulate cortices.

Aim 3 To correlate imaging measures with ratings on the Scale of Prodromal Symptoms (SOPS) obtained at baseline and at the 2-year follow-up in prodromal patients.

Hypothesis 3a We hypothesize that clinical ratings of positive symptoms will be associated with abnormalities of surface morphology in the superior and middle temporal gyri and that they will correlate inversely with cortical thickness in these areas.

Hypothesis 3b We also hypothesize that clinical ratings of negative symptoms will be associated with abnormal morphological measures of the medial prefrontal and right temporal cortex and that they will correlate inversely with cortical thickness in these areas. Ratings of disorganization symptoms will be associated with abnormal morphological measures in the dorsolateral prefrontal cortex and they will correlate inversely with cortical thickness in this region.

B. BACKGROUND AND SIGNIFICANCE

B1. Significance The study described in this K23 proposal will clarify the anatomical changes that occur in healthy adolescents and in individuals at risk for psychosis during adolescent development; this knowledge will further our understanding of the pathophysiological events that accompany the prodromal phase of schizophrenia, and it will help to identify the anatomical biomarkers for conversion to psychosis. This study may have far reaching consequences for our understanding of vulnerability to psychosis and possibly for treatment, as the identification of biomarkers is a prerequisite in the selection of those prodromal cases that may benefit from preventative interventions. Furthermore, because confounds are minimized, this study may identify anatomical endophenotypes that could be the target of novel therapeutics.

Innovative aspects of this study include its longitudinal prospective design, its unique sample of individuals who are deemed at ultra-high risk to develop psychosis, and the use of sophisticated imaging techniques that assess simultaneously both cortical morphology and cortical thickness in order to define the subtle anatomical changes that accompany normal development and the conversion to psychosis. Imaging studies conducted prior to the onset of illness inherently minimize possible confounds, such as medication use, disease chronicity, and compensatory responses. Furthermore, given that a risk factor is a measurable characteristic of a population that precedes an event (illness in this case),¹² only studies in high risk populations can offer substantive hope of identifying biomarkers of conversion. Cross-sectional comparisons, which are common in the prodromal literature, cannot establish temporal antecedence; although they ultimately can guide longitudinal studies, they cannot in themselves clearly identify risk factors. In other words, although prodromal cases and patients with schizophrenia are conceptually on a temporal continuum, cross-sectional findings from these different groups cannot be interpreted longitudinally as if those abnormalities found in the prodromal group were the actual “precursors” of the abnormalities found in ill-patients. Furthermore, as is common in cross-sectional studies, these two groups may have differing ascertainment biases, or they may differ systematically on any unrelated variables, with the possibility of either obscuring real differences or generating spurious ones.

This proposal builds on findings from prior imaging studies of the prodrome. Although these studies have yielded promising preliminary results, most have been cross-sectional, some have lacked a control group, and very few have used two time points in their design.

B2. Background

Overview We will summarize anatomical findings in healthy brain development and the array of anatomical abnormalities found in first-episode psychosis and established schizophrenia, in childhood- and adolescent-onset schizophrenia, and in the relatives and siblings of patients with schizophrenia. We will then proceed to discuss whether these abnormalities evolve over time, and we will finally review in detail the available imaging literature on individuals with prodromal illness.

The brain undergoes anatomical reorganization during normal adolescence Although brain development in healthy persons has only recently become the focus of imaging studies, an overall picture is beginning to emerge according to which the brain undergoes dynamic reorganization well into early adulthood. Following an initial increase in gray matter (GM) volume,¹³ association cortices undergo progressive loss of GM during the second decade.¹⁴⁻²⁵ These changes involve the parietal and the frontal cortices.¹⁶ Within the frontal lobe, orbitofrontal thinning occurs first, followed by thinning of ventrolateral prefrontal and later dorsolateral prefrontal cortex (DLPFC).²⁶ Conversely, GM in language-related areas thickens²¹ in the perisylvian and inferior frontal cortices. White matter (WM) appears to increase linearly with age^{14, 27} with WM volumes in the frontal and temporal lobes increasing especially during adolescence.²⁸ Fractional anisotropy (FA) also increases,²⁹ probably reflecting the progressive anatomical organization of WM tracts, such as the corpus callosum.³⁰ Furthermore, during this progressive maturation of the cerebrum, the correlation between measures of cortical thickness in areas that are functionally related increases over the course of development,³¹ in line with the suggested maturation of anatomical networks, such as the cortico-striatal-thalamic-cortical loops.^{5, 17}

Schizophrenia is associated with a distributed pattern of anatomical abnormalities Morphometric abnormalities have long been documented in schizophrenia.³²⁻³⁴ Reduced total brain volume and ventricular enlargement,³⁵ as well as volume reductions in the prefrontal cortex, temporal lobe,³⁶ amygdala,³⁷ hippocampus,³⁸ parahippocampus,^{39, 40} thalamus,⁴¹ and cingulate gyrus⁴²⁻⁴⁴ have all been reported. Temporal and prefrontal regions seem especially affected³⁴ with consistent reductions reported in the sizes of the planum temporale, the middle temporal gyrus, the superior temporal gyrus, and the prefrontal cortex.^{45, 46} Regional thinning of gray matter is present in frontal, temporal, parietal,⁴⁷ cingulate, and occipital cortices.⁴⁸ Finally, nearly every study has found reduced total brain and hippocampal volumes, and increased ventricular volumes.⁴⁹ These anatomical abnormalities are reliably detectable early in the illness as smaller total cerebral volumes, reduced temporal lobe gray matter, decreased thalamic volumes, and larger third and lateral ventricles.^{50, 51}

Anatomical abnormalities in associative and limbic cortices are present in early-onset variants of the illness Early-onset variants of the illness have been studied in the hope that they may reveal more definitive pathogenic abnormalities than those present in adult-variants, assuming that the earlier the onset, the less the influence of environmental confounds. Findings in childhood-onset schizophrenia indicate the presence of reduced volumes of the frontal, parietal, and temporal lobe, with a dynamic wave of gray matter loss starting in parietal association cortices and spreading frontally, eventually enveloping dorsolateral prefrontal and temporal regions.⁵² A multimodal study employing diffusion tensor imaging (DTI) and voxel based morphometry (VBM) in adolescent-onset schizophrenia⁵³ reported gray and white matter abnormalities in the same regions involved in adult schizophrenia (Heschl's gyrus, parietal operculum, left Broca's area, and left arcuate fasciculus) as well as abnormalities in primary sensorimotor and premotor cortices, consistent with the known presence of neurological soft signs.⁵⁴ In another study, participants with adolescent-onset schizophrenia showed a selective and severe loss of gray matter bilaterally across the medial surface of the brain, with frontal regions affected relatively early, and cingulate cortices affected later in adolescence.⁵⁵

Studies in relatives of patients with schizophrenia suggest that genetic and environmental factors are associated with different sets of anatomical abnormalities A different approach to the study of the pathogenesis of schizophrenia is to study populations at high familial risk for developing the disorder. Shared anatomical abnormalities between these subjects and patients are presumed to reflect genetic processes that confer vulnerability to schizophrenic illness. These are different from "disease-specific" abnormalities only present in the ill family member.⁵⁶ In a study in twins and siblings discordant for schizophrenia, for example, the affected twin presented deficits in GM density in the dorsolateral prefrontal cortex, the superior parietal and left superior temporal gyri, relative to the healthy twin. A map capturing variation associated with genetic proximity of the unaffected (mono- or dizygotic) twin to the affected co-twin suggested the presence of reduced GM density, mostly in polar and dorsolateral prefrontal regions, allowing the authors to conclude that abnormalities in different sets of regions are associated either with disease or with the genetic vulnerability to disease.⁵⁷ In another study, healthy siblings of patients with childhood-onset schizophrenia exhibited decreased GM thickness in the left prefrontal and bilateral temporal cortices, and smaller deficits in the right prefrontal and inferior parietal regions, compared with controls.⁵⁸ Finally, a study of GM and WM density measured using voxel based morphometry (VBM) in monozygotic and same-sex dizygotic twins discordant for schizophrenia reported focal decreases of GM density and increased WM density in the left medial orbitofrontal gyrus and left sensorimotor gyrus in the discordant twin pairs compared with healthy twin pairs.^{59, 60} A recent meta-analysis of 25 studies has shown that abnormalities in first-degree relatives are reproducible, especially in the hippocampus, which tends to be smaller in this population compared with normal controls.⁶¹

Anatomical abnormalities in patients with schizophrenia progress after the first psychotic break Taken together, these prior findings suggest that anatomical abnormalities within limbic regions and association cortices (frontal, parietal and temporal) in persons with schizophrenia are to some extent present very early in the course of the illness. More limited evidence indicates that these same regions are somewhat abnormal in the unaffected siblings of patients, making them good candidates for the status of biological markers, or endophenotypes, of schizophrenia. Whether these anatomical disturbances are fixed or whether they evolve over time has not been settled definitively, although the bulk of evidence suggests some degree of temporal progression. Tissue loss has been noted in patients with schizophrenia after the first episode,⁶²⁻⁶⁴ with reports

of progression in the posterior superior temporal gyrus^{65, 66} and frontal lobe.⁶⁷ Accelerated frontotemporal cortical GM decline and lateral ventricular expansion has been observed later in the illness, with greater clinical severity associated with faster rates of change in frontotemporal volumes.⁶⁸ This temporal pattern of GM reduction seems to differ from that found in normal aging, in that most of the loss, in schizophrenia, occurs in the first 10-20 years of the illness.⁶⁹ This trajectory of change in GM loss over time may also differ across different diagnostic groups that can present initially with psychotic symptoms.^{70, 71}

The prodromal phase of schizophrenia offers unique research advantages, but it is relatively unexplored Prodromal or high-risk populations are particularly promising, in that they allow the identification of brain disturbances (morphological, functional, metabolic) that are true risk factors present before the onset of illness. Nevertheless, in contrast to the yield of studies performed in first episode and established patients, relatively little is known about the nature of the neuroanatomical abnormalities in persons at ultra-high risk for psychosis. Evidence from PET⁷² and MRS⁷³ data is either scant or negative. Studies using fMRI in these populations implicate the presence of either aberrant functional connectivity,⁷⁴ reduced frontostriatal function,⁷⁵ hyperactivation of the parietal lobe,^{76, 77} or abnormal prefrontal cortex activation in theory-of-mind tasks.⁷⁸ Finally, DTI has not yet been used to study a prodromal sample.

Anatomical abnormalities especially within associative and limbic cortices may be present during the prodrome More evidence for the existence of brain abnormalities in prodromal patients who convert to psychosis ("converters") is available from anatomical MRI studies, pointing to more frequent radiological abnormalities^{79, 80} and reduced gray matter within the prefrontal, temporal, and cingulate cortices. VBM studies,⁸¹ for example, have reported reduced gray matter density in converters, when compared cross-sectionally to prodromals who do not go on to develop psychosis ("non-converters"), within the right medial temporal, lateral temporal, inferior frontal, and bilateral cingulate cortices. When re-scanned, the converters had reduced gray matter in the left parahippocampal, fusiform, orbitofrontal, cingulate, and cerebellar cortices. In those who had not become psychotic, longitudinal changes were restricted to the cerebellum. The group-by-time interaction, however, did not reach statistical significance. Another longitudinal study⁸² (2 time points, 2 years apart) reported a reduction of GM density in high risk subjects in the temporal, right frontal, and right parietal cortices. In the control group, decreased GM density was found in the right gyrus rectus. There was no significant difference over time, when healthy controls were compared to subjects who developed schizophrenia. Individuals who experienced psychotic symptoms had a different spatial distribution of gray matter loss than did those who did not have psychotic symptoms, mainly involving the left temporal lobe.

Recently, a comparison⁸³ of individuals at risk for psychosis with first episode patients and healthy controls revealed smaller gray matter volumes in the at-risk group in the left insula, superior temporal gyrus, cingulate gyrus, and precuneus. These deficits were not present when prodromals were compared with the first episode patients. Within the high risk group, converters had less gray matter in the right insula, inferior frontal, and superior temporal gyrus when compared to non-converters. Reduction in the volume of the right temporal lobe has been found in a cross-sectional comparison between converters and non-converters⁸⁴ and GM density decrease in the inferior temporal gyrus has been shown by one group to have a good predictive value for developing schizophrenia.⁸⁵ Anatomical perturbations in the right frontal gyrus have been suggested to be a distinguishing feature between converters and non-converters^{86, 87} in line with findings of right frontal hypergyria in patients with schizophrenia and their unaffected siblings^{88, 89} and hypergyria of the right superior frontal cortex in first episode patients.⁹⁰ Finally, abnormalities of the paracingulate and cingulate sulci have been found in a cross-sectional study⁹¹ of prodromal subjects. However, these morphological abnormalities did not distinguish converters from non-converters, and therefore they may reflect a predisposition to psychopathology rather than psychosis per se. Nevertheless, some have argued that anatomical pathology of the cingulate cortex is a promising candidate marker for future conversion.⁹²

Hippocampal and pituitary abnormalities are inconsistently reported in the prodrome Although smaller hippocampal volumes are a well replicated finding in persons with schizophrenia, available studies in the prodromal literature are inconclusive as to the nature and role of hippocampal abnormalities in prodromal samples.⁹³ In one study,⁹⁴ left hippocampal volumes were smaller in subjects at risk for psychosis than in normal controls. However, converters had larger hippocampi than did the non-converters and first episode

patients. No difference was found between converters and healthy subjects. Later, when the effect of family history was assessed, the results were even more puzzling, as shown by a study⁹⁵ examining hippocampal volume and anterior cingulate volume in 79 prodromal males (of these, 35 had a family history of schizophrenia). Surprisingly, a family history of schizophrenia was not associated with a greater degree of brain abnormalities, and indeed it was the high risk individuals with no family history who had smaller hippocampal volumes. More recently, another study found no differences among groups comparing converters, non converters, and healthy controls using an ROI-based approach for measuring volumes of the amygdala, hippocampus, and total cerebral volume.⁹⁶ A review of findings from the original Melbourne study group concludes that these inconsistencies may be due to the fact that smaller hippocampus volumes may not be a specific marker to psychosis.⁹⁷

Second, changes in pituitary volume have been reported⁹⁸ in high risk subjects who converted to psychosis when compared to non-converters. Enlarged pituitary volumes were present at the first episode and then decline later in the course of illness.⁹⁹ Some have speculated that these volumetric changes may be associated to experienced stress from around the time of illness onset and could reflect aberrant HPA axis function.^{97, 100} A recent study has not found any correlations, however, between cortisol levels and hippocampal or pituitary volumes.¹⁰¹

In conclusion, although evidence points in the direction of anatomical abnormalities in the prodromal group, especially in the prefrontal cortex, the cingulate cortex and the medial temporal lobe,^{92, 93, 102, 103} the findings have been highly variable. Part of the variability is a consequence of the different statistical comparisons carried out cross-sectionally among different diagnostic groups: subjects at risk or prodromals as a whole, prodromals who convert to psychosis ("converters"), prodromals who do not convert to psychosis ("non converters"), patients with first episode schizophrenia, and normal controls. Furthermore, the few longitudinal studies available either lack a control group or employ suspect morphometric techniques such as VBM¹⁰⁴ that are inadequate for capturing complex and distributed abnormalities¹⁰⁵ and that are especially prone to artifacts caused by errors in inter-subject registration.¹⁰⁶

C PRELIMINARY STUDIES

C1. Patterns of covariance among gray matter volumes, which are present in the normal brain and may be altered in schizophrenia, seem to follow functional and anatomical paths within neural circuits.

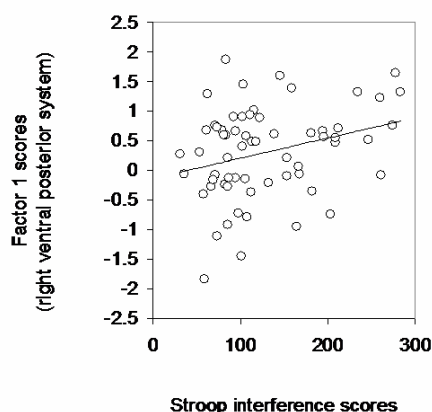
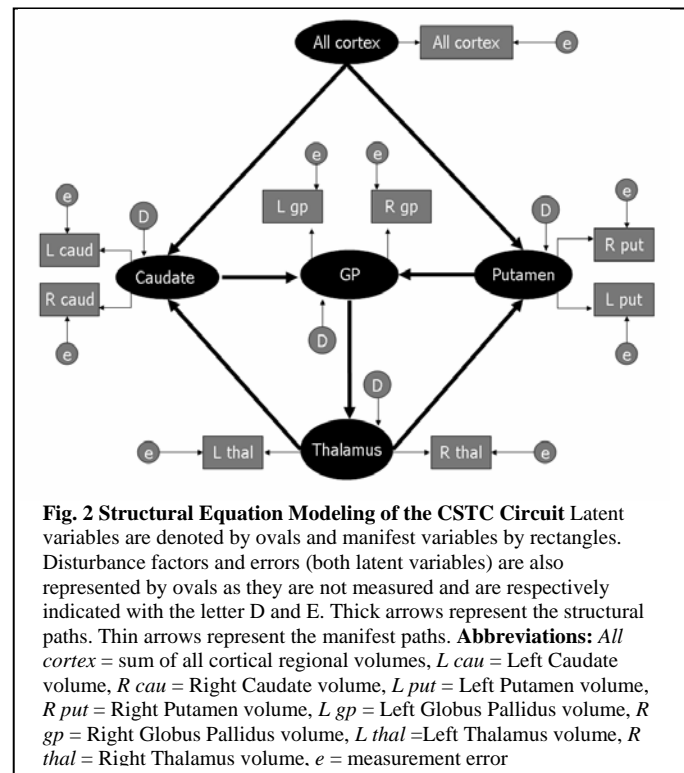


Fig. 1. Correlation of factor scores with behavioral measures (Stroop scores). Right hemisphere. Scatterplot representing the relationship between scores for the ventral-posterior system (factor 1) on the y-axis and Stroop scores on the x-axis. The scatterplot indicates that larger latent volumes for the ventral posterior system are correlated with worse performance on the Stroop task (i.e. inability to suppress automatic responses).

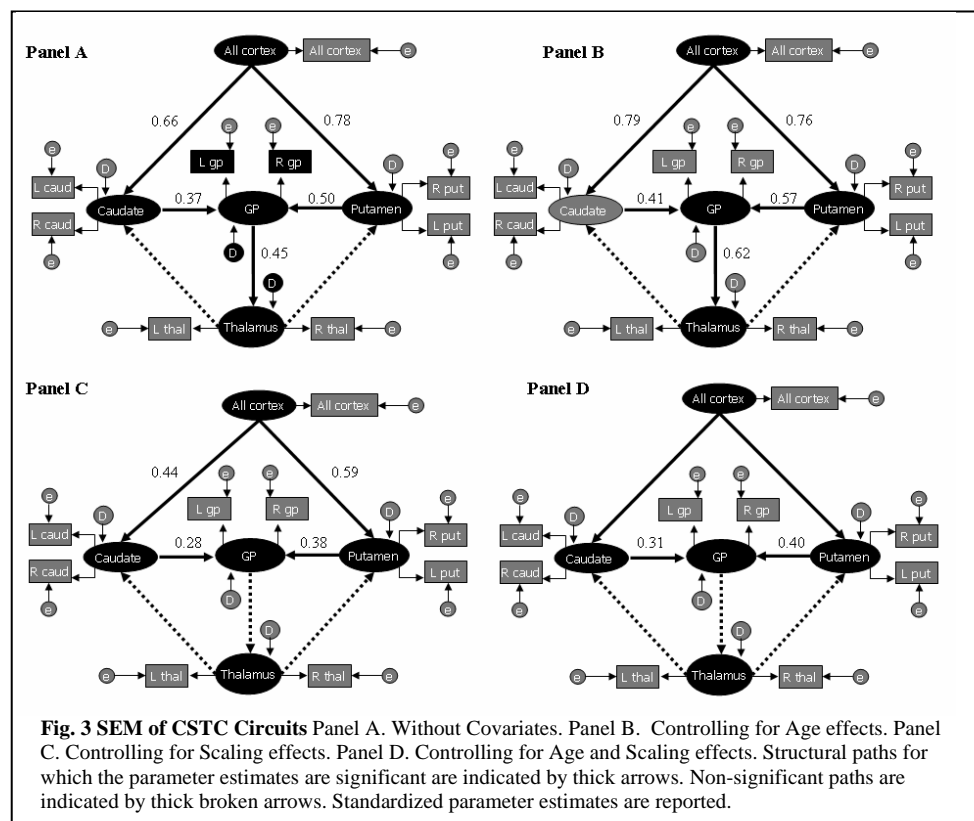
Previous studies³ have investigated patterns of volumetric covariance (i.e. intercorrelation) across brain regions. Methodological issues, however, have limited the validity and generalizability of findings from these prior studies. Additionally, patterns of volumetric covariance have often been assumed to reflect the presence of structural networks, but this assumption has never been tested formally. We identified patterns of volumetric covariance, correlated these patterns with behavioral measures, and tested the hypothesis that observed patterns of covariance reflect the presence of underlying networks. Our goal was to characterize normal patterns of volumetric covariation in the brain that could then be the basis for future comparison in a schizophrenia sample.

We performed exploratory factor analysis on regional brain volumes of 99 healthy children and adults, and we correlated factor scores with scores on the Stroop Word-Color Interference Test. Our sample consisted of healthy subjects who ranged in age from 7 to 57 years (mean 22.8 years, SD: 13.5 years). We identified 4 latent volumetric systems in each hemisphere: dorsal cortical, limbic, posterior, and basal ganglia. We observed a positive association between scores on the Stroop task and factor scores for the posterior cortical system in the

right hemisphere (which included amygdala, orbitofrontal cortex, thalamus, and occipital cortex) ($p = 0.02$, Adjusted $R^2 = 0.069$) (Fig. 1). We postulated that this system constituted an emotional-attentional network and that higher factor scores accompanied worse performance on the Stroop task, suggesting that larger latent volumes of this system are associated with poorer emotional-attentional control (Fig. 1). This finding is consistent with prior evidence that better intellectual performance accompanies decreasing thickness of the cortical mantle.^{15, 18, 20, 21} We also applied Structural Equation Modeling (SEM) to our dataset to test whether a model based on the anatomical pathways within cortico-striatal-thalamic-cortical (CSTC) circuits accounts for the covariances observed in our sample (Figs. 2 & 3). The degree to which SEM predicted volumetric covariance in the CSTC circuit depended on whether we controlled for age and whole brain volume in the analyses. Removing the effects of age worsened the fit of the model, pointing to a possible developmental component in the establishment of connections within CSTC circuits.



Thus, we demonstrated that cortico-subcortical volumetric correlations change during development, consistent with similar studies showing increasing structural correlations among functionally related areas over development.³¹ Taken together these findings also suggest that volumetric covariance can be helpful in identifying latent volumetric systems. Those systems, in turn, are arguably best suited to study brain-behavior correlations, because complex behaviors are likely subserved by circuits, rather than by individual brain



regions. Furthermore modeling techniques such as SEM, may prove useful in the future for the study of structural networks in schizophrenia where volumetric correlations among different regions are altered.^{4, 34} Finally, the volumetric modeling of entire circuits over the course of development may prove an important tool in understanding this illness, thought by some to be the consequence of a dysfunction of distributed neural networks.¹⁰⁷ These findings are published in *Human Brain Mapping*.⁵

I am in the process of extending these techniques to the study of developmental psychopathology (Tourette disorder) and ultimately to volumetric data in patients with schizophrenia and in adolescents prodromal for

psychosis. Further, as part of my training in morphometry, I want to deepen my understanding of how these multivariate techniques can be used to probe structural connectivity in the brain.

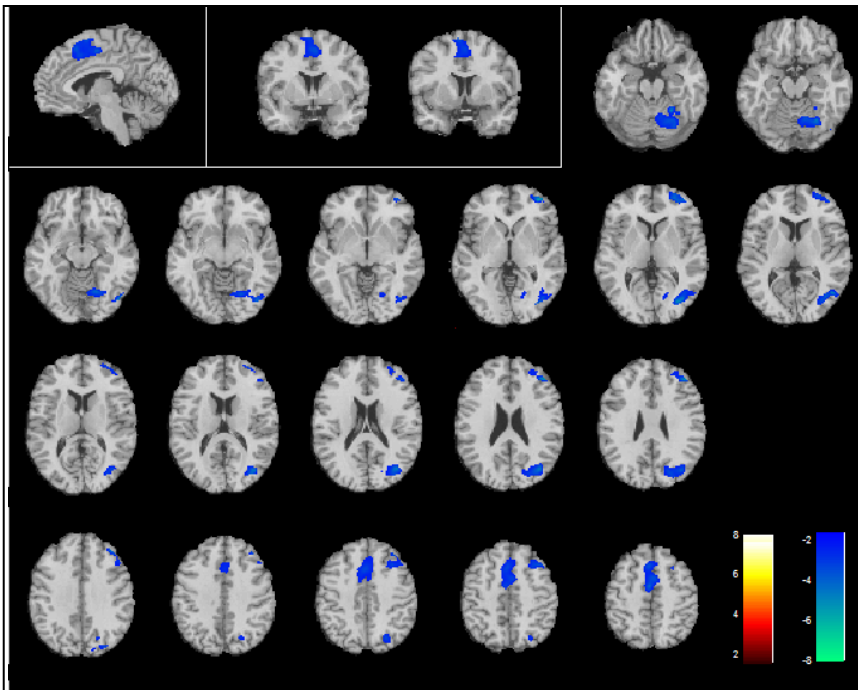


Fig. 4 Statistical Parametric Maps showing areas where BOLD signal intensity is directly or inversely correlated to valence ratings. Left to right and top to bottom: 1 sagittal section, 2 coronal sections and 18 axial sections. Direct correlations are in warm colors and inverse correlations are in cold colors. Different shades of colors correspond to different T values at each voxel. Images are displayed according to the neurological convention (the left and right side of the picture correspond to the left and right side of the brain).

C2 fMRI identifies two different neural systems that subserve the affective dimensions of valence and arousal and that comprises many of the same regions implicated in schizophrenia.

Negative symptoms in schizophrenia, now considered a fundamental dimension of the illness, are highly disabling and characteristically unresponsive to treatment.¹⁰⁸ Affective flattening, one the most prominent of these negative symptoms, is one aspect of the more general deficit in emotional processing reported in these patients.¹⁰⁹ These deficits in emotional processing, which also include a characteristic difficulty in understanding affective signals conveyed by social stimuli,¹⁰⁹⁻¹¹² perhaps reflect structural pathology in limbic regions^{44, 113} and a failure to activate them when processing emotional valence.¹¹⁴

We set out to develop an fMRI paradigm to investigate the neural processing of emotions in healthy subjects which could subsequently be applied to our patient cohort. Although imaging studies in affective neurosciences rely mostly on a basic emotion theory,^{115, 116} the limitations of this approach¹¹⁷ led us to prefer dimensional models of affect, which posit that all emotions derive from a combination of two or more underlying “dimensions.”¹¹⁷⁻¹²⁰ One of these models, the circumplex model of affect, posits that a linear combination of two independent neurophysiological systems,¹²¹ valence and arousal, produces a continuous range of sensations that cognitive systems interpret within a temporal and experiential context as a particular emotion.

We used functional Magnetic Resonance Imaging (fMRI) to identify the neural networks that subserve valence and arousal during the experience of a wide range of induced emotions. We scanned 10 normal subjects (5 men, 5 women; mean age of 25.51 ± 4.58 years; age

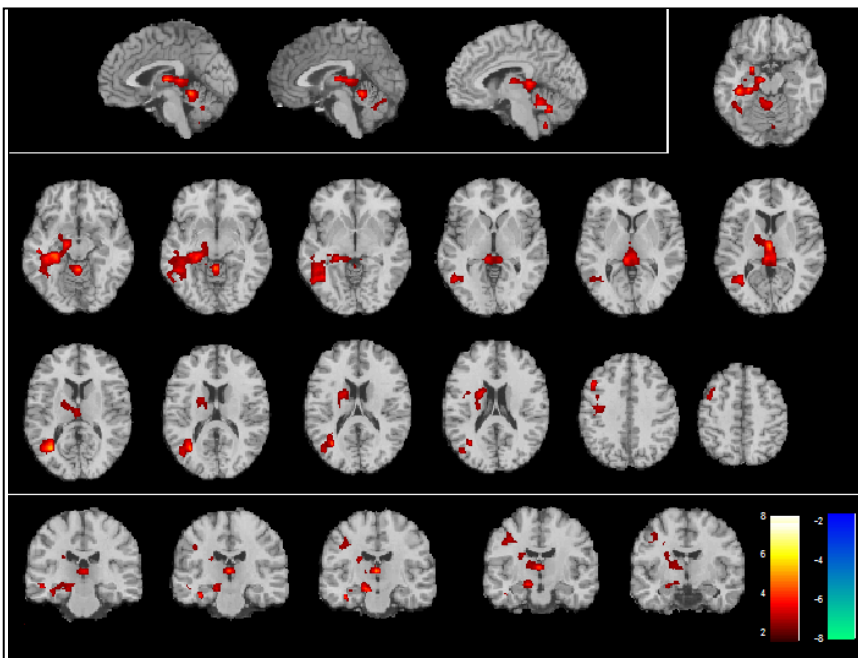
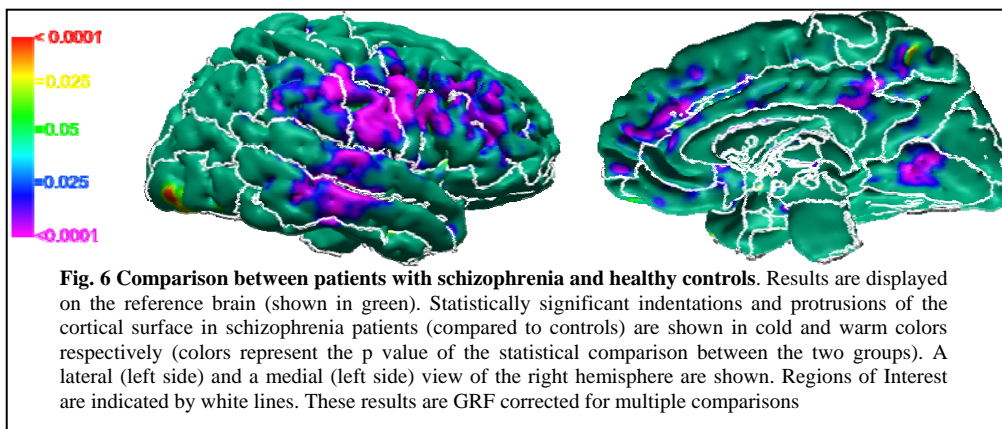


Fig. 5 Statistical Parametric Maps showing areas where BOLD signal intensity is directly or inversely correlated to arousal ratings. Left to right and top to bottom: 3 sagittal sections, 13 axial sections and 5 coronal sections. Direct correlations are in warm colors and inverse correlations are in cold colors.

range 19 to 34 years). Each of these individuals was screened for the presence of psychiatric disorders using the Structured Clinical Interview for DSM IV (SCID IV).¹²² Using a mood induction paradigm, subjects were shown a sentence intended to evoke a specified emotional state (e.g. "Imagine that you just won the lottery and you will have all the money you could ever wanted.") and were asked to try to experience the affective state that they would feel if the situation were real. Participants were then shown a grid displaying the dimensions of valence and arousal and were asked to rate these dimensions in circumplex space. We then assessed the correlations of BOLD (Blood Oxygen Level Dependent) response, an indirect index of neural activity, with ratings of valence and arousal given by the participants.

Inverse correlations of valence ratings with BOLD signal intensities were detected in the supplementary motor and midcingulate cortices, as well as in the right dorsolateral prefrontal cortex (DLPFC) and frontal pole, right occipito-temporal junction, inferior parietal cortex, and right cerebellar hemisphere (Fig. 4). *Positive* correlations of arousal ratings with BOLD signal intensities were detected in the left thalamus, globus pallidus and caudate, left parahippocampal gyrus, left amygdala, left premotor cortex, and cerebellar vermis (Fig. 5). Taken together, our findings suggest that the two affective dimensions of the circumplex model are supported by two distinct sets of neural structures. Progressively unpleasant emotions seem to engage the cingulate gyrus and the dorsal cortices which are part of an attentional system. On the other hand, highly intense emotional experiences engage the amygdala, the medial temporal lobe, where they are stored and later retrieved,^{123, 124} and the thalamus which alerts the cortex by virtue of its role in regulating overall cortical activity.¹²⁵ We plan to extend this paradigm to the study of patients with schizophrenia also because many of the regions we have identified are known to be anatomically or functionally altered in this illness. Two similar paradigms have also been developed in our laboratory using faces and affectively laden words in an identical fMRI design. Results from these two other studies are presented in two different manuscripts, of which one is currently in press.¹²⁶

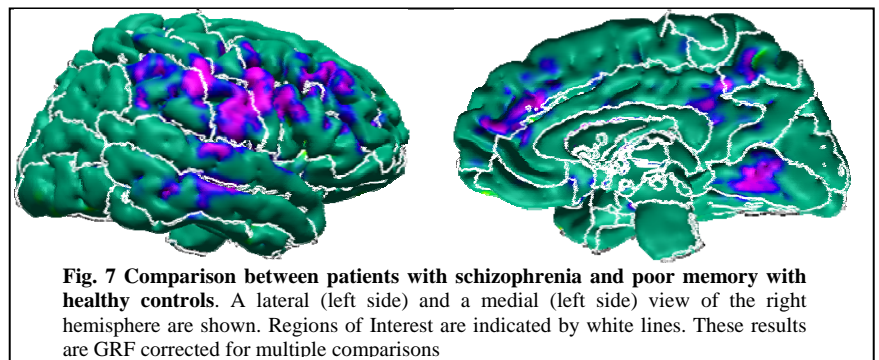
C3. Patients with schizophrenia exhibit abnormalities of the cortical surface that are correlated with working memory deficits as well as with positive and negative symptoms



The analysis of cortical and subcortical surfaces complements and expands classic volumetric analyses, in that it detects subtle and localized anatomical perturbations that may not be evident if we analyzed only volumes. We sought to explore the differences in the morphological features of the cortical surface between patients with schizophrenia

and healthy controls to determine whether the two groups differ significantly in shape. Furthermore, we wanted to test whether abnormalities in the shape of the cortical surface could be correlated with neuropsychological and clinical variables (working memory, and positive and negative symptoms).

Our sample included 66 patients meeting DSM IV TR criteria for schizophrenia and 76 healthy controls between the ages of 22 and 57 years old. Measures of working memory (Serial Position Task or SPT)¹²⁷ and of positive and negative symptoms (Positive and Negative Symptom Scale or PANSS)¹²⁸ were available for this sample. The SPT is



composed of 2 verbal and 2 nonverbal position working memory tasks. In each, 3 or 4 stimuli are presented with an interstimulus interval of 1 sec. One of the stimuli is repeated after a 3 -9 seconds delay. Subjects had to indicate in what position the stimulus had been in the original sequence. The four type of stimulus were: words and sounds (which are easy to label verbally) and birdsongs and snowflakes (which are not easily

labeled). Patients perform better when the stimulus is not easily labeled with a verbal tag (as in the case of snowflakes or birdsongs) reflecting impaired language-based memory processing¹²⁷. Participants were divided into two groups: “poor memory” and “good memory.” Assignment to these groups was based on performance: patients with good memory (n=20) had an overall score on the four tests within 0.5 SD

of the mean score of healthy subjects. Patients with poor memory had overall scores on the four tests more than one standard deviation below the mean score of healthy subjects. Surface analyses were carried out according to an algorithm detailed in the methods section. Protrusions and indentations identified in the surface are interpreted as volume increases or decreases respectively.

Our results indicate that patients with schizophrenia have statistically significant indentations of the cortical surface, which we interpret as localized volume decrements, spanning an arc of cortex including the DLPFC, the sensorimotor cortices, the inferior parietal lobule, and the superior and middle temporal gyri.

Significant volume reductions were also detected in the medial aspect

of the superior frontal gyrus, the cingulate gyrus abutting the superior parietal lobule, the anterior cingulate gyrus, and the lingual gyrus. These areas have already been found to be abnormal in patients with schizophrenia both in structural and functional studies^{39, 83, 129} (Fig. 6). Furthermore, when we analyzed only the subgroup of schizophrenia patients who have “poor memory” (Fig. 7), we found prominent indentations of the cortical surface in these same regions, although the temporal lobe was not affected to the same degree.

These topological abnormalities appeared much less prominent in those with “good memory”, who exhibited only a localized abnormality in the middle frontal gyrus (Fig. 8).

Finally, higher PANSS scores on the positive symptoms subscale were found to be significantly associated with indentations in the cortical surface of the left hemisphere within the middle temporal gyrus (and in the uncorrected analysis within the

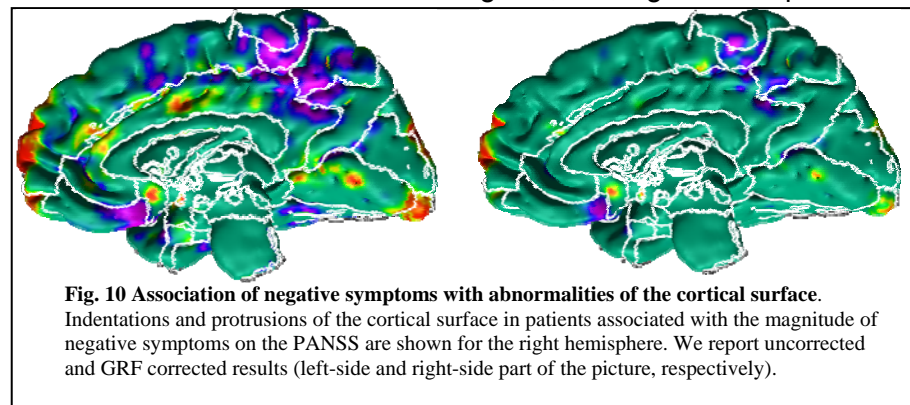


Fig. 8 Comparison between patients with schizophrenia and good memory with healthy controls. A lateral (left side) and a medial (left side) view of the right hemisphere are shown. Regions of Interest are indicated by white lines. These results are GRF corrected for multiple comparisons

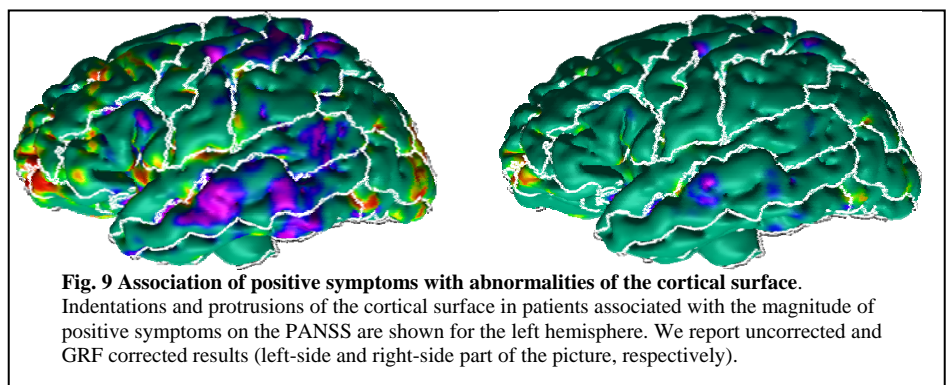


Fig. 9 Association of positive symptoms with abnormalities of the cortical surface. Indentations and protrusions of the cortical surface in patients associated with the magnitude of positive symptoms on the PANSS are shown for the left hemisphere. We report uncorrected and GRF corrected results (left-side and right-side part of the picture, respectively).

Fig. 10 Association of negative symptoms with abnormalities of the cortical surface. Indentations and protrusions of the cortical surface in patients associated with the magnitude of negative symptoms on the PANSS are shown for the right hemisphere. We report uncorrected and GRF corrected results (left-side and right-side part of the picture, respectively).

posterior part of the superior temporal gyrus). This finding is in line with evidence from neuroimaging literature in schizophrenia indicating that both anatomical and functional abnormalities in the superior and middle temporal gyri are related to positive symptoms.¹³⁰⁻¹³⁶

Higher PANSS scores on the negative symptom subscale, on the other hand, correlated with morphological abnormalities in the medial surface of the right hemisphere, specifically in the gyrus rectus, in the medial aspect of the superior parietal lobule, and at the border of the posterior cingulate and precuneus (Fig. 9). We also found prominent abnormalities in the right middle and inferior temporal gyri, although these did not survive correction for multiple comparisons (Fig. 10). Although little is known on the structural and functional correlates of negative symptoms, some have argued that abnormalities of limbic, paralimbic and medial prefrontal areas,^{32, 137} and the inferior temporal gyri,¹³⁸ may be involved.

Taken together, these preliminary results suggest that 1) Surface analysis is able to reveal the presence of highly localized volumetric abnormalities in regions that are known to be affected in schizophrenia and that distinguish patients from normal controls. 2) The extent of morphological abnormalities in these very same areas seem to correlate with functional impairment on neuropsychological measures (the SPT) and with clinical symptoms as measured on the PANSS. We plan to obtain estimates of cortical thickness at each point of the cortical surface to determine whether these localized volumetric losses are due to cortical thinning.

This preliminary work in patients with schizophrenia has provided me with hands-on experience in applying sophisticated structural techniques, such as surface analysis, to real world data. Furthermore, these findings are useful to inform our hypotheses as to which areas in the brain may be affected during the prodromal phase of schizophrenia. Under the auspices of this K23 Award, I plan to extend this work to the prodromal sample we have been currently scanning, with the aim of identifying anatomical biomarkers for the conversion to psychosis.

D. RESEARCH DESIGN AND METHODS

D1 Overview This project aims to study the developmental trajectories of brain structure in healthy adolescents and prodromal subjects. In a single year, we have already scanned 10 prodromal subjects and 4 healthy controls with a dropout rate in prodromal subjects of 10% per year, thus demonstrating the feasibility of this endeavor. The project complements the proposed training plan in that it will allow the application of techniques in anatomical imaging and modeling of longitudinal data that I will learn through didactics and mentor-based teaching. The data collected during this award period will be the basis of an RO1 application in Years 4 or 5 of the K23.

D2 Subject Sample In addition to the 10 prodromal subjects we have already enrolled and the 10 control subjects we will have enrolled before the beginning of this Award, I will recruit a total of 30 prodromal cases and 30 healthy controls, scanning each of them twice, 2 years apart. With a recruitment rate of 2 patients /month at the COPE clinic, we can safely estimate we will be able to recruit at least 10 prodromal cases per year for each of Years 1 and 2 and 3. An estimated dropout rate of 10% per year will leave us with 32 subjects who will have completed the two scans. Estimating a conversion rate of 30 – 40 %, we will have roughly 10-12 converters at the end of Year 5, similar to the number of converters in a prior longitudinal study with two time points.¹³⁹ Although in the first year we have scanned less healthy controls than prodromals, this mostly reflects both the need to first scan all the prodromals already enrolled in COPE when we started the study, as well as the need to match the controls by age and sex with those prodromals that had already been recruited in COPE. We expect that the rate of scanning will now be comparable in both study groups. We acknowledge that the total number of scans acquired during the Award may be considered high, however both normal controls and prodromal subjects are recruited through COPE, and our imaging study is part of their umbrella protocol, ensuring that everyone who is recruited into COPE is also offered a baseline and follow-up scan. Furthermore, members of the research staff at COPE also help with scheduling the scans and conducting the screening procedures. The entire Award period will be devoted to acquiring the anatomical scans and processing data. Clinical scores are also collected by the COPE staff. Although processing of structural data will start during Year 1, both Year 4 and 5 will be completely devoted to structural processing (recruitment will end in Year 3). Scanning 10 subjects each year will require processing only less than one person's dataset each 2 weeks, which poses little difficulty.

Inclusion criteria Prodromal cases will be 12-30 years old. They will be identified as prodromal on the basis of the Structured Interview for Prodromal Symptoms (SIPS/SOPS),⁸ as specified below.

Exclusion criteria Exclusion criteria for both prodromal cases and healthy participants will be:

1) Current or past diagnosis of any Axis I psychotic disorder, as gathered by a clinical diagnostic interview (schizophrenia, schizophreniform disorder, bipolar disorder, schizoaffective disorder, major depression with psychotic features, substance-induced psychosis, psychosis due to a medical condition or psychosis NOS); 2) History of neurological or major medical disorders (including prior seizure or head trauma with loss of consciousness) known to affect the brain, as putative prodromal symptoms could be secondary to these and unrelated to the risk of developing schizophrenia; 3) Risk of suicidal or violent behavior for the protection of subjects and staff; 4) IQ < 70; 5) Pregnancy or planning pregnancy during the study period; 6) Any metallic device or dental braces; 7) Ongoing substance abuse and lifetime substance dependence. Because the use of medication is not an exclusion criterion in our study, we will assess the effects of medication use as a possible confound.

D3 Subject Recruitment Prodromal patients will be identified through referral sources currently available to the Center of Prevention and Evaluation (COPE), the prodromal research program at NYSPI. This prodromal program recruits new patients at a rate of 2 cases per month. These subjects are extensively characterized within the COPE clinic and followed prospectively for 4 years. Referral sources have included 1) other clinical and research programs at Columbia/NYSPI, including the Children's Day Unit (NYSPI-based school) and the NIMH Child Psychiatry IRC (screens 450 adolescents/year), 2) counseling programs and mental health clinics at schools and universities, and in communities in NY and NJ; 3) pediatricians and general practitioners in NY and NJ; 4) school-based programs (a) the Children's Day Unit, (a school based at NYSPI), and b) the Alternative Services Program in NYC, with 4 middle schools and 2 high schools, and the c) Queens Children's School in Manhattan, a research center/education program for 325 children with psychiatric disability) and 5) referral by self or family through websites for NYSPI and NARSAD.

Healthy control adolescents will be recruited from community-based telemarketing lists of households characterized by zip code, age, gender, ethnicity, and income level (Donnelley Marketing, ph: 1-800-846-7338). Introductory letters will be sent to randomly selected households, with the constraint that the household contains a potential subject with the demographic profile that would match the clinical sample. These mailings will be followed up by phone calls that describe the study and address questions in detail. Using these same recruitment methods in the past, approximately 10% of eligible control families contacted have ultimately participated in studies conducted in Dr. Peterson's laboratory.

Sample characteristics Presently, the COPE clinic is following 32 prodromal cases ages 12- 30, with an average age of 18.8 (3.6) years, and with 81% male. Patients come from a range of socioeconomic backgrounds in the NY metropolitan area. Ethnicity is 43.8% white, 15.6% African-American, 25.0% Hispanic, 9.4% Asian, 6.3% other. All cases met criteria for the prodromal category of attenuated psychotic symptoms, and 25% also had genetic high risk with functional decline. This prodromal sample had serious functional impairment, with a modified-GAF of 45 (SD 7, range 34-60), similar to other prodromal programs.

D4 Screening All participants and healthy controls will have already been screened through the COPE clinic before entering our study. In addition, screening for this study will include an MRI questionnaire, in which the patients will be asked if they have any metal on or in their body that would preclude them from participation.

D5 Core Characterization All eligible adolescents are characterized systematically and thoroughly with structured diagnostic interviews by the COPE staff before entering our study. These measures are used to assess prodromal symptom severity and evaluate for the presence of other psychiatric disorder. Demographic information is collected (age, sex, ethnicity, family history). Baseline diagnostic assessment includes the K-SADS-PL (ages 12-15) and the Diagnostic Interview for Genetic Studies (>15 years of age), which encompasses the SCID. Life events are assessed using the Life Events Checklist. The Social Adjustment Scale probes social function. The neuropsychological battery includes attention (CPT), executive function (Wisconsin Card Sort Test, Stroop, Trails B), processing speed (Trails A), and IQ (WAIS or WISC), and explicit

memory (WMS). At COPE, patients are followed prospectively for up to 4 years, with quarterly assessments of symptoms (Hamilton depression and anxiety; SOPS for positive, negative, disorganization and general symptoms), life events (Life Events Checklist) and quantity of substance use (Quantitative Substance Use Inventory). Because we will only be using scores from the SOPS (described below), only baseline diagnostic scales and the SIPS/SOPS are described in detail.

Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL) is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to DSM-IV criteria. It will be used to establish neuropsychiatric diagnoses.¹⁴⁰

The Diagnostic Interview for Genetic Studies (DIGS) for participants older than 18 is a Research Instrument used by the NIMH genetics Initiative Consortium. Diagnoses are generated algorithmically using DSM IV and ICD 10 criteria.¹⁴¹

Structured Interview for Prodromal Symptoms and the Scale of Prodromal Symptoms (SIPS/SOPS)

Operationalized criteria for a psychosis prodrome define a group at heightened and imminent risk for psychosis (rate of conversion to psychosis is 40-50% in 1-2 years, and 68-80% in more recent studies).^{10, 11, 142} The Scale of Prodromal Symptoms (SOPS) is embedded in the Structured Interview for Prodromal Symptoms (SIPS) which is necessary to assess Global Assessment of Functioning (GAF), family history and the presence of schizotypal personality disorder. Psychometric properties of the SIPS/SOPS include excellent interrater reliability, with a kappa of 0.82.^{8, 10, 143} The SIPS/SOPS is also used to quantify the severity of prodromal positive, negative, disorganization, and general symptoms. Symptoms are rated 0-6 with 0= absent, 1= questionably present; 2 = mild; 3 = moderate; 4=moderately severe; 5=severe but not psychotic; 6 = psychotic.

Positive Symptoms include 1) unusual thought content, 2) suspiciousness 3) grandiosity 4) perceptual abnormalities 5) conceptual disorganization. Symptoms are rated 0-6 with 3-5 considered to be in the prodromal range and 6 = psychotic. Conversion to Psychosis is determined using the SIPS/SOPS when any positive symptom item is rated 6. *Negative Symptoms* include 1) social isolation and withdrawal 2) avolition 3) decreased emotional expression 4) decreased experience of emotion and self 5) decreased ideational richness 6) deterioration in role function. *Disorganization Symptoms* include 1) odd behavior and appearance 2) bizarre thinking 3) trouble with focus and attention 4) problems with personal hygiene and social attentiveness. *General symptoms* include 1) sleep disturbance 2) dysphoric mood 3) motor disturbance and 4) impaired tolerance to normal stress

Criteria for Prodromal Categories Based on the SIPS/SOPS, an individual may be deemed prodromal if belonging to any of three categories 1) individuals with attenuated positive or psychotic-like symptoms 2) individuals with brief intermittent psychotic symptoms 3) subjects with genetic high risk in addition to decline in function. Neither the symptoms nor the decline in function should have occurred solely as a consequence of substance use.

1) Brief Intermittent Psychotic States (also known as "BLIPS"). This category is defined by symptoms of psychotic intensity (SOPS score = 6 on any positive or disorganization item), which have begun or worsened in the past year, and which occur for less than 1 hour at a time and with a frequency of less than 3-6 times a week; alternatively symptoms can occur for longer than 1 hour but with a frequency of or less than twice a week. In either case each episode must be present for less than one week and symptoms must spontaneously remit.

2) Attenuated positive prodromal state This category is defined by a SOPS score of 3 to 5 for any positive or disorganization symptom occurring at least once in the past month, and which began or worsened in the past year.

3) Genetic risk and recent deterioration. This category is defined by DSM IV TR criteria for schizotypal personality disorder and/or the presence of a first-degree relative with psychosis. Either case must be accompanied by a decline in function (drop in GAF of at least 30 points in past year) or mood or deficit symptoms. Symptoms must have begun or worsened in the past year. There is no positive or psychotic symptom requirement for this category.

D6 Structural MRI

MRI Pulse Sequence Images will be acquired on GE Signa EXCITE HDx 3.0T whole body scanner with 16-channel MGD hardware platform, 8-channel head coil, and ASSET (Array Spatial Sensitivity Encoding Technique) software.

3 Plane Localizer TR = 23.4msec, TE = 1.7 msec, Flip angle = 30, Bandwidth = 31.3 MHz, FOV = 24 x 24 cm², thickness = 5.0 mm, Spacing = 0.0 mm, 9 slices per volume (3 axials, 3 sagittals and 3 coronals), Matrix 256 X 128, Scan Time: 10 sec.

High resolution high contrast T1 weighted Anatomical Fast Spoiled Gradient recall (FSPGR) Acquisition of head images along the desired direction is achieved in sagittal orientation. 3D high- resolution fast spoiled gradient recall (fSPGR) images are acquired with the following parameters: TI 900 ms, TR 2300 ms, TE Minimum full, Flip angle 8, Band width 31.25 KHz, FOV 26 x 26 cm², Phase FOV 1.0, Slice thickness 1.0 mm, Spacing 0.0, 170 slices per volume, 1 NEX images x 2 (these acquisitions are averaged off line – doing so allows us to salvage one of them if subjects should move during the other acquisition), Matrix 256 x 256, scanner acceleration factor =2 (Scan Time: 18 minutes)

Quality Control (QC) Subjects will be positioned similarly for each and every scan, with a stereotactic marker on the left side of the head. QC will be performed regularly to ensure the stability of image acquisition across time. Specifically, this will be assessed by scanning at regular intervals (every 12 months) an agar phantom for the detection of intensity distortions and a structured phantom (with an internal geometric structure) for the detection of geometric distortions. Finally, images will be processed with their temporal order of acquisition randomized so as to avoid bias.

D7 MRI Data Analysis

Preprocessing After applying the default correction in our GE scanner to correct spatial distortion, nonuniformities in image intensity will be corrected using a validated algorithm developed at the Montreal Neurological Institute.¹⁴⁴ Extracerebral tissues are removed using an automated tool for extracting the brain. This tool first smoothes image intensity using an anisotropic filter, detects three-dimensional edges using a Marr-Hildreth edge detector, and then selects as the brain the largest connected component with closed boundary. Connecting dura is removed manually on each slice in sagittal, coronal, and axial views. The brainstem is transected at the pontomedullary junction. All morphometric analyses are performed with the MRI dataset resliced to correct for any residual head rotation, tilt, or flexion/extension.

Cortical Gray and White Matter Segmentation Every tenth slice, the gray-scale values of "pure" representations of cortical gray matter and white matter are sampled bilaterally at 4 standard locations throughout the brain (frontal, temporal, occipital, parietal) using an 8 x 8 = 64 pixel array, sufficiently large to provide statistical stability but small enough to avoid partial volume effects that include other tissue types. These 4 values are then averaged for each tissue type and a threshold value halfway between the mean gray matter and mean white matter values is computed for a slice in the imaging volume. The threshold values for every tenth slice are then interpolated to determine the threshold values for every slice throughout the brain. We invoke these threshold values on a slice by slice basis to provide an initial rough classification of cortical gray and white matter throughout the cerebrum. This classification is then hand edited in all 3 views. White matter is defined by the subtraction of all other tissues (cortical gray, subcortical gray and ventricular CSF). ICC's are all >0.98.

Surface Analysis Following a rigid registration, (Translation, Rotation and Scaling) using an algorithm that maximizes mutual information between gray scale intensities values in the origin and in the target image,¹⁴⁵ the cortical surface of each subject is warped onto the cortical surface of a reference brain using a high-dimensional, non-rigid warping algorithm based on fluid dynamics. Warping a source image to the template brain will produce a cortex in the source brain that is exactly the same size and shape as the cortex of the reference brain, thereby permitting identification of precisely corresponding points on the surfaces of the subject and reference cortices. The warped subject cortices are then unwrapped by simply reversing the high-dimensional, nonlinear warping performed to identify point correspondences, but bringing along with the surface the labels that identified corresponding points on the surfaces of the subject and the reference cortex. Because all subject brains are normalized into the coordinate space of the reference and because we use high-dimensional nonlinear warping for surface analysis, region definitions in subject brains, other than the reference, are not needed. Within-subject longitudinal warping onto the reference brain will be performed. Scans for each subject acquired at t_1 , and t_2 will not be warped onto the reference brain separately one at a time. Instead, the first scan (t_1) will be warped onto the second scan (t_2). Only the final scan will be warped onto the reference brain.

Region definition on the reference brain is achieved by applying a template where Regions of Interest (ROIs) have been previously defined. After the unwarping is completed, we calculate the distance from each point on the cortical surface of each subject to the corresponding point on the cortical surface of the reference subject (signed Euclidean distances). Thus, at a group level this procedure allows the generation of a set of signed Euclidean distances at each point of the cortical surface whose variability we then subject to statistical modeling. Signed euclidean distances can be regressed with neuropsychological or clinical variables (see preliminary data) as well as group membership (i.e. prodromal, converter, non converter etc).

Cortical Thickness After determining the corresponding points on the surfaces of the reference and source brains, we subtract the cortical mantle from the coregistered brain of each subject. We then use a three-dimensional morphological operator to distance-transform this brain without the cortex from the coregistered brain of the same subject that contained the cortex.^{146, 147} This operation calculates cortical thickness as the smallest distance of each point on the external cortical surface from the outermost surface of the white matter in the coregistered brain. Because these thicknesses are measured in template space, their values inherently account for generalized scaling effects within the cerebrum, because the brain and its local features, such as cortical thickness, will have already been scaled during the similarity transformation of that brain to the template brain. Finally, the established point correspondences on the cortical surfaces will yield a set of values of cortical thickness at every point on the surface of the reference brain. Statistical analysis of these sets of values will detect locations where cortical thickness differs significantly between groups of subjects. Indentations or protrusions are understood to represent respectively subtle volume decreases and increases; by simultaneously obtaining values of cortical thickness at these same locations, we will be able to discern whether these morphological abnormalities are associated with thinning or thickening of the cortex, respectively.

Choice of the reference subject for surface analysis and cortical thickness We first select a reference subject who is as demographically representative as possible of the sample studies. The brains of the remaining healthy subjects are then coregistered to this preliminary reference. The point correspondences on the cortical surfaces are established and distances between corresponding points are calculated. A final reference brain is selected for which all points across the cortical surface are closest to the average computed distance (in terms of least squares). This method offers advantages over synthetic average brain which lose in anatomical detail.

Correction for Multiple Comparisons in Surface Analyses and Studies of Cortical Thickness Testing the linear model at each voxel entails multiple statistical comparisons. We will correct for the multiple statistical comparisons performed across the cerebral surface using the theory of Gaussian Random Fields (GRF). The signed distances determine a T statistic at each cortical point which across the surface compose a random field f . The expected value of the Euler Characteristic (EC) of the random field f is used to approximate the critical point for determining locations on the surface where the t statistics differs between groups at a predefined significance level. Surface locations where the statistics is larger than the estimated critical point

are considered significant. Because the expected EC is evaluated for a GRF, t statistics at each location on the cortical surface are converted into values from a Gaussian random variable. These methods have been shown to have excellent sensitivity and specificity for detecting morphological abnormalities at the cortical surface.¹⁴⁸⁻¹⁵⁰ After correction, a threshold of $\alpha < 0.0001$ will be set to minimize type I error. We will then color encode the p values and display them across the surface of the reference structure to visualize the local differences in surface morphology (or cortical thickness) across groups, while controlling for covariates at each voxel.

Scaling Scaling effects typically contribute in large extent to the inter-individual variability in size between different subregions of the brain. We scale each individual brain to the reference brain in order to account for this portion of variance. However, if whole brain volume (WBV) differs by diagnosis or group, this approach can obscure true differences in size of subregions between groups or it can lead to the erroneous detection of spurious differences. Therefore, we will confirm all results using height as the scaling factor, preferring this in the presence of known group differences in WBV, and with analyses that do not rescale individual brains.

D8 Biostatistics Following is a plan for testing a priori hypotheses listed in the Specific Aims. The statistical techniques used will also be part of the coursework that I am proposing in the training plan. Because the project is a pilot study, it is powered to detect mostly moderate effect sizes. However, the analyses from this project will inform later work, which will be powered to detect small effect sizes within the framework of an R01 application. Mixed random effects models with repeated measures will be developed to test our a priori hypotheses. These longitudinal models will assess the effects of an independent variable on the dependent variable as the latter changes over time. To identify significant component terms in each of the models, we will examine the parameter estimates, 95% confidence intervals, and p-values of the component terms. Residual plots will be generated to assist in the selection of the models. Before undergoing statistical modeling, we will perform descriptive analyses and examine the distributions of all our variables.

1. Aim 1: Gray Matter Development in Healthy Controls This hypothesis will test the effects of age and gender on cortical thickness and surface topology over time. The longitudinal structure of the data will be used and statistical modeling will be applied at each point on the surface of the reference brain. Signed Euclidean distances or values of cortical thickness will be entered as the dependent variable at each voxel in a linear mixed effects model with repeated measures obtained at baseline and at year 2. The mixed model will have the form

$$Y_i(t) = \beta_{0i} + \beta_{1i} * \text{age}_i(t) + \beta_{2i} * \text{age}_i^2(t) + \beta_{3i} * \text{sex}_i + \beta_{4i} * (\text{age}_i(t) \times \text{sex}_i) + \text{CORR}_i(t) + \varepsilon_i(t)$$

Here we are testing the null hypothesis that there is no relationship between age or age^2 and the change over time in cortical thickness or surface topology. We are also using age^2 because evidence from prior findings and our preliminary data show quadratic relationship of gray matter volumes with age. In this model, both the regression coefficients and the intercept are allowed to vary between subjects so that conclusions can be generalized outside of this sample. The assumption is that the variation in intercept and slope are normally distributed with an average of zero. Only some variables in the model are time- dependent (age for instance), while others (sex) are not.

Y_i is the signed Euclidean distance at each point of the brain surface of the i^{th} subject at time t. Alternatively, it is the value of cortical thickness for subject i at time t. β_{0i} is the random intercept for subject i; β_{1i} is the random regression coefficient for the term representing the linear effect of age, β_{2i} is the random coefficient for the quadratic effect of age for subject i; β_{3i} is the random regression coefficient for the term representing the effects of gender for subject i; β_{4i} is the random regression coefficient for the interaction term of age and sex for subject i and ε_i is the error term for subject i; **CORR_i(t)** is a nuisance variable representing the within-subject correlation structure of subject i over time.¹⁵¹ This term models correlated errors caused by correlated observations over our 2 time points. The correlation structure will be assumed to be exchangeable with

correlations between subsequent measures (ρ) set to be the same between time points. We will not model the correlation between hemispheres, as each hemisphere will be analyzed separately. Based on prior structural studies with comparable sample sizes and comparable conversion rates that detected differences between converters and non-converters at stringent levels of p values (0.002),⁸³ we can estimate that our sample size is adequate, especially in light of our use of repeated measures, which enhances statistical power. Under a linear mixed model with repeated measures, I will test whether the regression coefficients β_{1i} or β_{2i} or β_{3i} or β_{4i} differ significantly from zero. In this case, an approximate F-test can be applied. With 40 subjects per group and a power of 80%, a Type I error α of 0.05 allows detection of moderate effect sizes (between 0.58 and 0.67, based on different values of ρ ranging from 0 to 0.9).

2. Aim 2: Gray Matter Changes in prodromal cases (converters and non-converters) We will compare changes in surface morphology or cortical thickness between healthy controls and prodromal subjects, and between converters and non-converters. In each of these comparisons, these groups will be represented by a dummy independent variable (diagnostic group membership). Because group membership may change over time due to conversion, we are modeling this variable as time-dependent. The set of signed Euclidean distances or of the values of cortical thickness at each voxel will be entered as a continuous dependent variable and a test statistic will be obtained to measure how significantly the rate of change in the dependent measure differs between the groups. We will covary for age, age², and sex of the subject, having first ensured the absence of significant interactions among group, age, and sex.

$$Y_i(t) = \beta_{0i} + \beta_{1i} * \text{age}_i(t) + \beta_{2i} * \text{age}_i^2(t) + \beta_{3i} * \text{sex}_i + \beta_{4i} * \text{group}_i(t) + \text{CORR}_i(t) + \varepsilon_i(t)$$

β_4 is estimated in this model and the p value is then obtained for this coefficient using the T-statistic. We are here testing the null hypothesis that the difference in the rate of change of the dependent variable between groups is not statistically significant. Subsequently, we will also carry out a secondary analysis within the group of converters, comparing those individuals who develop schizophrenia versus those who develop affective psychoses. With our sample size, a one-tailed t-test for zero difference between slopes, with a one-sided significance level of 0.05, a power of 80%, allows detection of a small to moderate differences in slopes (effect size between 0.46 and 0.61 based on different values of ρ).

Aim 3 Association of Structural Changes with Prodromal Symptom Severity We will assess the contribution of SOPS scores to changes in cortical thickness and surface topology over time by introducing a regressor that captures the effects of these scores, as specified below:

$$Y_i(t) = \beta_{0i} + \beta_{1i} * \text{age}_i(t) + \beta_{2i} * \text{age}_i^2(t) + \beta_{3i} * \text{sex}_i + \beta_{5i} * \text{SOPS score}(t) + \text{CORR}_i(t) + \varepsilon_i(t)$$

Here we will test the null hypothesis that no association exists between the longitudinal variation of SOPS scores and the longitudinal change in cortical thickness or surface morphology. Scores assessing different symptom subscores (positive, negative, disorganization, and general) will not be entered simultaneously within the same model if collinearity between these dimensions is found. Under a linear mixed model with repeated measures, I will test whether the regression coefficient β_{5i} is different than zero. In this case, an approximate F-test can be applied. With 40 subjects per group and a power of 80%, a Type I error α of 0.05 allows detection of small effect sizes (between 0.05 and 0.11 based on different values of ρ).

Assessment of possible confounds We will include also in our initial model handedness, IQ, socioeconomic status, minority status, medication use, and past substance abuse as covariates (main effects and interactions). If no appreciable main effects or interactions are detected and if the measures have negligible effects on the parameter estimates for other variables in the model, they will not be included in the final models.

E. PROTECTION OF HUMAN SUBJECTS

E1. Involvement of Human Subjects. I will recruit a total of 30 prodromal cases and 30 healthy controls, scanning each of them twice, two years apart. These are in addition to the 10 prodromal subjects we have already enrolled and to the 10 control subjects we will have enrolled before the beginning of this Award. Both men and women will be recruited. I will group match the healthy control subjects for important biological variables, such as age, sex, socio-economic status, IQ, and handedness (these measures are collected in the COPE clinic).

Inclusion criteria Prodromal cases will be 12-30 years old and they will be identified as prodromal on the basis of the SIPS/SOPS.⁸

Exclusion criteria Exclusion criteria for both prodromal cases and healthy subjects will be : 1) Current or past diagnosis of any Axis I psychotic disorder, as gathered by a clinical diagnostic interview (schizophrenia, schizophreniform disorder, bipolar disorder, schizoaffective disorder, major depression with psychotic features, substance-induced psychosis, psychosis due to a medical condition or psychosis NOS); 2) History of neurological or major medical disorders (including prior seizure or head trauma with loss of consciousness) known to affect the brain, as putative prodromal symptoms could be secondary to these and unrelated to schizophrenia risk. 3) Risk of suicidal or violent behavior for the protection of subjects and staff; 4) IQ < 70 5) Pregnancy or planning pregnancy during the study period; 6) Any metallic device or dental braces; 7) Ongoing substance abuse and lifetime substance dependence. Because the use of medication is not an exclusion criterion in our study, we will assess the effects of medication use as a possible confound.

E2. Sources of Research Material Research material will include: (1) MRI scans; (2) the SIPS/SOPS; and (3) questionnaires measuring demographic characteristics such as age, sex, race, medical history, medications, psychiatric history, substance abuse history and parental occupation.

E3. Recruitment Procedures Please see the Research Plan for further details. Briefly, prodromal subjects will be recruited through the COPE clinic at the New York State Psychiatric Institute. Healthy control subjects will be recruited through the COPE clinic and through mailings and subsequent telephone calls to addresses that have been purchased from a national telemarketing company.

E4. Consent Procedures The nature of the research protocol, including potential risks and benefits, will be explained verbally to all potential subjects by the PI. The consent forms for participation will be reviewed with the legal guardian of adolescents under age 18, or directly with those over 18. Adolescents under 18 years will be asked to read an assent form, and parents or legal guardians will be asked to read and sign a consent form. An authorization form to Access PHI under the Health Insurance Portability and Accountability Act (HIPAA) will be presented to a legal guardian of adolescents under the age of 18 and directly to individuals over the age of 18 to access PHI information from the COPE clinic where each patient currently receives psychiatric care. Adolescents will be encouraged to ask questions about any aspect of the study that is unclear to them, and those questions will be addressed carefully to clarify any uncertainties. Prodromal patients are evaluated and treated within the COPE clinic, regardless of the subject's decisions regarding participation in the protocol. Prodromal cases are usually offered a standardized treatment consisting of weekly supportive psychotherapy and symptom-focused pharmacotherapy.

E5. Potential Risks The risks associated with MRI scanning can be classified into one of four categories: a) Acoustic Noise Levels, b) Gradient or Time-Varying Magnetic Fields, c) Radiofrequency (RF) Magnetic Fields, and d) Static Magnetic Fields. Also Possible incidental risks (e) and Risks associated with longitudinal scanning (f) are considered.

a) Acoustic Noise The acoustic noise associated with MR imaging is related to the mechanical movement of the gradient coils during the scanning process.

FDA Guidelines: "The acoustic noise levels associated with the device must be shown to be below the level of concern established by pertinent Federal Regulatory or other recognized standards setting organizations. If the acoustic noise is not below the level of concern, the sponsor must recommend steps to reduce or alleviate the noise perceived by the patient." Current FDA guidelines follow the regulations of the International Electrotechnical Commission (IEC) Standard 601-2-33, which stipulate that for MR equipment used in medicine, hearing protection is required when the system can produce acoustic sound levels above 99 dBA (maximum A weighted r.m.s.) and that the protection should be able to reduce noise levels to below 99 dBA.

The FDA has approved systems for which noise levels have been quantified, ranging up to 105 dB RMS for scanners operating at field strengths of 1.5 Tesla. It is important to note that the static magnetic field strength is only one factor, and not necessarily the most important one, in determining acoustic noise. Among the factors listed above, the design and construction of the gradient coils plays a major role in the noise level that MRI scanning produces. Therefore, noise levels are not necessarily greater when scanning at 3.0 T compared with 1.5 T field strengths. It is nevertheless possible that, in some circumstances, our system could produce noise levels higher than 99 dB, as do many clinical systems operating at lower field strengths.

Summary: The acoustic noise levels perceived by human subjects when undergoing MRI examination in our 3.0 Tesla magnet constitutes a non-significant risk; specifically, our system will not be operated in a way that will present more noise to human subjects than is recommended by the FDA.

b) Time-Varying Magnetic Fields The concern about the time-varying magnetic fields used in MRI is that these can, in some instances, induce stimulation of peripheral nerves, thereby producing sensations such as 'twitching' or 'tingling'. In very rare instances, this nerve stimulation can be painful. Nerve stimulation is particularly likely when subjects are physically positioned in a way that increases the likelihood of inducing stimulation, such as with hands clasped or arms folded. It should be noted that the parameter of interest here, dB/dt (the rate of change in the magnetic field per unit time), is not a function of the strength of the static magnetic field, so evaluating risk in a 3T MRI scanner involves the same considerations as evaluating other MRI systems operating at lower magnetic field strengths (i.e., the same issues apply to all the commercially available, FDA approved scanning systems). Thus, it is the *gradient system only* that needs to be evaluated to determine the risk of producing nerve stimulation.

FDA Guidelines: The FDA Guidance of 1995 was developed specifically to consider the fact that many clinical systems were capable of exceeding levels of dB/dt that could produce nerve stimulation. It was originally considered that a warning level should be implemented to guard against peripheral nerve stimulation, but the FDA finally concluded that: '*... this warning level is not considered critical since there are no harmful effects associated with mild peripheral nerve stimulation*'. The current guidelines therefore include monitoring procedures to help avoid painful peripheral nerve stimulation, and without specific dB/dt limitations.

Summary: The gradients used in our 3.0 Tesla MRI system will typically be operated at levels below those considered to be negligible according to FDA guidelines. Our system, like most commercially available, FDA-approved systems, does have the capacity to exceed this level, but it will include the same safeguards that are included in other FDA-approved clinical systems. Furthermore, policies and procedures will be implemented according to FDA guidelines to avoid the possibility of painful peripheral nerve stimulation. Therefore, in all circumstances the system will be operated in a way that poses nonsignificant risk to the participant.

c) Specific Absorption Rate (SAR) MRI scanning induces some heating of body tissues. This specific absorption rate (SAR) that determines heating is the amount of radiofrequency (RF) energy deposited (typically by a coil or "helmet"-like apparatus placed over the subject's head) per unit volume of tissue per unit time. The SAR for RF radiation is primarily related to the amplitude of RF power, the duration of the RF pulse, the type of RF coil used, the frequency of RF radiation, the resistivity of the tissue, the configuration of the anatomical region being examined, and several other parameters.

FDA Guidelines: "The following are levels of concern at which the reviewer shall exercise appropriate actions

to ensure that the safety of the device is substantially 0.4 W/kg whole body; and if SAR equivalent to a predicate device: A) If SAR 3.2 W/kg averaged 8.0 W/kg spatial peak in any 1 gram of tissue; and if SAR over the head: **below level of concern**. Or B) If exposure to radiofrequency magnetic fields is insufficient to produce a core temperature increase in excess of 1°C and localized heating to greater than 38°C in the head, 39°C in the trunk and 40°C in the extremities: **below level of concern**. The parameter SAR cited above must be shown to fall below either of the two levels of concern by presentation of valid scientific measurement or calculation evidence sufficient to demonstrate that SAR is of no concern."

It should be noted that this guideline is based on the calculation of a system that has no thermoregulatory response, and thus it is a very conservative estimate compared with the temperature change that would be experienced in any living subject. Normal diurnal temperature variations in humans, for example, are about +/- 1°C from the normal set point 37°C, and healthy people with normal thermoregulatory responses can easily dissipate any excess (or, in this instance, deposited) heat by increasing their peripheral blood flow or sweat rate. Thus, the heating effect of MRI with the SARs used in accord with these guidelines is extraordinarily unlikely to cause any acute effects in healthy human subjects. Furthermore, our scanner console calculates SAR based on the subject's body weight before running any pulse sequence and prohibits running of the sequence if exceeds the FDA-approved limit.

Summary: Because all experiments performed on the 3.0 Tesla system will comply with FDA guidelines with regard to SAR, and because appropriate RF power safety checks are in place, this criterion for classification of NSR is satisfied.

d) Static Magnetic Fields The possible risks of static magnetic fields have received much attention in the lay press, but scientific consensus on these risks has yet to be fully reached. The FDA has deemed that systems operating at 8.0 Tesla or less do not pose a significant risk. Moreover, experience with thousands of clinical studies over the past decade, and with multiple human investigations carried out at higher field strengths over this period, have not revealed risks of exposure to higher static magnetic fields. The most significant risk associated with static magnetic fields is that ferromagnetic objects, such as aneurysm clips or heart valves, can interact with the magnetic field of an MRI scanner, causing the device to malfunction or to move, and injuring the subject.

FDA Guidelines: "Studies conducted at 8T or less are not considered significant risk" (FDA Center for Devices and Radiological Health, memorandum 7-14-03).

Summary: This category of risk applies to work conducted around superconducting magnets of any kind (including standard clinical diagnostic MRI units). It is not unique to our 3.0 Tesla facility, which will maintain a safety policy to safeguard subjects and staff members from these incidental risks. Systems with static magnetic field less than 8 Tesla have been considered to represent a nonsignificant risk by the FDA. The static magnetic field of our system (3.0 Tesla) is therefore to be classified as posing NSR to human subjects.

e) Possible Incidental Risks The physical confinement and isolation produced by the scanner could cause mild to moderate emotional distress, although in our past experience, subjects generally tolerated the procedures remarkably well.

f) Risk associated with repeated scanning The effects of exposure for the first 4 components of MRI scanning (section a, b, c, d above) are **non-cumulative** – i.e. exposure on multiple occasions is no greater than exposure on a single occasion). Furthermore, as indicated above, the risks of MRI are considered minimal by the FDA, and the risks of repeat scanning are therefore minimal as well. Although the incidental risks associated with scanning (section e. above) conceivably could accrue across time with repeat scanning, in our past experience we have found that these risks actually decline rapidly with time due to sensitization to the scanning environment and procedures.

E6. Protecting Against Potential Risks Our 3.0 Tesla scanner satisfies FDA criteria for nonsignificant risk (NSR) in all risk categories:

i. Acoustic Noise: As suggested by the FDA, I will take steps to reduce or alleviate the noise levels experienced by subjects in this protocol. The easiest and most reliable means of preventing hearing loss is to use disposable earplugs, which I intend to do for all scans. I will also be using acoustically shielded headsets, which further attenuate noise.

ii. Nerve Stimulation: All consent forms for studies that might induce peripheral nerve stimulation also will provide this information. A record of dB/dt value will also be included with the imaging data to help in analysis of levels of peripheral nerve stimulation possibly perceived by subjects. In addition, I will conduct detailed calculations of the changes in magnetic field over time that our gradient system is capable of, and conservative values will be selected as limits that will be used to determine when special additional monitoring is indicated. In these cases, I will use the monitoring procedures recommended by the FDA. The gradient switching times and strengths will also be monitored together with the routine assessment of all electrical components of the system, as described previously.

MR technologists will also receive special training to prevent peripheral nerve stimulation and before any scanning procedure that might stimulate peripheral nerves, a technologist will:

- a) Inform the subject that peripheral nerve stimulation may occur
- b) Describe the nature of the sensation to the subject
- c) Instruct subjects not to clasp their hands, since this may create a conductive loop which will increase the possibility of stimulation
- d) Maintain constant verbal contact with the subject
- e) Instruct subjects to inform the MR technologist if they experience discomfort or pain
- f) Terminate the scan if the subject complains of discomfort or pain
- g) Complete a report of any incidents involving severe discomfort or pain, including a description of the associated circumstances (imaging parameters, dB/dt value, level of pain, etc.), and submit this report immediately to the IRB.

iii. SAR Absorption The magnitude of temperature increase during MRI scanning is minimal. Increases are always within FDA guidelines, which include core temperature increases less than 1°C, as well as localized heating to less than 38°C in the head, 39°C in the trunk, and 40 °C in the extremities. Our 3.0 Tesla system has in place a means to monitor RF power levels and ensure that energy deposition is sufficiently low to stay well within these guidelines for temperature increases. First, a "system security" unit is employed to integrate the output of the RF amplifiers. This integration takes into account the amplitudes and duty cycle of the transmitter. If system security detects an output that might exceed the guidelines noted above, it automatically shuts down the entire RF power system. Secondly, all pulse sequences are evaluated, based on calculations and sound scientific measurements, to ensure that SAR remains within FDA-approved guidelines, prior to their use in humans. Any experiment performed on our 3.0 Tesla system will comply with all FDA guidelines with regard to RF power deposition. Proper and routine monitoring of all RF electronics (e.g., coils, transmitters, system security, etc.) will be performed on a regular basis. All pulse sequences will be evaluated (by calculation and by valid scientific measurement) prior to use in humans.

iv. Static Magnetic Fields The minimization of risks associated with the static magnetic field of 3.0 Tesla is mainly related to incidental risks (see below). These risks are the same as in other commercially available clinical systems, and like other clinical MRI centers, our facility will incorporate a complete range of procedures to assure security of the restricted access area, careful screening of potential subjects before they enter the restricted access area, and a metal detector positioned at the doorway leading into the magnet room within the MRI suite. Access to the MRI suite will be tightly controlled, allowing access only to personnel and research subjects who have legitimate reason to be there. Doors to the unit will be securely locked, with only MR technologists, physicists, or physicians controlling entry of ferromagnetic and other materials that could possibly cause injury to patients, research subjects, personnel, or equipment. In addition, entry-ways to the unit will be labeled with clear visible signs warning of the presence of the magnetic field and the exclusion from

entry by individuals with implanted metal objects such as prostheses, pins, clips, IUD's, etc.

v. Incidental MRI Risks All subjects will be able to communicate directly with technologists and study staff to inform them of any emotional or physical distress during the scanning procedure. If they wish, the scan will be terminated immediately and the subject will be removed from the scanner.

vii. Risk associated with repeated scanning The effects of exposure for the first 4 components of MRI scanning (section a, b, c, d above) are **non-cumulative** – i.e. exposure on multiple occasions is no greater than exposure on a single occasion). Furthermore, as indicated above, the risks of MRI are considered minimal by the FDA, and the risks of repeat scanning are therefore minimal as well. Although the incidental risks associated with scanning (section e. above) conceivably could accrue across time with repeat scanning, in our past experience we have found that these risks actually decline rapidly with time due to sensitization to the scanning environment and procedures.

vii. Confidentiality All the information obtained from the subjects will be coded by number and kept in locked, confidential files. This information will not be accessible to anyone but the study investigators. Furthermore, all of the data (including MRI scans) will be stored behind firewalls at the New York State Psychiatric Institute. Finally, to ensure protection of confidentiality of the sensitive information that will be obtained in this project, I will apply for a Certificate of Confidentiality from NIH. Dr Corcoran already has a certificate of confidentiality for the prodromal research program (COPE). All subjects will be identified by subject number only. Finally, to ensure protection of confidentiality of the sensitive information that will be obtained in this project, I will apply for a Certificate of Confidentiality from NIH.

viii. Clinical Issues I will make necessary referrals during the course of the study if the need arises and I will notify the treating clinician if abnormalities are found on the MRI.

Special Human Subjects Concerns in a Prodromal Sample

Research on the schizophrenia prodrome raises special concerns, given that the prodrome is not yet a well-defined diagnosis or clinical entity.

Special concerns include:

1. Risk of stigma
2. Appropriate crisis interventions and sufficient monitored protection for those who develop psychosis
3. Informed consent (see above)

These concerns have been addressed in the following ways:

1. Stigma: Only help-seeking patients will be involved in the study as prodromal subjects. In general, patients and their families who participate in COPE clinic research are told that 1) there may be some chance of the further development of symptoms, including psychosis, but that the actual risk is not known and 2) there are effective treatments for any further symptoms that do develop. Experience at our and other prodromal research programs – Dr. McGlashan's PRIME clinic in New Haven, Dr. Cornblatt's RAP clinic in Queens, NY and Dr. McGorry's PACE clinic in Melbourne, Australia - suggests that prodromal patients already suffer stigma among their peers for odd and unusual behavior, and that identification as "prodromal for psychosis" has not been found to be stigmatizing.

2. Appropriate crisis intervention and monitored protection for those who develop psychosis:

Subjects will be referred for treatment as needed at any point during study participation (i.e. crisis intervention and emergency services for suicidal or violent ideation and behavior, or frank psychosis or mania). There is a 24-hour crisis service and emergency room for both children and adults.

E7. Risk/Benefit Ratio The information generated by this study will offer important insights into the structural brain abnormalities that may underlie the development of symptoms during the prodrome and which may lead to the identification of predictors of conversion to psychosis. Subjects and parents will be informed of any clinically significant findings from the MRI. Each subject will receive payment for participating in the study. The risks of participating in this study are minimal, especially in relation to the potential benefits and public health importance of improved understanding of the schizophrenia prodrome and of our ability to predict conversion to psychosis.

E8. Inclusion of Females and Minorities In keeping with NIH policy, women will be included in this project. Subjects at COPE are now 81% male and 19% female. A strong effort will be made to increase the percentage of girls and women. I will oversample females so that I can assess gender effects as a possible confound in our findings. Strategies to increase the percentage of females enrolled in COPE include recruiting from counseling centers at all local women's colleges (i.e. *Barnard College, College of New Rochelle*) guidance counselors at high schools for girls (e.g. *Spence School, Young Women's Leadership School, Girls Preparatory Charter School,*) women's health centers at co-ed colleges (e.g. *New York University, LaGuardia Community College, Brooklyn College*) women's health centers in local communities (e.g. *Iris Cancor Women's Health Center at Weil Medical College and New York-Presbyterian Hospital, The Center for Women's Health at Columbia University Medical Center*), and directors of clubs/organizations for girls (e.g. *Girls Club of New York, Girls Incorporated*). There are no specific hypotheses about gender differences in outcome, but any potential interaction of sex and hypothesized associations of brain imaging findings and symptoms will be analyzed. No exclusions will be made on gender.

In keeping with NIH policy, members of minority groups will be included in this project. Subjects at the COPE are 25% Hispanic or Latino, 9% Asian, 41% Black or African American, and 50% White. There are no specific hypotheses about ethnic differences in outcome, but any potential interaction of racial/ethnic subgroups and hypothesized associations of brain imaging findings and symptoms will be analyzed. No exclusions will be made on ethnicity or race. Self-reporting and self identification will be used for collecting data on ethnicity and race. Should the rate of recruitment of minority subjects drop below our targets, we will intensify recruitment efforts at participating recruitment sites that serve predominantly minority subjects (e.g., Columbia Presbyterian and our affiliates, St. Luke's & Roosevelt, both in Harlem).

Inclusion of Children The sample will not consist of children but only of adolescents and young adults aged 12 through 30, as this is the range when prodromal symptoms typically appear. I have had experience in clinical research with and treatment of prodromal individuals. Further, I have had, as part of this fellowship, oversight and training in the appropriate ethical conduct of research with prodromal individuals, by Dr. Cheryl Corcoran, the director of COPE (weekly). Additionally, COPE will continue to collaborate with the child psychiatry experts on the Children's Day Unit at NYSPI. COPE employs clinical staff with considerable experience assessing and treating teens and young adults, as well as staff with specific experience with prodromal patients.

E9. Collaborating Sites None.

F. VERTEBRATE ANIMALS None**G. SELECT RESEARCH AGENT** None**F. LITERATURE CITED**

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