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Decreased functional connectivity with aging and disease duration in schizophrenia

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DECREASED FUNCTIONAL CONNECTIVITY WITH AGING AND DISESEAE DURATION IN SCHIZOPHRENIA

BY

CHRITOPHER ABBOTT

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THESIS

Submitted in Partial Fulfillment of the
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ABSTRACT

Objective: Progressive brain changes late in the disease course of shizophrenia may be detected with functional connectivity. This study compared functional connectivity between patients with schizophrenia late in the disease course with matched healthy controls.

Method: Subjects included 18 patients with schizophrenia with minimum 15 years disease duration and 28 matched healthy controls from the MIND Clinical Imaging Consortium database. The functional magnetic resonance imaging paradigm was the auditory oddball task. We used independent components analysis to identify temporally cohesive but spatially distributed neural networks. We selected the executive control and default mode networks for additional analysis. The temporal course of each spatial component was then regressed with a model of the hemodynamic time course based on the experimental paradigm to measure functional connectivity. The beta weights from this regression were used for additional group level analyses.

Results: The anterior default mode network had a main effect by group (patients with schizophrenia and healthy controls) and an interaction with group and aging. As the patient group aged, they had less negative modulation of the anterior

default mode network. The patient group also had significantly less positive modulation of the executive control network.

Conclusions: These results show evidence of progressive changes in functional connectivity in the anterior default mode network late in the disease course of schizophrenia. The decreased functional connectivity may be attributable to the progressive disease course of schizophrenia.

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CHAPTER 1 GENERAL INTRODUCTION

Schizophrenia is a chronic, debilitating disease affecting one percent of the world's population [1]. The signs and symptoms of schizophrenia include hallucinations, delusions, disorganized thought, and abnormalities in emotional expression, social interaction, and drive [2]. Treatment consists of a variety of antipsychotic medications that share the common property of antagonizing the dopamine receptor [1]. Pharmacologic treatment successfully attenuates the hallucinations and delusions but unfortunately fails to significantly attenuate the cognitive and negative symptoms. Cognitive symptoms correlate strongly with the level of functioning [3]. The affected individuals subsequently fail to return to their premorbid level of functioning. A better understanding of the longitudinal course of schizophrenia is a necessary step in the development of more effective treatments.

The disease course of schizophrenia has generated considerable debate for the last 100 years. Emil Kraepelin (1855-1926) emphasized a poor prognostic view when he emphasized the onset, course, and outcome of the illness and labeled the disorder *dementia praecox*. *Dementia praecox* had a heterogeneous symptom profile, a deteriorating course, and a poor outcome [4]. Kraepelin emphasized the progressively deteriorating longitudinal course was essential in differentiating this illness from manic-depressive disorder [5]. Eugene Bleuler (1857-1939) had a more optimistic view of the illness and did not believe that

dementia was an essential component of the illness. He subsequently changed the name of the diagnosis to schizophrenia (splitting of the mind).

Today, schizophrenia is often viewed as a “limited neuroprogressive” illness balancing the conceptualizations from Kraepelin and Bleuler [6, 7]. The longitudinal course of schizophrenia is summarized as follows[7]. A prodromal period precedes the onset of psychotic symptoms. This period consists of mood symptoms, cognitive symptoms, and social withdrawal. The onset of psychotic symptoms marks the onset of first-episode schizophrenia and further functional decline. The early years of the illness are characterized by intermittent psychotic exacerbations that correlate with worsening periods of functioning, psychiatric hospitalizations, and incomplete recovery. After the first five to ten years of the illness, the disease stabilizes with no further decline in cognitive deficits or decline in functioning [8-12]. The disease course of schizophrenia is presented in Figure 1.

In contrast, poor-outcome patients with schizophrenia have an entirely different disease course. These patients with schizophrenia have no symptom remission and are dependent on others for activities of daily living [13]. This poor-outcome group also has more cognitive deficits at the onset of the illness [14]. In late-life, this group has an increased rate of cognitive and functional deterioration qualifying these individuals for an additional diagnosis of dementia [14-18]. The cognitive and functional decline of this group of patients in late-life suggests that the neuroprogressive aspects of schizophrenia may not be limited to the early

part of the disease. These changes in level of functioning are contrasted with the classic disease course in Figure 2.

Schizophrenia has been intensively studied with structural and functional neuroimaging. The collective evidence of these studies suggests that schizophrenia is not a product of a specific, structural lesion affecting one part of the brain, but multiple neuronal pathologies resulting in a failure of neural networks or functional interaction between networks [19]. The complexity of the disease is the catalyst for the development of new neuroimaging modalities and data analysis techniques. One such data analysis technique is functional connectivity. Functional connectivity correlates the activity in one anatomic area or network with other brain regions or a model of brain activity [20]. This technique has been widely used with electroencephalography and magnetoencephalography. These imaging modalities sacrifice spatial resolution for superior temporal resolution (milliseconds). Recently, investigators have measured functional connectivity with functional magnetic resonance imaging (fMRI). This imaging modality has inferior temporal resolution (seconds) relative to the aforementioned imaging modalities, but the vastly improved spatial resolution of fMRI promises to add significantly to our understanding of the pathophysiology of schizophrenia.

The following study is an fMRI investigation of an older sample of community dwelling patients with schizophrenia. We hypothesized that these patients will show evidence of neuroprogressive changes late in the illness. Specifically, we hypothesized that the older group of patients will have less

functional connectivity correlating with age relative to the healthy control group. After introducing the challenges in more detail, we will describe the methodology with particular emphasis on independent component analysis, a sophisticated method of blind source separation that we used to identify spatially independent but temporally coherent networks. We will then contextualize our findings with previous studies using related methodologies in schizophrenia and healthy aging.

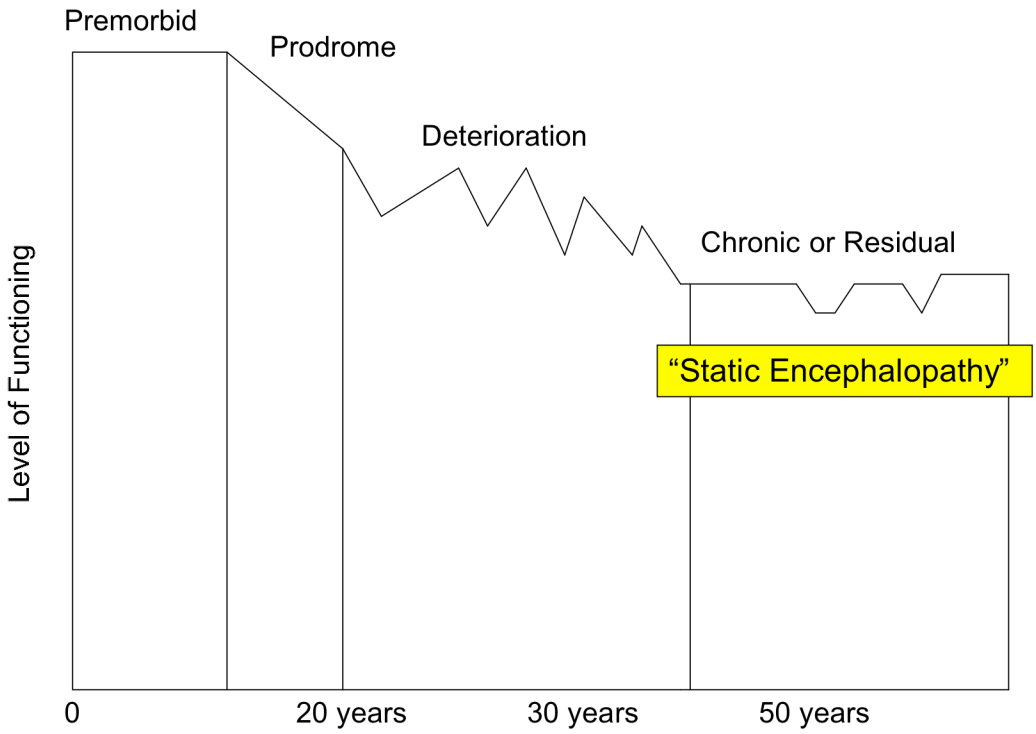

Figure 1. The disease course of schizophrenia includes the "static" period in late-life. The figure is adapted from Lieberman *et al* [7].

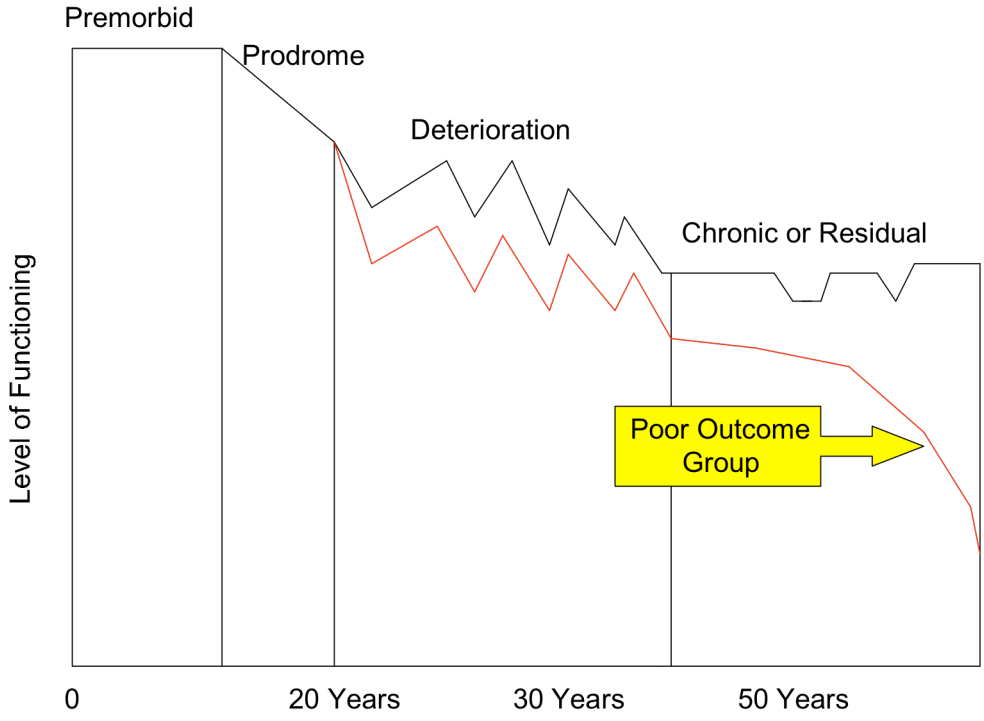

Figure 2. In contrast to the typical disease course of schizophrenia, the poor outcome group has a progressive decline in cognition and function in late-life.

CHAPTER 2 MANUSCRIPT

INTRODUCTION

Over the next decade, the number of elderly patients with schizophrenia will increase dramatically [21]. The costs associated with schizophrenia are substantial, and these costs increase with age and disease duration [22]. A better understanding of disease progression and aging in schizophrenia is necessary to develop interventions that effectively modify the disease course and improve functioning in late-life.

In mid- and late-life, patients with schizophrenia have significant variability in their level of functioning. Some patients with schizophrenia have a modest but stable level of functioning with intermittent psychotic exacerbations [7]. Others are less fortunate and are plagued with chronic, treatment-resistant symptoms. This poor-outcome group also has more cognitive deficits at the onset of the illness, but progressive cognitive deterioration is not always evident until late-life [14]. In late-life, this group has an increased rate of cognitive and functional deterioration qualifying these individuals for an additional diagnosis of dementia. However, large postmortem studies of these patients do not show a significant increase in senile plaques or neurofibrillary tangles [23]. The progressive functional and cognitive decline in this patient group may be related to the natural disease course of schizophrenia as opposed to another neurodegenerative co-morbidity [14].

The progressive changes associated with the level of functioning in schizophrenia can be detected earlier in the disease course with functional Magnetic Resonance Imaging (fMRI) and functional connectivity. Functional connectivity measures the temporal correlation of the blood oxygen level dependent signal with different brain areas or a model of the hemodynamic response [20]. The region of interest method correlates the time course of an *a priori* region with the rest of the brain with voxel by voxel correlations [24]. Previous investigators have used this method to measure differences in functional connectivity between patients with schizophrenia and healthy controls. These results have been variable and are often attributable to methodological differences including the choice of *a priori* defined region(s) of interest [25-30].

Functional connectivity can also be assessed with the blind source separation methods such as independent component analysis (ICA). Based on the assumption that fMRI data represents a linear mixture of source signals, ICA extracts these source signals from the fMRI data. ICA assumes that different source signals or components are from different physical processes [31]. Spatial ICA separates fMRI data into statistically independent spatial components along with their respective ICA time courses. The temporal course of each spatial component is then regressed with a model of the hemodynamic time course based on the experimental paradigm to measure functional connectivity [32]. For more information regarding the application of ICA to fMRI data, we refer the reader to these references [31, 33-35].

Several canonical components have been repeatedly identified in previous ICA studies [36, 37]. These include primary vision, somatosensory, auditory, executive control and default mode networks [36]. These networks may be further subdivided based on their response to an attention-demanding task. For example, the executive control networks, which include the frontal and parietal cortical areas, are positively modulated during an attention-demanding task [38]. In contrast, the default mode networks, which include the posterior cingulate, retropslenial cortex, medial prefrontal cortex, and the inferior parietal lobule, are negatively modulated during an attention-demanding task. Functions of the default mode network include autobiographical memory and self-referential thought.

Studies using independent component analysis have assessed functional connectivity in patients with schizophrenia. Garrity *et al.* found differences in the spatial and temporal aspects of the default mode in patients with schizophrenia [39]. Using a large sample of patients and controls in a modified auditory oddball task, Kim *et al.* found differences in functional connectivity in a variety of networks including auditory, executive control, and default mode networks [32]. The executive control networks failed to activate as robustly in the patient group to target detection relative to healthy controls. Independent component analysis has yet to be utilized to study the effects of aging and disease duration on functional connectivity in schizophrenia.

Previous investigators have used ICA to study healthy aging. Damoiseaux *et al.* assessed resting state brain activity in the default mode network in a group

of young adults (mean age 22.8 years) and a group of older adults (mean age 70.7 years) [40]. Using ICA, the default mode network was split into an anterior portion that included the superior and middle frontal gyrus and a posterior portion that included the posterior cingulate as well as the bilateral superior parietal regions. In both networks, the older group had significantly decreased blood oxygen level dependent signal change compared with the younger subjects. The decreased activity in the anterior default mode network was associated with cognitive decline only in the older group.

In the present study, we compared functional connectivity with a group of older patients with early-onset schizophrenia and matched healthy controls. We used an auditory oddball task that required subjects to actively attend and respond to target or “oddball” stimuli. Previous studies have shown that target detection in the auditory oddball task positively modulates executive control networks while negatively modulating the default mode networks [32, 39]. We hypothesized that patients with schizophrenia will have significantly less positive modulation of the executive control networks and less negative modulation of the default mode networks with aging and disease duration. We also hypothesized that the loss of modulation of these networks will correlate with positive and negative symptoms.

METHODS

Participants

The patients and controls were from the MIND Clinical Imaging Consortium database. This database included over 300 first episode and chronic patients with schizophrenia and matched healthy controls from four different sites: University of Iowa (IOWA), Harvard/Massachusetts General Hospital (MGH), University of Minnesota (MINN), and the University of New Mexico (UNM). For this study, we included all of the patients with schizophrenia with minimum disease duration of 15 years and matched healthy controls that performed the auditory oddball task with a minimum behavioral response of 60% correct response to targets for each experimental run.

The demographic characteristics of the patients with schizophrenia (n = 18) and healthy controls (n = 28) are presented in Table 1. The two groups did not differ with age, maternal or paternal education, or parental socioeconomic status. The patient group scored less than controls on a test premorbid intelligence (t_{44} = 4.47, P < 0.01). The patient group also had less education than the controls (t_{43} = 3.55, P < 0.01). The subjects were from all four sites (patents/controls): IOWA (2, 0), MGH (2, 10), MINN (8, 9), and UNM (6, 9). The patients were all treated with antipsychotics at the time of data acquisition: aripiprazole (1), clozapine (5), fluphenazine (1, this patient was also taking risperidone), haloperidol (2), olanzapine (1), quetiapine (3), risperidone (3), ziprasidone (2). Positive and negative symptoms for the patient group were assessed with the Scale for the Assessment of Negative Symptoms (SANS) and

the Scale for the Assessment of Positive Symptoms (SAPS) [41, 42]. These scores are summarized in Table 2.

Auditory Oddball Paradigm

The auditory oddball task was a randomized, event-related design that consisted of frequently occurring standard tones (1000 Hz, frequency rate 82%), infrequently occurring target or "oddball" tones (1200 Hz, frequency rate 9%), and the equally infrequent novel noises. Subjects had to press a button every time they heard a target tone, and the percentage of correct hits was recorded as a behavioral measure. Stimuli was presented sequentially in a pseudorandom order for 200 milliseconds (ms) each with an interstimulus interval that varied randomly from 550 to 2050 ms with a mean of 1200 ms. The sequence allowed the BOLD response evoked by each stimuli (targets, novels, and standards) to be tested separately. An experimental run consisted of 90 stimuli (standards, novels, and targets). Each subject completed four runs. The attention demands of responding to target stimuli generate a significant hemodynamic response in a variety of cortical and subcortical networks [43].

Imaging Parameters

IOWA, MINN, and MGH used a Siemens 3 Tesla Trio Scanner. UNM used a Siemens 1.5 Tesla Sonata. The fMRI pulse sequences were the same for all four sites and consisted of the following: repetition time (TR) = 2 s, echo time (TE) = 30 ms, field of view (FOV) = 22 cm, acquisition matrix 64 x 64, flip angle = 90^{o}, voxel size = 3.44 x 3.44 x 4 mm^{3}, slice thickness = 4 mm, slice-gap = 1 mm, number of slices = 27, slice acquisition = ascending.

FMRI Preprocessing

We used SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/) to preprocess the fMRI data. Images were realigned using INRIalign, a motion correction algorithm unbiased by local signal changes [44]. Images were spatially normalized into the standard Montreal Neurological Institute space [45] and slightly sub sampled to 3 x 3 x 3.4 mm^3, resulting in 53 x 53 x 46 voxels. The images were spatially smoothed with a 9 x 9 x 9 mm full width at half-maximum Gaussian kernel.

Independent Component Analysis

We used the Group ICA fMRI Toolbox (GIFT), version 2.0b (http://icatb.sourceforge.net) to analyze the fMRI data with spatial ICA. GIFT used a minimum description length algorithm to determine the optimal number of spatially independent components [46]. The data was compressed with principal component analysis. Spatial ICA was then performed on all of the subjects at once with the infomax algorithm [47]. The output consisted of series of spatial maps and their respective time courses.

Component Selection

We were interested in identifying the executive control and default mode networks. After discarding the components that were related to artifact, we used the methods from Stevens *et al.* to select the components of interest in the following manner [48]. We compared each component spatial map with *a priori* maps of white matter and cerebral spinal fluid. Components that had a higher correlation with this map ($r^2 > 0.015$) were not considered to be meaningful activations and were discarded. We then compared the remaining components

with spatial maps of the executive control and default mode networks that have been previously identified by Damoiseaux [37]. We selected the components that matched these spatial maps for additional analysis.

Statistical Analysis of Component Time Course

We used SPM5 to generate a general linear model design matrix for the four experimental runs of the auditory oddball task. We regressed the ICA time course with this design matrix to generate a series of beta weights for every experimental parameter (targets, novels, and standards). The beta weights from the regression represented the degree of modulation of the task relative to baseline. These beta weights also measured the functional connectivity of the components of interest. We used the beta weights for targets from the regression with the SPM design matrix for additional group level analysis [32]. Groups that had more positive or negative modulation of the components of interest were more functionally connected. We performed a three-factor analysis of covariance (ANCOVA) with the beta weights of each component of interest as the outcome variable. Age (continuous data), group (healthy controls and patients with schizophrenia), and the interaction term were the independent variables. We then performed another three-factor ANCOVA for the subjects with schizophrenia with the beta weights for component of interest as the outcome variable. Disease duration (continuous data), positive and negative symptoms (categorical data), and the interaction term were the independent variables. Positive and negative symptoms were dichotomized into high (> 8 for the total of the four factors of the

SAPS, > 10 for the total of the five factors of the SANS) and low categorical variables.

Demographics	Schizophrenia (Mean/SD)	Controls (Mean/SD)	Statistics (*t*)/*P*
Sex (M/F)	13/5	20/8	
Age	44.9 (7.54)	45.8 (6.0)	t_{44} = 0.45/0.66
Education	13.78 (1.96)	15.92 (1.98)	t_{42} = 3.55/0.001
Maternal education	13.25 (3.19)	13.11 (2.86)	t_{41} = 0.15/0.88
Paternal education	14.29 (3.87)	13.88 (4.22)	t_{41} = 0.32/0.75
WRAT-3	46.5 (5.89)	52.64 (3.43)	t_{44} = 4.47/0.0001
SES	3.35 (1.00)	2.57 (0.74)	t_{43} = 3.01/.004
Parent SES	2.82 (0.95)	2.68 (0.86)	t_{43} = 0.53/0.60

Table 1. This table displays demographic information for patients with schizophrenia and healthy controls (WRAT-3, Wide Range Achievement Test, Third addition; SES, socioeconomic status).

	Mean (SD)
Scale for the Assessment of Positive Symptoms (total)	**5.17 (2.36)**
Hallucinations: Global Rating	2.33 (1.81)
Delusions: Global Rating	2.83 (1.34)
Bizarre Behavior: Global Rating	0.94 (1.06)
Thought Disorder: Global Rating	1.17 (1.38)
Scale for the Assessment of Negative Symptoms (total)	**7.39 (2.99)**
Affect: Global Rating	1.72 (1.13)
Alogia: Global Rating	0.72 (0.89)
Avolition: Global Rating	2.56 (1.25)
Anhedonia: Global Rating	2.39 (1.20)
Attention: Global Rating	1.67 (1.32)

Table 2. This table displays global rating symptom scores for the patients with schizophrenia using the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS).

RESULTS

Behavioral Findings

Both patient and control groups performed the task correctly. The controls had a near perfect response to target detection and precluded the use of a t-test. Seventy-five percent of the patients with schizophrenia performed the task correctly 90% of the time. The healthy controls and the patients with schizophrenia had significant differences in reaction times (patients = 551.68 ms, SD = 110.71; controls = 463.16 ms, SD = 29.51; $t_{45} = 2.93$, $P < 0.01$).

Components

The minimum description length algorithm determined that the optimal number of components for our data set was 18. For the 46 subjects, our output consisted of 3,312 spatial maps and respective time courses (46 subjects x 4 runs x 18 components = 3,312). From the 18 components, we identified one executive control network and two components of the default mode network for additional analysis. Similar to Damoiseaux [40], independent component analysis divided the default mode networks into an anterior and posterior network. The executive control network and the default mode networks are shown in Figure 3 and Table 3.

Between-Group Differences and Aging

For the anterior default mode network, we found a significant main effect for group ($F_{1, 42} = 4.56$, $P < 0.05$) and a group x age interaction ($F_{1, 42} = 4.54$, $P < 0.05$). As the patients with schizophrenia aged, they had less negative modulation of this network during target detection. In contrast, as healthy controls

aged, they had more negative modulation of this network during target detection. These results are presented in Figure 4.

For the executive control network, we did not find a main effect for group with the interaction term. We repeated the ANCOVA without the interaction term. We found a main effect for group ($F_{1, 43} = 4.76$, $P < 0.05$). The patients with schizophrenia had less positive modulation of their executive control networks relative to healthy controls. These results are shown in Figure 5. The posterior default mode network had no main effects for group or interactions.

Disease Duration and Symptoms

Age strongly correlated with disease duration in the patients with schizophrenia ($r = 0.71$, $P < 0.001$). We used disease duration to assess changes in connectivity that may be related to positive or negative symptoms. For the anterior default mode network, we found trend level significance for a main effect of positive symptoms (high/low) ($F_{1, 14} = 4.56$, $P = 0.052$). We also found trend level significance for the interaction of positive symptoms x disease duration ($F_{1, 14} = 4.45$, $P = 0.062$). As the patients with schizophrenia had longer disease duration and more positive symptoms, they had more negative modulation of their anterior default mode networks with target detection. We did not find this trend for negative symptoms. We did not find this relationship with positive or negative symptoms for the posterior default mode network or the executive control networks.

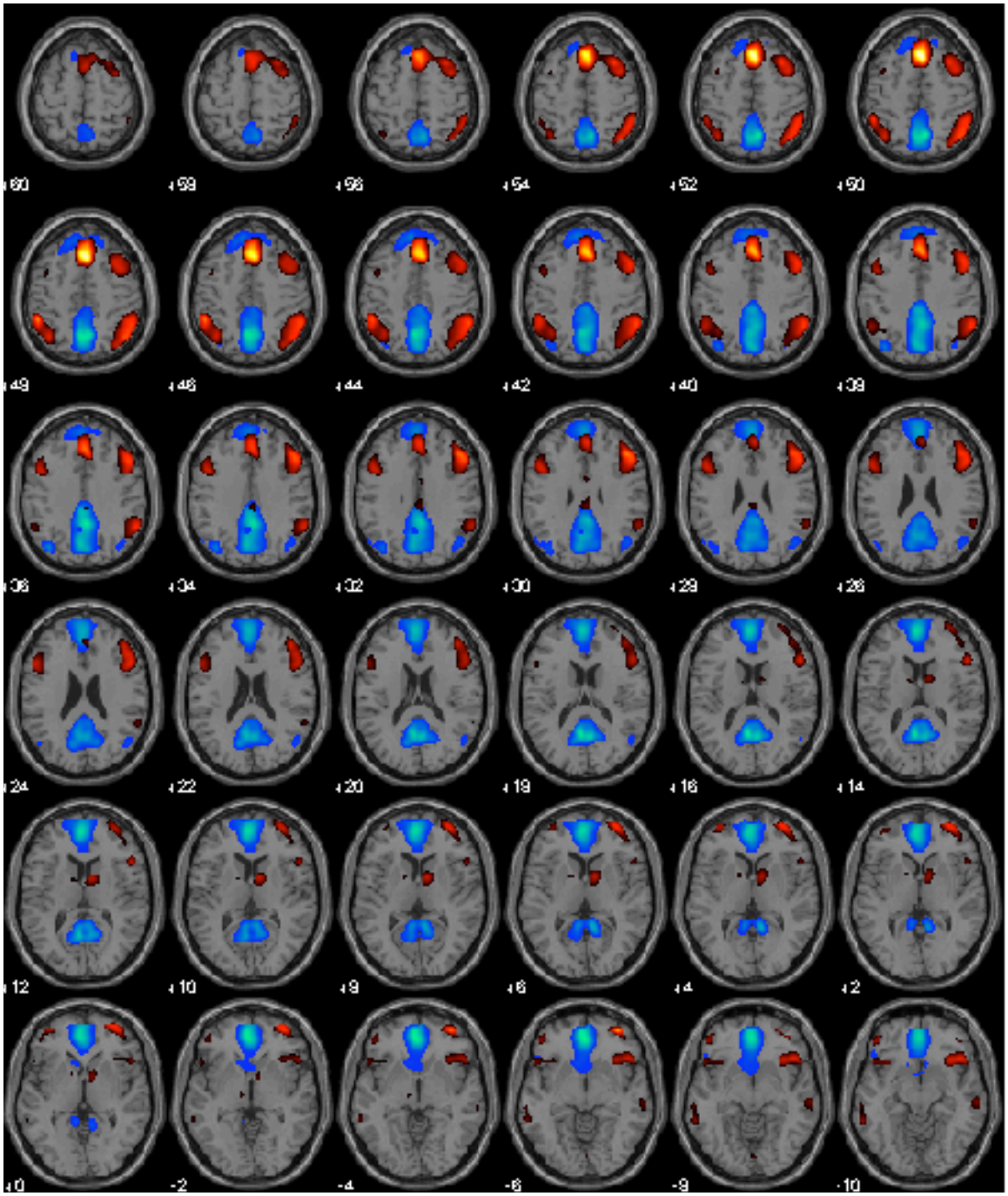

Figure 3. This figure is an overlay of the components of interest. The hot colors represent the executive control network. This network is positively modulated during target detection. The cool colors represent the default mode networks (anterior and posterior). These networks are negatively modulated during target detection.

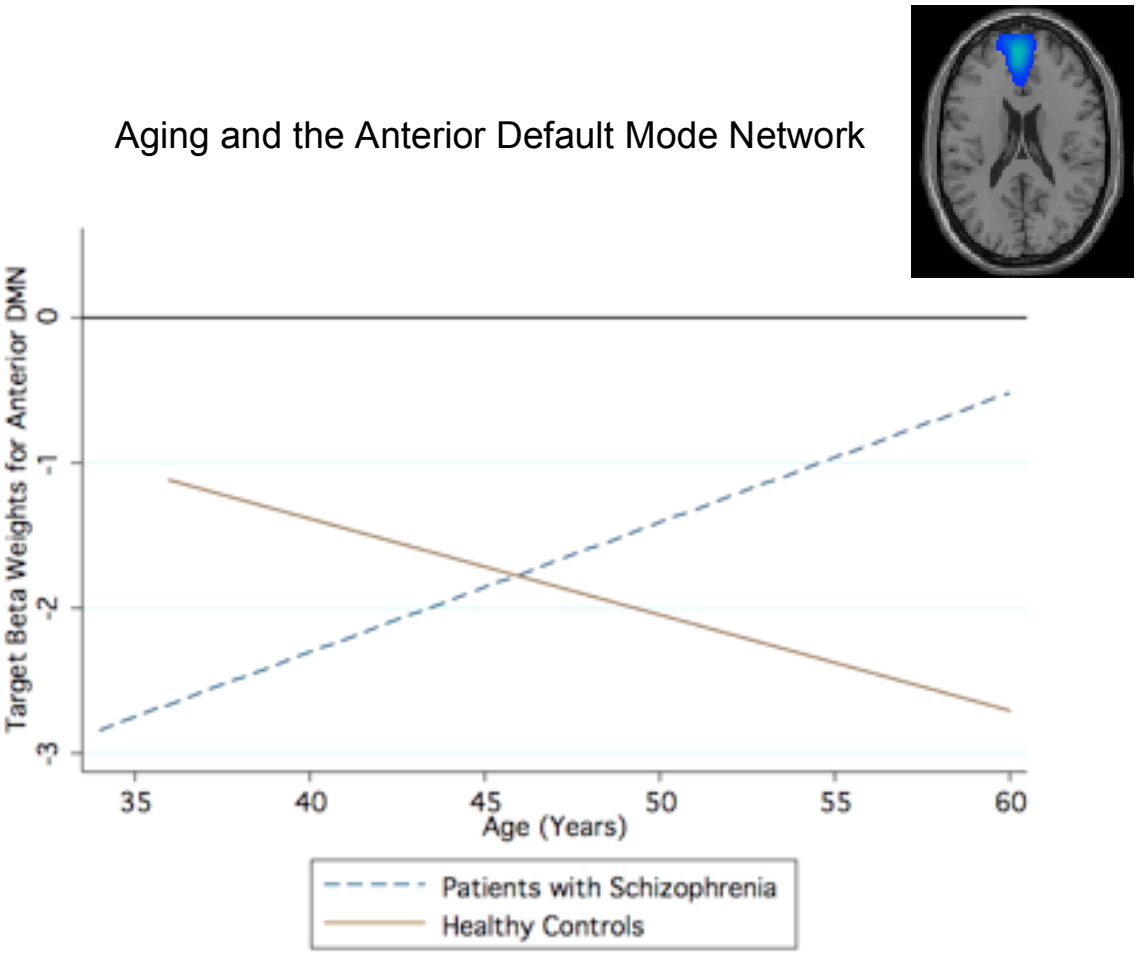

Figure 4. In an ANCOVA with the predictor variables group and age and the dependent variable beta weights of the anterior default mode network, group had a main effect ($F_{1, 42} = 4.56$, $P < 0.05$) and interaction of group with aging was also significant ($F_{1, 42} = 4.54$, $P < 0.05$). . As the patients with schizophrenia became older, they had less negative modulation of the anterior DMN. As healthy controls aged, they had more negative modulation of the anterior DMN during target detection.

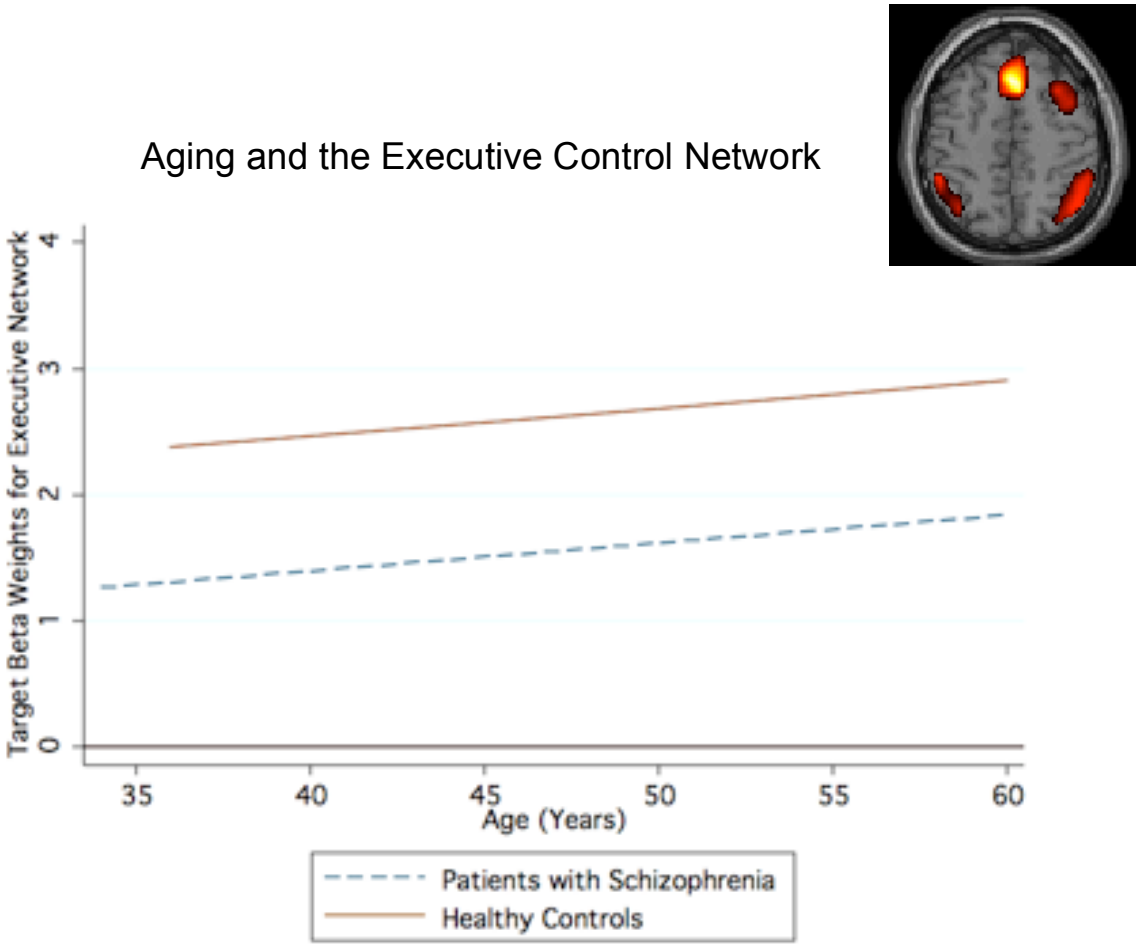

Figure 5. In an ANCOVA with the predictor variables aging and group and the dependent variable of beta weights for targets in the executive control network, group had a main effect ($F_{1, 43} = 4.76$, $P < 0.05$). The patients with schizophrenia had less positive modulation of the executive control network relative to healthy controls as they aged.

Default Mode Network (Ant.)	**Brodmann Areas**	**R / L (cm^3)**	**Maximum t Values (R / L)**
Medial Frontal Gyrus	10, 32, 11, 9, 6, 8	11.2 / 13.7	24.5 (-3, 43, -7) / 25.4 (3, 49, -5)
Anterior Cingulate	32,10, 24, 25	6.7 / 7.3	23.5 (-3, 40, -7) / 25.3 (3, 46, -5)
Superior Frontal Gyrus	9, 10, 8, 6	6.9 / 12.0	18.6 (-3, 54, 22) / 17.7 (3, 56, 22)
Superior Temporal Gyrus	38, 39	0.1 / 0.9	9.1 (-42, 19, -26) / 15.5 (42, 19, -19)
Inferior Frontal Gyrus	47, 11	0.1 / 3.1	8.9 (-39, 28, -17) / 14.3 (39, 22, -16)
Default Mode Network (Post.)			
Precuneus	7, 31, 23, 19, 39	19.0 / 16.6	21.2 (-6, -59, 50) / 14.3 (39, 22, -16)
Posterior Cingulate	23, 30, 31, 29	5.6 / 5.9	20.3 (-6, 57, 19) / 20.9 (3, -55, 17)
Cingulate Gyrus	31, 23, 24	6.6 / 4.3	20.7 (-3, -45, 35) / 17.6 (3, -33, 35)
Superior Parietal Lobule	7	0.8 / 0.5	17.3 (-9, -61, 53) / 13.9 (6, -64, 53)
Cuneus	7, 30, 19,18	0.8 / 1.1	15.2 (0, -65, 31) / 17.1 (6, -68, 31)
Executive Control Network			
Medial Frontal Gyrus	8, 6, 9	4.1 / 2.2	23.0 (-3, 26, 46) / 20.1 (3, 28, 43)
Superior Frontal Gyrus	8, 10, 6, 9	6.0 / 1.3	20.1 (-3, 26, 48) / 20.4(3, 29, 46)
Cingulate Gyrus	32, 9, 23, 24, 31	1.9 / 0.5	18.1 (-6, 22, 40) / 13.6 (3, 22, 40)
Middle Frontal Gyrus	10, 8, 46, 9, 6, 11	17.9 / 4.1	16.9 (-36, 52, -8) / 12.4 (45, 10, 30)
Inferior Parietal Lobule	40, 7, 39	8.9 / 5.5	15.1 (-45, -59, 47) / 16.3 (48, -38, 46)

Table 3. This table shows the top five regions within each component of interest. The anatomic regions are based off a one-sample *t* test using SPM5. A Talairach labeling system was used to determine regions of significance at a threshold of $P < 1.0 \times 10^{-9}$, FDR corrected.

DISCUSSION

We used independent component analysis to identify functionally connected networks. We regressed the ICA time course with the SPM design matrix to measure functional connectivity. We found a significant main effect as well as a group by age interaction for the anterior default mode network. As the healthy control group aged, they had *more* negative modulation of the anterior default mode network. As the patient group aged, they had the opposite pattern and *less* negative modulation of this network. The results for the executive control network contrasted with this pattern. The positive modulation of the executive control network increased as the healthy control group aged while the patient group had less positive modulation of this network. The decreased positive modulation in the patient group of the executive control network is consistent with a larger, more heterogeneous patient population using the same methodology [32]. The results suggest that certain networks have progressive changes in functional connectivity late in the disease course of schizophrenia.

In late-life, the natural disease course of schizophrenia is poorly understood. After the first five or ten years of the initial episode, some evidence suggests that the disease course of schizophrenia may “stabilize” with no further illness related decline in functioning or cognitive deficits [7]. In contrast, investigators focusing on institutionalized, poor-outcome group of patients have found evidence of cognitive decline and neuroprogression in this group very late in the disease [14]. Our study focused on older, community dwelling patients with

schizophrenia. We found evidence of continued disease progression in the anterior default mode network late in the disease process.

The decreased functional connectivity in the anterior default mode network in patients with schizophrenia is consistent with a previous study on functional connectivity and aging. Damoiseaux *et al.* used ICA to compare changes in the resting state connectivity in a younger and older cohort [40]. They found significantly less resting state connectivity in the anterior default mode network in the older cohort. Decreased resting state connectivity in the anterior default mode network was also associated with cognitive decline. The patients in our study were significantly younger (average age 44.9 years) than Damoiseaux's older cohort of normal aging (average age 70.7 years). Despite these age differences, the patient group had a similar pattern of decreased functional connectivity in the anterior default mode network. These results may be consistent with the hypothesis that schizophrenia is a syndrome of accelerated aging [49]. The decreased functional connectivity in the executive control network is consistent with previous studies in schizophrenia [32]. We have extended this finding by showing that patients with schizophrenia have consistently decreased positive modulation of this network as they age relative to healthy controls.

We also found trend level significance with changes in the anterior default mode network and positive symptoms. Garrity *et al.* also compared changes in the modulation of default mode network with positive symptoms [39]. Patients that had higher positive symptoms had more negative modulation of the medial

frontal gyrus, the precuneus, and the left middle temporal gyrus. They did not find any relationship with negative symptoms. Interestingly, we found a similar relationship (trend level significance) as Garrity *et al.* The patients with higher positive symptoms had more negative modulation with disease progression in the anterior default mode network. This relationship was not present with negative symptoms, nor was this relationship observed with the other components of interest. This pattern of the high positive symptom group contrasted with the overall trend group trend of patients with schizophrenia and diminished negative modulation of the anterior default mode network. Future studies with larger patient populations will help clarify the relationship between functional connectivity and symptoms.

Changes in functional connectivity can result from changes in gray and white matter. A recent study by Friedman *et al.* focused on white matter changes in a group of first episode patients and a group of chronic patients similar to the patient population in our study (average age = 45 years, disease duration = 20 years) [50]. These investigators did not find any significant differences in white matter integrity as measured by fractional anisotropy early in the disease. Late in the disease, they noted significant differences in several white matter tracts relative to matched controls. These white matter tracts included the right forceps minor and the left inferior longitudinal fasciculus. The forceps minor includes the genu of the corpus callosum and associated white matter radiations that interconnect the frontal lobes. The loss of white matter integrity of this tract may

affect functional connectivity of the frontally mediated networks such as the anterior default mode network and the executive control network.

Changes in functional connectivity have not been observed early in the disease course of schizophrenia. Lui *et al.* assessed changes in functional connectivity in a group of first episode patients using a novel region of interest approach [30]. These investigators used differences in voxel-based morphometry to select regions of interest in the right superior temporal gyrus, the right middle temporal gyrus, and right anterior cingulate gyrus. The anterior cingulate gyrus is part of the anterior default mode network. They did not find any differences in functional connectivity between the group of first episode patients and matched controls. These studies using functional connectivity and diffusion tensor imaging suggest that changes in functional connectivity are progressive throughout the disease course and may correlate with changes in white matter integrity.

Limitations of this study include the confounding effect of the antipsychotics. All patients were taking antipsychotics at the time of the scan, and the older patient population had a long history of medication compliance. We did not find any significant differences in network modulation attributable to high and low potency antipsychotics. Furthermore, the patient population had increased prevalence of other psychiatric co-morbidities such as chemical dependency that may have affected the functional connectivity. The patient group also had a slower reaction to the behavioral measure of the auditory oddball task relative to the healthy controls. This change might not have affected the relatively sluggish hemodynamic response function of the blood oxygen level dependent

signal, but other investigators have found a delayed response in patients with schizophrenia to target detection that may have affected our results [51]. We did not find any significant differences in component modulation between our four sites.

Despite such limitations, our findings point to a progressive of loss of functional connectivity in the anterior default mode networks late in the disease course of schizophrenia. Our findings also show diminished positive modulation of the executive control networks with aging. Further study will elucidate the relative contributions of grey and white matter pathology on this loss of connectivity by combining different imaging modalities such as fMRI and diffusion tensor imaging. Such studies will further our understanding of the neuronal basis of aging and disease duration in schizophrenia.

CHAPTER 3 CONCLUSION

Few investigators have used fMRI to assess changes late in the disease course of schizophrenia. We are the first investigators to use ICA in older patients with schizophrenia. Our patient sample consisted of older, community dwelling patients with schizophrenia. This patient group is in the “static” period of their illness with little further functional or cognitive decline as opposed to the poor outcome group that was expected to have further functional and cognitive decline. Despite this, our findings show evidence of progressive changes late in the disease course of schizophrenia. The progressive changes were only present in the anterior default mode network. The progressive nature of schizophrenia may affect only a discrete number of networks and not the entire brain. Our findings also had some remarkable similarities with Damoiseaux’s study of healthy aging in relation to loss of functional connectivity in the anterior default mode network [37].

Despite this significant finding, we would recommended some changes to our design to better assess the nature of disease progression on functional connectivity in schizophrenia. The MIND Clinical Imaging Consortium database has over 300 first episode and chronic patients with schizophrenia and matched healthy controls. We initially tried to use very stringent inclusion criteria with age > 50 years and disease duration > 20 years. Because we were only including subjects that had a successful behavioral response to the target stimuli (> 60 % correct for each run), we had to exclude a fair number of subjects. To be consistent with our power analysis, we had to relax our inclusion criteria to > 15

years of disease duration to obtain the requisite number of subjects. Despite the relaxed inclusion criteria, we only included 18 patients from this very large database. Ideally, we would have assessed changes in functional connectivity between the first episode group and a large group of chronic patients with disease duration > 10 years. Our patient sample size would have included approximately 30 first episode patients and significantly more chronic patients. We would have used a two-factor [group (patients, controls), age (young or first episode, older)] analysis of variance to assess for changes functional connectivity. These larger groups would have also allowed us to better assess relationships with symptoms and potential confounds such as medications.

We assessed the relationship of disease duration and symptoms with functional connectivity with each component of interest. We found trend level significance with positive symptoms and the anterior default mode network. We have some concerns about this analysis despite the consistency with previous investigators [39]. First, previous investigators have concluded that schizophrenia signs and symptoms have at least three dimensions: positive, disorganized, and negative [2]. We only used two of these dimensions: positive (included the disorganized dimension) and negative. Second, in an effort to make these symptoms measures categorical, we split them positive and negative symptoms into high and low categories based on the rating for the Scale for the Assessment of Positive Symptoms and the Scale for the Assessment of Negative Symptoms (global rating < = 2 was consistent with “mild” symptoms and our “low” category). We now recognize that the positive symptoms should have been split into

positive and disorganized symptoms. We could have than proceeded to split the three dimensions into high and low categorical variables. We performed a post-hoc regression on the functional connectivity measure of each component with these three dimensions. We did not find any significant results, which we attribute to our small sample size. Third, our results for our analysis of covariance appear inconsistent with our results with aging that included the healthy controls and larger sample size. The patient group had a *loss* of functional connectivity with aging. In contrast, the patient group with high positive symptoms had *increased* functional connectivity with disease duration. The patients with higher symptoms have a similar finding as the healthy control group. We performed a post-estimation analysis (Cooks D < 0.5), so we are confident that the results are not from an outlier. Nonetheless, we look forward to clarifying this relationship with a larger sample size.

FUTURE DIRECTIONS

This project represents a pivotal moment in my career trajectory. Over the last two years, I have learned fMRI data analysis methods using the general linear model and independent component analysis. I have also become very familiar with the growing body of psychiatric literature using neuroimaging in schizophrenia. I am now committed to pursuing a career focused on the translational aspects of neuroimaging. This project has already generated important preliminary data for two grants. In May 2009 I submitted an administrative supplement for Vince Calhoun's RO1 working with the MIND Clinical Imaging Consortium database. This grant will focus on the larger sample

sizes to overcome some of the limitations of this study. In October 2009 I will be submitting a career-training award (K23) to the National Institute of Mental Health that also utilizes this preliminary data. This project will focus on the relative contribution of white matter integrity on functional connectivity by combining diffusion tensor imaging with functional connectivity. Although I have learned a great deal in completing this project, I will have to devote many more years to the study of neuroimaging to be a potential contributor in this exciting field of neuroscience. The career-training award will be a necessary step in my continued development.

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