

Cortical Gray Matter Density in Patients with Schizophrenia, Psychotic and Severe Non-Psychotic Depression and Healthy Volunteers

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Author Note

Arash Nafisi recently graduated from the University of California, Los Angeles with a degree in Psychobiology. His interests in the fields of psychology and medicine led him to the Clinical Neuroscience Lab where he conducted research with Dr. Tyrone Cannon for three years. Among other future endeavors, Arash hopes to enter the field of medicine and provide comprehensive care for diverse patients in the Los Angeles community.

Cortical Gray Matter Density in Patients with Schizophrenia, Psychotic and Severe Non-Psychotic Depression and Healthy Volunteers

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Abstract

Psychosis in affective illnesses has been associated with a family history of schizophrenia, although its neural underpinnings have yet to be determined. Both schizophrenia and depression have been associated with reductions in brain gray matter volumes. To examine disease-specific abnormalities, high-resolution MRIs were obtained from patients with schizophrenia, depression with psychotic features, depression without psychosis, and healthy volunteers. Cortical gray matter density was examined using cortical pattern matching methods. The study aims to identify regional cortical gray matter abnormalities specific to psychosis and depression. Preliminary results indicate that compared to controls, patients with depression have a 15% reduction in cortical gray matter in the left and right anterior superior temporal gyri and an 8%-16% reduction in the right post-central gyrus.

Unearthing the precise relationship between schizophrenia and mood disorder has been one of the long-standing questions in the field of medicine. Many have wondered whether the psychosis associated with schizophrenia is related to the psychosis in individuals with mood disorders. Could they actually be variants of the same disorder? An instrumental study done by Kendler et al (1993) supported the notion that schizophrenia and affective disorders are indeed on the same etiological continuum.

Kendler's Roscommon family Study (1993) reported that schizophrenia was significantly more common in relatives of subjects with psychotic affective illnesses compared to controls. Moreover, relatives of schizophrenic probands with affective disorders were five times more likely to develop psychosis as were affectively ill relatives of controls. Lastly, individuals with schizophrenia have been found to develop affective disorders at a significantly earlier age than do relatives of controls. Another study done by Maier et al (1993) reported an increase in the occurrence of depression in relatives of schizophrenia patients.

Thus we can appreciate the common ground that exists between schizophrenia and affective disorders and execute further investigations to discover the underlying connections between these two broad disorders. Whereas researchers have focused on searching for a clinical and psychosocial basis to solve this mystery, this study hopes to find conclusive answers through the use of structural imaging in finding regional cortical gray matter abnormalities in the cortex.

A growing body of research collected through the means of structural magnetic imaging (sMRI) has indicated that structural brain abnormalities exist in patients diagnosed with schizophrenia (Cannon 1994) as well as in patients with affective

disorders, such as depression (Lange 2004) and bipolar disorder (Lopez-Larson 2002). Furthermore, Salokangas et al. (2002) report that there are numerous regions of overlap in structural brain abnormality between schizophrenics and individuals with affective disorders.

Many studies have exposed the structural brain abnormalities in patients with schizophrenia, compared to control subjects. One consistent abnormality detected in several studies involves differences in gray and white matter volumes in the temporal lobe. Cannon et al. (1998), Gur et al. (2000) and Okugawa (2002) have demonstrated white and gray matter alterations in schizophrenia.

The neocortical structure of the superior temporal gyrus has recently been a focus of many studies. In their meta-analysis, McCarley et al (1999) have reported that gray matter volume reduction in the posterior superior temporal gyrus is associated with thought disorders. Correlations have also been made between volume reductions in the anterior region and reported hallucinations in schizophrenics. A stunning 80% of the 15 studies McCarley et al. reviewed show abnormalities in this area -- the highest percentage of abnormality in any cortical region.

Moreover, schizophrenic subjects display various cognitive and behavioral deficits associated with frontal lobe damage (McCarley et al. 1999). Many of these deficits parallel deficits observed in patients diagnosed with depression. Both positron emission tomography and functional magnetic resonance imaging reports have shown that patients with schizophrenia have abnormal prefrontal cortex activity, much like patients with depression (McCarley et al), which suggests that underlying structural differences may exist. Therefore, sMRI studies can be of immense value when striving to

find the structural differences between patients with schizophrenia and/or depression, compared to controls in distinct areas of the frontal lobe.

Whereas there has been considerable interest in sMRI studies of the frontal lobe, evidence from these studies have been far from conclusive. Half of the 33 studies that McCarley et al (1999) review have reported structural abnormalities, while the other half found the opposite. One explanation for this ambiguity might lie in a lack of specificity of cortical volume studied. Previous studies have not segmented the frontal gyri into separate fractions. This approach could very well distinguish volume differences in specific areas of the frontal cortex associated with disease, differences that are obscured when trying to find structural differences in the aggregate frontal cortex volume.

Salokangas et al. reported brain variation in the temporal horn, the Sylvian fissure and volume in the occipital regions compared to first-episode and non-first episode schizophrenics. Moreover, in comparison with controls, male schizophrenics displayed reduced correlations in volume between various brain regions, especially between the volumes of the prefrontal and the superior temporal gyrus. These findings not only provide additional differences between schizophrenics and controls, but also imply that these regional differences can help in differentiating between schizophrenics and other disorders, such as severe depression.

The goal of the current study is to use cortical pattern matching methods in order to analyze in detail possible gray matter abnormalities on lateral brain surfaces in our different samples. Through this comprehensive brain mapping protocol, we will match cortical anatomy among each individual in our sample and measure local gray matter densities at each anatomically matched point on the cortical surface of each cerebral

hemisphere. The advantage of this technique compared to previous studies is as follows: our employed technique can detect subtle as well as spatially diffuse differences in regional gray matter. This is accomplished through matching structurally equivalent brain regions across our subjects by previously marking various sulcal territories on the brain surface of each individual. (Ballmaier et al 2004)

We hope to find regionally specific patterns of gray matter density disparities in the four sub-samples – patients with schizophrenia, severe psychotic depression, severe non-psychotic depression and healthy volunteers. Namely, we hypothesize that patients with severe non-psychotic depression have significantly larger gray matter densities in the frontal and temporal lobes, compared to severe psychotic depressive patients. Furthermore, we hope to locate significant cortical distinctions between patients with (psychotic) schizophrenia to patients with both psychotic and non-psychotic depression. We hope this study will prove to have notable implications on the way we survey various disorders and distinguish distinct cortical areas of focus for each group as well as provide new, detailed regions of overlap.

Methods

The participants in this study consist of patients between the ages of 16-64 (mean age=34.55, SD=10.76) who were selected from a larger group of first-contact patients admitted to out-patient or in-patient facilities of the Turku University Central Hospital and the Turku City Mental Health Center in Turku, Finland. These subjects were gathered within a four-year period, beginning in November of 1994. Written consent

from each participant was required in order to participate in the study. Moreover, the study was limited to first-ever psychiatric treatment due to this specific disorder.

Each subject was given a thorough interview by a psychiatrist. Interviews included taking the subject's medical history, providing a diagnostic evaluation and assessing the severity of the psychiatric symptoms using the DSM-IV. Particular emphasis was placed on making a distinction between schizophrenia and psychotic depression. The patients were then given an MRI.

In this study, only patients with the DSM-IV criteria of schizophrenia, severe psychotic depressive disorder, and severe non-psychotic depressive disorder were included. The sample consisted of 11 subjects with schizophrenia, 20 with psychotic depression, 17 with non-psychotic depression, and 19 healthy control subjects who had no first-degree relatives with any major psychiatric disorder.

Magnetic resonance imaging scans of each subject in the study were completed using a Siemens 1.5T scanner at the Turku University Central Hospital. An SPGR sequence was used to obtain approximately 160 sagittal slices with a thickness of 1.3mm and no interslice gap. The image matrix size was 256 x 256 with an in-plane resolution of 0.9 x 0.9mm.

The images were processed in the following fashion: an automated whole brain extraction with removal of non-brain tissue was completed; each brain slice was also manually edited such that only brain tissue and CSF remained in each image volume and was corrected for signal intensity variances. A radiofrequency bias field correction algorithm detected and eliminated intensity drifts due to scanner field inhomogeneities. (Ballmaier et al 2004)

We traced 17 sulcal and gyral landmarks on the lateral surface of each hemisphere, using a validated surface curve protocol. In addition to tracing the major sulcal and gyral landmarks, a set of seven midline landmark curves bordering the longitudinal fissure were outlined on each hemisphere. Interrater reliability was measured as the three-dimensional root mean square difference in millimeters from each sulcal landmark from the right hemisphere of four previously traced brains. Comparisons of these tracings were made to a gold standard created by a consensus of raters. Intrarater reliability was found by comparing the three-dimensional root mean square distance between equidistant surface points from sulcal landmarks in a similar fashion. The disparities between the various lateral brain tracings were less than 4mm.

Cortical gray matter was quantified by measuring the density of voxels segmenting as gray matter within a local sphere of a fixed radius of 15mm at similar cortical surface points in each individual. Thus, at each point on the lateral hemispheres, a local measurement of gray matter was made that was averaged and statistically contrasted to find differences in tissue proportion within and between groups. (Ballmaier et al 2004)

Results

Figure 1 represents the average change in cortical gray matter density of patients with severe, non-psychotic depression versus healthy volunteers. Probability values from t-tests have also been mapped onto the cortical surface, indexed in color, with areas in red that reflect greater decreases in gray matter, as seen in figure 2. The exact magnitude of difference in gray matter is shown as a percentage on the right side of the figure.

Looking at the pattern of results displayed in Figure 1, it appears that depressed subjects in general, were significantly more likely to have decreased gray matter density in the right parietal lobe, right sensory cortex and both the left and right anterior superior temporal gyri compared to controls. The precise degree of gray matter loss was dependent on the exact region of lateral cortex. More specifically, we observed an increased percent loss in gray matter in the anterior superior temporal gyrus in both the left and right sides of the cortex, whereas we see a more diffuse loss in the parietal lobe. No other main effects have been detected in any other regions as of yet, but results may change after the full sample has been analyzed.

Numerically, we found that patients with severe, non-psychotic depression displayed a 15 percent reduction in the anterior superior temporal gyrus on both the left and right sides of the cortex. The decrease on the left side of the brain was more posterior than the decrease on the right side. Moreover, we observe a 7-15 percent reduction on the right sensory cortex, with greater margins of reduction on the medial surface. Considerably higher decreases are seen on the right side, compared to the left. Lastly, there is a significant 7-15 percent reduction in gray matter in the right parietal lobe, with increased losses on the lateral portion of the brain.

Although we observed deficits in various regions of the brain, we must also be cognizant of the significance of our pilot data, as seen in Figure 2. The areas of the brain that have so far proved to be significant include the anterior superior temporal gyrus on both sides of the cortex and some areas in the sensory cortex, showing $p < 0.05$ in each respective region.

Discussion

Our preliminary results have been encouraging. As predicted, we found gray matter deficits in specific parts of the cortex of patients with non-psychotic depression compared to controls.

One area of interest has been the deficit in gray matter in the sensory region (post-central gyrus) in patients with depression. This is one of the first studies to find reductions in this region that is known to impair emotional experience, arousal and imagery for emotion. In addition, patients with tumors in the temporoparietal cortex have reported an increase in negative mood states after surgery, which correlates to the negative symptoms of depression (Ballmaier et al 2004). These findings are consistent with Ballmaier's study of patients with late-onset depression.

It is still unclear whether gray matter reductions in patients with depression cause the onset of depression or whether they appear with the progression of stressors that accumulate later in life due to natural aging processes. One confound in our study involves the age difference in our two sub-samples. Our control group is almost ten years younger than our patients with depression. This could mean that the difference observed in the two samples is due to the older age of our patients with depression; because they are older, they have a greater chance of natural neural decay.

One area of surprise was found in the frontal lobe, where we found no significant gray matter differences between the two sub-samples. Previous studies have found that patients with severe depression have significantly reduced gray matter in the frontal lobe. There are at least two explanations for this finding. First, although patients with depression are significantly older than our controls, they are still young relative to

patients in other studies. Previous studies have shown that patients with late-onset depression have more atrophy in the frontal cortex compared with younger patients. (Almeida, 2003) Secondly, because our sample is still relatively small and has yet to be completed, there are limitations to the statistical significance of our data. However, with more subjects, results could very well reach significance.

Our findings thus far have shown that individuals with non-psychotic depression do indeed show reductions in cortical gray matter in distinct locations in the temporal and parietal lobes, compared to healthy volunteers. We are even more excited to conclude our study so that we may begin to uncover the quantitative and qualitative differences in cortical gray matter between patients with schizophrenia, psychotic depression, non-psychotic depression and controls.

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Figure Captions

Figure 1 illustrates the average change in cortical gray matter density of patients with severe, non-psychotic depression, compared to the healthy volunteer control group.

Figure 2 confirms areas of statistical significance of patients with severe, non-psychotic depression, compared to the healthy volunteer control group.

Figure 1:

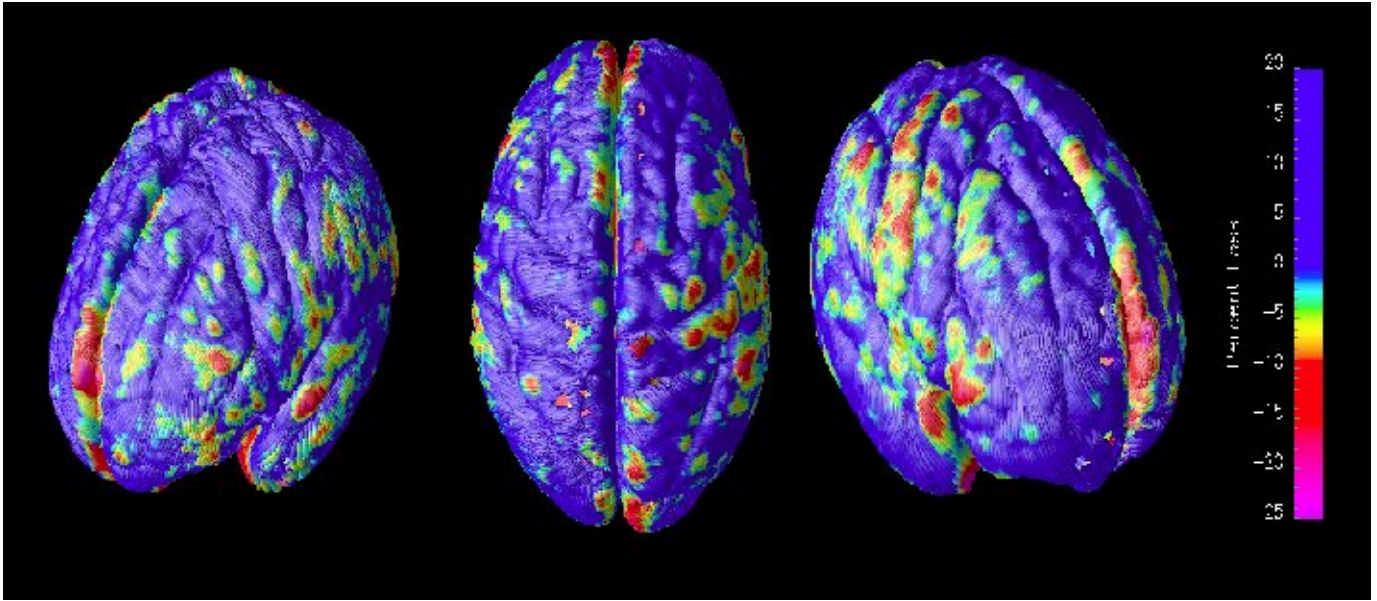


Figure 2:

