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Untreated Illness Duration Correlates with Gray Matter Loss in First Episode Psychoses

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Abstract

Frontolimbic neural circuit dysfunction has been thought to underlie schizophrenia. Prolonged duration of untreated illness is associated with frontolimbic structural changes. We present data addressing this question in minimally treated first episode patients with psychoses. To determine the relationship between Duration of Untreated Illness (DUI) and gray matter changes in schizophrenia, we analyzed the structural magnetic resonance images of 82 minimally treated first episode patients with psychotic disorder using optimized voxel based morphometry. DUI inversely correlated with gray matter in the left fusiform gyrus extending into the lingual gyrus, cerebellum and the parahippocampal gyrus. The observed inverse relationship between DUI and temporal gray matter density is consistent with a progressive process during the early course of schizophrenia.

Keywords

prodrome; psychosis; illness duration; outcome; schizophrenia

1. Introduction

Early treatment in the course of schizophrenia has been an important focus of researchers worldwide. Interest in early intervention has been stimulated by observations by our group [1] and others [2] that treatment delay (i.e. DUI), may be associated with poor outcome. Treatment delay has been variously defined as DUI, beginning with the onset of prodromal symptoms, and Duration of Untreated Psychosis (DUP) beginning from the onset of psychosis. It has been noted that DUI is typically between 1–3 years across studies [3]. With regards to clinical outcome it has been suggested that the relationship of DUP to clinical outcome is strongest during the initial period of psychosis [4]. Recent data suggest that DUI may also be related to progressive brain changes early in the illness, a topic central to this investigation.

There have been several studies showing an association between DUP and gray matter loss in patients with schizophrenia. In an earlier study by our group using region of interest

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approach, we had shown that an inverse relationship existed between duration of untreated psychosis and left superior temporal gyrus volume [5]. Further, an association between prolonged duration of illness and decreased temporal volume has been reported [6]. A reduction in the volume of left medial temporal structures was noted in a prospective study of transition of patients clinically determined to be at ultra-high risk (operationally defined as having prodromal symptoms) to first episode psychosis [7]. A recent study has shown that temporal gray matter reductions are marked in patients with a long DUP [8]. However, few studies which have looked at volumetric measures have found no association between DUI and gray matter changes in schizophrenia [9,10].

There is evidence that antipsychotic medications can affect brain structure [11,12]. It has also been noted that shorter duration of untreated psychosis has been associated with greater response to antipsychotic treatment, and may therefore underlie a subgroup with better prognosis [13]. Studies examining the relation between DUI and brain structure are therefore more likely to be informative if conducted in previously untreated patients.

In this study, we tested the hypothesis that an inverse correlation would exist between DUI in first episode minimally treated psychotic patients and brain structure using optimized voxel based morphometry. We also sought to address several potential confounding factors. First, minimally treated subjects represent a unique population without the potential confounds of illness chronicity and medication on structural changes. Second, age may have a differential effect on brain structure in schizophrenia [14]. However, earlier studies have failed to investigate the effect of chronological age between the time period of onset of psychosis and the time of scan. Third, gender differences in brain structure in healthy individuals and patients with schizophrenia have been well documented [15]. In this study, we wanted to investigate the effect of DUI on brain structure over and above the effect of age and gender.

2. Methods

2.1. Subjects: clinical and demographic characteristics

The study sample consisted of (N=82) 61 males and 21 females with first episode psychoses; age 23.7 ± 6.5 years. The diagnostic break down was as follows: 48 schizophrenia spectrum subjects [schizophrenia (N=41), schizophreniform (N=1), and schizoaffective disorder (N=6)] and 34 other psychotic disorder subjects [delusional disorder (N=4), psychosis not otherwise specified (N=15) and affective psychosis (N=15)]. The mean DUI was 213.5 ± 216.9 weeks and DUP was 132.0 ± 173.3 weeks. A consecutive series of patients with a first episode of psychoses, (N= 82) were recruited into our study from the inpatient or outpatient services at the Western Psychiatric Institute and Clinic. The Institutional Review Board at the University of Pittsburgh, School of Medicine approved the protocol. All patients provided written informed consent. The patients were diagnosed by DSM-IV criteria at consensus conference meetings of senior diagnostician/clinical researchers approximately one month after entry into the study incorporating all available clinical information and data gathered using the Structured Clinical Interview for DSM disorders (SCID) [16]. Exclusion criteria were: age greater than 50 or less than 12, significant medical illness affecting the central nervous system function, IQ lower than 75 and a current diagnosis of substance use disorder. To avoid confounding effects of sustained medication treatment, we excluded subjects who had received more than 2 weeks (lifetime) of antipsychotic treatment. There were 2 patients who had received typical antipsychotics and 6 who had received atypical antipsychotics among the schizophrenia group. There was 1 patient who had received typical antipsychotics among the other psychotic group. Antipsychotic use was minimal among these patients (1–2 day period prior to scan). These

patients participated in a longitudinal, prospective study that allowed a careful diagnostic re-review with at least 6 months followup data to confirm diagnostic stability.

DUI and DUP were assessed in each case by the same raters using all clinical information, including medical records, reports by family members or significant others, and the SCID interviews. Using these, the most likely date of illness onset was determined in consensus diagnostic conferences. The onset of the prodrome was defined as first appearance of prodromal symptoms of the illness contiguous (i.e. clearly discernible period (s) of wellness intervening) with the subsequent onset of psychosis. In defining prodromal symptoms, we included both attenuated or brief positive symptoms and attenuated negative symptoms (as defined in SCID). The term “attenuated” was used to refer to symptoms that were severe enough to be considered by the patient or significant others to need treatment. Non-specific symptoms such as depression or attentional impairment were not included. DUI was defined as the time interval (weeks) between onset of prodromal symptoms and index admission (enrollment) into this study (there was no significant interval between index admission and treatment initiation, which was typically 2–5 days after admission), while DUP was defined as the time interval (in weeks) between onset of psychotic symptoms (hallucinations, delusions or disorganization of thinking; bizarre or catatonic behavior) and index admission into this study.

2.2. MRI Parameters

Structural MRI scans were acquired using a General Electric 1.5T whole body scanner (GE Medical Systems, Milwaukee, Wisconsin). Briefly, the scans were three-dimension spoiled gradient recalled (SPGR) acquired in a steady-state pulse sequence (124 coronal slices, 1.5 mm thickness, TE=5 msec, TR=25msec, acquisition matrix=256×192, FOV=24 cm, flip angle 40°). Images were scored for motion/inhomogeneity artifacts on a scale of 0 to 2 for increasing artifacts; those that scored more than 0 were not included in the analysis.

2.3. Image Processing

Voxel based morphometric (VBM) analysis was performed using SPM2 software. VBM is an automated technique for MR-image processing that measures differences in local concentrations of brain tissue by performing a voxel-by-voxel comparison of multiple brain images that are fitted in to a common stereotactic space, such as MNI space (Montreal Neurological Institute). All structural T1 weighted images were manually checked for motion artifacts. The images were then preprocessed using the optimized VBM protocol [15]. Briefly, a study specific group and tissue specific templates were created from the set of subject images to reduce spatial normalization biases. The images were segmented into tissue classes and extracted to remove non-brain matter voxels. The segmented gray matter images were then normalized to the study specific gray matter templates to ensure optimal normalization of gray matter. The normalized segmented images were smoothed with a 12 mm full width at half-maximum (FWHM) Gaussian kernel.

2.4. Statistical Analysis

Multiple regression analysis was conducted to assess the correlation between gray matter density maps and DUI with age and gender as covariates. To covary the effect of diagnostic heterogeneity, we grouped patients into schizophrenia-related (schizophrenia, schizophreniform, schizoaffective) or other psychotic disorders (affective psychotic disorders and psychosis not otherwise specified). We conducted multiple regression analysis covarying the effect of age, gender and diagnostic category. We separated the groups into first episode schizophrenia patients and other psychotic disorders and did multiple regression with age and gender as covariates. Further, to assess age related gray matter density change, we regressed age with gender as covariate. The analyses were thresholded

for a significance level of $p < 0.001$ uncorrected and a spatial extent of 50 voxels. Only cluster peaks that survived multiple comparison correction with family wise error corrected p of < 0.05 ($p_{\text{FWE-corr}} < 0.05$) were considered. The MNI coordinates that corresponded to the significant peak voxel intensity across the analysis were used to determine the gray matter regions using WFU PickAtlas's Talairach Daemon labels [17].

3. Results

DUI inversely correlated with gray matter (i.e., longer the DUI, lower the gray matter density) in the left fusiform gyrus ($p_{\text{FWE-corr}} = 0.001$, $p_{\text{FDR-corr}} = 0.003$ and $t_{77} = 6.03$) (Brodmann area 37) extending into the left lingual gyrus, left declive and right parahippocampal gyrus ($p_{\text{FWE-corr}} = 0.046$, $p_{\text{FDR-corr}} = 0.005$ and $t_{77} = 4.98$) (Brodmann area 36). This was significant after multiple comparison correction at the voxel level. Multiple regression analysis with age, gender and diagnostic categories as covariates showed significant cluster peaks in the left fusiform gyrus ($p_{\text{FWE-corr}} = 0.001$, $p_{\text{FDR-corr}} = 0.003$ and $t_{77} = 6.12$) and right parahippocampal gyrus ($p_{\text{FWE-corr}} = 0.054$, $p_{\text{FDR-corr}} = 0.005$ and $t_{77} = 4.94$) (Figure 1a).

Multiple regression analysis of age with gender as covariate showed significant clusters in right superior frontal gyrus ($p_{\text{FWE-corr}} = 0.000$, $p_{\text{FDR-corr}} = 0.000$ and $t_{77} = 6.73$), left superior temporal gyrus ($p_{\text{FWE-corr}} = 0.015$, $p_{\text{FDR-corr}} = 0.000$ and $t_{77} = 5.30$), right extranuclear ($p_{\text{FWE-corr}} = 0.036$, $p_{\text{FDR-corr}} = 0.000$ and $t_{77} = 5.05$) and left inferior frontal gyrus ($p_{\text{FWE-corr}} = 0.049$, $p_{\text{FDR-corr}} = 0.000$ and $t_{77} = 4.95$) (Figure 1b). We did not notice any significant increases in gray matter density with DUI in any brain region.

DUI inversely correlated with gray matter density in the left fusiform gyrus ($p_{\text{FWE-corr}} = 0.055$, $p_{\text{FDR-corr}} = 0.023$ and $t_{44} = 5.29$) extending into the left lingual gyrus, left declive and right parahippocampal gyrus (Brodmann area 36) in minimally treated first episode subjects with schizophrenia (Figure 1c). There was no significant area which showed a decrease in gray matter density in patients with other psychotic disorders ($p_{\text{FWE-corr}} = 0.157$, $p_{\text{FDR-corr}} = 0.477$ and $t_{30} = 5.27$) (Figure 1d).

Post hoc analysis was conducted including age, gender, diagnostic category, total Brief Psychiatric Rating Scale (BPRS) scores, substance use and average IQ as covariates. Given some missing data the total number of subjects decreased substantially from 82 to 68. Not surprisingly the significance of the p -value ($p_{\text{FWE-corr}} = 0.088$ and $p_{\text{FDR-corr}} = 0.113$) was reduced, perhaps related to loss of statistical power due to reduced degrees of freedom. However these results were seen in the same cluster area that was significant before, the left fusiform gyrus. To clarify whether psychotic symptoms influenced brain structural changes, we repeated the analysis using age, gender and total BPRS score as covariates. Although, the BPRS scores differed significantly between the two groups ($p = 0.40$), we did not see any change in the main findings.

4. Discussion

Our findings confirmed our prediction of an inverse correlation between DUI and gray matter density. This was noted to be significant in the left fusiform gyrus extending into the lingual gyrus and cerebellum. This indicates the possibility of structural changes that might be taking place in the early phase of the illness. We wanted to explore the effect of age related gray matter reductions in the patient sample and to differentiate its effect from that of DUI. Multiple regression analysis correlating age to gray matter density maps show significant reduction in the superior and inferior frontal gyrus, extra-nuclear and superior temporal gyrus. This age related decrease in the fronto-temporal gray matter has been

previously demonstrated [14]. To allay our suspicion that age could be strongly correlated with DUI, we did correlational analysis between age and DUI. We did not find any significant correlations between them.

The results of multiple regression VBM analysis did not show any significant overlap between age and DUI. Hence, we can infer that the effect of DUI on brain structure after covarying age is that of DUI alone.

We found significant reductions in gray matter density of fusiform area when DUI was regressed with age and gender in patients with first episode schizophrenia. DUI did not have any major effects on the brain structure in patients with other psychotic disorders. One could speculate that patients with schizophrenia have either a more severe neurodevelopmental delay either at onset of psychosis or a more severe ongoing pathophysiological process during the first episode with the DUI contributing to significant reductions in gray matter density that was noted only in patients with first episode schizophrenia as compared to the other psychotic group.

Post-hoc analyses of other potential confounding factors such as psychotic symptom scores, substance use and average IQ continued to show decreases in gray matter density in the left fusiform gyrus. However, the results were not significant, perhaps due to reduction of statistical power caused by sample size reduction. Significant differences in psychotic symptoms were present between schizophrenia and other psychotic group. However this did not influence changes in brain structure when total BPRS was substituted for diagnostic category as a covariate.

Our findings suggest that neurobiologic changes may begin in the prodrome and continue with the first episode of psychosis, and are consistent with three separate lines of evidence from the recent literature pointing to progressive neuropathology in the early phases of schizophrenia. First, a prospective study of subjects at genetic risk of schizophrenia who later developed schizophrenia showed more gray matter loss in the left inferior temporal gyrus and right cerebellum, two years before the onset of psychosis [18]. Second, VBM analyses in a longitudinal study of clinically high risk patients having prodromal signs showed significant decrease in gray matter in the left fusiform gyrus and left cerebellum [19]. Third, our findings are also consistent with the results of a recent study reporting decreased gray matter in left middle and inferior temporal, left occipital and left fusiform cortices [8].

Bilateral fusiform gyrus gray matter volume reduction was reported in patients with first episode schizophrenia at the time of initial hospitalization [20]. Bilateral decrease in the inferior temporal gyrus gray matter volume in patients with chronic schizophrenia has been reported [21]. The inferior temporal gyrus has been shown to be important in the processing of language and semantic memory and representation of visual shapes. The fusiform gyrus has been shown to regulate face recognition and has been shown to be decreased in patients with chronic schizophrenia.

To our knowledge this is the first study analyzing structural changes associated with DUI in minimally treated psychotic patients, and several strengths are worth noting. First, we applied stringent multiple comparison correlations to analyze our sample. Second, our study tried to address the effect of DUI on gray matter beyond the effect of age. Third, our study included a cohort of minimally treated first episode psychotic patients. The advantages of first episode strategy are that estimates of illness duration, unlike retrospective studies, are estimated from the recent past, and the prospective design ensures that patients are followed up over time to measure outcome. Finally, to our knowledge, no published studies have

examined the relation between illness duration as defined by prodromal onset as well as that measured by onset of psychotic symptoms.

A limitation of our study is the difficulty to ascertain prodromal and psychoses onset and the reliance on history for assessments of prodromal and psychosis onset. However, we used multiple sources of information and a best estimate, consensus approach to determining onset to improve reliability. We did not compute volumetric analyses as part of our study in lieu of the rather diffuse boundaries of the significant cluster of decreased gray matter density with DUI.

The cross-sectional nature of the dataset limits the possibility of assessing the true effect of DUI on gray matter. Future studies need to utilize standardized methods of assessing onset timing such as IRAOS [22], and the Royal Park Instrument. Instruments that tap into the more subtle aspects of psychopathology seen in the prodromal phase [23] are likely to be of particular value.

Conclusion

We found significant inverse correlation between DUI and gray matter density in the left fusiform gyrus extending into the lingual gyrus and cerebellum. These results indicate structural changes in the brain occurring early during the course of illness.

Acknowledgments

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Figure 1.

Overlay of Negative correlation between (a) DUI and gray matter covarying for age, gender and diagnostic categories in patients with first episode psychosis, (b) age and gray matter density covarying for gender in patients with first episode psychosis, (c) DUI and gray matter density covarying for age and gender in patients with Schizophrenia and (d) DUI and gray matter density covarying for age and gender in patients with other psychotic disorders.