Original Article

Duration of Illness, Regional Brain Morphology and Neurocognitive Correlates in Schizophrenia

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Abstract

Introduction: Previous studies examining brain effects of duration of illness in schizophrenia have focused on either cortical or subcortical structures. Hence this study sought to elucidate the regional grey matter changes (both cortical and subcortical) and neurocognitive correlates with increased duration of illness in a large sample of patients with schizophrenia using voxel-based morphometry. Materials and Methods: Ninety patients (72 males and 18 females) with DSM-IV diagnosis of schizophrenia were recruited and assessed using magnetic resonance imaging and a battery of neuropsychological tests. Results: A longer duration of illness was associated with smaller grey matter volumes in the left superior frontal gyrus, bilateral putamen, right superior temporal gyrus, right superior occipital gyrus as well as the right thalamus. No region showed increased grey matter volume above threshold with longer duration of illness. Longer duration of illness was correlated with poorer attention. Conclusions: The grey matter reductions in different brain regions highlighted that a distributed network of cortical and subcortical regions was associated with duration of illness. This is consistent with neural models that implicate involvement of thalamo-cortical circuitry as the disruption in these neural pathways can result in specific deficits such as poorer attention. The results have implications for the understanding of brain changes in schizophrenia, and with further studies, may guide better tailored and targeted clinical management in terms of reducing the impact of duration of illness on neural substrates in schizophrenia in the future.

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Key words: Duration of Illness, Grey Matter, Magnetic resonance imaging, Voxel-based Morphometry

Introduction

Schizophrenia is a potentially devastating illness with a tremendous impact on the lives of both patients as well as the caregivers. Conceptualised as a lifelong disorder,[1] the specific effects of schizophrenia on the brain and cognition are still being actively studied using modern imaging techniques such as magnetic resonance imaging (MRI).[2-4] Earlier studies have provided evidence for specific brain grey matter changes in patients compared to healthy controls, mostly implicating the frontal and temporal regions,[5,6] as well as brain grey matter changes in these regions over the time course of the disease. Reductions in frontal grey matter volumes are found to be associated with longer duration of illness in stable outpatients,[6] chronic[7,8] as well as patients with first episode schizophrenia.[5] Longitudinal studies reveal a decrease in prefrontal grey matter and that further progressive frontal grey matter losses can occur with greater number of psychotic episodes.[9] Recent studies have used voxel-based morphometry (VBM) to investigate the relationship between prefrontal grey matter volumes and duration of illness.[10,11] Looking at a younger adolescent population with a mean duration of illness of 14 months, Burke et al[10] found that the duration of illness was inversely related to regional grey matter in the left inferior frontal

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gyrus. In a separate study of an adult patient population with a mean duration of illness of 13.7 years, Premkumar et al[11] found inverse associations between duration of illness and grey matter volumes in the left dorsomedial prefrontal, and right middle frontal cortex. In addition, lower grey matter volume in the temporal lobe,[12] occipital lobe,[5] and thalamus[13] are also observed with an increased duration of illness in schizophrenia. These diverse findings from extant studies seem to suggest that duration of illness is associated with grey matter volume changes in a distributed pattern involving both cortical (such as frontal and temporal regions) and subcortical structures (such as thalamus).

With regard to neurocognition, frontal lobe based cognitive impairments have been noted in chronic patients with schizophrenia,[14] suggesting that increased duration of illness may have a deleterious effect on the frontal lobe-based structure and functional relationship. A review by Goldberg et al[15] suggests that the course of cognitive impairments is akin to that of 'static encephalopathy'. Subsequent studies appear to support this notion. For example, Heaton et al[16] administered a comprehensive neuropsychological battery covering 7 neurocognitive domains but found no change in neurocognitive performance scores within patients with schizophrenia between baseline and follow-up (mean follow-up period of 37 months). Similarly, DeLisi et al[17] also found no significant deterioration in neurocognitive performance within patients with schizophrenia after a four-year follow-up. These studies suggest that cognitive deficits, once present at onset, do not further deteriorate with the course of the disease.

To date, most studies examining brain effects of duration of illness have focused on either cortical or subcortical structures (Table 1). Adding to previous studies, this study sought to elucidate the regional grey matter changes (both cortical and subcortical) and their neurocognitive correlates with an increased duration of illness in a bigger sample of patients with schizophrenia using VBM. In view of the relationship between age, severity of illness and medication use with chronicity of illness as well as with grey matter volumes,[15,18] these factors were taken into account and adjusted as covariates during the analyses.

Materials and Methods

Ninety patients who met the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) diagnosis of schizophrenia were recruited from the Institute of Mental Health in Singapore. Confirmation of the diagnosis was made for all patients by a psychiatrist using information obtained from the clinical history, existing medical records, interviews with significant others as well as the administration of the Structured Clinical Interview for DSM-IV Disorders-Patient Version (SCID-P).[19] The patients were maintained on a stable dose of antipsychotic medications for at least 2 weeks, and did not have their medication withdrawn for the purpose of the study. There was no history of any significant neurological illness such as seizure disorder, head trauma or cerebrovascular accident and no subject met DSM-IV criteria for alcohol or other substance abuse within the preceding 3 months. The duration of illness was calculated in years by deducting the age of onset of illness (age when having the first evident psychotic symptoms as reported by the patient and confirmed with other sources wherever possible) from the age at date of MRI. Neuroleptic doses, including depot preparations, were converted to approximate chlorpromazine equivalents (CPZ mg eq) based on established guidelines.[20-23] Written, informed consent was obtained from all the participants after a detailed explanation of the study procedures. The study protocol was approved by the Institutional Review Boards of the Institute of Mental Health, Singapore, as well as that of the National Neuroscience Institute, Singapore.

Structural images, obtained using T1-weighted turbo field echo sequence (TR 7.2 ms, TE 3.3 ms, flip angle 8°, FOV 23 cm, 256 x 256 acquisition matrix), were acquired with a 3-Tesla Philips Achieva whole body scanner (Philips Medical System, Eindhoven, The Netherlands) at the National Neuroscience Institute, Singapore. Each volume consisted of 180 axial slices of 0.9 mm thickness with no gap. Voxel-based morphometry of grey matter was performed using SPM5 software (http://www.fil.ion.ucl.ac.uk/spm/software/), based on a unified framework for segmentation.[24] Images were spatially normalised to MNI (Montreal Neurological Institute, McGill University) space using 12-parameter affine (linear) and 7 × 8 × 7 discrete cosine transform basis functions (nonlinear) transformation, and segmented using the grey matter, white matter and cerebral spinal fluid templates provided by SPM5 as priors. The grey matter images were modulated by the Jacobian determinant of the deformation field to account for volume changes due to normalisation, and resliced to isotropic voxels of 1 mm^3. The images were then smoothed with a 8 mm FWHM isotropic Gaussian kernel prior to statistical analysis. To disentangle various possible confounding effects, voxel-wise grey matter volumes were subjected to multiple regression analysis. Duration of illness was entered as the predictor of interest. The covariates included within the model were age, sex, years of education, medication dosage (CPZ mg equivalents), and severity of psychopathology (as measured by PANSS total score).[25] Global adjustment for total intracranial volume was done using the ANCOVA approach. The resulting t-map for the regression coefficient for duration of illness was thresholded

Table 1. Summary Table of Findings of Relationships Between Duration of Illness and Brain Regions

Year	Authors	Subjects (Age in years)[a]	Duration of illness[b]	Imaging parameters	Findings
2003	Hietala et al[12]	14 first-admission SZ (29.9 ± 7.3)19 HC	Median DOI 36 months (range 5-120)	1.5T, 5 mm	Negative relationship between DOI and left temporal lobe, and right posterior region grey matter volume.
2004	Molina et al[7]	22 FES (23 ± 3.5) 29 short term SZ (28.9 ± 7.8) 30 long term SZ (41.0 ± 10.9)	FES: 0.6 years SZ: 3.9 to 15.1 years	1.5T, 1.1 or 1.5 mm	Negative log-relationship between DOI and left & right PFCgrey matter in the patient group as a whole.
2005	Preuss et al[13]	25 FES (27.9 ± 8.9) 43 SZ (30.2 ± 8.8) 50 HC (30.2 ± 8.8)	FES: 13.7 months SZ: 94.2 months	1.5T, 1.5 mm	Negative correlation between DOI and left, right and total thalamic volumes for chronic patients only.
2006	Lopez-Garcia et al[8]	22 FES (22.6 ± 5.7) 21 SZ (36.7 ± 8.9) 47 HC	FES: 3.33 years SZ: 12.74 years	3T, 1.5 mm	Negative correlation between DOI and right BA 6, and right SMA in chronic patients. No significant correlation for first episode patients.
2006	Premkumar et al[5]	34 FES (median 23) 49 SZ (median 39) 39 HC	FES: Max. 3 years SZ: Min. 3 years	1.5T, 1.5 mm	Negative log-relationship between DOI and whole brain, PFC total, PFC grey matter, parietal-occipital cortex grey matter in patients as a whole.
2007	Sapara et al[6]	28 SZ (39.0 ± 10.5) 20 HC (35.9 ± 13.7)	13.7 years	1.5T, 5mm with 2.5 mm gap	Negative correlation between DOI and total & left PFC, total & left superior frontal, total, left & right orbitofrontal grey matter volumes.
2007	Van Haren et al[9]	96 SZ (32.2 ± 11.1) 113 HC (35.3 ± 12.3)	10.9 years	1.5T, 1.2 mm	Grey matter density loss occurred along course of illness, predominantly in left frontal and temporal cortices.
2008	Burke et al[10]	40 EOS (16.1 ± 1.4)	14.3 months	1.5T, 5 mm with 2.5 mm gap	Negative correlation between DOI and left inferior frontal gyrus grey matter volume.
2008	Premkumar et al[11]	64 outpatient SZ (38.6 ± 9.6) 25 HC (36.4 ± 11.1)	13.7 years	3T, 1.5 mm	Negative relationship between DOI and left dorsomedial PFC, right middle front al cortex, left fusiform gyrus, and left cerebellum grey matter volumes.

DOI: duration of illness; EOS: early-onset schizophrenia; FES: first-episode schizophrenia; HC: healthy control; PFC: pre-frontal cortex; SZ: schizophrenia.
[a] Denotes mean +/-SD unless otherwise indicated.
[b] Mean duration of illness unless otherwise indicated.

at $P = 0.0005$ (uncorrected). We only retained clusters larger than 200 voxels in size. Anatomical regions were assigned using the Automated Anatomical Labeling (AAL) atlas[26] toolbox for SPM.

Patients were also administered the following neuropsychological scales by a psychometrist trained in standardised assessments: (i) Raven's Progressive Matrices;[27] (ii) Conners' Continous Performance Test II;[28] (iii) Wisconsin Card Sorting Test;[29] (iv) Digit and Spatial Span subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III);[30] and (v) Block Design subtest of the WAIS-III. Testing generally took 1.5-2 hours and when necessary, occurred over 2 sessions. Pearson's correlation analysis was used to identify significant corrrelations between neurocognitive measurements and duration of illness. Spearman's rho was used for the analysis of non-parametric data. Partial correlation coefficients controlling for age, sex, years of education, medication dosage, and PANSS total score were also estimated to adjust for confounding by covariates. Variables were inspected for deviations from normality. Duration of illness, PANSS total score, and medication dosage were found to have highly skewed distributions, thus a natural logarithmic transformation[31] was applied to them before further analyses.

Results

Figure 1 shows the distribution and histograms of the duration of illness before and after transformation. It can be seen that the duration of illness is much more normally distributed after transformation. Table 2 presents the

Duration of illness	*n* (%)
Less than 2 Years	22 (24.4%)
Between 2 to 5 Years	21 (23.3%)
Between 5 to 7 Years	13 (14.4%)
Between 7 to 15 Years	17 (18.9%)
Between 15 to 30 Years	14 (15.6%)
More than 30 Years	3 (3.3%)
Total	90 (100%)

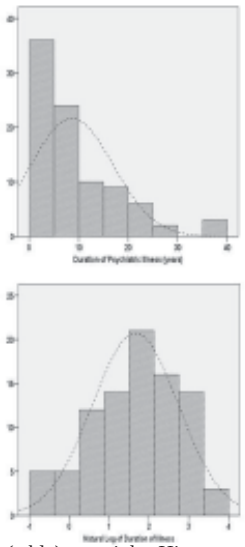

Fig. 1. Left: Distribution of duration of illness (table); top right: Histogram of duration of illness in years; bottom right: Histogram of duration of illness after a natural logarithm transformation.

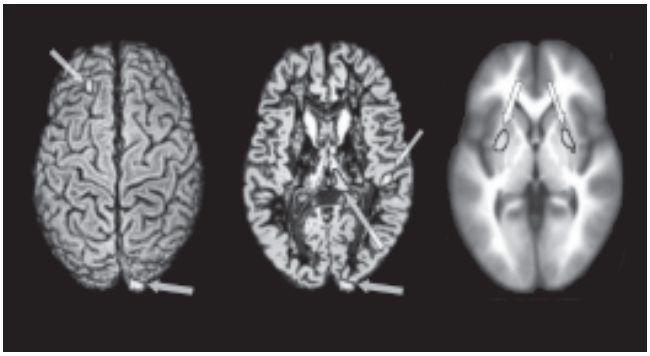

Fig. 2. Grey matter volume reductions (highlighted in red) which are found in patients with a longer duration of illness. Left image: Surface rendered image showing correlations with SFG and SOG; middle image: Grey matter image (axial slice) showing correlations with Thalamus, STG and SOG; right image: Averaged structural image (axial slice) showing correlations with bilateral Putamen.

demographic and clinical characteristics of the participants. There were 72 male and 18 female patients, and most of them (80 out of 90) were right handed. Out of the 90 patients, 33 (36.7%) were on typical oral antipsychotics, 40 (44.4%) were on atypical oral antipsychotics, and 17 (18.9%) were on depot typical antipsychotics only.

Figure 2 shows the grey matter regions that were negatively correlated with duration of illness, after age, sex, years of education, medication dosage and PANSS scores were controlled for. A longer duration of illness was associated with smaller grey matter volumes in the left superior frontal gyrus, bilateral putamen, right superior temporal gyrus, right superior occipital gyrus/right cuneus as well as the right thalamus (Table 3). No region showed increased grey matter volume above threshold with a longer duration

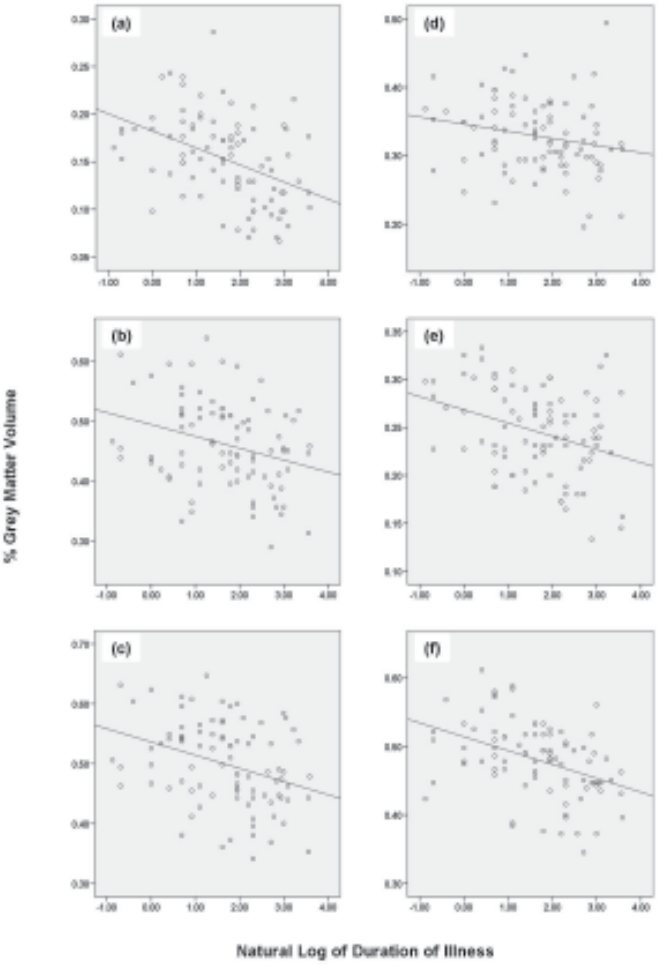

Fig. 3. Scatterplots of grey matter volume with duration of illness for (i) left superior frontal gyrus, (ii) right putamen, (iii) left putamen, (iv) right superior temporal gyrus, (v) right superior occipital gyrus and (vi) right thalamus. All correlations are significant at $P < 0.01$.

Table 2. Demographic and Clinical Characteristics of Participants

Variable	Mean (SD)	Range	Skewness (Std. Error)
Age (y)	34.4 (9.1)	21 – 56	0.33 (0.25)
Age at onset	25.6 (6.9)	15 - 46	0.93 (0.26)
Years of education (y)	11.4 (2.5)	1 – 16	-0.78 (0.25)
Duration of illness (y)	8.6 (8.3)	0.4 – 36	1.50 (0.25)
natural logarithm	1.66 (1.08)	-0.87 – 3.58	-0.34 (0.25)
Medication (CPZ mg eq)	227 (206)	50 – 1100	2.15 (0.25)
natural logarithm	5.10 (0.91)	1.61 – 7.00	-1.00 (0.25)
PANSS Total[a]	40.9 (9.9)	30 – 74	1.47 (0.25)
natural logarithm	3.69 (0.22)	3.40 – 4.30	0.93 (0.25)

PANSS: Positive And Negative Symptom Scale; CPZ: chlorpromazine

Table 3. Brain Regions with Significant Grey Matter Volume Reduction

Brain region	L/R	BA	Cluster Size[a] (voxels)	MNI coordinates (mm)			*t*-value
				x	y	z	
Superior Frontal Gyrus	L	9	296	-25	40	50	4.11
Putamen	R	-	538	24	4	-2	3.82
Putamen	L	-	320	-29	-1	-3	3.90
Superior Temporal Gyrus	R	22	245	49	-27	8	4.28
Superior Occipital Gyrus / Cuneus	R	17	388	14	-102	12	4.32
Thalamus	R	-	296	11	-30	9	4.02

[a] Cluster size have been adjusted for voxels that lie outside the parenchyma.
BA: Brodmann Area; MNI: Montreal Neurological Institute

Table 4. Neurocognitive Assessments and Correlation with Duration of Illness

Variable	Mean (SD)	Correlation[a]	*P* value
Raven's Progressive Matrices	45.5 (9.4)	-0.10	0.380
CPT Hit Reaction Time	53.0 (12.6)	0.29	0.013
CPT Discriminability	51.6 (8.2)	-0.19	0.106
WCST Total Errors	40.6 (25.6)	-0.03	0.792
WCST Perseverative Errors	24.4 (18.7)	-0.02	0.853
Digit Memory Span (forward)	11.2 (2.6)	0.08	0.476
Digit Memory Span (backward)	6.9 (206)	0.06	0.586
Spatial Memory Span (forward)	9.1 (1.8)	-0.05	0.693
Spatial Memory Span (backward)	7.8 (2.0)	-0.08	0.483
Block Design of WAIS-III	40.3 (13.3)	-0.17	0.133

[a] The correlations reported are partial correlations controlled for age, sex, years in education, medication and PANSS total score. Since CPT scores are already age- and sex-adjusted T-scores, they are only adjusted for years in education, medication and PANSS total score.
CPT: Continuous Performance Task; WCST: Wisconsin Card Sort Test; WAIS: Weschsler Adult Intelligence Scale

of illness. Figure 3 shows the scatterplots of implicated grey matter volumes (Table 3) with duration of illness (natural log).

As for neuropsychological assessments, a longer duration of illness was associated with lower scores on the Raven's Progressive Matrices (r = -0.25, P = 0.022), WAIS-III Block Design subtest (r = -0.34, P = 0.002) and greater hit reaction time on the Conners' Continous Performance Test (r = 0.27, P = 0.018). Correlation analysis performed using Spearman's rho revealed the same results. After statistically adjusting for the covariates (age, sex, years in education, medication, and severity of psychopathology), only the performance on the Conners' Continous Performance Test was significantly correlated with duration of illness. Table 4 presents the covariates-adjusted partial correlations.

Discussion

There were several main findings. Within patients with chronic schizophrenia, we found that a longer duration of illness was associated with grey matter reductions in a distributed network of cortical and subcortical regions involving the superior frontal gyrus, superior temporal gyrus, superior occipital gyrus, thalamus and putamen. We also found that an increased duration of illness was correlated with poorer attention in patients with schizophrenia. No brain region showed an increased grey matter volume with an increased duration of illness.

Our finding of grey matter reduction in the frontal lobe region of patients with chronic schizophrenia is consistent with earlier cross sectional studies which also found decreases in frontal lobe grey matter in chronic patients compared to patients with first onset illness. Molina et al[7] and Lopez-Garcia et al[8] found less prefrontal lobe grey matter being associated with an increased duration of illness in chronic patients and not in patients with first episode schizophrenia. Of note, Premkumar et al[5] found a smaller prefrontal cortex with an increased duration of illness in 49 patients with chronic schizophrenia and 34 patients with first episode schizophrenia. These findings suggest that neurodevelopmental brain changes may be present at the onset of illness with further neurodegenerative changes occurring with the progression of the illness. In addition, longitudinal studies of patients with schizophrenia have lent support for the illness specific effects on frontal lobe grey matter reduction[2,4] and progressive grey matter loss in frontal lobe was noted with an increased frequency of relapse of illness.[9] Three studies found a lack of relationship between frontal lobe grey matter volume and duration of illness.[12,32,33] A possible explanation may relate to the smaller number of patients studied. Other explanations could be a relatively longer maturation period for the frontal lobe that can extend into the fifth decade of life, and specific brain changes that may only occur with further progression of the illness.[34,35]

Previous studies have found grey matter reductions in the

temporal lobe region which is associated with an increased duration of illness[12,36] and this is further supported by findings from our study. Decreases in the temporal lobe grey matter were also noted in some,[9,37,38] but not all longitudinal studies,[2,39] perhaps suggesting different cortical developmental trajectories and disease vulnerability profiles which can vary with different individuals over time. In regard to the occipital lobe, we found a decrease in superior occipital gyrus whereas Tanskanen et al[36] found grey matter reduction in more extensive regions involving the cuneus, fusiform gyrus and lingual gyrus in their study sample.

We found thalamic grey matter reduction with an increased duration of illness which is in line with the finding by Preuss et al.[13] This is consistent with several other studies which have implicated the thalamus in the pathophysiology of schizophrenia.[40,41] As for the basal ganglia, extant studies have either found increased grey matter volume which is thought to be related to neuroleptic use,[42-44] no change[45-47] or even decrease in volume[36] in patients with schizophrenia. Neuroimaging studies showing the basal ganglia volume increase have localised it further to the caudate and putamen;[42,44,48] and this supports previous post mortem findings of increased striatal volumes.[49,50] We found decreased putamen volumes bilaterally and Taskanen et al[36] have reported similar findings. Several explanations may be posited for the discrepancy between our findings and that of increased basal ganglia volume in previous studies. First, we are not comparing patients receiving neuroleptic medication with patients not receiving medication, or with patients who are drug naïve. Second, there may be compensatory changes in response to different treatment along the course of illness. Third, the changes in the basal ganglia may be specific to the phase of the illness. This may explain the spectrum of previous findings including that of no change in striatal volume in the context of differing duration of illness and treatment.

The grey matter reductions in different brain regions in this study highlighted that a distributed network of cortical and subcortical regions was associated with duration of illness. This is consistent with neural models that implicate involvement of thalamo-cortical circuitry as the disruption in these neural pathways can result in specific deficits.[51] Being a central relay station of the brain, the thalamus has reciprocal connections with the frontal, temporal, occipital lobes and basal ganglia.[51] Furthermore, attentional tasks overlap and tap on executive[52] and working memory functions[53] which are subserved by these interconnected brain regions. In a recent fMRI study, Salgado-Pineda et al[54] found significant hypoactivation in several brain regions (especially in the right hemisphere) in patients with schizophrenia when performing the continuous performance task, including dorsolateral prefrontal areas, temporal lobes, inferior parietal lobe and thalamus which partially correspond with the involved brain regions within current findings. Our finding of correlation between deficits in sustained attention with increased duration of illness is consistent with the findings of study by Loberg et al[55] who reported that duration of illness predicted attentional modulation and is thought to reflect the involvement of frontal temporal networks.

The absence of association between illness duration and neurocognitive measures of working memory and executive function is in line with a recent meta-analysis of 10 studies of 834 patients.[56] The analysis indicated that although deficits in cognition are present at onset in schizophrenia, there appears no marked deterioration in cognitive function greater than that associated with aging in the first decade following onset within community-dwelling outpatients. Hence, as in previous studies, the absence of a linear relationship between duration of illness and the majority of neuropsychological tests in this study is expected. Contrary to working memory and executive function, there has been evidence in the literature that deficits in sustained attention represent a stable vulnerability marker of the illness, and the association between sustained attention and duration of illness is in line with these evidences. Deficits in CPT performance have been shown in patients with schizophrenia from prodrome across all stages of illness,[57-61] and it appears that they are not amenable to treatment with traditional or atypical neuroleptics.[62,63] Family studies suggest that performance deficits are observable in unaffected family members of patients with schizophrenia.[64] Hence, CPT may be particularly sensitive to the underlying disease trait that is associated with reductions in key structures including frontal, temporal and thalamus that are important in complex attention.

Several limitations need to be considered for this study. First, this was a cross sectional study and a longitudinal design would allow a better understanding of the impact of duration or chronicity of illness on regional brain structures and neurocognitive measures. Second, no definite causality can be drawn between duration of illness and morphometric brain abnormalities. Third, the findings need to be replicated in a bigger sample of patients. Fourth, other confounders such as impact of genetic markers on the duration of illness were not considered in the analysis. Fifth, we had a greater proportion of males in the sample, and although sex was included as a covariate in the analysis, we cannot rule out completely the alternative explanation that the grey matter loss may reflect a sex bias.

In summary, an increased duration of illness was associated with regional brain reductions involving cortical and subcortical structures and poorer attention in a relatively

larger sample of patients with chronic schizophrenia. Future studies may want to consider using multi-modality imaging (such as structural MRI, diffusion tensor imaging, magnetic resonance spectroscopy) to better document and understand the nature of brain changes over time in patients with schizophrenia. It is hoped that this will ultimately guide clinicians in better-tailored and targeted clinical management in terms of reducing the impact of duration of illness on neural substrates in schizophrenia in the future.

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