

Neuropsychological function–brain structure relationships and stage of illness: An investigation into chronic and first-episode schizophrenia

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Abstract

Neuropsychological function–brain structure relationships may differ as a function of illness stage because of progressive brain matter loss through the course of schizophrenia. In this study, we tested whether neuropsychological function–brain structure relationships differed as a function of illness stage. In addition, we tested whether these relationships differed between older and young healthy controls. Function–structure relationships were examined in 35 first-episode patients (31 with schizophrenia, 4 with schizoaffective disorder), 54 chronic schizophrenia patients, 21 older healthy controls and 20 young healthy controls. MRI volumes of frontal and temporal lobe structures, as well as the whole brain, were estimated using a region-of-interest approach. Hierarchical multiple regression analyses were performed between the MRI and neuropsychological measures. Stronger relationships of immediate memory–total prefrontal cortex (PFC) volume in chronic than first-episode patients, and in older than young controls were observed. The abstract reasoning (WCST perseverative errors)–total temporal lobe volume relationship was stronger in older than young controls. These function–structure relationships appeared unexplained by whole brain volume or age in chronic patients. A similar dissociation between young and older subjects of both healthy and patient groups suggests that a ‘bigger-is-better’ relationship style is present in older individuals regardless of a diagnosis of schizophrenia.

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1. Introduction

Neuropsychological function–brain structure relationships have been observed in both first-episode and chronic schizophrenia patients (Seidman et al., 1994; Bilder et al., 1995; Antonova et al., 2005). However, it is not known whether similar function–structure relationships occur at different stages of illness. Determining

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whether different function–structure relationships exist at different illness stages would inform us about the emergent nature of function–structure relationships in people with schizophrenia.

The hypothesis that neuropsychological function–brain structure relationships may differ as a function of illness stage is based on evidence for progressive brain matter loss through the course of schizophrenia (DeLisi et al., 2004; Premkumar and Sharma, 2005; Premkumar et al., 2006), with reports of further volumetric reduction following illness onset (Gur et al., 1998; Mathalon et al., 2001; Bachmann et al., 2004), but a neuropsychological impairment that is relatively stable over time (see Antonova et al., 2004 for a detailed review and table exploring the consistency of the relationship between specific brain regional volumes and specific neuropsychological functions; Kurtz, 2005).

In patients with chronic schizophrenia, fewer Wisconsin Card Sorting Test (WCST) perseverative errors and better Wechsler Memory Scale (WMS)-Logical Memory immediate recall and WMS Visual Reproduction-immediate recall scores have been associated with larger dorsolateral prefrontal cortex (DLPFC) volume (Seidman et al., 1994). Better immediate verbal and visual memory (temporal lobe measures) and verbal fluence (frontal lobe measure) have also been associated with larger prefrontal cortical (PFC) grey matter volume in patients with chronic schizophrenia (Baaré et al., 1999). In males with first-episode schizophrenia, executive and motor function associated positively with anterior hippocampal volume leading to the suggestion that abnormalities of the anterior hippocampus predict frontal lobe dysfunction in schizophrenia (Bilder et al., 1995; Szeszko et al., 2002). Poorer executive function has been associated with smaller anterior cingulate gyrus volume in first-episode schizophrenia males (Szeszko et al., 2000). No association between neuropsychological function and the cerebellum has been found in first-episode patients (Szeszko et al., 2003).

In healthy individuals, function–structure relationships are characterised by an age-related decline (Brickman et al., 2006; Zimmerman et al., 2006). Poorer executive function is found to be associated with smaller lateral frontal grey matter volume in individuals older than 40 years, but not in individuals younger than 40 years (Zimmerman et al., 2006). A high number of perseverative errors on the WCST has been linked with an age-related decline in PFC volume in middle-aged and older healthy individuals (Gunning-Dixon and Raz, 2003). A meta-analysis of studies on the relationship between memory and hippocampal volume across the life-span suggests a positive association only in older adults and not in young adults (Van Petten, 2004).

In the present study, we aimed to determine whether there are differences in function–structure relationships between first-episode and chronic patients after controlling for normal age-related differences in function–structure relationships. We hypothesized that in first-episode patients, poorer executive function would be related to smaller temporal lobe and hippocampal volumes based on previous findings in first-episode patients (Bilder et al., 1995; Szeszko et al., 2002). In chronic patients, we hypothesized that poorer executive function, attention and immediate memory would be related to smaller PFC volume based on previous findings in patients with chronic schizophrenia (Seidman et al., 1994; Baaré et al., 1999). In older healthy adults, we hypothesized that better executive function, attention and immediate memory would be related to larger PFC volume and that better delayed memory would be related to larger temporal lobe and hippocampal volumes because of a normal age-associated decline relating these functions to these structures (Gunning-Dixon and Raz, 2003; Zimmerman et al., 2006). In young adults, we hypothesized that there would be no function–structure relationships because the investigated function–structure relationships do not appear to be present in young adults (Zimmerman et al., 2006).

2. Method

2.1. Participants

Groups of 35 first-episode psychosis patients and 20 healthy controls matched on age, gender, ethnicity and parental socio-economic status who had both MRI and neuropsychological data were investigated. DSM-IV diagnoses were as follows: 14 patients satisfied criteria for schizophrenia, 17 for schizophreniform disorder and four for schizoaffective disorder. The 17 patients with a diagnosis of schizophreniform disorder were re-classified as meeting DSM-IV (1996) criteria for schizophrenia after 6 months. Recruitment details and MRI findings on this patient cohort have been previously reported (Fannon et al., 2000; Ettinger et al., 2002; Sumich et al., 2002, 2005).

In addition, 54 patients with chronic schizophrenia and 21 healthy controls matched on age, gender, ethnicity and parental socio-economic status who had both MRI and neuropsychological data were also considered in this analysis. Patients had a DSM-IV (1996) diagnosis of schizophrenia. The description of these patients as having chronic schizophrenia was based on the patients having a duration of illness longer than 3 years (range 3 to 37 years). MRI and neuropsychological data (separately)

from these patients were included in two previous reports (Sharma et al., 2003; Premkumar et al., 2006).

Patients were recruited from London and surrounding areas by referral from their psychiatrist and healthy controls by advertisements placed in the local press. Suitability criteria (in both studies) were an Axis I diagnosis as determined by the Structured Clinical Interview for Axis I diagnosis (First et al., 1996a) among patients, an absence of previous or current psychiatric problems as determined by the non-patient version of the Structured Clinical Interview for DSM-IV (First et al., 1996b) among controls and an absence of a history of neurological disease, a positive urine drug screen test and a lifetime DSM-IV diagnosis of substance abuse or dependence in both patients and controls.

The study procedures for both first-episode and chronic schizophrenia studies were approved by the Institute of Psychiatry and South London and Maudsley Foundation research ethics committee. All subjects provided written informed consent. The use of data for the purpose of this investigation (MPhil research of PP) was approved by the Department of Psychology, Goldsmith's College London.

2.2. MRI measurements

2.2.1. Image acquisition

MRI scans for both studies were acquired at the Maudsley Hospital, London using a 1.5-T G.E. Signa system. A series of sagittal and axial scout views were acquired to correct for head tilt and to localize imaging coordinates. For participants from the first-episode study, a three-dimensional, inversion recovery prepared, fast spoiled gradient/recall in the steady state scan of the whole brain was performed to acquire a T1-weighted data set. These T1-weighted images were obtained in the axial plane (parallel to the z axis of the magnet) with 1.5-mm contiguous sections (TR=11.3 ms, TI=300 ms, TE=2.2 ms, and flip angle=20° with one data average and a 256×256×128 pixel matrix). The MRI protocol for participants in the chronic study was exactly the same as described for the first-episode study, except that the images were initially acquired in the coronal view.

2.2.2. Brain regions of interest (ROIs)

With the software MEASURE (Barta et al., 1997) stereological assessment was performed by trained raters blind to participant diagnosis, including one of the authors (PP), in the following ROIs: whole brain, total PFC, grey matter of PFC, total premotor cortex (PMC), grey matter of PMC, total temporal lobe, matter of the temporal lobe, and the hippocampus (see

Premkumar et al., 2006 for illustrations). Inter-rater reliability (calculated as intra-class correlation coefficient [ICC]) were as follows: whole brain (range 0.98–0.96), cortical grey matter (range 1.0–0.96) and hippocampus (range 1.0–0.95). Left and right ROI measurements were derived from the total ROI measurements by performing plane cutaways using the 'COMBINE MEASURE' option in MEASURE. Separate ICCs were therefore not calculated for each side. Existing criteria were used for the measurement of the whole brain (excluding cerebrospinal fluid), total and grey matter of the temporal lobe (DeLisi et al., 1995), the total and grey matter of the PFC and the PMC (DeLisi et al., 1995; Sharma et al., 1998) and the hippocampus (Stephanis et al., 1999). Grey matter measurements were carried out on total ROI measurements by unmarking pixels that covered the white matter. The criterion for including a pixel was that the pixel be more than 60% in grey matter, a decision made by viewing each coronal slice from both a large and small scale 'zoom'. The total PFC and total PMC were derived from the whole brain volume measurements, while the grey matter for the PFC and PMC were derived from measurement of the cortical grey matter.

2.2.2.1. Prefrontal cortex. The PFC included all slices frontal to the genu of the corpus callosum. It consisted of the first four to five coronal slices.

2.2.2.2. Premotor cortex. The PMC was defined as the area between the PFC and the sensorimotor cortex. The PMC extended from the first coronal slice at which the corpus callosum appeared to the slice before the thalamus.

2.2.2.3. Temporal lobe. The first coronal slice of the temporal lobe was visible at the 4th or 5th coronal slice from the front. The last coronal slice of the temporal lobe was the slice at which the sylvian fissure extended less than halfway across the temporal lobe in both the left and right hemispheres.

2.2.2.4. Hippocampus. As seen in the coronal view, the hippocampus was bounded by the subiculum posteriorly and the amygdala anteriorly. The white matter bordering the hippocampus anteriorly, the alveus posteriorly, and the parahippocampal gyrus ventrally, were excluded from the measurement. The hippocampal–amygdala boundary was used to separate the hippocampus and amygdala at the anterior end of the hippocampus.

Table 1
Demographic characteristics of the patient and control groups

	FE patients (N=35)	Young healthy controls (N=20)	Test	Statistic	P^a	Chronic patients (N=54)	Older healthy controls (N=21)	Statistic	P^a
Age in years [mean (S.D.)]	23.57 (4.95)	26.15 (5.52)	ANOVA	3.18	0.08	38.61 (10.87)	36.19 (11.27)	7.61	0.007
Education (years)	12.06 (1.77)	15.75 (1.86)	ANOVA	53.55	<0.001	12.91 (2.6)	14.86 (3.10)	0.73	0.39
Gender (% male)	71.43	70.00	χ^2	4.22	0.38	68.52	71.43	0.06	0.81
Handedness (% right)	91.43	90.00	χ^2	0.07	0.79	94.44	100.00	1.22	0.27
Parental socio-economic status ^b									
Professional	3	4				8	1		
Intermediate	8	5				6	6		
Skilled	17	8				21	9		
Semi-skilled manual	4	0				8	1		
Unskilled	0	1				3	2		
Missing	3	2				8	2		
Diagnosis				–			–		
Schizophrenia						54			
Paranoid	12								
Disorganised	2								
Schizophreniform	17								
Schizoaffective	4								
Duration of illness in months [mean (S.D.)]	7.79 (7.65)	–				152.16 (83.52)	–		
PANSS [mean (S.D.)]		–					–		
Total	82.85 (16.82)					54.67 (19.71)			
Positive	21.47 (5.34)					12.67 (5.44)			
Negative	19.77 (5.77)					13.98 (6.17)			
General psychopathology	40.56 (8.40)					28.02 (9.29)			
Current antipsychotic mediation type	17	–				54	–		
Typical	8								
Atypical	10								
Neuroleptic naïve									
Taking anticholinergics	0	–				10	–		

^a $P < 0.05$.

^b Parental socio-economic status categories: Professional — doctor, lawyer; Intermediate — teacher, nurse; Skilled — secretary, bus driver; Semi-skilled manual — agricultural, bus conductor; Unskilled — labourer, cleaner.

2.3. Neuropsychological measures

Measures of executive functioning, attention and memory were selected from the originally administered battery of tests (Riley et al., 2000) that were common to both the studies, namely, the National Adult Reading Test (NART), Wisconsin Card Sorting Test (WCST) perseverative errors, WMS Visual Reproductions-immediate recall, WMS Visual Reproductions-delayed recall, Verbal fluency-letters (phonemic verbal fluency) and Trail Making Test — part B.

2.4. Statistical analysis

Group differences in demographic variables were assessed with ANOVAs and chi-square tests.

2.4.1. Function–structure relationships

To test the hypothesis that there are group differences in function–structure relationships, three-step hierarchical regression analyses were performed for the six neuropsychological variables (see Table 2, NART-IQ was used as a control variable). The neuropsychological variable was the dependent variable. Participant group was the step 1 predictor, the seven brain sub-regions (see Table 3) were the step 2 predictors entered in a stepwise manner, and NART-predicted IQ, years of education and whole brain volume were the step 3 predictors entered in a stepwise manner.

Within-group Pearson correlations were performed for significant function–structure relationships that were predicted in the regression analysis. Fisher z transformations were performed to test for group

Table 2
Means (S.D.) of the neuropsychological test scores in first-episode (FE) and chronic schizophrenia

	FE patients		Young healthy controls		Chronic patients		Older healthy controls	
		<i>N</i>		<i>N</i>		<i>N</i>		<i>N</i>
NART-IQ	107.75 (7.68)	27	118.35 (6.51)	16	108.05 (10.21)	53	112.39 (6.01)	21
VFLT	29.03 (11.16)	32	48.55 (9.87)	20	30.96 (11.14)	52	44.19 (10.64)	20
VR-Imm ^a	32.83 (6.42)	34	36.15 (5.07)	19	25.99 (8.23)	54	31.51 (8.53)	20
VR-Del ^a	29.31 (8.37)	33	36.90 (4.72)	19	21.05 (9.46)	54	28.72 (10.01)	20
TMT-I	61.14 (66.91)	35	28.75 (22.36)	20	50.57 (48.87)	42	30.81 (30.39)	17
WCST PE	21.16 (17.21)	31	15.58 (19.44)	15	28.17 (20.91)	42	17.40 (12.31)	18

NART-IQ: National Adult Reading Test-predicted IQ; VFLT: Verbal fluency-letters test — number of words; VR-Imm: WMS Visual Reproduction-immmediate recall; VR-Del: WMS Visual Reproduction-delayed recall; TMT-I: Trail Making Test interference (time taken on Part A minus time taken on Part B); WCST PE: WCST perseverative errors.

^a WMS Visual Reproductions — Revised version was used for first-episode patients and young controls. WMS Visual Reproductions — Original version was for chronic patients and older controls and scores were made equivalent to the revised version for the purpose of comparison with first-episode patients and young controls.

differences in the strength of the correlations using the following formula (Howell, 2002):

$$z = [r'_1 - r'_2] \div \sqrt{[(1/N_1 - 3) + (1/N_2 - 3)]}.$$

To determine whether the observed function–structure relationships in the chronic patients were independent of an age-associated decline, partial correlations controlling for age were performed. When more than one brain region predicted neuropsychological performance and to test whether specific brain regional volume–neuropsychological function relationships are explained by whole brain volume effects, multiple regression analyses were performed with the neuropsychological variable as the dependent variable and whole brain volume and the significant brain ROIs as predictors entered in a stepwise manner.

All statistical analyses were performed using the Statistical Package for the Social Sciences, version 15.0 (SPSS Inc., Chicago).

3. Results

Table 1 presents the demographic characteristics of the four participant groups. Table 2 presents the mean scores on the neuropsychological measures in the four participant groups. The distribution of the neuropsychological data was also normal in the chronic patient (skewness range=1.45 to –0.46, standard error=0.33; kurtosis range=2 to –0.74, standard error=0.64) and older control groups (skewness range=–1.28 to 0.23, standard error=0.50; kurtosis range=2.74 to –1.05, standard error=0.97). The distribution of the neuropsychological data was less normal in the first-episode patient (trails interference: skewness=3.32, kurtosis=13.4; other variables: skewness range=1.76 to –1.56; kurtosis range=3.48 to 2.57, standard error of all skewness values=0.4, standard error of all kurtosis values=0.78) and young control groups (WCST perseverative errors: skewness=3.16, kurtosis=11.33; WMS Visual Reproduction-immmediate

Table 3
Mean (S.D.) volumes of brain regions of interest in first-episode (FE) and chronic schizophrenia (volumes in cm³)

	FE patients	Young healthy controls	Chronic patients	Older healthy controls
	(<i>N</i> =35)	(<i>N</i> =20)	(<i>N</i> =54)	(<i>N</i> =21)
Whole brain	834.73 (71.99)	897.07 (97.89)	820.67 (120.13)	855.76 (115.95)
Total PFC	112.28 (17.11)	118.25 (18.14)	97.59 (19.39)	111.94 (21.94)
PFC grey	71.56 (10.87)	74.01 (13.27)	57.67 (11.14)	67.76 (10.36)
Total PMC	156.32 (17.67)	167.10 (24.77)	173.25 (31.54)	160.97 (28.26)
PMC grey	75.23 (14.32)	82.68 (15.09)	81.29 (18.76)	80.26 (16.49)
Total t. lobe	100.94 (16.13)	112.58 (18.29)	99.43 (20.95)	99.23 (19.34)
T. lobe grey	72.60 (10.84)	81.09 (12.00)	66.75 (12.62)	69.09 (13.97)
Hippocampus	4.34 (0.50)	5.04 (0.43)	3.94 (0.95)	4.63 (0.57)

T. lobe grey = Grey matter of temporal lobe; PMC = Premotor cortex; PMC grey = Grey matter of premotor cortex; T. lobe = Temporal lobe; PFC = Prefrontal cortex; PFC grey = Grey matter of prefrontal cortex.

recall: skewness = -3.04, kurtosis = 11.35; WMS Visual Reproduction-delayed recall: skewness = 2.69, kurtosis = 8.64; trails interference: skewness = 2.06, kurtosis = 5.44; skewness range of other variables = 0.78 to -1.92; kurtosis range of other variables = 1.16 to 4.99; standard error of all skewness values = 0.51, standard error of all kurtosis values = 0.99).

Table 3 presents the mean volumes of the brain regions of interest in the four participant groups. The distribution for the ROI volumes was mostly normal in all participant groups (skewness range = 1.22 to -0.55, standard error range = 0.5–0.32; kurtosis range = 3.17 to -1.1, standard error range = 0.99 to 0.64).

3.1. Function–structure relationships

3.1.1. WMS Visual Reproduction-immediate recall–total PFC volume relationship

In the first step, group predicted 6% of the variance in WMS Visual Reproduction-immediate recall ($r = -0.24$, $P = 0.006$). In the second step, larger total PFC volume predicted a further 14% of the variance ($r = 0.39$, $P < 0.001$). In the third step, NART-IQ predicted a further 8% of the variance ($r = 0.29$, $P < 0.001$). PFC volume remained a predictor in the third step ($r = 0.33$, $P < 0.001$).

Immediate recall correlated with total PFC volume in the chronic patients and older controls (see Table 4). The size of the immediate recall–total PFC volume correlation was different between the two patient groups ($z = 2$, $P = 0.02$) and between the two control groups ($z = 1.8$, $P = 0.04$). Controlling for age, immediate recall did not correlate with total PFC volume in chronic patients ($r = 0.23$, $P = 0.10$), but correlated with total PFC volume in older controls ($r = 0.49$, $P = 0.03$).

Multiple regression analyses predicting delayed memory were performed in the chronic patient and older control groups, with whole brain and total prefrontal cortex as stepwise predictors. In chronic patients, only prefrontal cortex volume predicted delayed memory

($r = 0.29$, $P = 0.03$). In older controls, only whole brain volume predicted delayed memory ($r = 0.66$, $P = 0.001$).

3.1.2. WMS Visual Reproduction-delayed recall–total PFC and hippocampal volume relationship

In the first step, group predicted 5% of the variance in WMS Visual Reproduction-delayed recall ($r = -0.23$, $P = 0.008$). In the second step, larger total PFC volume predicted a further 15% of the variance ($r = 0.39$, $P < 0.001$). Larger hippocampal volume predicted an additional 3% of the variance ($r = 0.23$, $P = 0.03$). In the third step, years in education ($r = 0.28$, $P = 0.001$) and whole brain volume ($r = 0.23$, $P = 0.04$) increased the variance prediction by a further 3% and 2%, respectively. In the third step, total PFC volume and hippocampal volume no longer predicted delayed recall ($r = 0.13$, $P = 0.25$ and $r = 0.11$, $P = 0.22$, respectively).

Delayed recall correlated with total PFC volume in chronic patients (see Table 4). The size of the delayed recall–total PFC correlation was different between the two patient groups at a trend level ($z = 1.45$, $P = 0.07$), but was not different between the two control groups ($z = 0.92$, $P = 0.18$). Controlling for age, delayed recall partially correlated with total PFC volume in chronic patients ($r = 0.29$, $P = 0.04$), but not in older controls ($r = 0.32$, $P = 0.17$). Controlling for duration of illness, delayed recall partially correlated with total PFC volume ($r = 0.31$, $P = 0.02$).

Delayed recall correlated with hippocampal volume in older controls (see Table 4) even after controlling for age ($r = 0.52$, $P = 0.02$). The size of the delayed recall–hippocampal volume correlation was not different between the two patient groups ($z = 0.37$, $P = 0.36$) or between the two control groups ($z = 0.79$, $P = 0.22$).

Multiple regression analyses predicting delayed memory were performed in the chronic patient and older control groups with whole brain, total prefrontal cortex and hippocampus as stepwise predictors. In chronic patients, prefrontal cortex volume predicted delayed

Table 4

Pearson correlations, r , (P) between neuropsychological variables and brain regional volumes that were significant predictors based on multiple regression analysis

Correlates	FE patients ^a		Chronic patients		Young healthy ^a controls		Older healthy controls	
	r (P)	N	r (P)	N	r (P)	N	r (P)	N
Verbal fluency-letters and hippocampal volume	-0.23 (0.21)	32	-0.003 (0.98)	52	0.06 (0.79)	20	0.13 (0.59)	20
WMS VR immediate recall and total PFC	0.15 (0.38)	34	0.29 (0.03)	54	-0.10 (0.71)	18	0.53 (0.01)	21
WMS VR delayed recall and total PFC	0.02 (0.91)	33	0.34 (0.01)	54	0.08 (0.75)	18	0.38 (0.09)	21
WMS VR delayed recall and hippocampus	0.15 (0.39)	33	0.07 (0.63)	54	0.20 (0.41)	19	0.44 (0.05)	21
WCST perseverative errors and total temporal lobe	-0.13 (0.49)	31	-0.26 (0.10)	42	0.008 (0.98)	15	-0.60 (0.01)	18

^a Spearman correlations because of non-normal distribution in these groups remained non-significant.

memory ($r=0.34$, $P=0.01$). In older controls, whole brain volume predicted delayed memory ($r=0.52$, $P=0.02$).

3.1.3. WCST perseverative errors–total temporal lobe volume relationship

In the first step, group predicted 3% of the variance in WCST perseverative errors ($r=0.05$, $P=0.57$). In the second step, smaller total temporal lobe volume predicted a further 4% of the variance ($r=-0.19$, $P=0.03$). In the third step, NART-IQ predicted a further 3% of the variance ($r=-0.19$, $P=0.03$). In the third step, total temporal lobe volume remained a predictor ($r=-0.19$, $P=0.03$).

WCST perseverative errors correlated with total temporal lobe volume in older controls (see Table 4) even after controlling for age ($r=-0.56$, $P=0.02$). The WCST perseverative errors–total temporal lobe volume correlation was not different between the first-episode and chronic samples ($z=0.44$, $P=0.33$), but was different between the two control groups ($z=1.8$, $P=0.04$).

A multiple regression analysis predicting WCST perseverative errors was performed in the older control groups with whole brain and temporal lobe as stepwise predictors. Only temporal lobe volume predicted perseverative errors ($r=-0.57$, $P=0.007$).

3.1.4. Phonemic verbal fluency–hippocampal volume relationship

In the first step, group predicted 4% of the variance in phonemic verbal fluency ($r=-0.23$, $P=0.008$). In the second step, larger hippocampal volume predicted a further 6% of the variance ($r=0.24$, $P=0.01$). In the third step, NART-IQ predicted a further 20% of the variance ($r=-0.19$, $P=0.03$), although hippocampal volume no longer predicted phonemic verbal fluency ($r=0.1$, $P=0.22$).

None of the within-group Pearson correlations were significant (see Table 4). The size of the verbal fluency–hippocampus correlation was not different either between the two patient groups ($z=0.97$, $P=0.17$) or between the two control groups ($z=1.37$, $P=0.09$).

3.1.5. Trail Making interference — no correlation

Only NART-IQ was a significant predictor ($r=-0.40$, $P<0.001$), accounting for 16% of the variance in Trail Making interference.

4. Discussion

The study aimed to determine whether there are differences between patients with chronic schizophrenia and first-episode psychosis and between older and young

healthy controls in neuropsychological function–brain structural volume relationships. The immediate memory–total prefrontal cortex (PFC) volume relationship was stronger in chronic than first-episode patients and in older than young controls. The abstract reasoning (WCST perseverative errors)–total temporal lobe volume relationship was stronger in older than young controls. The delayed memory–total PFC volume relationship tended to be stronger in chronic than first-episode patients. Better delayed recall was related to larger hippocampal volume in older controls, but this relationship was not stronger than in young controls. These function–structure relationships were not explained by a whole brain volume effect in chronic patients, but were mostly explained by whole brain volume in older controls (except for the abstract reasoning–total temporal lobe volume relationship). Additionally, age explained only the immediate recall–PFC volume relationship in chronic patients and the delayed recall–PFC volume relationship in older patients.

In the chronic patients, the delayed memory–PFC volume relationship was not explained by age, duration of illness or whole brain volume. In contrast, in older controls, the delayed memory–PFC volume relationship was explained by age and whole brain volume. Our finding that poorer delayed memory was associated with smaller PFC volume in chronic schizophrenia, which tended to differentiate chronic from first-episode patients, is consistent with previous findings of a relationship between delayed memory and the volume of the dorsolateral prefrontal cortex (DLPFC) in chronic schizophrenia (Seidman et al., 1994; Baaré et al., 1999). The DLPFC has been related to memory in patients with chronic schizophrenia, but not in controls (Seidman et al., 1994). Furthermore, the observation that this function–structure relationship remained significant after partialling out the effect of age shows that this relationship was not mediated by a normal process of aging. An earlier finding (in the same sample) showed the effect of duration of illness on PFC volume (Premkumar et al., 2006). However, the present findings suggest that the delayed memory–PFC volume relationship among chronic patients is not abolished by the influence of the duration of illness.

Our delayed memory–PFC volume relationship finding in chronic patients may be considered in terms of a protracted effect of the PFC on temporal lobe function, although only one measure of memory was used to examine temporal lobe function. According to the ‘evolutionary cytoarchitectonic trends’ model of the cerebral cortex (Sanides, 1969, 1972), the frontal lobe is thought to develop from the hippocampus (archicortical

trend) and the olfactory cortex (paleocortical trend). The archicortical trend consists of the hippocampal formation, the cingulate gyrus and the dorsal PFC, and is thought to be defective in schizophrenia (Bildler et al., 1995; Szeszko et al., 2000). Following this model, the fronto-temporal connection within the archicortical system may be compromised in schizophrenia, requiring projectional control of the frontal lobe over temporal lobe functions.

A diminished immediate memory–PFC volume relationship after partialling out age effects, and a dissociation between older and young healthy control groups on the PFC volume–immediate memory relationship, would suggest a normal age-mediated relationship of this function–structure relationships among schizophrenia patients. However, the presence of this relationship in older controls after partialling out age effects would suggest that such relationships are not only due to normal aging, but are also due to neurodegenerative changes that occur concomitant with aging.

The delayed memory–hippocampal volume relationship in older healthy controls supports evidence that better long-term memory is associated with a larger hippocampal volume (Van Petten, 2004; Van Petten et al., 2004). Memory may be reliant on overall hippocampal integrity in older adults, but not in young adults. The small samples may have reduced the power and the likelihood of making a distinction between the older and young control groups. Additionally, this relationship may be influenced by the integrity of the whole brain volume, as suggested by a reduced relationship when the effect of whole brain volume was partialled out. Our findings suggest that cognitive function may be influenced by general brain volume effects in older healthy adults. This did not appear to be the case for the chronic schizophrenia group where cognitive functions were related only to specific regional volumes. It is possible that in healthy adults, function–structure relationships emerge as a result of a decline in general brain volume, whereas in people with schizophrenia, the function–structure relationships may be partly caused by the effect of schizophrenia on specific brain functions (Seidman et al., 1994; Baaré et al., 1999; Manoach, 2003).

The abstract reasoning–total temporal lobe volume relationship in older healthy controls differentiated the older from young healthy groups, such that more perseverative errors were associated with a smaller temporal lobe volume in older controls. While WCST performance is typically associated with DLPFC function (Stuss et al., 2000), projections from the DLPFC to the mesolimbic system do exist (Adinoff, 2004; Pogarell et al., 2006) and functional networks may continue to form in older adults.

The absence of function–structure relationships in the first-episode and young control groups may be attributable to the fact that neuropsychological function at this period relies on the functioning of specific neural circuits, rather than on gross structural volume. The absence of function–structure relationships in the first-episode group may also reflect difficulty with performing neuropsychological tasks in a reliable manner at a time of poor stability where the patient is adapting to the stress associated with the experience of psychotic symptoms.

Our investigation has a number of limitations. Except for the PFC–immediate memory and WCST perseverative errors–temporal lobe relationships, the function–structure relationships entering the regression analyses did not survive the effect of general cognitive function, suggesting that these relationships are confounded by a generalised cognitive decline. The function–structure correlations were of moderate effect size and our analyses were exploratory. Therefore, correction for multiple comparisons was not made. Chronic patients had a less severe symptom profile as measured by the PANSS and a longer duration of medication that would have confounded neuropsychological performance, since the chronic patients would have been more stabilized compared with the first-episode patients. The investigation was opportunistic in that we were able to include only those neuropsychological variables that were common to both studies. The boundaries of some of the ROIs were arbitrary rather than anatomical (e.g., the PFC measurement included all slices frontal to the genu of the corpus callosum). Replication of the findings from the present study in larger samples is needed.

In conclusion, age rather than illness chronicity differentiate older patients and healthy adults from young patients and healthy adults. General brain volume mediates this relationship in older healthy adults, but not in patients with chronic schizophrenia, leading to the inference that function–structure relationships emerge as a result of general decline in brain volume in older healthy adults, and as a result of schizophrenia illness on specific brain functions in chronic patients.

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References

- Adinoff, B., 2004. Neurobiologic processes in drug reward and addiction. *Harvard Review of Psychiatry* 12, 305–320.
- Antonova, E., Sharma, T., Morris, R., Kumari, V., 2004. The relationship between brain structure and neurocognition in

- schizophrenia: a selective review. *Schizophrenia Research* 70, 117–145.
- Antonova, E., Kumari, V., Morris, R., Halari, R., Anilkumar, A., Mehrotra, R., Sharma, T., 2005. The relationship of structural alterations to cognitive deficits in schizophrenia: a voxel-based morphometry study. *Biological Psychiatry* 58, 457–467.
- Baaré, W.F., Hulshoff Pol, H.E., Hijman, R., Mali, W.P., Viergever, M.A., Kahn, R.S., 1999. Volumetric analysis of frontal lobe regions in schizophrenia: relation to cognitive function and symptomatology. *Biological Psychiatry* 45, 1597–1605.
- Bachmann, S., Bottner, C., Pantel, J., Schroder, J., Amann, M., Essig, M., Schad, L.R., 2004. MRI-morphometric changes in first-episode schizophrenic patients at 14 months follow-up. *Schizophrenia Research* 67, 301–303.
- Barta, P.E., Dhringra, L., Royall, R., Schwartz, E., 1997. Improving stereological estimates for the volume of structures identified in three-dimensional arrays of spatial data. *Journal of Neuroscience Methods* 75, 111–118.
- Bilder, R., Bogerts, B., Ashtari, M., Wu, H., Alvir, J., Jody, D., Reiter, G., Bell, L., Lieberman, J., 1995. Anterior hippocampal volume reductions predict frontal lobe dysfunction in first episode schizophrenia. *Schizophrenia Research* 17, 47–58.
- Brickman, A.M., Zimmerman, M.E., Paul, R.H., Grieve, S.M., Tate, D.F., Cohen, R.A., Williams, L.M., Clark, C.R., Gordon, E., 2006. Regional white matter and neuropsychological functioning across the adult lifespan. *Biological Psychiatry* 60, 444–453.
- DeLisi, L.E., Tew, W., Xie, S., Hoff, A.L., Sakuma, M., Kushner, M., Lee, G., Shedlack, K., Smith, A.M., Grimson, R., 1995. A prospective follow-up study of brain morphology and cognition in first-episode schizophrenic patients: preliminary findings. *Biological Psychiatry* 38, 349–360.
- DeLisi, L.E., Sakuma, M., Maurizio, A.M., Relja, M., Hoff, A.L., 2004. Cerebral ventricular change over the first 10 years after the onset of schizophrenia. *Psychiatry Research: Neuroimaging* 130, 57–70.
- DSM-IV, 1996. *Diagnostic and Statistical Manual of Mental Disorders — Fourth Edition (DSM-IV)*. American Psychiatric Association, Washington, D.C.
- Ettlinger, U., Chitnis, X.A., Kumari, V., Fannon, D.G., Sumich, A.L., O’Ceallaigh, S., Doku, V.C., Sharma, T., 2002. Magnetic resonance imaging of the thalamus in first-episode psychosis. *American Journal of Psychiatry* 158, 116–118.
- Fannon, D., Chitnis, X.V.D., Tennakoon, L., O’Ceallaigh, S., Soni, W., Sumich, A., Lowe, J., Santamaria, M., Sharma, T., 2000. Features of structural brain abnormality detected in first-episode psychosis. *American Journal of Psychiatry* 157, 1829–1834.
- First, M.B., Gibbon, M., Spitzer, R.L., Williams, J.B.W., 1996a. *User’s Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders— Research Version (SCID-I, Version 2.0, February, FINAL Version)*.
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B., 1996b. *Structured Clinical Interview for DSM-IV Axis I Disorders — Non-Patient Edition (SCID-I/NP), version 2.0*. New York State Psychiatric Institute, Biometrics Research, New York.
- Gunning-Dixon, F.M., Raz, N., 2003. Neuroanatomical correlates of selected executive functions in middle-aged and older adults: a prospective MRI study. *Neuropsychologia* 41, 1929–1941.
- Gur, R.E., Cowell, P., Turetsky, B.I., Gallacher, F., Cannon, T., Bilker, W., Gur, R.C., 1998. A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. *Archives of General Psychiatry* 55, 145–152.
- Howell, D.C., 2002. *Statistical Methods for Psychology*. Duxbury, California.
- Kurtz, M.M., 2005. Neurocognitive impairment across the lifespan in schizophrenia: an update. *Schizophrenia Research* 74, 15–26.
- Manoach, D.S., 2003. Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. *Schizophrenia Research* 60, 285–298.
- Mathalon, D.H., Sullivan, E.V., Lim, K.O., Pfefferbaum, A., 2001. Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance imaging study. *Archives of General Psychiatry* 58, 148–157.
- Pogarell, O., Koch, W., Popperl, G., Tatsch, K., Jakob, F., Zwanzger, P., Mülert, C., Rupprecht, R., Moller, H.J., Hegerl, U., Padberg, F., 2006. Striatal dopamine release after prefrontal repetitive transcranial magnetic stimulation in major depression: preliminary results of a dynamic [123I] IBZM SPECT study. *Journal of Psychiatric Research* 40, 307–314.
- Premkumar, P., Sharma, T., 2005. Neuropsychologic functioning and structural MRI of the brain in patients with schizophrenia. *Expert Reviews in Neurotherapeutics* 5, 85–94.
- Premkumar, P., Kumari, V., Corr, P.J., Sharma, T., 2006. Frontal lobe volumes in schizophrenia: effects of stage and duration of illness. *Journal of Psychiatric Research* 40, 627–637.
- Riley, E.M., McGovern, D., Mockler, D., Doku, V.C.K., Óceallaigh, S., Fannon, D.G., Tannakoon, L., Santamaria, M., Soni, W., Morris, R.G., Sharma, T., 2000. Neuropsychological functioning in first-episode psychosis — evidence of specific deficits. *Schizophrenia Research* 43, 47–55.
- Sanides, F., 1969. Comparative architectonics of the neocortex of mammals and their evolutionary interpretation. *Annals of the New York Academy of Sciences* 167, 404–423.
- Sanides, F., 1972. Representation in the cerebral cortex and its areal lamination patterns. In: Boume, G.H. (Ed.), *The Structure and Function of Nervous Tissue*. Academic Press, New York.
- Seidman, L.J., Yurgelun-Todd, D., Kremen, W.S., Woods, B.T., Goldstein, J.M., Faraone, S.V., Tsuang, M.T., 1994. Relationship of prefrontal and temporal lobe MRI measures to neuropsychological performance in chronic schizophrenia. *Biological Psychiatry* 35, 235–246.
- Sharma, T., Lancaster, E., Lee, D., Lewis, S., Sigmundsson, L.T., Takei, N., Gurling, H., Barta, P., Pearson, G., Murray, R., 1998. Brain changes in schizophrenia: volumetric MRI study of families multiply affected with schizophrenia — The Maudsley family study 5. *British Journal of Psychiatry* 173, 132–138.
- Sharma, T., Hughes, C., Soni, W., Kumari, V., 2003. Cognitive effects of olanzapine and clozapine treatment in chronic schizophrenia. *Psychopharmacology* 169, 398–403.
- Stephanis, N., Frangou, S., Yekely, J., Sharma, T., O’Connell, P., Morgan, K., Sigmundsson, T., Taylor, M., Murray, R.M., 1999. Hippocampal volume reduction in schizophrenia: effects of genetic risk and pregnancy and birth complications. *Biological Psychiatry* 46, 697–702.
- Stuss, D.T., Levine, B., Alexander, M.P., Hong, J., Palumbo, C., Hamer, L., Murphy, K.J., Izukawa, D., 2000. Wisconsin Card Sorting Test performance in patients with focal frontal and posterior brain damage: effects of lesion location and test structure on separable cognitive processes. *Neuropsychologia* 38, 388–402.
- Sumich, A., Chitnis, X.A., Fannon, D.G., O’Ceallaigh, S., Doku, V.C., Falrowicz, A., Marshall, N., Matthew, V.M., Potter, M., Sharma, T., 2002. Temporal lobe abnormalities in first-episode psychosis. *American Journal of Psychiatry* 159, 1232–1234.

- Sumich, A., Chitnis, X.A., Fannon, D.G., O’Ceallaigh, S., Doku, V.C., Faldrowicz, A., Sharma, T., 2005. Unreality symptoms and volumetric measures of Heschl’s gyrus and planum temporal in first-episode psychosis. *Biological Psychiatry* 57, 947–950.
- Szeszko, P.R., Bilder, R.M., Lencz, T., Ashtari, M., Goldman, R.S., Reiter, G., Wu, H., Lieberman, J.A., 2000. Reduced anterior cingulate gyrus volume correlates with executive dysfunction in men with first-episode schizophrenia. *Schizophrenia Research* 43, 97–108.
- Szeszko, P.R., Strous, R.D., Goldman, R.S., Ashtari, M., Knuth, K.H., Lieberman, J.A., Bilder, R.M., 2002. Neuropsychological correlates of hippocampal volumes in patients experiencing a first episode of schizophrenia. *American Journal of Psychiatry* 159, 217–226.
- Szeszko, P.R., Gunning-Dixon, F., Goldman, R.S., Bates, J., Ashtari, M., Snyder, P.J., Lieberman, J.A., Bilder, R.M., 2003. Lack of normal association between cerebellar volume and neuropsychological functions in first-episode schizophrenia. *American Journal of Psychiatry* 160, 1884–1887.
- Van Petten, C., 2004. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. *Neuropsychologia* 42, 1394–1413.
- Van Petten, C., Plante, E., Davidson, P.S.R., Kuo, T.Y., Bajuscak, L., Glisky, E.L., 2004. Memory and executive function in older adults: relationships with temporal and prefrontal gray matter volumes and white matter hyperintensities. *Neuropsychologia* 42, 1313–1335.
- Zimmerman, M.E., Brickman, A.M., Paul, R.H., Grieve, S.M., Tate, D.F., Gunstad, J., Cohen, R.A., Aloia, M.S., Williams, L.M., Clark, C.R., Whitford, T.J., Gordon, E., 2006. The relationship between frontal gray matter volume and cognition varies across the healthy adult lifespan. *American Journal of Geriatric Psychiatry* 14, 823–833.