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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 differ 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.

Key Words: magnetic resonance imaging, neuropsychological function, function-structure relationships, illness stage

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 the illness. Determining 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 has been associated with larger dorsolateral prefrontal cortex (DLPFC) volume (Seidman et al., 1994). Better immediate verbal and visual memory (temporal lobe measures) and verbal fluency (a frontal lobe measure) has 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 associate positively with anterior hippocampal volume leading to the suggestions that abnormalities of the anterior hippocampus predict frontal lobe dysfunction in schizophrenia (Bilder et al., 1995; Szeszko et al., 2002). Poorer executive function was associated with smaller anterior cingluate gyrus volume in first-episode schizophrenia males (Szeszko et al., 2000). No association between neuropsychological function and cerebellum was 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). More 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 controlling for normal age-related differences in function-structure relationships. We hypothesised 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 with these structures (Gunning-Dixon and Raz, 2003; Zimmerman et al., 2006). In young adults, we hypothesized that there would be no function-structure relationship because the investigated function-structure relationships do not appear to be present in young adults (Zimmerman et al., 2006).

2. Method

2.1. Participants

Thirty-five first-episode psychosis patients and twenty healthy controls matched on age, gender, ethnicity and parental socio-economic status who had both MRI and neuropsychological data were considered suitable for this investigation. Fourteen patients satisfied the DSM-IV (1996) criteria for schizophrenia, seventeen for schizophreniform disorder and four for schizoaffective disorder. The seventeen patients with a diagnosis of schizophreniform disorder were reclassified as meeting DSM-IV (1996) criteria for schizophrenia after six 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; Sumich et al., 2005).

Fifty-four patients with chronic schizophrenia and twenty-one 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).

First-episode were recruited from London and surrounding areas. Chronic patients were recruited from the Bethlem Royal and Maudsley National Health Services Trust, London. Patients were recruited 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 Structure Clinical Interview for Axis I Diagnoses (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 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=11.3msec, TI=300msec, TE=2.2msec, and the 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)

Using 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, grey matter of temporal lobe, hippocampus. Inter-rater reliability (calculated as intraclass correlation coefficient [ICC]) rates were: 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 whole brain (excluding cerebrospinal fluid), total and grey matter of temporal lobe (DeLisi et al., 1995), total and grey matter of PFC and PMC (DeLisi et al., 1995; Sharma et al., 1998) and 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 (see Premkumar et al., 2006 for illustrations). It consisted of the first 4-5 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 (see Premkumar et al., 2006 for illustrations).

2.2.2.3. Temporal lobe

The first coronal slice of the temporal lobe was visible 4-5 coronal slices 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 (see Premkumar et al., 2006 for illustrations).

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 (see Premkumar et al., 2006 for illustrations).

2.3. Neuropsychological measures

Measures of executive functioning, attention and memory were selected from the original battery of tests that was administered (Riley et al., 2000) that were common to both the studies, namely 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-one predictor, the seven brain sub-regions (see Table 3) were the step-two predictors entered in a stepwise manner, and NART-predicted IQ, years of education and whole brain volume were the step-three 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 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 in the chronic patient group for the significant function-structure relationships that were predicted in the regression analysis. 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 1 about here

Table 2 presents the mean scores on the neuropsychological measures in the four participant groups. 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). 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 immediate 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 2 about here

Table 3 about here

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 also 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). Controlling for age, delayed recall correlated with hippocampal volume in older controls (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 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). Controlling for age, WCST perseverative errors correlated with total temporal lobe volume in older controls (r = -0.56, *P* = 0.02). The WCST perseverative errors-total temporal lobe 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 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.

Table 4 about here

4. Discussion

The study aimed to determine whether brain structural volume-neuropsychological function relationships differ between patients with chronic schizophrenia and first-episode psychosis and between older and young healthy controls. 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 dorsolateral prefrontal cortex (DLPFC) in chronic schizophrenia (Seidman et al., 1994; Baaré et al., 1999). 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 findings in the present study suggest that this function-structure 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 prefrontal cortex 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, cingulate gyrus and the dorsal PFC, and is thought to be defective in schizophrenia (Bilder 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 relationship 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 also due to neurodegenerative changes that occur concomitant with aging.

The delayed memory-hippocampal volume relationship in older healthy controls supports evidence that a larger hippocampal volume is associated with better long-term memory (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). (insert Manoach 2003)

The abstract reasoning-total temporal lobe volume relationship in older healthy controls differentiated the older from young healthy groups, such that a smaller temporal lobe volume was associated with more perseverative errors 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 because neuropsychological function at this period may rely on the functioning of specific neural circuits, rather than on gross structural volume. The absence of a function-structure relationship 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 when compared to 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 regions of interest 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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