Structural Disconnectivity in Schizophrenia: Diffusion Tensor Imaging Study

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The corpus callosum (CC) is the major white-matter tract that crosses the interhemispheric fissure in the human brain. It connects homologous regions of the cerebral cortex. Dysfunction of the corpus callosum can lead to deficits in sensory and cognitive integration. Magnetic resonance Diffusion Tensor Imaging (DTI) provides information about the microstructural organization of white matter integrity in vivo through measurement of directionality of motion of water molecules in the brain. The most commonly used index in DTI is "fractional anisotropy" (F.A.).The aim of this study is: to determine fraction anisotropy (F.A.) of genu and splenium of the corpus callosum in a sample of patients with schizophrenia and in control healthy individuals and to correlate clinical findings with F.A. in different parts of the corpus callosum within the patient group. We are testing the hypothesis of structural disconnectivity in schizophrenia using fractional anisotropy maps of corpus callosum. We found significant reductions of F.A. in genu and splenium in patient group compared to control group. We also found significant statistical correlations of F.A. with synonymous clinical symptoms in patients group reflecting degradation of myelinated fibers in the C.C. We conclude that DTI of water molecules within the human brain may provide valuable in vivo tool in examining the previously unknown clues to the microstructure of white-matter tracts in schizophrenia. Our findings suggest structural disconnectivity hypothesis of schizophrenia.

Introduction

In the last century, psychiatrists tried to define the neuropathology of schizophrenia through postmortem studies. Although histopathological characterization of schizophrenia proved to be elusive, identifiable neuropathological features were clearly and consistently associated with the illness. The findings of studies in the late nineteenth and early twentieth centuries were remarkably ambiguous in describing both diffuse and focal abnormalities in multiple brain structures (but failed actually to describe " single-lesion model "), which were subtle in magnitude and did not exactly explain the pathophysiology of schizophrenia nor different symptom-matology and hence the discovery of influential pharmacotherapy has been delayed.

Following this initial progress and with the advent of modern neuroimaging techniques, which enabled relatively non-invasive in vivo studies of brain structure and function, in the search for the neuropathology of schizophrenia, scientific discovery of the pathology of schizophrenia is meaningfully resumed. These techniques facilitate the emergence of different theoretical hypotheses of the illness. By virtue of these advanced neuroimaging methods, the new hypotheses of neuropathology of schizophrenia are now testable and could be elucidated.

More than 90 years ago, Bleuler (1911) proposed the term "schizophrenia" to describe a disease process that produces a *"splitting* of the psychic functions*"*. More recently, Friston KJ (1999) has renewed this concept and he described one of the most up-to-date hypotheses named *"disconnection syndrome"* models of schizophrenia.

These models draw on recent neuroscientific findings and highlight a lack of *"functional connectivity"* across multiple brain systems. These hypotheses could be tested over the past few years (Crespo-Facorro, et al., 1999; Andreas et al., 2001; Lee et al., 2003; Friston 2005 and Matthew et al., 2005). By aid of advanced neuroimaging techniques, the other face of the coin, *"structural connectivity hypothesis "*, has been emerged. One of the novels recently used in testing this hypothesis is Diffusion Tensor Imaging (D.T.I.) which is a new non-invasive structural imaging modality that measures the mobility of brain water molecules and the organization of fibers in white matter tracts in vivo (Basser et al, 1995).

Diffusion tensor imaging (DTI) provides information about the microstructural organization of deep tissues in vivo. Specifically, DTI provides information about white matter integrity through measurement of directionality of motion of water molecules in the brain. In the absence of barriers, water molecules in tissues undergo Brownian motion along all possible directions. This is referred to as "*isotropic diffusion"*. However, in the presence of barriers such as axonal membranes, myelin sheaths and microfilaments the diffusion of water molecules exhibits directional preference. This is referred to as "*anisotropic diffusion"*. Organized structures such as white matter fiber tracts exhibit a large anisotropy since the water diffusion is restricted along the length of the tracts rather than across them. A reduction in the anisotropy implies less restraint of water molecules that may be related to subtle white matter pathology and loss of integrity in fiber tracts that are not evident with other radiological modalities, including conventional MRI (Taber et al, 2002). The most commonly used index for quantifying the anisotropy is "*fractional anisotropy"* (F.A.) (deviation from pure *isotropic diffusion*), which varies from *zero* (diffusion equal in all directions) to *unity* (diffusion purely unidirectional). It has been recently shown to be rotationally invariant, provides excellent gray matter–to–white matter contrast, and has a high contrast to noise ratio than other measures (Hasan et al, 2004).

Any pathological factors (as oedema, demyelination or axonal loss) that alter the structural organization and / or reduce the density of axonal membranes [like acute cerebral ischemia (Huisman, 2003), multiple sclerosis (Ge et al., 2004), alcoholism (Pfefferbaum et al., 2004; 2005) and dementia (Sullivan et al., 2001; Head et al., 2004)] might be expected to cause a reduction in diffusion anisotropy values

compared with those measured in normal brain.

Thus, fractional anisotropy is taken to be a useful sensitive marker of neuronal integrity, with high fractional anisotropy values indicating healthy, intact white matter fiber tracts and is typically higher in fibers with a homogeneous or linear structure than in tissue with an inhomogeneous structure, such as areas with pathology (Lansberg et al., 2001) or crossing fibers (O'Sullivan et al, 2001; Pfefferbaum and Sullivan, 2003).

In white matter with relatively homogenous structure, such as the corpus callosum, the diffusion of the water molecules is restricted and bound in a structure with a primarily linear organization resulting in high F.A. (Pfefferbaum et al., 2003; Pfefferbaum and Sullivan, 2003).

Because D.T.I. may detect the pathology of white matter despite absence of macrostructural size variation measured with conventional neuroimaging techniques (like C.T.; M.R.I.; f.M.R.I. and M.R. Spectroscopy), so it may have the potential to identify structural correlates of impaired structural connectivity in schizophrenia.

The corpus callosum (CC) is the major white-matter tract that crosses the interhemispheric fissure in the human brain. It consists of approximately 200 million interhemispheric fibers, most of which connect homologous regions of the cerebral cortex (Biegon et al., 1994). Dysfunction of the corpus callosum can lead to deficits in sensory and cognitive integration (Yamauchi et al., 1997; Fabri et al., 2001and Pfefferbaum et al., 2003). Therefore, it has been a region of much interest in schizophrenia researches. Early post mortem studies indicated an increased thickness of the CC in patients, possibly reflecting a *"hyperconnection"* between the hemispheres as Rosenthal and Bigelow stated at 1972.

In vivo studies by using conventional neuroimaging techniques, neuroanatomic structural abnormalities and the morphology of the corpus callosum have been thoroughly investigated. Most investigators have studied callosal length and width (Nasrallah et al., 1986; Uematsu et al., 1988; Woodruff et al., 1995; Jacobsen et al., 1997), while few have investigated callosal shape (Casanova et al., 1990; DeQuardo et al., 1996). Volumetric methods are less sensitive to across subject variability (like sex differences and wide differences between whole brain volume) (Rauch and Jinkins, 1994; Jäncke et al., 1997) and less likely to capture subtle differences in anatomy between different groups of schizophrenic patients. Clinical and psychopathological heterogeneity in schizophrenic patients may also account for inconsistencies in results when assessing structural morphology, including morphology of the callosum. For example, patients with negative symptoms show smaller callosal sizes (Gunther et al., 1991; Woodruff et al., 1993), thicker callosa (Coger and Serafetinides, 1990) or no difference relative to other groups. Similarly, early-onset schizophrenic

patients have been shown to have larger total, anterior and posterior callosal areas compared to controls (Coger and Serafetinides, 1990; Jacobsen et al., 1997). As shown, the results have been inconclusive and controversial in proving the disconnection hypothesis of schizophrenia.

By using diffusion tensor imaging technique, our objectives in this study are: to determine fraction anisotropy (F.A.) of genu and splenium of the corpus callosum in a sample of patients with schizophrenia and in control healthy individuals and to correlate clinical findings with F.A. in different parts of the corpus callosum within the patient group.

We are testing the hypothesis of structural disconnectivity in schizophrenia using fractional anisotropy maps of corpus callosum.

Subjects and Methods

Twenty schizophrenic patients (12 males and 8 females; mean age 39.0±9.1 years; with mean duration of illness 12.0±7.3 years) and twenty normal controls (12 males and 8 females; mean age 39.9±8.1 years) were included in the study.

Patients were randomly recruited from outpatient services of Psychological Medicine Hospital in Kuwait. They were diagnosed by using the Structured Clinical Interview for Diagnostic and Statistical Manual (DSM-IV) criteria (First et al., 1996). We used the Arabic version (Al-Sammak A. and Mustafa A., 2001). Semi-structured sheet including socio-demographic data; past psychiatric, medical and surgical histories; family history and history of used neuroleptic medications was included. All patients were on antipsychotic medication (7 patients were on typical and 14 were on atypical antipsychotics at the time of the study). Psychiatric symptoms were assessed using the Brief psychiatric rating scale (BPRS) (Overall and Gorham 1962). Interviews verified absence of any current or past other Axis I diagnoses in those patients.

Healthy control subjects were recruited and selected to match the patient group for sex and age from the neuro-radiology department at Ibn Sina hospital -by one researcher- after completing the semi-structured sheet and the General Health Questionnaire (cut-off point = 7) (Goldberg 1972) and after exclusion of any past or current Axis-I psychiatric disorders or family history of psychiatric illness.

Exclusion criteria for both patients and controls included head trauma; drug abuse; hereditary neurological disorders; gross neurological or systemic disorders (evidenced by clinical and M.R.I. examinations); mental retardation and contraindication for M.R.I. All subjects gave informed written consent for their participation in this study after complete description of the procedure.

Corpus Callosum as a region of interest (ROI):-

The corpus callosum was the focus of this study, based on many factors. First, the corpus callosum is easily and reliably

identifiable on DTI images due to the large concentration of white matter fiber tracts. It is large enough for the ROI to be reliably placed with minimal intersubject variability in the directionality and spread of fiber tracts. This allows for a clear separation of white matter from gray matter and CSF, which are significant confounding factors in the DTI analysis. Second, corpus callosum white matter tracts are significantly influenced by cortical damage, thus subtle dysfunction of the prefrontal cortex or other brain regions by the effect of schizophrenia may be seen in changes in corpus callosum FA. Third، in order to compare regions of the corpus callosum and thereby examine fiber tracts connecting different cortical regions. Fourth, callosal pruning and myelination as well as interhemispheric coherence continue to develop into early adulthood, a factor that may be relevant to age of onset in schizophrenia (Njiokiktjien *et al.*, 1994). Lastly, callosal myelination begins prenatally and is susceptible to malnutrition, asphyxia and toxins of infectious origin; also, these same events are linked with aberrant neuro-developmental events in schizophrenia (Njiokiktjien et al., 1994).

Why Genu and Splenium?

Witelson (1989) divided C.C. into nine discriminated areas according to the connecting fibers passing through C.C. namely anterior genu (the most anterior area); middle genu; posterior genu; anterior body; posterior body; isthmus; anterior splenium; middle splenium and posterior splenium (the most anterior area). Anterior genu contains the connecting fibres of prefrontal cortices. While, middle splenium contains the fibers connecting superior and inferior temporal gyri together. Other areas of the C.C. contains fibers connecting premotor; precentral; post-central; posterior parietal and occipital areas on both hemispheres respectively (anteriorly to posteriorly).

Many recent studies have demonstrated abnormal brain structure and function in the frontal and temporal lobes of patients with schizophrenia. Functional imaging and D.T.I. studies show abnormal frontotemporal activations on various neuropsychological tasks lending support to the hypothesis that the core feature of schizophrenia is a disruption of fronto-temporal structural disconnectivity (Honey et al, 2002 and Burns et al., 2003). Hence, we chose anterior genu and middle splenium as R.O.Is because they contain the fibers which are convenient to test our hypothesis and because they are the most widened areas of the C.C. so can be described easily through axial images.

Why axial plane?

We obtained the anisotropy images in the axial plane rather than in the sagittal plane, with multiple sections through the corpus callosum. We believe that this approach results in more representative images of the entire corpus callosum than the acquisition of a single mid-sagittal image.

M.R. Imaging data acquisition and analysis

DTI was performed with a 1.5 Tesla scanner (Signa; GE, medical system, Milwaukee, Wis) by using 8 Channel head Coil, landmark to the nasion and pad the patient to reduce the likelihood of artifacts related to motion. The diffusion tensor MR imaging protocol consisted of 3-plane localizer series and ASSET calibration scan taking into consideration that the entire brain anatomy included in the ASSET calibration scan. Optimization of TE to ensure that the lowest TE possible is utilized base on the gradient amplitude applied (B-Value). Single-shot spin- echo echo-planar sequence with ASSET series in axial plane using the following parameters Time to repeat (TR) was 6200msec, Time to echo (TE) was 111msec. Diffusion sensitization gradient encoding was applied in 25 directions by using B-Value 1000sec/mm2. A total 25 diffusion weighted images were obtained for each image section, and images through the whole brain were obtained. The slice thickness was 5mm with no intersection gap, the matrix size was 128 X 128 and Field of view was 24X24 cm2. The imaging time for the diffusion tensor MR sequence was approximately 2 minutes. In addition to diffusion tensor MR sequence, conventional MR imaging sequence was performed to exclude white matter lesions. Axial FSE T2 weighted sequences with the following parameters Time to repeat (TR) 700msec, Time to echo (TE) 88msec, Matrix size 512X512, FOV 24X24cm2 with slice thickness 5mm and intersection gap 1.5mm.

Image analysis

The raw diffusion tensor data were transferred to an independent workstation (Advantage Windows; GE Medical Systems) and processed with a computer software program (Functool; GE Medical Systems) to get index of anisotropy, we chose to use fractional anisotropy (FA). FA represents the anisotropic portion of total diffusion. To get FA, A uniform ovoid regions of interest (ROIs) were placed by using the functool software. All ROIs used in this study were manually placed by one neuroradiologist who was blinded to the patients' characteristics. The ROIs were drawn in mid part of genu and splenium on the section showing maximum thickness; it was at least 70 mm2. Slices contiguous with the one selected were examined to avoid the partial volume effects of cerebrospinal fluid (CSF) fig (1 and 2).

The FA value is unitless because it represents a ratio of diffusion coefficients. The calculations for FA were performed for each voxel and displayed as an anisotropy map, which was appropriately scaled for display.

Statistical Analysis

Data were collected and coded then entered into an IBM compatible computer, using the SPSS version 12 for Windows. Entered data were checked for accuracy then for normality, using Kolmogorov-Smirnov and Shapiro-Wilk tests, and proved to be normally distributed. Qualitative variables

were expressed as number and percentage while quantitative variables were expressed as median, mean ($\overline{X}$) and standard deviation (S).

The arithmetic mean ($\overline{X}$) was used as a measure of central tendency, while the standard deviation (S) was used as a measure of dispersion.

The following statistical tests were used:-

1-Independent samples t-test was used as a parametric test of significance for comparison between two sample means, after performing the Levene's test for equality of variances.

2-The χ^2-test (or likelihood ratio =LLR) was used as a non-parametric test of significance for comparison between the distribution of two qualitative variables.

3-The Spearman's rank correlation coefficient (r) was used as a non-parametric measure of the mutual relationship between two not-normally distributed quantitative or ordinal variables.

A 5% level is chosen as a level of significance in all statistical significance tests used.

Results

There was no significant difference between patients and their matched healthy control subjects regarding age and gender differences ($p > 0.05$). 70% of patients were currently single or divorced compared to only 20% of the control group (Likelihood Ratio = 16.9 and $p=0.001$). 40% and 10% of the patients finished only primary and preparatory schools respectively compared to 40% and 35% of the controls who finished secondary schools or graduated from the university respectively (Likelihood Ratio = 26.8 and $p=0.000$). Also, 70% of patients were currently unemployed or retired compared to 60% of the controls who were working currently at senior level works (Likelihood Ratio = 22.9 and $p=0.000$).

Fractional Anisotropy of the corpus callosum

By comparing Fractional Anisotropy (F.A.) in both the genu and splenium of the corpus callosum in both groups using t-test, we found that , F.A. of genu in schizophrenia group (0.552 ± 0.119) was significantly less than F.A. in controls (0.641 ± 0.075) (t = 2.8 and $p=0.008$) and that F.A. of splenium in schizophrenia group (0.596 ± 0.102) was significantly less than F.A. in controls (0.778 ± 0.030) (t = 7.9 and $p=0.000$)(Figure 3).

Table (2) demonstrates the correlation between F.A. (in both genu and splenium) with duration of illness; total score of Brief Psychiatric Rating Scale (B.P.R.S.) and subscores of items of B.P.R.S. in patients group. No significant correlations were found between all of these variables ($p > 0.05$).

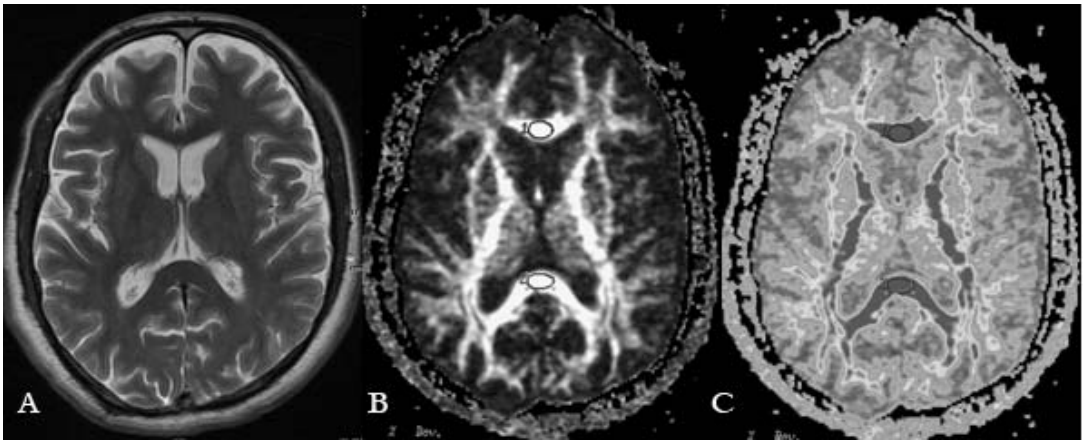

Figure (1): Normal control subject Male 39ys. old; (A) Ax T2w image at the level showing maximum thickness of corpus callosum at genu anterior and splenium posterior, (BandC) are fractional anisotropy maps (FA maps) in gray (A) and colour (B) scales where white matter is white and red in the coloured image ROI is seen placed at mid part of genu and splenium measuring FA values.

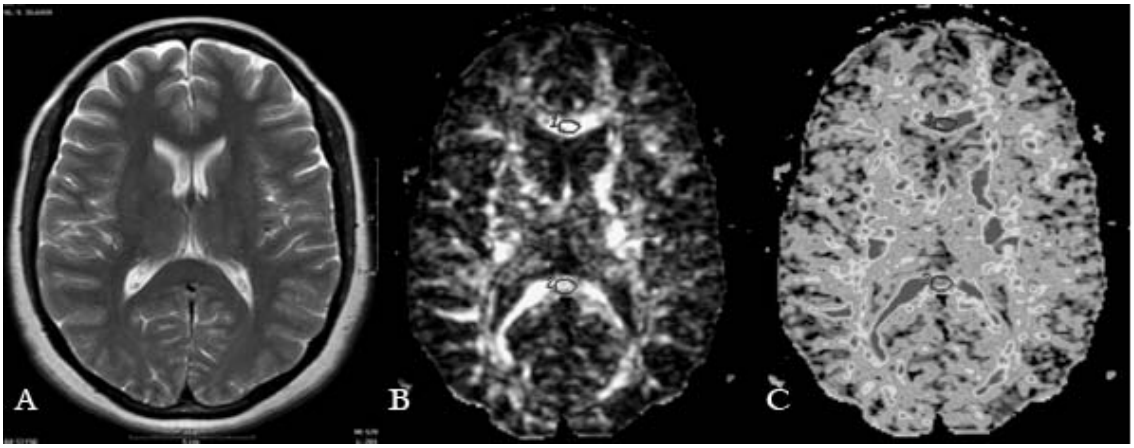

Figure (2): Male 37ys. old patient with schizophrenia; (A) Ax T2w image at the level showing maximum thickness of corpus callosum at genu anterior and splenium posterior and no abnormality, (BandC) are fractional anisotropy maps (FA maps) in gray (A) and colour (B) scales showing the thinned out white matter tracts and the ROI seen at mid part genu and splenium measure the FA values.

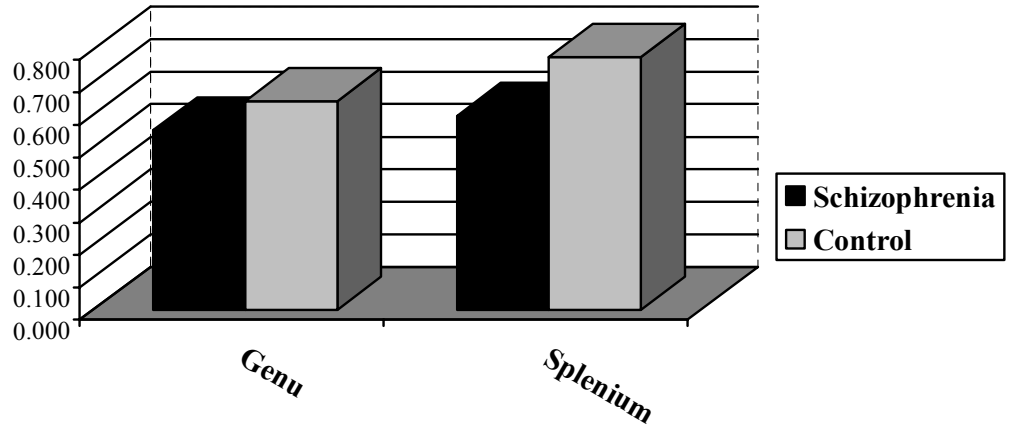

Figure (3): Comparison between F.A.* in genu and splenium in both groups

* F.A. = Fractional Anisotropy (dimensionless units)

Correlating F.A. with age and gender differences in both groups

Using Spearman's rho test, there were no significant statistical correlations between age and F.A. of genu or splenium in both studied groups ($p > 0.05$). As shown in table (1), there were no significant statistical differences between males and females of each group regarding F.A. in genu and splenium ($p > 0.05$).

Table (1):- Correlation between gender and F.A. in genu and splenium in each group

F.A.	Schizophrenia group				Control group			
	Male (n=12)	Female (n=8)	t	*p*	Male (n=12)	Female (n=8)	t	*p*
Genu	0.546 ± 0.139	0.568 ± 0.364	.44	*0.67*	0.653 ± 0.074	0.613 ± 0.069	1.23	*0.23*
Splenium	0.578 ± 0.114	0.596 ± 0.070	.40	*.69*	0.772 ± 0.026	0.745 ± 0.030	1.52	*0.19*

F.A. = Fractional Anisotropy (dimensionless units)

t = t-value (Independent sample t-test)

Correlation is significant at the 0.05 level (p value)

Correlating F.A. with clinical findings in patient group

Table (2):- Correlation between genu and splenium F.A. with clinical findings

Clinical variables	Genu F.A.		Splenium F.A.	
	r	*p*	r	*p*
Duration of illness(years)	0.583	0.57	0.230	0.82
B.P.R.S. score	0.168	0.48	0.076	0.75
Conceptual disorganization	0.733	0.000 **	0.218	0.36
Hostility	0.580	0.02 *	0.804	0.000 **
Suspiciousness	0.696	0.01 *	0.777	0.000 **
Hallucinatory behaviour	0.624	0.003 *	0.700	0.002 *
Emotional withdrawal	- 0.631	0.003 *	- 0.429	0.09
Blunted affect	- 0.566	0.009 *	- 0.393	0.19
Motor retardation	- 0.620	0.004 *	- 0.369	0.06
Anxiety	0.291	0.21	0.582	0.02 *
Unusual thought content	0.706	0.001 **	0.242	0.30

F.A. = Fractional Anisotropy (dimensionless units)

r = r-value (Spearman's rho test)

* Correlation is significant at the 0.05 level (p value)

* * Correlation is significant at the 0.05 level (p value)

(-) = Negative correlation

N.B.:- Other symptoms of B.P.R.S. not included in the table, were found to have statistical insignificance when correlated with F.A.

By correlating all items of B.P.R.S. with F.A. in genu and splenium, the most evident significant correlations were as follows:-

- Out of 16 items of B.P.R.S. have significant correlations with genu F.A. The highest significance was for conceptual disorganization and unusual thought content.
- Only 4 items of B.P.R.S. showed significance when correlated to splenium F.A. The highest significance was for hostility and suspiciousness.
- Scores of emotional withdrawal; blunted affect and motor retardation had the only negative correlations with F.A. in both of genu and splenium.

Discussion

The present study examined whether there are regionally C.C. abnormalities in patients with schizophrenia compared to control subjects, and whether schizophrenia results in an aberration in age; gender or duration of illness related alterations in C.C. We applied current analysis techniques to fractional anisotropy maps obtained from D.T.I. data to test the hypothesis that these specific white matter tracts of C.C. would be disrupted in patients with schizophrenia due to structural disconnectivity of the illness. Such a disruption would manifest itself as a reduction in fractional anisotropy values in patients with schizophrenia compared with controls.

We found a statistical significant reduction of F.A. in genu of schizophrenic group compared to control group ($p = 0.008$) and a high significant statistical reduction of splenium of schizophrenic group compared to control group ($p= 0.000$). Our results are in agreement with previous researches which found the same reduction in F.A. in schizophrenia group in both the genu and splenium (Lim et al., 1999; Agartz et al., 2001 and Price et al., 2006). Others found the significant difference in patients with schizophrenia only in the genu (Kitamura et al., 2005 and Buchsbaum 2006) or only in the splenium (Foong et al., 2000 and Mitelman et al., 2006). While, other researchers did not find any statistical difference between F.A. in both groups (Steel et al., 2001 and Foong et al., 2002). Different methods in measuring F.A.; patient populations and difference in the numbers of the studied cases may explain these differences.

Our findings about the reduction in F.A. in the genu and the splenium suggest a disruption of axonal integrity likely to be related to the density or organization of fibers. It is possible that DTI changes may also reflect myelin abnormalities. However, Miranda et al., (1998) demonstrated similar F.A. values in partially myelinated or unmyelinated white matter structures in the infant brain compared with the fully myelinated adult brain indicating that the contribution of myelin abnormalities to changes in anisotropy may be less significant than that from axonal abnormalities.

From the results, it is evident that F.A. is less in genu than in splenium in both of the schizophrenia and control groups. The explanation for this finding may lie in the regional differences of the microscopic structure of the corpus callosum that are due to regional variations in normal development or regional variations in age-related effects. This finding may be an important clue regarding the organization of the corpus callosum, and it may help to explain the behavior of the corpus callosum in schizophrenia. Neeraj et al., (2002) conducted a D.T.I. study in forty two healthy individuals and they found the average values of the F.A. for the genu, body, and splenium of the corpus callosum were 0.400, 0.456, and 0.539, respectively. The differences between these values are statistically significant ($P < .01$). They

proposed that these anisotropic variations in the corpus callosum may be due to a combination of the following physical and geometric factors in splenium: 1) tighter packing of axons, 2) less permeable myelin sheaths, 3) fewer obliquely oriented axons, 4) altered radius of individual axons, and 5) the presence (or absence) of structures other than myelin sheaths within the splenium that restrict water diffusion as collagenous fibers.

Our finding regarding gender ; age; type of antipsychotics mainly used (typical or atypical) and duration of illness and their correlations to F.A. failed to predict the DTI changes in schizophrenic patients and in control group suggesting that these abnormalities are unlikely to be progressive although this would need to be confirmed by longitudinal studies. These findings may be due to the relatively small number of our sample. The same results were found also by Price et al., (2005).

By correlating the clinical findings of the patients (total score of Brief Psychiatric Rating Scale -B.P.R.S.- and subscores of the sixteen items of B.P.R.S.) with F.A. in both the genu and splenium to specify which symptoms are correlated significantly more to the genu and / or splenium. We found 8 and 4 symptoms out of 16 were significantly correlated to F.A. for the genu and splenium respectively (as shown in table 2). Other symptoms did not reach the statistical level of significance ($p > 0.05$). The most significant correlations for the genu were conceptual disorganization and unusual thought content and for the splenium were hostility and suspiciousness. It is to be noted that the main negative symptoms of B.P.R.S. namely blunted affect; emotional withdrawal and motor retardation were negatively correlated to F.A. in both the genu and splenium, reaching the significance level only for the genu.

It is well evidenced now that the main function of corpus callosum is to organize the transfer of information between the two homologous hemispheres. Anterior genu is responsible for connecting both prefrontal cortices involved in higher-order processing of motor control, planning, cognitive and executive functions. Lesions in prefrontal areas lead to some symptoms as change in personality; loss of inhibitions; poor judgment; apathy; indifference and poor abstraction. Body and isthmus of C.C. connects premotor; precentral; postcentral and posterior parietal areas on both sides of the brain. They are involved mainly in motor and sensory functions; cortical inhibitions of bladder and bowel; language and other skills like calculation and construction. While middle splenium connects bilateral temporal gyri (including the limbic system) which are involved in memory; learning and emotions (Lindsay et al., 1997).

So, the results of our study can be explained by either of two points of view. Firstly, Thomalla et al., (2004) found reduced F.A. in the anterior regions of C.C. in cocaine-dependant subjects and he supposed that this reduction is due to damage in prefrontal cortex. Their hypothesis is supported by an

earlier post mortem study which showed that the anterior corpus callosum exhibits Wallerian degeneration after injury to the inferior frontal and anterior inferior parietal regions of the brain (De Lacoste et al, 1985). So the degeneration of the white matter tracts is secondary to the cortical pathology. Following this hypothesis in interpretation of our results is less plausible because it necessitates the presence of bilateral pathology in many lobes of the brain at the same time to explain different symptomatology of schizophrenia group.

Second explanation is more powerful and instructive. Reduced F.A. in genu and splenium is due to reduced function ("hypoconnectivity" or "disconnection hypothesis") of the corpus callosum itself rather than damage to the prefrontal and temporal cortices. This hypothesis is supported by many histopathological studies which found the numbers of axonal fibers connecting the cortical regions across the C.C. to be smaller in schizophrenia which disrupt the connection in the cortical neurons or axons in focal areas in C.C. (Nasrallah et al., 1983; Casanova et al., 1989; Friston et al., 1998 and Diwadkar et al., 2001).

Other studies suggested region specific differences in fiber composition of C.C. association higher cortical regions (as prefrontal and temporal cortices) project via small axons (<2 mm in diameter) to the genu and splenium respectively. These axons found to be affected mainly in schizophrenia and lead to reduced F.A., while other visual; somatosensory; primary motor and sensory cortices project via large axons (>2 mm) to other areas of C.C. (Aboitz et al., 1992a and1992b). Hence, significant correlations between some symptoms as conceptual disorganization; unusual thought content; blunted affect; motor retardation and emotional withdrawal and other symptoms as hostility; suspiciousness and anxiety in our schizophrenic sample with F.A. of genu and splenium respectively are convenient.

It remains possible that DTI abnormalities may have been present in other regions of the corpus callosum and in other areas mainly prefrontal and temporal white matter in the brain which need more sophisticated techniques. Therefore, our findings in this study suggest the structural disconnectivity hypothesis in schizophrenia but certainly do not exclude the possibility of abnormalities in other regions of white matter.

Conclusion

DTI of water molecules within the human brain may provide valuable in vivo tool in examining the previously unknown clues to the microstructure of white-matter tracts in schizophrenia. The significant reductions of F.A. in genu and splenium of the C.C. and the statistical correlations of F.A. with synonymous clinical symptoms in patients group reflect degradation of myelinated fibers in the C.C. and suggest structural disconnectivity hypothesis of schizophrenia.

Limitation of the study

However, there are some methodological limitations in this study:

1- Relatively small number of patients.

2- F.A. was assessed only in genu and splenium of the C.C. No other areas of the white matter were studied.

Future researches

1- To study the connectivity hypothesis in schizophrenia by using more advanced techniques like tractography and the planar model which describes the spread of heterogeneous fibers in term of planar architecture other than uniaxial model.

2- D.T.I. of other white matter tracts as arcuate fasciculus; uncinate fasciculus; U shaped fibers; longitudinal fascicule; cingulated fascicule and long associative fibers will throw more light on the nature of connection pathology in schizophrenia.

3- Combining DTI with neuro-physiological tests of inter-hemispheric processing.

References

Aboitz F; Scheibel AB and Fisher RS. (1992b): Individual differences in brain asymmetries and fiber composition in the human corpus callosum. Brain Res; 598:154–61.

Aboitz F, Scheibel AB, Fisher RS, et al. (1992a): Fiber composition of the human corpus callosum. Brain Res; 598:143–53.

Agartz I, Andersson JLR, Skare S. (2001): Abnormal white mater in schizophrenia a diffusion tensor imaging study. Neuroreport; 12:2251–4.

Andreas M., Jean-Baptiste P., Philip D., John L. et al. (2001): Evidence for Abnormal Cortical Functional Connectivity during Working Memory in Schizophrenia. Am J Psychiatry 158:1809-1817, November

Basser, P. J. and Pierpaoli,C. (1998): A simplified method to measure the diffusion tensor from seven MR images. Magnetic Resonance Medicine, 39, 928-934.

Basser, P. J. (1995): Inferring microstructural features and the physiological state of tissues from diffusion weighted images. NMR in Biomedicine, 8, 333-344.

Biegon A, Eberling JL, and Richardson BC, et al. (1994): Human corpus callosum in aging and Alzheimer's disease: a magnetic resonance imaging study. Neurobiol. Aging; 15:393–397

Bleuler E (1911): Dementia Praecox or the Group of Schizophrenias. Translated by Zinkin J. New York, International Universities Press, 1950

Buchsbaum MS, Friedman J, Buchsbaum BR et al., (2006): D.T.I in schizophrenia. Biol Psychiatry. Dec 1; 60(11):1181-7.

Burns J, Job D., Bastin M. E. et al., (2003): Structural disconnectivity in schizophrenia: a diffusion tensor magnetic resonance imaging study. Br. J. Of Psych., 182, 439 – 443

Casanova MF, Sanders RD, Goldberg TE, Bigelow LB, Christison G, Torrey EF and Weinberger DR (1990): Morphometry of the corpus callosum in monozygotic twins discordant for schizophrenia: a magnetic resonance imaging study. J Neurol Neurosurg Psychiat 53:416–421.

Casanova MF, Zito M, Bigelow LB, et al. (1989): Axonal counts of the corpus callosum of schizophrenic patients. J Neuropsychiatry Clin Neurosci; 1:391–93.

Coger RW and Serafetinides EA (1990): Schizophrenia, corpus callosum, and interhemispheric transfer: a review. Psychiat Res 34:163–184.

Crespo-Facorro B, Paradiso S, Andreasen NC, O'Leary DS, Watkins GL, Boles Ponto LL and Hichwa RD (1999): Recalling word lists reveals "cognitive dysmetria" in schizophrenia: a positron emission tomography study. Am J Psychiatry; 156:386–392

De Lacoste MC, Kirkpatrick JB, Ross ED (1985). Topography of the human corpus callosum. J Neuropathol Exp Neurol 44: 578–591.

DeQuardo JR, Bookstein FL, Green WD, Brunberg JA and Tandon R (1996): Spatial relationships of neuroanatomic landmarks in schizophrenia. Psychiat Res 61:81–95.

Diwadkar VA, Dick EL, Harenski KA, et al. (2001): Abnormalities in corpus callosum signal intensity in schizophrenia. Proceedings of the International Society for Magnetic Resonance in Medicine; 9:430.

Fabri M, Polonara G, Del Pesce M, Quattrini A, Salvolini U, Manzoni T (2001): Posterior corpus callosum and interhemispheric transfer of somatosensory information: an fMRI and neuropsychological study of a partially callosotomized patient. J Cogn. Neurosci. 13: 1071-1079.

First MB, Spitzer RL, Gibbon M, Williams JBW (1996): Structured Clinical Interview for DSM-IV Axis I Disorders For Patient Edition (SCID-I/P, Version 2.0), Biometrics Research Department, New York State Psychiatric Institute: New York.

Foong J, Maier M, Clark C A et al., (2000): Neuropathological abnormalities of the corpus callosum in schizophrenia: a diffusion tensor imaging study. J Neurol Neurosurg Psychiatry 2000; 68:242–244

Foong J, Symms MR, Barker GJ, et al. (2002): Investigating regional white matter in schizophrenia using diffusion tensor imaging. Neuroreport; 13:333–6.

Friston KJ (1999): Schizophrenia and the disconnection hypothesis. Acta Psychiatr. Scand. Suppl.; 395:68–79.

Friston KJ. (1998): The disconnection hypothesis. Schizophr Res; 30:115–25.

Ge Y, Law M, Johnson G, Herbert J, Babb JS et al., (2004): Preferential occult injury of corpus callosum in multiple sclerosis measured by diffusion tensor imaging. J. Magn. Reson. Imaging 20:1-7.

Goldberg D.(1972). The detection of psychiatric illness by questionnaire (GHQ).

Mandsley Monograph.21 London: Oxford University.

Gunther W, Petsch R, Steinberg R, Moser E, Streck P, Heller H, Kurtz G, Hippius H (1991): Brain dysfunction during motor activation and corpus callosum alterations in schizophrenia measured by cerebral blood flow and magnetic resonance imaging. Biol. Psychiat. 29:535–555.

Hasan KM, Alexander AL, Narayana PA (2004). Does fractional anisotropy have better noise immunity characteristics than relative anisotropy in diffusion tensor MRI? An analytical approach. Magn Reson Med 51: 413–417.

Head D, Buckner RL, Shimony JS, Williams LE, Akbudak E, Conturo TE, et al., (2004): Differential vulnerability of anterior white matter in non-demented aging with minimal acceleration in dementia of the Alzheimer type: evidence from diffusion tensor imaging. Cereb. Cortex 14:410-423.

Honey, GD, Bullmore, E.T. and Sharma, T. (2002): :De-coupling of cognitive performance and cerebral functional response during working memory in schizophrenia. Schizophrenia Research, 53, 45-56.

Huisman TA (2003): Diffusion-weighted imaging: basic concepts and application in cerebral stroke and head trauma. Eur Radiol 13:2283-2297.

Jacobsen LK, Giedd JN, Rajapakse JC, Hamberger SD, Vaituzis AC, Frazier JA, Lenane MC, Rapoport JL (1997): Quantitative magnetic resonance imaging of the corpus callosum in childhood onset schizophrenia. Psychiat. Res. 68:77–86.

Jäncke L, Staiger JF, Schlaug G, Huang Y, Steinmetz H (1997): The relationship between corpus callosum size and forebrain volume. Cereb. Cortex 7:48–56.

Kitamura H, Matsuzawa H, Shioiri T, et al., (2005): Diffusion tensor analysis in chronic schizophrenia. A preliminary study on a high-field (3.0T) system. Eur Arch Psych. Clin Neurosci. Oct; 255(5):313-8.

Lansberg MG; Thijs VN; O'Brien MW; Ali JO, et al., (2001): Evolution of apparent diffusion coefficient, diffusion-weighted and T2-weighted signal intensity of acute stroke. AJNR Am J Neuroradiol. 22:637-644.

Lee KH, Williams LM, Breakspear M, and Gordon E: Synchronous gamma activity (2003): a review and contribution to an integrative neuroscience model of schizophrenia. Brain Res Brain Res Rev.; 41:57–78

Lim KO, Hedehus M, Moseley M, et al. (1999): Compromised white matter tract integrity in schizophrenia inferred from diffusion tensor imaging. Arch Gen Psychiatry; 56:367–74.

Lindsay K; Bone I and Callander R (1997): Neurology and neurosurgery illustratrated. 3rd edition.Churchil Livingstone. 105 – 113.

Matthew B., Anthony W., Evian G. and Leanne M. (2005): "Gamma Synchrony" in First-Episode Schizophrenia: A Disorder of

Temporal Connectivity? Am J Psychiatry 162:459-465, March.

Mette R.; Henrik B and Larssonand M.; Van J. (2000): Fiber Crossing in Human Brain

Miranda MJ, Born P, Wiegell MR. (1998): White matter tract visualization in infants by diffusion tensor MRI. 528.

Mitelman SA, Torosjan Y, Newmark RE et al., (2006) : Internal capsule, corpus callosum and long associative fibers in good and poor outcome schizophrenia: A diffusion tensor imaging survey. : Schizophr Res. , Dec. (for publication) (abstr.).

Nasrallah HA, Andreasen NC, Coffman JA, Olson SC, et al., (1986): A controlled magnetic resonance imaging study of corpus callosum thickness in schizophrenia. Biol. Psychiat. 21:3:274–282.

Nasrallah HA, McCalley-Whitters M, Bigelow LB, et al. (1983): A histological study of the corpus callosum in chronic schizophrenia. Psychiatry Res; 8:251–60.

Neeraj B. C, Yi-Fen Y, Jonathan H. et al., (2002): Diffusion Anisotropy in the Corpus Callosum. Am J Neuroradiol 23:803–808, May.

Njiokiktjien C, de Donneville Land Vaal J (1994): Callosal size in children with learning disabilities. Behav Brain Res 64:213–218.

O'Sullivan M; Jones DK; Summers PE; Morris RG; Williams SCand Markus HS (2001): Evidence for cortical 'disconnection' as a mechanism of age related cognitive decline. Neurology 57:632-638.

Overall JE and Gorham DR. (1962): The Brief Psychiatric Rating Scale. Psychol Rep. ; 10:779–82.

Pfefferbaum Aand Sullivan EV (2003): Increased brain white matter diffusivity in normal adult aging: relationship to anisotropy and partial voluming. Magn. Reson. Med. 49:953-961.

Pfefferbaum Aand Sullivan EV (2004): Disruption of brain white matter microstructure by excessive intracellular and extracellular fluid in alcoholism: evidence from diffusion tensor imaging. Neuropsychopharmacol.

Pfefferbaum A, Adalsteinsson E, Sullivan EV (2003): Replicability of diffusion tensor imaging measurements of fractional anisotropy and trace in brain. J. Magn. Reson. Imaging, 18:427-433.

Pfefferbaum A, Sullivan EV, et al., (2005): Corpus Callosal Microstructural Integrity Influences Interhemispheric Processing: A Diffusion Tensor Imaging Study. Cerebral Cortex September; 15:1384-1392.

Price G, Bagary M.S., Cercignani M., Altmann D.R., Ron M.A. (2005): The corpus callosum in first episode schizophrenia: a diffusion tensor imaging study. J. Neurol. Neurosurg. Psychiatry; 76:585–587

Price G, Cercignani M, Parker GJ, et al., (2006): Abnormal brain connectivity in first episode psychosis: a diffusion MRI

tractography study of the corpus callusum. Neuroimage: Dec. (for publication) (abstr.).

Rauch RA and Jinkins JR (1994): Analysis of cross-sectional area measurements of the corpus callosum adjusted for brain size in male and female subjects from childhood to adulthood. Behav Brain Res 64:65–78.

Steel RM, Bastin ME, McConnell S, et al., (2001): Diffusion tensor imaging (DTI) and proton magnetic resonance spectroscopy (1H MRS) in schizophrenic subjects and controls. Psychiatry Res; 106:161–70.

Taber KH, Pierpaoli C, Rose SE, Rugg-Gunn FJ, Chalk JB, Jones DK et al (2002). The future for diffusion tensor imaging in neuro-psychiatry. J Neuro-psychiatry Clin Neurosci 14: 1–5.

Thomalla G, Glauche V, Koch MA, Beaulieu C, Weiller C, Rother J (2004). Diffusion tensor imaging detects early Wallerian degeneration of the pyramidal tract after ischemic stroke. Neuroimage 22: 1767–1774.

Uematsu M, Kaiya H (1988): The morphology of the corpus callosum in schizophrenia: a MRI study. Schizophr Res 1:391–398.

Witelson SF (1989): Hand and sex differences in the isthmus and genu of the human corpus callosum. Brain; 112:799–835.

Woodruff P, McManus IC and David AS (1995): Meta-analysis of corpus callosum size in schizophrenia. J Neurol Neurosurg Psychiat 58:457–461.

Woodruff PWR, Pearlson GD, Geer MJ, Barta PE, Chilcoat HD (1993): A computerized imaging study of corpus callosum morphology in schizophrenia. Psychol Med 23:45–56.

Yamauchi H, Fukuyama H, Nagahama Y, Katsumi Y, Dong Y, Konishi J, Kimura J (1997): Atrophy of the corpus callosum, cognitive impairment, and cortical hypometabolism fin progressive supranuclear palsy. Ann Neurol 41:606-614.

الـدليل التشخيصـي والإحصـائي الرابـع للاضـطرابات النفسية_ المعايير التشخيصية، الرابطية الأمريكية للطب النفسي، ترجمة د. أمينة السماك، مدرس علم النفس، كلية العلوم الاجتماعية، الكويت، ود. عادل مصطفى محمد اخصائي الأمراض النفسية، مستشفى الطب النفسي ، الكويت،مكتبة المنار الإسلامية، الكويت،(٢٠٠١) .

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عسر الأتصال التركيبي في الفصام: دراسة بإستخدام تصوير الأنتشار المتوتر

يعتبرالجسم المتصلب هو أهم المسالك ذات المادة البيضاء التي تربط المناطق المتشابهه بين فصي من الانسان. والخلل في هذا الجسم يؤدي الي العديد من العجز في الإحساس والقدرات المعرفية. تصويرالأنتشار المتوتر هو من أحدث الوسائل التي تمكننا من دراسة البنية بالدقة الصحيحة لتكامل المادة البيضاء عن طريق قياس إتجاهات حركة جزيئات الماء بالمي أثناء الحياة. ومن أهم المؤشرات التي تستخدم في هذا القياس هو الأنيزوتروب الجزيئي. دراسة الأنيزوتروب الجزيئي في أجزاء من الجسم المتصلب عند عينة من مرضي الفصام ومجموعة من الأصحاء كعينة ضابطة وذلك لإختبار فرضية عسر الأتصال التركيبي في الفصام.تمت دراسة الأنيزوتروب الجزيئي في أجزاء من الجسم المتصلب في ٢٠ من المرضي الذين يعانون مرض الفصام. وتم تشخيص الحالات عن طريق المقابلة المقننة للتقسيم الأمريكي الرابع للأمراض النفسية .

أختير عدد ٢٠ فرد من أناس لا يعانون أي أمراض أو أعراض نفسية حالية بعد خضوعهم إلى إختبار مقياس الصحة العامة كعينة ضابطة . - تم دراسة بعض العوامل الشخصية والإكلينيكية المختلفة ومدى إرتباطها وعلاقتها بالأنيزوتروب الجزيئي . وجد أن إنخفاض الأنيزوتروب الجزيئي لأجزاء مختلفة من الجسم المتصلب في مرضي الفصام قد إنخفض بدرجة إحصائية واضحة عن الأفراد بالعينة الضابطة . كما أن هناك إرتباطا إحصائيا هاما بين إنخفاض الأنيزوتروب الجزيئي في هذة الأجزاء المختلفة وبين الأعراض الإكلينيكية المختلفة في مرضي الفصام. تصويرالانتشار المتوتر لحركة جزيئات الماء بالمي هو من أحدث التقنيات الفريدة والتي يمكن أن تمدنا بمعلومات بالدقة عن حالة المسالك ذات المادة البيضاء في مرضي الفصام والتي كان لايمكن الوصول إليها عن طريق تقنيات التصوير المعتادة.

- نتائجنا أكدت فرضية عسر الأتصال التركيبي في الفصام. نحتاج إلى رؤية أكثر وضوحا لتأثير الذهان على الأنيزوتروب الجزيئي في المسالك ذات المادة البيضاء الأخري بالمي وإرتباطها بالقدرات المعرفية للمرضي وبحجم عينة أكبر من المرضي .