The Prevalence of Cavum Septum Pellucidum in Brain Imaging of Mental Health Referrals in a South African Population

Dr Kathleen Louise Jacobs

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Diagnostic Radiology.

Johannesburg, 2015

Declaration

I, Kathleen Louise Jacobs, declare that this research report is my own work. It is being submitted for the degree of Mmed (RadD) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

DR KATHLEEN LOUISE JACOBS

On this 31st day of October 2015.

To my husband, Rudolf.

Publications and presentations

This work has never been published.

It has never been presented at a congress.

Abstract

INTRODUCTION:

The cerebral anomaly of a cavum septum pellucidum (CSP) has been the subject of controversy in neuroimaging since the hallmark study by DeGreef in 1992. The association of CSP with schizophrenia and postulation of CSP as a marker of cerebral midline maldevelopment has been studied extensively with no consistent outcome. The storm of debate underlies the requirement for a reliable objective imaging marker as an organic cause of mental illness.

AIM:

This study aims to determine the prevalence of cavum septum pellucidum in mental health referrals in South Africa and determine the significance thereof.

METHOD:

This was a retrospective, observational study based at Baragwanath Hospital, including 114 mental health referrals and 114 controls, matched for age and sex. The CT scans of these patients' brains were anonymously reviewed by three independent radiologists/radiologists in training to determine the prevalence of CSP, and the length and width of CSP's, if present.

RESULTS:

There was no statistical significance in the difference in prevalence of CSP between the mental health referrals and controls. The anteroposterior length of CSP was not a statistically significant determinant of mental illness but an increased average axial width was a statistically significant measurement in the mental health referrals.

CONCLUSIONS:

The axial width of CSP is a statistically significant determinant of mental illness.

Acknowledgements

My heartfelt gratitude is expressed to my supervisors, Dr Tanusha Sewchuran, Prof Savvas Andronikou and Prof Yasmien Jeenah. I especially thank Tanusha who has rewritten and improved my thesis several times and been supportive throughout the process.

I extend my gratitude to the Wits Diagnostic Radiology Department which has been encouraging of this project; especially Professor Mngomezulu and Dr Su Lucas, who have accommodated research time and commitments, allowing this thesis to reach completion. The staff of Chris Hani Baragwanath Hospital, including Dr Hlabangana, the Head of the Radiology Department, who allowed me access to their PACS system and the use of multiple images for this study.

Thanks also to Petra Gaylard, who assisted with the statistical analysis of my results, and Noleen Gordon, who was always available to help with printing, delivering of documents and being a shoulder to cry on; also to the artist, Minette Eiselen, who designed an original diagram to demonstrate the anatomy of a CSP for this document.

Finally, my appreciation must be expressed to my family and husband, who were unwaveringly sympathetic and supportive.

Table of Contents

List of Tables

List of Figures

1. Literature review

1.1. Cavum Septum Pellucidum

1.1.1. Definition

The septum pellucidum is a component of the limbic system, composed of two laminae that fuse to form a thin plate, which separates the lateral ventricles in the midline (1, 2). The septum pellucidum functions as a connection between the hypothalamus and habenular commissure, hippocampus and amygdala, as well as reticular formation of the brainstem (3, 4).

Fusion of the two leaflets of the septum pellucidum occurs in 85% of individuals within 6 months of birth, most likely due to rapid growth of the hippocampus and corpus callosum (2, 5). If the laminae fail to fuse, a residual cavity remains, termed a cavum septum pellucidum (1, 2, 6, 7). A CSP has been postulated to serve as a marker of disturbed brain development (2, 5), and an unusually large CSP may reflect callosal and limbic abnormalities specifically (3).

1.1.2. Anatomy

The cavum septum pellucidum has the following boundaries:

- Anteriorly it extends to the genu of the corpus callosum.
- Superiorly it is bounded by the body of the corpus callosum.
- Inferiorly, the rostrum of the corpus and the anterior commissure form its borders.

- Posteriorly, the CSP extends into the anterior limb and pillars of the fornix (8, 9).
- Laterally the cavum is bounded by the two laminae of the septum pellucidum (9).

The diagrams below (10) demonstrates the morphology of a brain with a CSP, compared to a normal brain without a CSP.

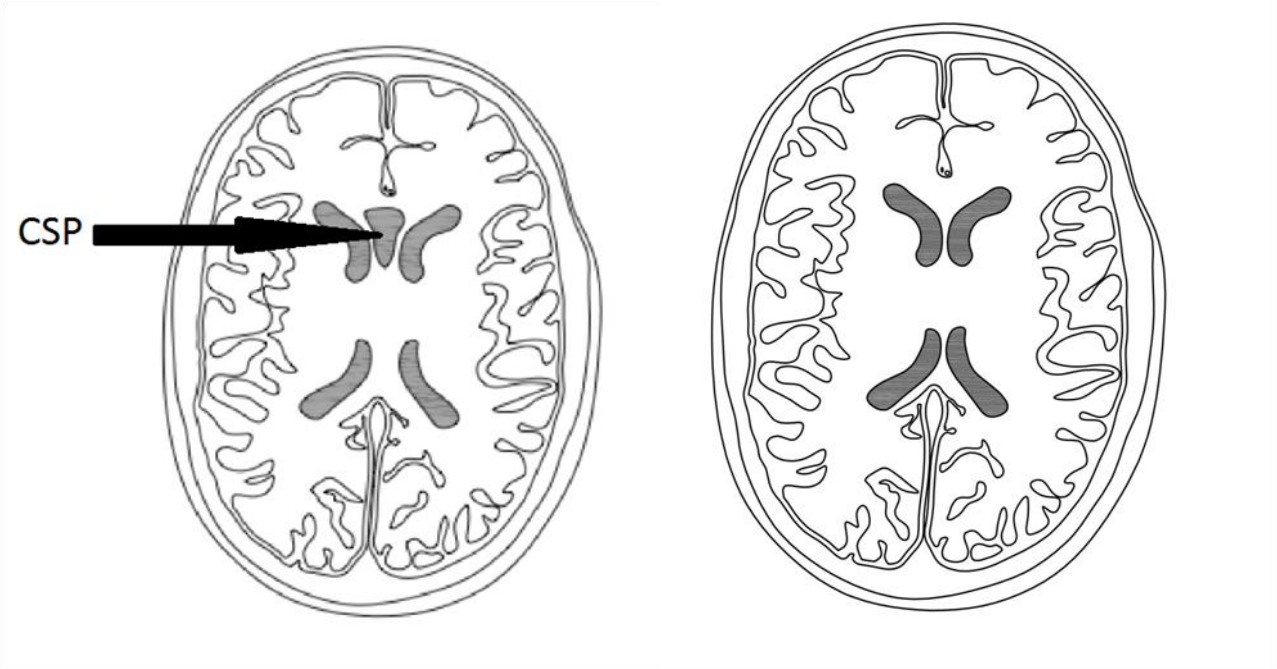

Figure 1.1. Diagram demonstrating axial views of a brain with and without a CSP, at the level of the frontal horns of the lateral ventricles
(10)
(Image by artist, Minette Eiselen; used with permission)

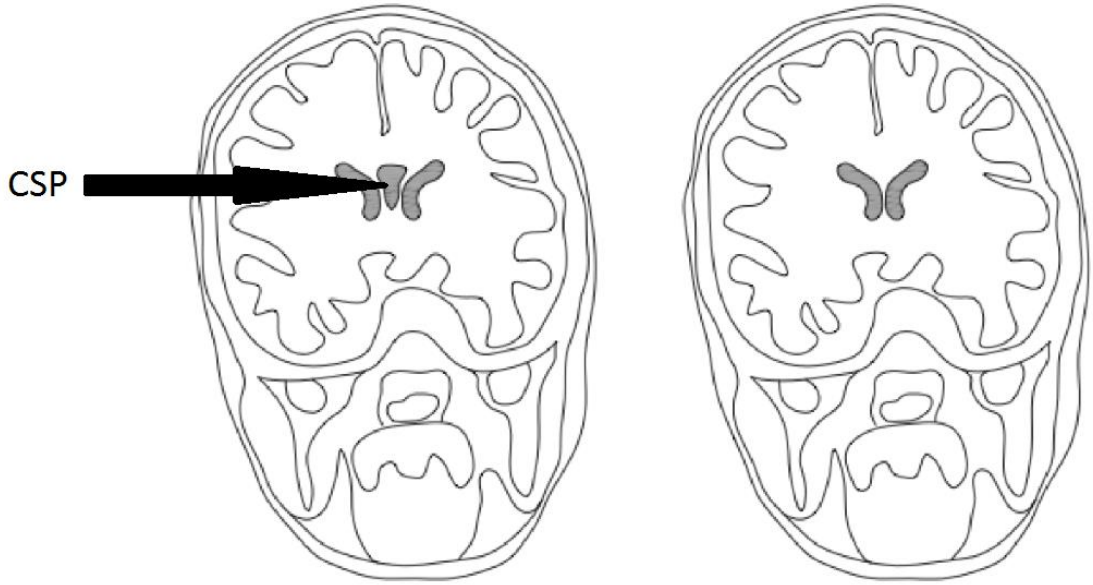

Figure 1.2. Diagram demonstrating coronal views of a brain with and without a CSP, at the level of the frontal horns of the lateral ventricles
(10)
(Image by artist, Minette Eiselen; used with permission)

The CSP is also referred to as "the fifth ventricle", as it is fluid-filled (11); however there is no connection to the ventricles (11, 12). In the sagittal and coronal planes, the CSP appears triangular with its base as the corpus callosum (8, 9).

The most extreme form of CSP occurs when there is a complete lack of fusion of the two septal laminae (13). This is referred to as a combined cavum septum pellucidum and cavum vergae (13).

1.1.3. Grading of CSP

Various grading scales are used for CSP (13). The most common method referenced in the literature involves measuring the anterior-to-posterior length of the cavum on consecutive coronal slices, and grading its length into the following categories:

- 1.5 – 4.4 mm: variant
- 4.5 – 5.9 mm: borderline
- >6mm: enlarged (3, 11, 14, 15), as demonstrated on the selected pre-contrast axial and coronal slices of a CT Brain below.

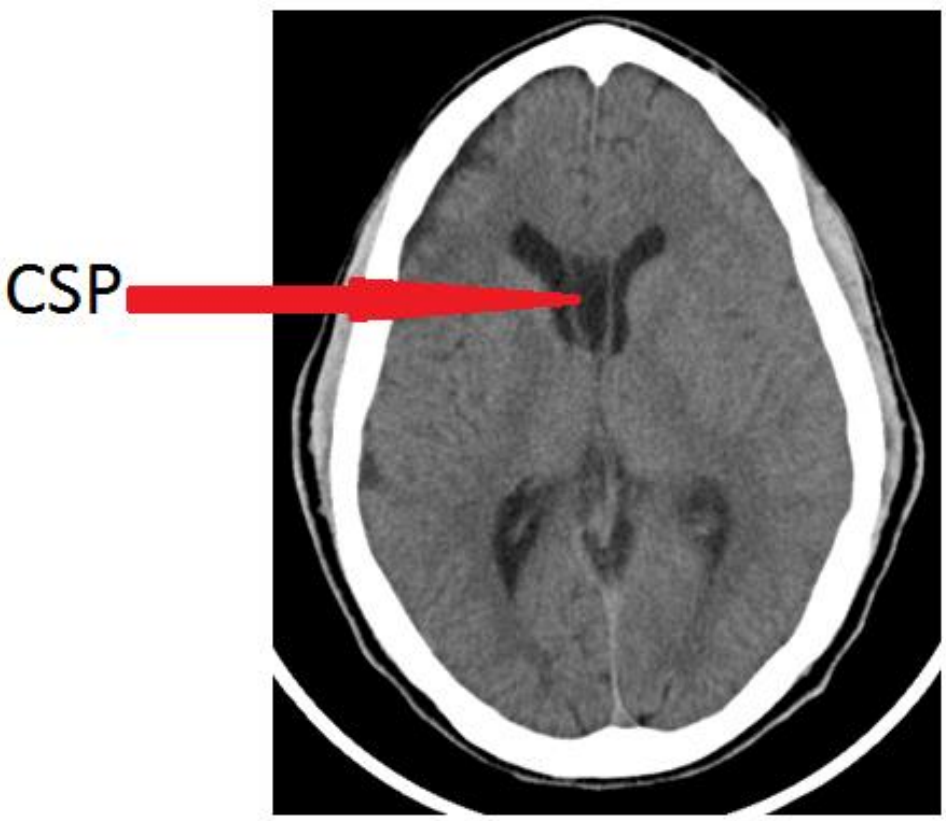

Figure 1.3. Enlarged CSP (axial slice of a pre-contrast CT scan of the brain at the level of the frontal horns of the lateral ventricles)
(16)
(Source: Chris Hani Baragwanath PACS System; used with permission)

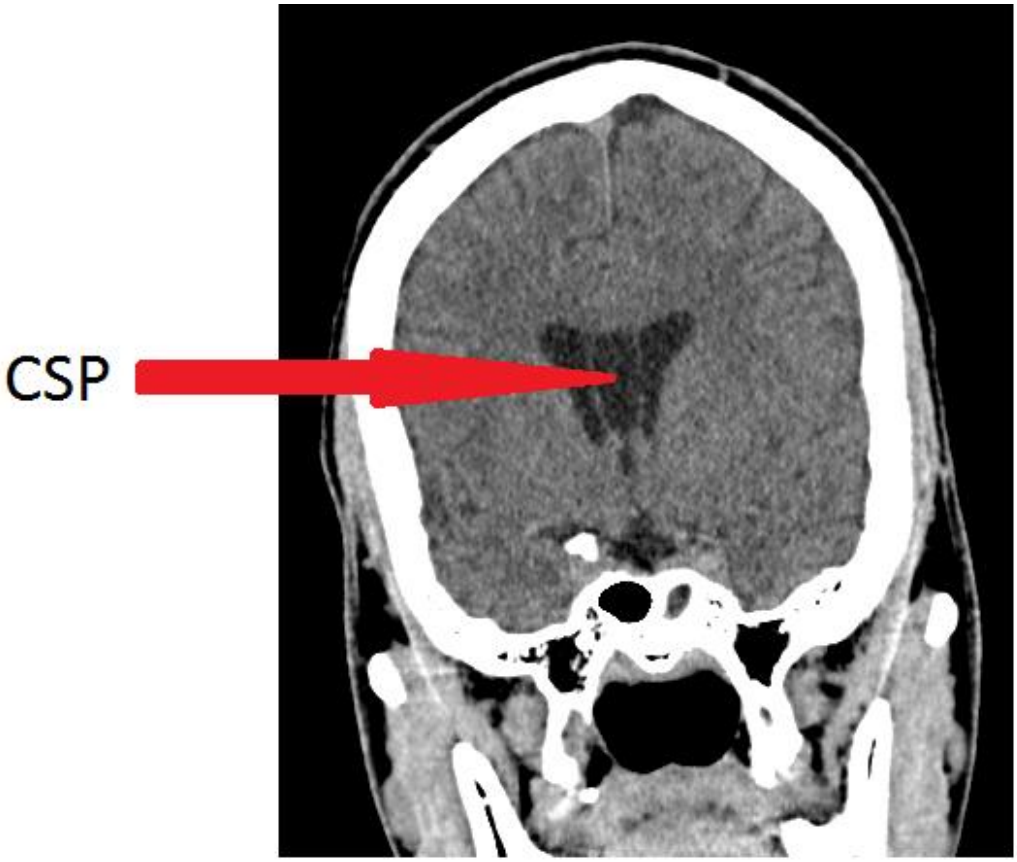

Figure 1.4. Enlarged CSP (coronal slice of a pre-contrast CT scan of the brain at the level of the frontal horns of the lateral ventricles)
(16)
(Source: Chris Hani Baragwanath PACS System; used with permission)

Due to the lentiform contour of a CSP, it cannot be visualised completely on a single axial slice. Mitigating factors for possible inaccuracy include partial voluming and slice thickness, where the latter is specific for MRI (2, 30).

1.1.4. Technique of imaging and measurement of CSP

There is a wide variation in the techniques used for imaging and measurement of CSP (13). The reported prevalence varies between 0.1% and 85% depending on the method of identification (11), which includes the use of CT and MRI, as well as pneumoencephalography (PEG) and post-mortem examination (11). PEG sequences demonstrate the lowest sensitivity for the evaluation of CSP, while post-mortem studies have the highest sensitivity overall (4, 11). The increase in prevalence of CSP in autopsied specimens is theorised to be due to the swelling of the post-mortem septum pellucidum which consequently separates into its constituent leaflets and fills with fluid , as well as the higher spatial resolution of histology specimens (17).

Most of the MRI studies in the literature make use of a 1.5 Tesla MRI scanner (13, 18). Various sequences are used, namely:

- 3D spoiled GRE steady-state imaging, with axial, sagittal and coronal reconstructions (14, 18);
- 3D T1 GRE FLASH with 1mm coronal reconstructions (3).

There is also a great variation in the slice thickness utilized, ranging from 0.94 mm to 5 mm (13). Thick slice studies exhibit a lower yield because the resultant voxel dimensions exceed the CSP dimensions, causing a partial volume artefact, thus decreasing sensitivity of CSP detection and accuracy of measurement (19). Consequently thin slice MRI has a higher sensitivity for imaging evaluation of CSP (11).

MRI data can be obtained as a 3D data set and resampled in 1 mm slices. The coronal, sagittal and axial planes are inspected simultaneously to allow for a thorough examination and identification of CSP (3, 14, 18).

A quantitative measurement technique has been adopted whereby the antero-posterior length of the CSP is measured by counting the coronal views (with no gaps) on which it appears (3, 13, 18). The number of slices is then multiplied by their thickness to calculate the size of the CSP. This is the most sensitive and reliable method of classifying CSP (18), due to the distinctive sickle-shape of a CSP.

Neuroimaging with CT scan has higher spatial resolution, albeit lower contrast resolution than MR-imaging (20). It is also the neuroimaging modality primarily used in the South African context due to its availability (21). Although CT imaging has not been used in studies in the literature review, it is the ideal imaging modality for visualising a small structure with high intrinsic contrast resolution, such as a CSP (20).

1.1.5. Causes and Prevalence of CSP

The prevalence of CSP is controversial. A wide range has been reported, dependant on the method of identification, the criteria for CSP characterization and the population sampled (1). The inability to define an accurate prevalence has resulted in further uncertainty regarding the significance of a CSP (9).

The literature does support an increased prevalence of CSP in the following populations:

- Males (9, 11)

- Professional boxers: postulated to be secondary to acceleration-deceleration forces causing detachment of the fornix with consequential splaying of the forniceal bodies (8)
- Psychiatric disorders (6, 13, 18)

1.2. CSP and Psychiatry

1.2.1. Diagnosis of Psychiatric Disorders

The basis of psychiatric diagnosis hinges on clinical manifestations of mental illness and the categorisation of these symptoms using the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (22). According to the DSM-IVR, the differentiation between normality and pathology can present a diagnostic challenge, hence the conceptualization of the DSM criteria to provide objectivity regarding psychiatric illness (23). Each mental illness is a "clinically significant behavioural or psychological syndrome or pattern" that results in "present distress... or disability.... or with a significantly increased risk of suffering death, pain, disability or an important loss of freedom" (23).

The controversial, newly published DSM V (24) demonstrates subtle changes regarding the diagnosis of schizophrenia (25). The crux of the diagnosis of schizophrenia includes positive symptoms, namely "delusions, hallucinations, disorganized thinking and behaviour", as well as negative symptoms (the absence of normal emotional function or behaviour) present over a continuous 6 month period, with one month of active symptoms (25, 26). The elimination of causative organic pathology has remained a diagnostic criterion (25).

Various medical conditions can masquerade as psychiatric pathology, as depicted by the table below. This table has been modified from Psychiatric emergencies (part III): psychiatric symptoms resulting from organic diseases (27).

Table 1.1. Organic Disease producing Psychiatric Symptoms

Disorder	Psychosis	Depression	Mania	Anxiety
Hypopituitarism	+	-	-	+
Hyperprolactinaemia	-	+	-	+
Hypothyroidism	+	+	+	+
Hyperthyroidism	+	+	+	+
Addison's disease	+	+	-	-
Cushing's disease	+	+	-	+
Phaeochromocytoma	-	-	-	-
Fluids and electrolyte disorders	+	+	-	+
Wernicke-Korsakoff	+	+	+	+
EDH, SDH	+	+	+	+
Cerebral contusion, haematoma	+	+	+	+

Disorder	Psychosis	Depression	Mania	Anxiety
TIA	-	+	-	+
Stroke	+	+	+	+
Meningitis, encephalitis	+	+	+	+
Neurosyphilis	+	+	+	+
Degenerative brain disease	+	+	+	+
Epilepsy	+	+	+	+

The exclusion of organic pathology during psychiatric work-up requires the investigating physician to take a detailed history, perform a mental state examination as well as a physical examination, and request appropriate investigations (28). Brain imaging with CT or MRI may be performed, if clinically indicated (28).

1.2.2. CSP and Psychiatric Disorders

The cavum septum pellucidum (CSP) has been postulated to be a potential marker of brain maldevelopment (especially midline abnormalities and limbic system dysgenesis) and has been linked with multiple psychiatric disorders (6, 9, 18). A small CSP is

considered a normal variant; however an enlarged CSP may be related to schizophrenia (1, 9) amongst other disorders listed below:

- Schizotypal personality disorder (6)
- Bipolar disorder (6, 29)
- Tourette's Syndrome (6, 7)
- Obsessive-Compulsive Disorder (6)
- Mental retardation (14, 30, 31)
- Developmental delay (14, 31)
- Seizures (14, 31)
- Macro/microcephaly (14, 31)
- The use of illicit drugs, particularly adolescent-onset opiate use (32)
- Apert's Syndrome (18)
- Antisocial personality disorder (33)
- Psychopathy (33)
- Fetal alcohol syndrome (13)

1.2.3. CSP and Schizophrenia

Within the schizophrenic population, an enlarged CSP has been associated with poor verbal learning and memory (14, 31), as well as more severe thought disturbances (5). An increase in CSP length correlated positively with an increase in negative symptoms and poorer comprehension of sentences (31).

Several studies have associated CSP with specific subcategories of the schizophrenic population:

- Women (12)
- Chronic patients (15, 17)
- First episode psychotics (5, 34)
- Childhood-onset schizophrenics (18)
- Poor prognosis schizophrenics with a history of long-term institutionalization (5, 30, 31)
- An increased rate of successful suicide, especially hanging (35)
- A family history of psychosis (13).

Despite this extensive amount of information regarding CSP in schizophrenia, several questions remain:

- What is the role of antipsychotic medication in the structural changes that take place in the psychotic brain (13)?

- Does disease progression influence these morphological abnormalities (36)?

1.2.4. Aetiology of Schizophrenia

Schizophrenia is a debilitating psychiatric disease (25), affecting 1% of the population worldwide (37). Despite this, its aetiology remains complex and controversial (38). An interaction between genetic and environmental factors is currently accepted, whereby multiple DNA loci and contextual factors interact to increase vulnerability the development of schizophrenia (3, 37, 38).

Several environmental elements have been implicated in the multifactorial pathogenesis of schizophrenia. These include: perinatal complications, malnutrition, intrauterine infections (1, 25), childhood trauma and sexual abuse (39). The incidence of schizophrenia has also been shown to be higher in those raised in an urban setting and among minority ethnicities (25). The use of Marijuana is also considered an important aetiological component (37) and has been recognised to double the risk of psychosis (39).

The complex genetic factors involved in an individual's susceptibility to psychosis are considered to be interactive and confer an increased risk of psychosis without being causative independently (37). They may be divided into direct and indirect factors, referring to genetic endophenotype and a family history of the disease respectively (39). Currently the most accurate indicator of a future diagnosis of schizophrenia or bipolar mood disorder is a family history of the disorder, although the exact genetic origins remain unknown (37). The catechol-O-methyl-transferase gene has been linked to an increased susceptibility to schizophrenia (39), as well as other hereditary structural lesions, which are contributory in familial schizophrenia (37).

The neurodevelopmental model of schizophrenia is prominently featured in the literature, where it has been postulated that brain dysgenesis interacts with normal neurodevelopment over a protracted period to result in psychosis (38, 39). Nopoulos et al. in 1998 suggested that the more severe the neurodevelopmental aberrations, the younger the age of onset of schizophrenia (18). Evidence for the neurodevelopmental hypothesis is provided in several categories (5):

- Aetiological: perinatal complications, viral infections of the pregnant mother

- Phenotypic: cognitive, behavioural, kinetic, physical pathology pre-psychosis
- Structural neuropathology: gray matter heterotopias, cavum septum pellucidum (5, 15, 17).

The controversy still remains whether schizophrenia is the result of a physical or physiological anomaly (12), though the most likely explanation is a complex interaction of deranged structure and dysfunction, neither of which would be sufficient to cause disease in isolation (37).

1.2.5. Structural Correlates of Schizophrenia

Numerous structural anomalies have been associated with schizophrenia through imaging and post-mortem studies (12, 17), although whether they are causative or a consequence of the disease remains unclear (15). In keeping with the neurodevelopmental theory, a marker of distorted neurodevelopment (though not necessarily the underlying cause) should be evident (15) from birth (18).

Brain abnormalities associated with schizophrenia in the literature are mainly of limbic and midline origin (5), including:

- Cavum septum pellucidum, especially the enlarged variant which may act as a marker for limbic system or midline abnormalities (2, 15, 17, 18),
- Corpus callosum agenesis/ dysgenesis (9, 15, 18),
- Gray matter heterotopia (9, 18),
- Interruptions of the cingulate sulcus (2) with decreased neuronal density (12),
- Poorly-defined paracingulate sulcus in the left hemisphere (2),

- Asymmetrical lateral ventricles (2),
- Generalised atrophy (2),
- Disorganised pyramidal cells of the hippocampus (9, 12),
- Decreased volume of the white matter in the parahippocampal region (3, 12),
- Decreased volume of amygdala and hippocampus (3, 12), as well as hippocampal gliosis (12) which appears more significant in male schizophrenics (4),
- Cerebellar pathology (14),
- Decreased gray matter volume (13),
- Increased third and lateral ventricular volume (9, 13, 17, 38),
- Arachnoid cysts (13),
- Absence of the interthalamic adhesion, which interestingly has been associated with more severe negative symptoms, longer illness duration and higher antipsychotic dosages (38),
- Gray matter volume loss (13).

Hippocampal and parahippocampal abnormalities are associated with a higher prevalence of positive symptoms in schizophrenia. As such, neurodevelopmental anomalies in this region are considered a possible cause for the positive symptoms of psychosis (5).

1.2.6. Schizophrenia in South Africa

The diverse South African population has a prevalence of schizophrenia similar to the reported international prevalence of between 0.3 (25) and 1% (40). 90% of untreated schizophrenics reside in developing countries (41), such as South Africa. Our indigenous

epidemiology is quite unique in that the South African Afrikaans community has been identified as a founder population with a genetically identifiable aetiology of the disease (37, 42). There is a lack of data regarding Black South Africans (43).

Afrikaners immigrated to South Africa from the Netherlands from 1652 onward, settling in the Cape. The 1000-2000 individuals formed small communities, which remained culturally, religiously and geographically isolated over the next 13-15 generations. The increase to the current population of 3 million occurred mainly through reproduction and consanguinity early on. The genetic isolation of the Afrikaners has resulted in a high incidence of rare Mendelian disorders, as well as a relatively homogeneous variance of associated alleles and the conservation of disease-related haplotypes (42, 44).

In 2004, Abecasis et al. traced the genotype of 98 Afrikaner individuals diagnosed with schizophrenia and traced 87 of them to a common founder ancestor (42).

An exogenous factor, which is influential in South Africa, is the use of marijuana. Cannabis is second only to alcohol as the commonest substance of abuse in South Africa (44). As mentioned previously, the use of cannabis doubles the risk of developing schizophrenia (39).

2. Aim

This study aims to determine the prevalence of cavum septum pellucidum in mental health referrals in South Africa and classify this according to mental health diagnosis.

3. Study Objectives

- to determine the prevalence of CSP in a population of mental health referrals as well as in a control population, and to compare the prevalence of CSP in the above-mentioned groups
- to compare diagnostic subcategories of mental health referrals with regards to prevalence of CSP

4. Methods

4.1. Research Paradigm

This was a retrospective, observational, cross-sectional study with a control population.

4.2. Sample

The study population consisted of mental health referrals presenting for CT Brain scans at Chris Hani Baragwanath Academic Hospital over four months. Our sample size was 228 patients in total, comprised of 114 mental health referrals and an equal number of trauma patients, matched for sex and age, as controls.

4.2.1. Inclusion Criteria

Adult patients (≥18 years of age) who presented for CT Brain scans as a referral from the psychiatry department with a history of psychiatric symptoms for investigation were included in the study. Referrals from the emergency department who underwent CT brain scans for minor trauma and had no radiological evidence of intracranial injury, were used as the controls. These patients were selected from consecutive trauma referral CT Brain

scans to match the mental health referrals for sex and age, and were referred during the same period as the study patients.

4.2.2. Exclusion Criteria

In order for the radiologists reading images for the study to remain blinded to the study cohort, control scans with radiological evidence of acute intracranial injury were excluded from the controls by the primary investigator, who reviewed the included scans in the controls prior to radiologist readings. Illegible request forms and control patients with a history of mental illness, as described in the request for radiological investigation, were excluded from the study by the primary investigator, who accessed this data prior to assigning patients in the control group.

4.3. Materials and Methods

CT scans were performed using Toshiba Aquilon multidetector CT scanners (Yokohama, Japan) with 128 and 64 detector arrays. The CT Brain scans are performed using a standard brain protocol (120kV, 30mAs) with 0.5mm reconstructions on a brain window.

Data collection included copies of the requisition form and retrieving the DICOM-format CT scan on DVD. Images (CT data) from the DVD's were then reconstructed using Osirix (image viewing and manipulation freeware by Apple) into axial, sagittal and coronal 0.5mm thick slices of the brain by the primary investigator. Patient information was anonymised using Osirix software before presenting the images to CT readers.

Three readers (two radiology registrars in their first two years of specialization and a consultant radiologist) interpreted all the CT scans. The radiologists were blinded to the

referral information and to each other. They were asked to independently interpret the CT scans according to defined criteria stipulated below, on individual Apple Computers. A 'final' decision on the presence of CSP was then made once the primary investigator evaluated all three readers' data sets using a majority rule.

4.4. Data Collection

The following data was collected by the primary investigator:

- Demographics: age and gender.
- Only history provided by the referring physician on the request forms for CT brain scan was used: mental illness, specific diagnosis, treatment-resistance, as well as a history of other known contributory factors, such as a history of head injury, alcohol and drug abuse, or a family history of mental illness.
- CT findings were recorded by the three readers was merged into a 'final decision' based on a majority rule principal for the following: presence or absence of a cavum septum pellucidum.
- The maximum dimensions of the enlarged CSP in the axial and coronal planes using digital calipers in the following manner: the 'CSP length' was determined by three readers (a consultant radiologist and two radiology registrars), using the same method as similar studies from the literature (1, 4, 18), namely a quantitative measurement in the coronal plane calculating the number of consecutive coronal 0.5 mm slices on which a CSP is visible. The maximum axial width of the CSP was also measured. In the case of unanimous agreement, all three measurements were averaged for statistical analysis. In case of

disagreement regarding the presence of a CSP, when the majority decision was that it was present, only the measurements made by the two readers in agreement were averaged.

All CSP's that were considered present were measured; small CSP's (as depicted in Figure 4.1 below) which may be considered normal variants, were read as positive despite the lack of evidence regarding their significance.

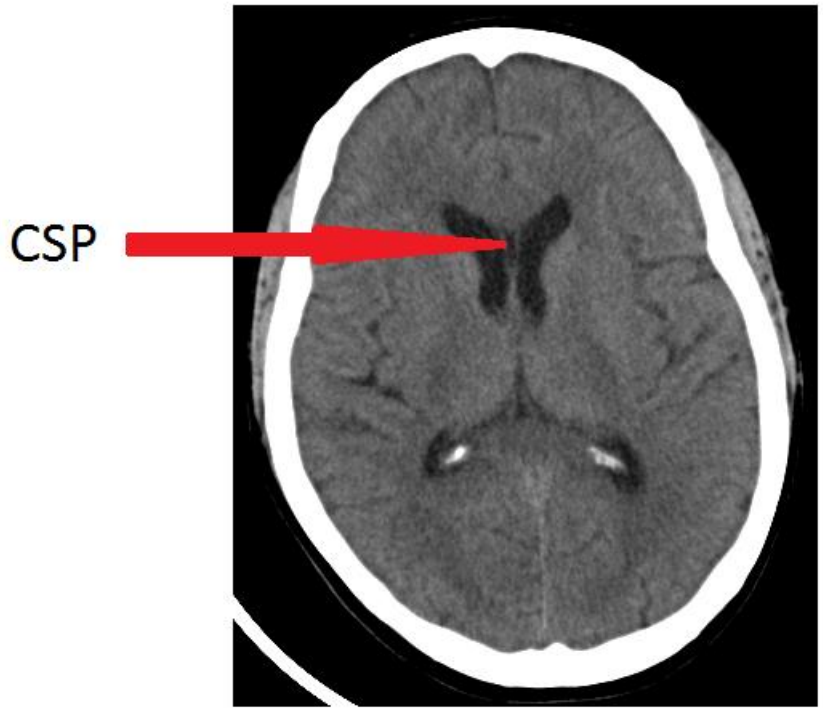

Figure 4.1. Small CSP (axial slice of a pre-contrast CT scan of the brain at the level of the frontal horns of the lateral ventricles)
(16)
(Source: Chris Hani Baragwanath PACS System; used with permission)

4.5. Statistical Analysis

The relationship between continuous and categorical variables was assessed by the t-test (or ANOVA for more than two groups). Where the data did not meet the assumptions of these tests, a non-parametric alternative, the Wilcoxon rank sum test (or the Kruskal-Wallis test for more than two groups) was used. The strength of the associations was measured by the Cohen's d-value for parametric tests and the r-value for the non-parametric tests.

In determination of predictive factors for CSP within the study population, logistic regression was used as CSP is a binary dependent variable. For this technique, the minimum size of the smallest DV class should be 10* the number of independent variable parameters to be estimated. The independent variable list given (age, gender, head injury, alcohol abuse, substance abuse, epilepsy, and HIV status) comprised 9 parameters, so some variable selection was done. Family history of mental illness as an independent variable was not used, since there were no cases. Given the large number of independent variables, and the sample size limitations, univariate logistic regression was first performed with each independent variable separately. Variables with a Wald statistic significant at $p<0.20$ were retained for multiple logistic regression analysis.

The mental health referrals were then divided according to the types of mental illness diagnosed. For the purposes of comparative analysis they were classified in the following diagnostic categories: schizophrenia spectrum disorders (which included schizophrenia, brief psychotic disorder, substance-induced psychosis); mood disorders (which included

bipolar and major depressive disorder); anxiety disorders (which included generalized anxiety disorder); and other (which included pseudocyesis and unsure diagnoses).

Between-group tests were conducted with the following statistical analyses:

- The X^2 test was used to assess the relationships between categorical variables.
- Fisher's exact test was used for 2 x 2 tables or where the requirements for the X^2 test could not be met.
- The strength of the associations was measured by Cramer's V and the phi coefficient respectively.

Interrater agreement on the CSP prevalence was determined by raw agreement values, as well as Kappa Chance Corrected measure of agreement. Interrater bias among the three raters was determined using Cochran's Q statistic. Where analysis involved continuous outcomes and all three raters, the Intraclass Correlation Coefficient (ICC) was used to calculate the proportion of variability in the data which is attributable to variation between patients.

5. Results

5.1. Comparisons between the Mental Health Referrals and Controls

The study comprised a total of 228 patients, consisting of 114 patients making up the mental health referrals and 114 patients making up the controls.

The mean age of the mental health referrals was 42.5 years (SD = 14.7) and that of the controls was 42.5 years (SD = 14.7). For both groups, the standard deviation was 14.7, the median value was 42 and the IQR was 31 – 53.

The gender distribution in the mental health referrals was 41.23 % males and 58.77 % females; that of the controls 41.23 % males and 58.77 % females. There were no significant differences between the two groups with respect to age and gender because the controls were chosen to match the study group.

5.1.1. Type of Mental Illness diagnosed in the Mental Health Referrals

The prevalence of the different types of mental illness in the mental health referrals is shown in Figure 5.1. Note that the percentages do not sum to 100% since some patients had more than one type of mental illness. Schizophrenia spectrum predominated (79.0%).

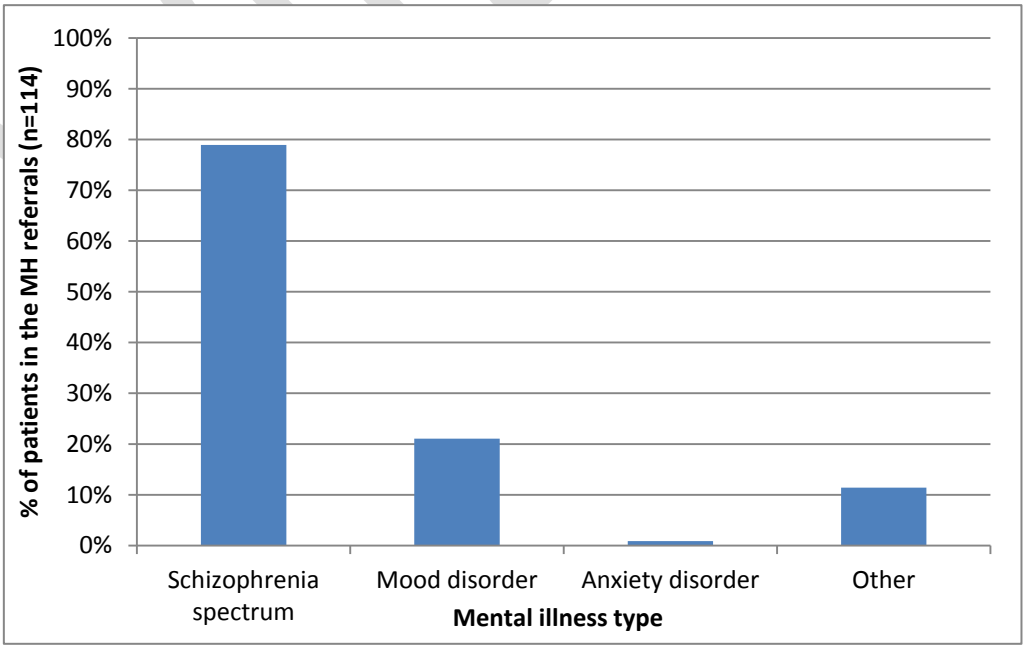

Figure 5.1. Distribution of different types of Mental Illnesses in the Mental Health Referrals

5.1.2. Prevalence of CSP in the Mental Health Referrals and Controls

42 of the 114 mental health referrals, comprising 36.8% (95% CI: 28.0-46.4%) of the group, had a CSP. By comparison, 28 of the 114 controls had a CSP comprising 24.6% (95% CI: 17.0-33.5%) of the group (Figure 5.2). The difference was not significant (p=0.06).

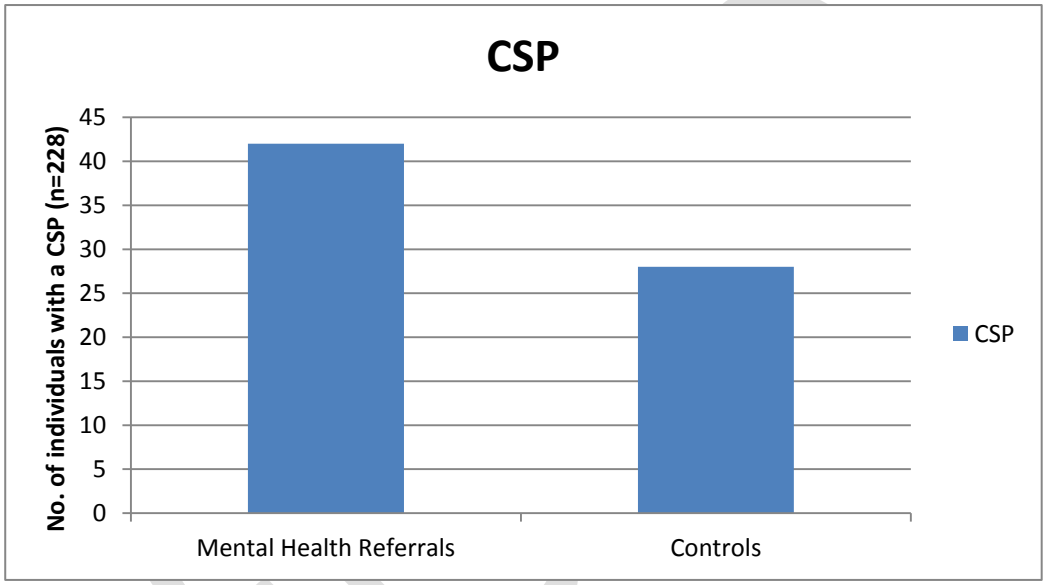

Figure 5.2. Prevalence of CSP in the Mental health referrals and Controls

Interrater Agreement

In determining the prevalence of CSP, the raw agreement (unanimous determination of CSP presence or absence) between all three raters was 92.5% (Table 5.1).

Table 5.1. Rater's Determination of CSP Prevalence

Rater	Number of patients read as having a CSP	Percentage of patients read as having a CSP
A	66	28.95
B	68	29.39
C	73	31.58

The kappa chance-corrected measure of agreement was 0.88, which corresponds to 'almost perfect' agreement (Table 5.2). The Cochran's Q statistic was not significant (p=0.16), indicating that there was no significant bias between the raters in determining the presence or absence of CSP. Although the agreement was very good and there was no significant bias, the agreement and bias between each pair of raters was determined. The agreement between all pairs of raters was high. There was no significant bias between any pair of raters.

Table 5.2. Interrater Agreement

Raters	Kappa	95% confidence interval for kappa	Interpretation of kappa	p-value for McNemar's test
A vs. B	0.88	0.82-0.95	almost perfect agreement	0.76
A vs C	0.88	0.81-0.94	almost perfect agreement	0.083
B vs C	0.89	0.82-0.95	almost perfect agreement	0.13

5.1.3. Anteroposterior Length of CSP in the Mental Health Referrals and Controls

The median anteroposterior length was 15.3 mm and 13.9 mm for the mental health referrals and controls respectively. The difference was not significant (p=0.39).

The mean and median anteroposterior lengths of CSP for the mental health referrals and controls, as well as the standard deviation and interquartile range are demonstrated in Table 5.3.

Table 5.3. CSP Anteroposterior Length Statistical Analysis

AP length analysis	Mental Health Referrals	Controls
Mean	25.38	17.01
Median	15.3	13.9
Standard deviation	26.67	9.66
IQR	10.67 – 32.33	9.42 – 23.83

Interrater Agreement

The kappa chance-corrected measure of agreement was 0.90 for determination of CSP anteroposterior length indicating 'almost perfect' agreement between the three raters, as demonstrated in Table 5.4.

Table 5.4. Assessment of Anteroposterior Length

Variable	A	B	C
Number of patients read as having a CSP	66	68	73
Mean AP length	25	23	20
Std Dev AP length	27	20	22
Median AP length	16	15	14
Interquartile range of AP length	10	12	10
	28	31	18
Minimum AP length	3	3	5
Maximum AP length	138	110	123

5.1.4. Axial Width of CSP in the Mental Health Referrals and Controls

The median axial width of CSP was 1.8 and 2.6 mm for the controls and mental health referrals respectively. The difference was significant (p=0.046), with a small effect size (r=0.24). The statistical analysis of axial widths is shown in Table 5.5.

Table 5.5. Statistical Analysis of Axial Width of CSP in Mental health referrals and Controls

Axial width analysis	Mental health referrals	Controls
Mean	3.85	2.51
Median	2.55	1.75
Standard deviation	3.12	1.81
IQR	1.75 – 5.60	1.23 – 4.07

Interrater Agreement

In measurement of CSP axial width, the agreement between all pairs of raters was excellent, as depicted in Table 5.6.

Table 5.6. Interrater Agreement in Assessment of Axial Width

Variable	A	B	C
Number of patients read as having a CSP	66	68	73
Mean axial width	3.8	3.3	3.1
Std Dev of axial width	3.3	2.7	2.7
Median axial width	2.3	2.4	2.3
Interquartile range of axial widths	1	2	2
	6	5	4
Minimum axial width	0	0	1
Maximum axial width	16	17	16

5.2. Comparison of Prevalence of CSP in the Mental Health Subgroups

For the purposes of comparative analysis the patients in the mental health referrals were classified in the following diagnostic categories: schizophrenia spectrum disorders (which included schizophrenia, brief psychotic disorder, substance-induced psychosis); mood disorders (which included bipolar and major depressive disorder); anxiety disorders (which included generalized anxiety disorder); and other (which included pseudocyesis and unsure diagnoses).

5.2.1. Prevalence of CSP in the Mental Health Subgroups

In the schizophrenia spectrum subgroup 36 of 90 patients, comprising 40.0% (95% CI: 29.8-50.9%) of the group, had a CSP. By comparison, 6 of 24 mental health referrals who did not have a schizophrenia-spectrum disorder, had a CSP, comprising 25.0% (95% CI: 9.8-46.7%) of the non-schizophrenia spectrum subgroup. The difference was not significant (p=0.24).

In the mood disorder subgroup, 7 of 24 patients had a CSP. This is calculated as 29.2% (95% CI: 12.6-51.1%) of the patients in the mood disorder subgroup, compared to 35 of 90 patients in the non-mood disorder subgroup, which comprises 38.9% (95% CI: 28.8-49.7%) of this subgroup. The difference was not significant (p=0.48).

The prevalence of CSP in these groups is demonstrated in Figure 5.3.

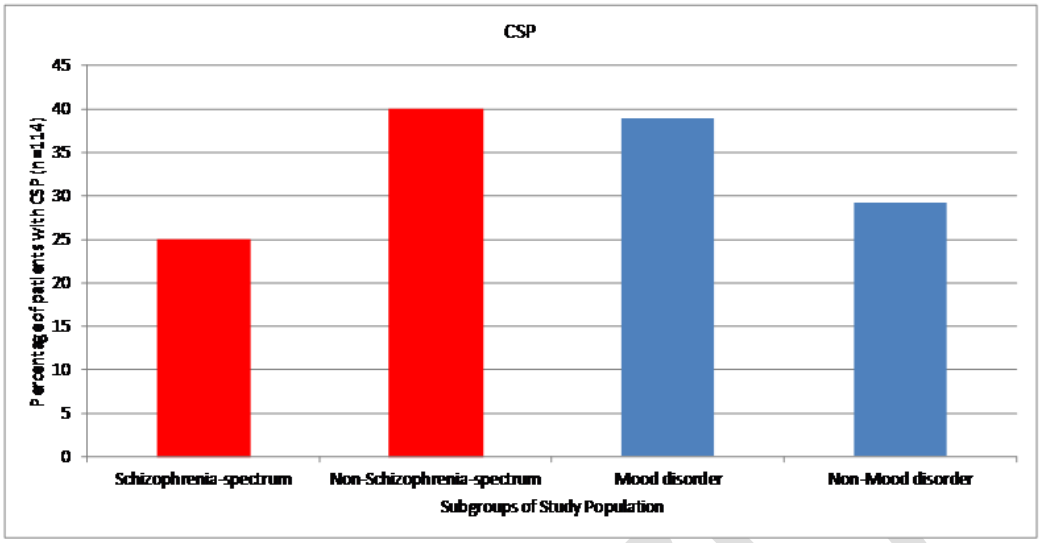

Figure 5.3. CSP prevalence in Mental Health Subgroups

5.2.2. Anteroposterior Length of CSP in the Mental Health Subgroups

The median anteroposterior length of CSP was 15.3 mm and 16.0 mm for the schizophrenia spectrum and non-schizophrenia spectrum subgroups respectively. The difference was not significant (p=0.75). The statistical analysis of the anteroposterior length of CSP is demonstrated in Table 5.7.

Table 5.7. The Statistical Analysis of CSP Anteroposterior Length in the Schizophrenia-Spectrum Subgroups

AP length analysis	Schizophrenia Spectrum Subgroup	Non-Schizophrenia Spectrum Subgroup
Mean	26.19	20.56
Median	15.33	16.00
Standard deviation	28.53	10.09
IQR	9.67 – 31.33	13.33 – 32.33

The median anteroposterior length was 13.3 mm and 16.0 mm for the mood disorder and non-mood disorder subgroups respectively. The difference was not significant (p=0.32). The statistical analysis of the anteroposterior length of CSP is demonstrated in Table 5.8.

Table 5.8. The Statistical Analysis of CSP Anteroposterior Length in the Mood Disorder Subgroups

AP length analysis	Mood disorder Subgroup	Non-Mood disorder Subgroup
Mean	25.17	25.42
Median	13.33	16.00
Standard deviation	37.54	24.68
IQR	9.00 - 18.00	11.33 – 32.67

5.2.3. Axial width of CSP in the Mental Health Subgroups

The median axial width was 5.2 and 2.2 mm for the non- schizophrenia spectrum and schizophrenia spectrum groups respectively. The difference was significant (p=0.049), with a small effect size (r=0.31). The statistical analysis of the axial width of CSP is demonstrated in Table 5.9.

Table 5.9. The Statistical Analysis of CSP Axial Width in the Schizophrenia-Spectrum Subgroups

Axial width analysis	Schizophrenia Spectrum Subgroup	Non-Schizophrenia Spectrum Subgroup
Mean	3.61	5.34
Median	2.18	5.20
Standard deviation	3.20	2.23
IQR	1.70 – 4.47	4.07 – 6.50

The median axial width was 3.7 and 2.0 mm for the non-mood disorder and mood disorder groups respectively. The difference was not significant (p=0.22). The statistical analysis of the axial width of CSP is demonstrated in Table 5.10.

Table 5.10. The Statistical Analysis of CSP Axial Width in the Mood Disorder Subgroups

Axial width analysis	Mood disorder Subgroup	Non-Mood disorder Subgroup
Mean	3.48	3.93
Median	2.03	3.73
Standard deviation	4.41	2.88
IQR	1.00 – 3.73	1.77 – 5.63

5.2.4. Predictive Clinical Factors for CSP within the Mental Health Referrals

There were no variables (HIV status, drug use, family history of mental illness) which were significant even at p<0.20 and thus we did not proceed to multiple logistic regression analysis. None of the independent variables were significant predictors of CSP within the mental health referrals.

6. Discussion

This study found no statistically significant difference in the prevalence of CSP in patients with mental illness (36.8%) compared to those with no mental illness (24.6%). The prevalence of CSP represented in the literature varies from 9.30% (45) to 85.10% (3) for mental health patients, and from 2% (17) to 85.7% (46) for controls. Our results of 36.8% and 24.6% respectively, are within this wide range, and are most similar to DeLisi's study of 1993 (15) and Fukuzako's research in 1998 (47). DeLisi had a total population of 132 (85 schizophrenic patients, 47 control patients) with CSP noted in 44.7% of schizophrenics

and 29.8% of control patients (15) . Fukuzako had a total population of 113 patients (72 schizophrenic patients and 41 control patients) with results of 47.2% and 38% respectively (47). A meta-analysis by Trzesniak in 2011 determined that a CSP of any size is not found more frequently in schizophrenic patients (13), and our findings are in agreement with this.

Further, this study found no significant difference in the prevalence with respect to the different types of mental illnesses (schizophrenia-spectrum group and mood disorder group). There are very few other studies that considered a comparative analysis of multiple mental illnesses. Kwon evaluated the prevalence of CSP in 67 mental health patients, including 30 schizophrenic patients, 16 affective disorder patients and 21 schizotypal disorder patients, which were compared to each other and 46 control patients, and did not find a difference in the prevalence of CSP between the four groups (48). However, he subsequently compared "abnormal" CSP prevalence (measuring 6mm or more in anteroposterior length) and found a statistically significant increase of CSP prevalence in schizophrenic patients, compared to controls (48). Takahashi has compared the prevalence of CSP in schizophrenics and patients with schizotypal disorder (3), as well as patients with first-episode psychosis to patients with chronic schizophrenia and asymptomatic individuals at ultra-high risk for schizophrenia due to genetic predisposition (45). He did not find a difference in the prevalence of CSP between these groups (3, 45).

There was no statistically significant difference in median anteroposterior length in the mental health referrals (15.3mm) compared to the controls (13.9mm) and with respect to the different forms of mental illnesses (schizophrenia spectrum subgroup and mood

disorder subgroup). Trzeniak's meta-analysis determined that only a large CSP is more common in schizophrenia-spectrum patients (13). Trzeniak's research contradicts the studies by Crippa (46), Flashman (31), Hagino (30) and Rajarethinam (19) which demonstrated findings similar to ours.

The median anteroposterior lengths for the controls and mental health referrals were much larger than those found in previous studies. This is most likely due to the higher spatial resolution of CT used in our study, compared to MRI and direct visualisation used in other earlier studies. The median length was 15.5 mm in the mental health referrals and 13.9 mm in the controls. The conventional parameters for an abnormally large CSP (i.e. more than 6 mm) could not be applied to our study, as 96% of the CSP's identified overall were longer than 6mm.

There is a statistically significant difference ($p=0.046$) with a small effect size ($r=0.24$) in the median axial width in the mental health referrals (2.6mm) and the controls (1.8mm) and a significant difference ($p=0.049$), with a small effect size ($r=0.31$) between the non-schizophrenia spectrum and schizophrenia spectrum subgroups. This significance of CSP width, though not as well documented as CSP length, has been noted in previous research both in conventional imaging as a volume measurement of CSP, (1) and on post-mortem samples as an axial width measurement (35). These studies determined that CSP width was increased in patients with schizophrenia-spectrum disorders (1, 35).

There were no clinical variables which were significant predictors of the presence of CSP, though this finding was limited by poor history supplied on the radiology requisition forms.

6.2. Results in context

This study was larger than the average sample populations reported in the literature, with 114 control patients and 114 study patients comprising at total of 228 individuals. The average size of studies included in the literature review is 150 individuals, with the smallest study comprising only 42 patients, and the largest 479 individuals (Appendix B). Of these studies, the report by Chon et al in 2010, matched study and control groups for sex and age whilst determining CSP prevalence in patients with obsessive compulsive disorder (6), as did Crippa et al in 2004 while doing similar research in patients with panic disorder (46) and in 2006, when he investigated the association between CSP and schizophrenia (1). The vast majority of studies, however, did not match the study and control groups for age and sex.

The main difference of note between the current research and previous research is the use of CT scan as the primary neuroimaging modality for psychiatric work-up compared to MRI, pneumoencephalography or post-mortem studies, as used in previous studies. This is advantageous in our context because of the relative widespread availability of CT scan compared to MRI. Furthermore, CT imaging is of a higher spatial resolution (albeit lower contrast resolution) than MRI (20), accounting for the increased CSP length measured in this study compared to previous research.

The current study is one of the few studies measuring the axial width of CSP's as a possible predictor of mental illness, a difference which was statistically significant between mental health referrals and healthy controls. Previously, only Filipovic consistently measured CSP width and advocated its use as a marker for mental illness

(35). Other studies have attempted volumetric CSP measurements (1), but this is much less common than CSP length measurements (13).

Due to the poor history supplied by referring clinicians regarding HIV status, drug use and previous head trauma, the multi-variant analysis performed was not performed. In the South African context where these three factors are ubiquitous, their influence in mental illness aetiology is possibly underestimated.

6.3. Current applications

The presence and length of CSP is not a reliable predictor of the diagnosis of a mental illness or a determinant of the type of mental illness diagnosed in our population. CSP width is a statistically significant determinant of mental illness, especially schizophrenia-spectrum disorders, and can be used as an independent marker of mental illness. This is a simple linear measure performed very quickly using callipers on CT scans but the ideal location for standardised measurement needs to be defined. Further prospective studies measuring CSP width are recommended with clear clinical definitions and workup to accompany the imaging interpretations.

6.4. Limitations of the current study

The largest limitation of the study is the use of trauma patients as the controls, as trauma has been associated with an increased prevalence of CSP (49). However, trauma patients with moderate or severe trauma, or radiological evidence of trauma, were excluded as control patients.

The main source of data regarding the patient's history and illness was provided by the radiology requisition form, which is often poorly completed especially in the emergency setting Thus there was a paucity of information regarding both diagnosis and history for study and control patients.

A further limitation was the incorrect registration of patients on the PACS system, which created difficulty in tracing the referral route of our patients.

The resource-limited South African medical environment severely hampers the adequate work-up of patients from the periphery due to transport and financial constraints, which may have biased the mental health referrals towards those with a higher socio-economic status who could afford transport.

The retrospective nature of the research caused a bias, as predominantly schizophrenic mental health referrals are investigated by imaging. Prospective work could include a more representative population of mental health referrals, with equal numbers of patients in the mental health subgroups to better investigate the prevalence of CSP in all the diagnostic categories of mental illness.

6.5. Future applications

The axial width of a CSP is a reproducible, single-step measurement, and is therefore simpler and faster than calculating the anteroposterior length of CSP by multiplying the number of reformatted coronal slices on which the CSP appears with the slice thickness. Axial width measurements could become routine on all CT Brain scans. The use of CSP

axial width could be utilised by CAD software to automatically measure the CSP width and highlight the abnormality as a potential marker of mental illness.

7. Conclusion

Our study aimed to determine the prevalence of CSP in mental health referrals and normal patients. Our study varied from previous published works in the use of CT as the primary investigation for brain imaging, as well as the measurement of CSP width. There was no statistically significant association noted between the prevalence or length of CSP and psychiatric diagnosis. The axial width of the CSP was a statistically significant predictor of mental illness. Further research evaluating CSP length and width is recommended. The length of CSP's in this study was larger than in previous studies, demonstrating either a larger baseline length in the South African population, or as a result of using CT as our imaging modality.

Appendix A: Ethics Clearance Certificate

M140413

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140413

NAME: (Principal Investigator)	Dr Kathleen Jacobs et al
DEPARTMENT:	Radiology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	The Prevalence of Cavum Septum Pellucidum in Brain Imaging of Mental Referrals in a South African Population
DATE CONSIDERED:	25/04/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Tanusha Sewchuran
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 18/07/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned researcl and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from th research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit** yearly progress report.

Principal Investigator Signature M140413Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B: Comparison of the Current Study to Literature Review of CSP and Mental Illness

Year	Author	Imaging Method	Total patients	Mental health group and diagnosis	Controls		CSP in mental health patients (Unless otherwise stated, refers to CSP of any size)		CSP in controls
2008	Choi	MRI	87	30 ultra high-risk for schizophrenia 23 genetic high-risk for schizophrenia	34		21/30 (70.0%) ultra high-risk 12/23 (52.2%) genetic high-risk	Abnormal CSP (Grade 2,3, 4)	13/34 (38.2%)
2010	Chon	MRI	142	71 Obsessive-compulsive disorder	71	Matched for sex and age	16/71 (22.5%)	Abnormal CSP (Grade 2,3, 4)	10/71 (14.1%)
2004	Crippa	MRI	42	21 Panic disorder	21	Matched for sex and age	16/21 (76.2%)		18 / 21 (85.7%)
2006	Crippa	MRI	76	38 schizophrenia	38	Matched for sex and age	30/38 (78.9%)- CSP of any size		33/38 (86.8%)- CSP of any size
							8/38 (21.1%) – CSP>6mm		1/38 (2.6%) – CSP>6mm

Year	Author	Imaging Method	Total patients	Mental health group and diagnosis	Controls		CSP in mental health patients (Unless otherwise stated, refers to CSP of any size)	CSP in controls
1993	DeLisi	MRI	132	85 schizophrenia	47	Matched for age	38/85 (44.7%)	14/47 (29.8%).
1992	DeGreef	MRI	108	62 schizophrenia	46		14/62 (23%)	1/46 (2%)
1992	DeGreef	MRI	127	81 schizophrenia	46		17/81 (21%)	1/46 (2%)
		Post-mortem studies	67	28 schizophrenia	39		17/28 (61%)	12/39 (31%)
2005	Filipovic	Post-mortem studies	479	30 schizophrenia	377		25/30 (83.33%)	4/377 (10.61%)
2007	Flashman	MRI	122	77 schizophrenia spectrum	55		53/77 (68.8%)	42/55 (76.4%)
1998	Fukuzako	MRI	113	72 schizophrenia	41		34/72 (47.2%)	16 / 41 (38%)
2004	Galarza	MRI	51 (females only)	32 schizophrenia	19		14/32 (43.75%)	2/19 (10.52%)
2001	Hagino	MRI	165	86 schizophrenia	79		64/86 (74.40%)	59/79 (74.70%)

Year	Author	Imaging Method	Total patients	Mental health group and diagnosis	Controls	CSP in mental health patients (Unless otherwise stated, refers to CSP of any size)	CSP in controls
2013	Hwang	MRI	132	65 opiate-dependent subjects	67	54/65 (83.1%) – any CSP 12/65 (18.5%) – large CSP (>6mm)	43/67 (64.2%)- any CSP 4/67 (6.0%) – large CSP (>6mm)
2004	Kasai	MRI	130	33 schizophrenia 41 affective psychosis	56	23/33 (69.7%) schizophrenia 33/41 (80.5%) affective psychosis	49/56 (87.5%)
2003	Kim	MRI	161 107	97 children with Tourette's Syndrome 43 adults with Tourette's Syndrome	64 children 64 adults	44/97 children (51%) 16/43 adults (37%)	43/64 children (67%) 38/64 adults (59%)
2007	Kim	MRI	82	41 bipolar mood disorder	41	8 /41 (19.5%) – large CSP (>6mm)	1/41 (2.4%) – large CSP (>6mm)

Year	Author	Imaging Method	Total patients	Mental health group and diagnosis	Controls	CSP in mental health patients (Unless otherwise stated, refers to CSP of any size)	CSP in controls
1998	Kwon	MRI	113	30 schizophrenia 16 affective disorder 21 schizotypal disorder	46	23/30 (76.7%) – any CSP 7/23 (30.4%) - large CSP (>6mm) 10/16 (62.5%)– any CSP 2/10 (20%)- large CSP (>6mm) 16/21 (76.2%)– any CSP 3/16 (18.8%)- large CSP (>6mm)	39/46 (84.8%)– any CSP 4/39 (10.3%)- large CSP (>6mm)
1997	Nopoulos	MRI	130	55 schizophrenia	75	32/55 (58.8%)- any CSP 6/29 (21.0%) – large CSP	44/75 (58.7%) – any CSP 1/39 (3.0%) – large CSP
1998	Nopoulos	MRI	119	24 adolescents with schizophrenia	95 adolescents	12.5% (3/24) – large CSP (>6mm)	1.1% (1/95) – large CSP (>6mm)
2010	Raine	MRI	87	19 with CSP, 68 without CSP	None	Increased antisocial personality disorder and psychopathy scores in pt's with CSP	

Year	Author	Imaging Method	Total patients	Mental health group and diagnosis	Controls	CSP in mental health patients (Unless otherwise stated, refers to CSP of any size)	CSP in controls
2001	Rajarethinam	MRI	116	73 schizophrenia	43	3/73 (4.1%) -large CSP>6mm	1/43 (2.3%) – large CSP (>6mm)
						44/73 (60.3%) -any CSP	18/43 (41.9%) – any CSP
2008	Rajarethinam	MRI	273	89 schizophrenia 64 genetic high-risk for schizophrenia	120	(60/89) 64% (41/64) 64.60%	77/120 (64.20%)
2007	Takahashi	MRI	364	154 schizophrenia 47 schizotypal disorder	163	117/154 (76.00%) - any CSP 10/154 (6.5%) - large CSP 40/47 (85.10%) - any CSP 5/47 (10.6%) - large CSP	133/163 (81.60%) - any CSP 12/163 (7.4%) - large CSP
2008	Takahashi	MRI	384	162 first episode psychosis	87	15/162 (9.30%)	10/87 (11.50%)
				89 chronic schizophrenia		10/89 (11.20%)	
				135 ultra high-risk		15/135 (11.10%)	

Year	Author	Imaging Method	Total patients	Mental health group and diagnosis	Controls	CSP in mental health patients (Unless otherwise stated, refers to CSP of any size)	CSP in controls
2014	Jacobs	CT	228	90 Schizophrenia spectrum 24 Mood disorder	114	42/114 (36.84%) 36/90 (40%) Schizophrenia spectrum 7/24 (29.17%) Mood disorder	28/114 (24.56%)

8. References

1. de Souza Crippa JA, Zuardi AW, Busatto GF, Sanches RF, Santos AC, Araujo D, et al. Cavum septum pellucidum and adhesio interthalamica in schizophrenia: an MRI study. European psychiatry : the journal of the Association of European Psychiatrists. 2006 Jul;21(5):291-9. PubMed PMID: 16406503. Epub 2006/01/13. eng.

2. Choi JS, Kang DH, Park JY, Jung WH, Choi CH, Chon MW, et al. Cavum septum pellucidum in subjects at ultra-high risk for psychosis: compared with first-degree relatives of patients with schizophrenia and healthy volunteers. Progress in neuro-psychopharmacology & biological psychiatry. 2008 Jul 1;32(5):1326-30. PubMed PMID: 18513845. Epub 2008/06/03. eng.

3. Takahashi T, Suzuki M, Hagino H, Niu L, Zhou SY, Nakamura K, et al. Prevalence of large cavum septi pellucidi and its relation to the medial temporal lobe structures in schizophrenia spectrum. Progress in neuro-psychopharmacology & biological psychiatry. 2007 Aug 15;31(6):1235-41. PubMed PMID: 17553605. Epub 2007/06/08. eng.

4. Nopoulos P, Swayze V, Flaum M, Ehrhardt JC, Yuh WT, Andreasen NC. Cavum septi pellucidi in normals and patients with schizophrenia as detected by magnetic resonance imaging. Biological psychiatry. 1997 Jun 1;41(11):1102-8. PubMed PMID: 9146821. Epub 1997/06/01. eng.

5. Kasai K, McCarley RW, Salisbury DF, Onitsuka T, Demeo S, Yurgelun-Todd D, et al. Cavum septi pellucidi in first-episode schizophrenia and first-episode affective psychosis: an MRI study. Schizophrenia research. 2004 Nov 1;71(1):65-76. PubMed PMID: 15374574. Pubmed Central PMCID: PMC2811876. Epub 2004/09/18. eng.

6. Chon MW, Choi JS, Kang DH, Jung MH, Kwon JS. MRI study of the cavum septum pellucidum in obsessive-compulsive disorder. European archives of psychiatry and clinical neuroscience. 2010 Jun;260(4):337-43. PubMed PMID: 19856198. Epub 2009/10/27. eng.

7. Kim KJ, Peterson BS. Cavum septi pellucidi in Tourette syndrome. Biological psychiatry. 2003 Jul 1;54(1):76-85. PubMed PMID: 12842311. Epub 2003/07/05. eng.

8. Pearce JM. Some observations on the septum pellucidum. European neurology. 2008;59(6):332-4. PubMed PMID: 18408379.

9. Born CM, Meisenzahl EM, Frodl T, Pfluger T, Reiser M, Moller HJ, et al. The septum pellucidum and its variants. An MRI study. European archives of psychiatry and clinical neuroscience. 2004 Oct;254(5):295-302. PubMed PMID: 15365704. Epub 2004/09/15. eng.

10. Eiselen M. Diagram of Cavum Septum Pellucidum. 2015.

11. Rajarethinam R, Miedler J, DeQuardo J, Smet CI, Brunberg J, Kirbat R, et al. Prevalence of cavum septum pellucidum in schizophrenia studied with MRI. Schizophrenia research. 2001 Mar 30;48(2-3):201-5. PubMed PMID: 11295373. Epub 2001/04/11. eng.

12. Galarza M, Merlo AB, Ingratta A, Albanese EF, Albanese AM. Cavum septum pellucidum and its increased prevalence in schizophrenia: a neuroembryological

classification. The Journal of neuropsychiatry and clinical neurosciences. 2004 Winter;16(1):41-6. PubMed PMID: 14990758. Epub 2004/03/03. eng.

13. Trzesniak C, Oliveira IR, Kempton MJ, Galvao-de Almeida A, Chagas MH, Ferrari MC, et al. Are cavum septum pellucidum abnormalities more common in schizophrenia spectrum disorders? A systematic review and meta-analysis. Schizophrenia research. 2011 Jan;125(1):1-12. PubMed PMID: 20965698. Epub 2010/10/23. eng.

14. Nopoulos P, Krie A, Andreasen NC. Enlarged cavum septi pellucidi in patients with schizophrenia: clinical and cognitive correlates. The Journal of neuropsychiatry and clinical neurosciences. 2000 Summer;12(3):344-9. PubMed PMID: 10956567. Epub 2000/08/24. eng.

15. DeLisi LE, Hoff AL, Kushner M, Degreef G. Increased prevalence of cavum septum pellucidum in schizophrenia. Psychiatry research. 1993 Oct;50(3):193-9. PubMed PMID: 8272454. Epub 1993/10/01. eng.

16. Chris Hani Baragwanath Picture Archiving and Communications System. 2015.

17. Degreef G, Bogerts B, Falkai P, Greve B, Lantos G, Ashtari M, et al. Increased prevalence of the cavum septum pellucidum in magnetic resonance scans and post-mortem brains of schizophrenic patients. Psychiatry research. 1992 May;45(1):1-13. PubMed PMID: 1410074. Epub 1992/05/01. eng.

18. Nopoulos PC, Giedd JN, Andreasen NC, Rapoport JL. Frequency and severity of enlarged cavum septi pellucidi in childhood-onset schizophrenia. The American journal of psychiatry. 1998 Aug;155(8):1074-9. PubMed PMID: 9699696. Epub 1998/08/12. eng.

19. Rajarethinam R, Sohi J, Arfken C, Keshavan MS. No difference in the prevalence of cavum septum pellucidum (CSP) between first-episode schizophrenia patients, offspring of schizophrenia patients and healthy controls. Schizophrenia research. 2008 Aug;103(1-3):22-5. PubMed PMID: 18248791. Epub 2008/02/06. eng.

20. Bushberg J. The Essential Physics of Medical Imaging. 3 ed. Philadelphia: Lippincott Williams and Wilkins; 2012.

21. Smith AB, Van Hoving DJ, Wallis LA. Emergency centre investigation of first-onset seizures in adults in the Western Cape, South Africa. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2013 Oct;103(10):723-7. PubMed PMID: 24079622.

22. Messinger JW, Tremeau F, Antonius D, Mendelsohn E, Prudent V, Stanford AD, et al. Avolition and expressive deficits capture negative symptom phenomenology: implications for DSM-5 and schizophrenia research. Clinical psychology review. 2011 Feb;31(1):161-8. PubMed PMID: 20889248. Pubmed Central PMCID: PMC2997909. Epub 2010/10/05. eng.

23. Association AP. Diagnostic and Statistical Manual of Mental Disorders. Arlington, VA: American Psychiatric Association; 2000. Available from: http://books.google.co.za/books?hl=en&lr=&id=w_HajjMnjxwC&oi=fnd&pg=PP1&dq=psychiatric+diagnosis+functioning&ots=i7TVcl5L8K&sig=wjYdilZ1Fr9jAf0R2epkAI7tlOg#v=onepage&q=psychiatric%20diagnosis%20functioning&f=false.

24. Rey J. Proposed changes to the psychiatric classification: towards DSM5. Australasian psychiatry : bulletin of Royal Australian and New Zealand College of Psychiatrists. 2010 Aug;18(4):309-13. PubMed PMID: 20645895.

25. Association AP. Schizophrenia Spectrum and Other Psychotic Disorders. Diagnostic and Statistical Manual of Mental Disorders. Arlington, VA: American Psychiatric Association; 2013.

26. Malaspina D, Walsh-Messinger J, Gaebel W, Smith LM, Gorun A, Prudent V, et al. Negative symptoms, past and present: A historical perspective and moving to DSM-5. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2013 Nov 21. PubMed PMID: 24314851. Epub 2013/12/10. Eng.

27. Testa A, Giannuzzi R, Daini S, Bernardini L, Petrongolo L, Gentiloni Silveri N. Psychiatric emergencies (part III): psychiatric symptoms resulting from organic diseases. European review for medical and pharmacological sciences. 2013 Feb;17 Suppl 1:86-99. PubMed PMID: 23436670.

28. Basant P. Organic Psychiatry. May 2011 [cited 04/12/2013]. In: Textbook of Psychiatry [Internet]. Churchill-Livingstone. 3. [cited 04/12/2013]; [95-134]. Available from: http://v5.books.elsevier.com/bookscat/samples/9780443070167/9780443070167.pdf.

29. Kim MJ, Lyoo IK, Dager SR, Friedman SD, Chey J, Hwang J, et al. The occurrence of cavum septi pellucidi enlargement is increased in bipolar disorder patients. Bipolar disorders. 2007 May;9(3):274-80. PubMed PMID: 17430302. Epub 2007/04/14. eng.

30. Hagino H, Suzuki M, Kurokawa K, Mori K, Nohara S, Takahashi T, et al. Magnetic resonance imaging study of the cavum septi pellucidi in patients with schizophrenia. The American journal of psychiatry. 2001 Oct;158(10):1717-9. PubMed PMID: 11579008. Epub 2001/10/02. eng.

31. Flashman LA, Roth RM, Pixley HS, Cleavinger HB, McAllister TW, Vidaver R, et al. Cavum septum pellucidum in schizophrenia: clinical and neuropsychological correlates. Psychiatry research. 2007 Feb 28;154(2):147-55. PubMed PMID: 17291728. Pubmed Central PMCID: PMC1858669. Epub 2007/02/13. eng.

32. Hwang J, Kim JE, Kaufman MJ, Renshaw PF, Yoon S, Yurgelun-Todd DA, et al. Enlarged cavum septum pellucidum as a neurodevelopmental marker in adolescent-onset opiate dependence. PloS one. 2013;8(10):e78590. PubMed PMID: 24205275. Pubmed Central PMCID: PMC3813473. Epub 2013/11/10. eng.

33. Toivonen P, Kononen M, Niskanen E, Vaurio O, Repo-Tiihonen E, Seppanen A, et al. Cavum septum pellucidum and psychopathy. The British journal of psychiatry : the journal of mental science. 2013 Aug;203(2):152-3. PubMed PMID: 23908342. Epub 2013/08/03. eng.

34. Degreef G, Lantos G, Bogerts B, Ashtari M, Lieberman J. Abnormalities of the septum pellucidum on MR scans in first-episode schizophrenic patients. AJNR American journal of neuroradiology. 1992 May-Jun;13(3):835-40. PubMed PMID: 1590179. Epub 1992/05/01. eng.

35. Filipovic B, Kovacevic S, Stojicic M, Prostran M, Filipovic B. Morphological differences among cavum septi pellucidi obtained in patients with schizophrenia and healthy individuals: forensic implications. A post-mortem study. Psychiatry and clinical neurosciences. 2005 Feb;59(1):106-8. PubMed PMID: 15679549. Epub 2005/02/01. eng.

36. Trzesniak C, Schaufelberger MS, Duran FL, Santos LC, Rosa PG, McGuire PK, et al. Longitudinal follow-up of cavum septum pellucidum and adhesio interthalamica alterations in first-episode psychosis: a population-based MRI study. Psychological medicine. 2012 Dec;42(12):2523-34. PubMed PMID: 22717008. Epub 2012/06/22. eng.

37. Roos JL. Genetics of schizophrenia: communicating scientific findings in the clinical setting. African journal of psychiatry. 2011 May;14(2):105-11. PubMed PMID: 21687908.

38. Trzesniak C, Kempton MJ, Busatto GF, de Oliveira IR, Galvao-de Almeida A, Kambeitz J, et al. Adhesio interthalamica alterations in schizophrenia spectrum disorders: A systematic review and meta-analysis. Progress in neuro-psychopharmacology & biological psychiatry. 2011 Jun 1;35(4):877-86. PubMed PMID: 21300129. Epub 2011/02/09. eng.

39. Burns JK. Pathways from Cannabis to Psychosis: A Review of the Evidence. Frontiers in psychiatry. 2013;4:128. PubMed PMID: 24133460. Pubmed Central PMCID: 3796266.

40. Trump LH, C. The Barriers Preventing Effective Treatment of South African mental health patients. S Afr Psychiatry Rev. 2006;9:249-60.

41. Organization WH. Mental Health: Schizophrenia [02/12/2013]. Available from: www.who.int/mental_health/management/schizophrenia/en/.

42. Abecasis GRB, R. A., Hall, D.; Bochum, S. Genomewide Scan in Families with Schizophrenia from the Founder Population of Afrikaners Reveals Evidence for Linkage and Uniparental Disomy on Chromosome 1. Am J Hum Genet. 2004;74:403-17.

43. Koen LN, D.J.H.; Emsley, R.A. Chromosome 22q11 in a Xhosa schizophrenia population. SAMJ. 2012;102(3).

44. Roos JL, Pretorius HW, Karayiorgou M. Clinical characteristics of an Afrikaner founder population recruited for a schizophrenia genetic study. Annals of the New York Academy of Sciences. 2009 Jan;1151:85-101. PubMed PMID: 19154519.

45. Takahashi T, Yung AR, Yucel M, Wood SJ, Phillips LJ, Harding IH, et al. Prevalence of large cavum septi pellucidi in ultra high-risk individuals and patients with psychotic disorders. Schizophrenia research. 2008 Oct;105(1-3):236-44. PubMed PMID: 18693084. Epub 2008/08/12. eng.

46. Crippa JA, Uchida R, Busatto GF, Guimaraes FS, Del-Ben CM, Zuardi AW, et al. The size and prevalence of the cavum septum pellucidum are normal in subjects with panic disorder. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas / Sociedade Brasileira de Biofisica [et al]. 2004 Mar;37(3):371-4. PubMed PMID: 15060705. Epub 2004/04/03. eng.

47. Fukuzako H, Kodama S. Cavum septum pellucidum in schizophrenia. Biological psychiatry. 1998 Mar 15;43(6):467. PubMed PMID: 9532354. Epub 1998/04/09. eng.

48. Kwon JS, Shenton ME, Hirayasu Y, Salisbury DF, Fischer IA, Dickey CC, et al. MRI study of cavum septi pellucidi in schizophrenia, affective disorder, and schizotypal personality disorder. The American journal of psychiatry. 1998 Apr;155(4):509-15. PubMed PMID: 9545997. Pubmed Central PMCID: PMC2826366. Epub 1998/04/18. eng.

49. Aviv RI, Tomlinson G, Kendall B, Thakkar C, Valentine A. Cavum septi pellucidi in boxers. Canadian Association of Radiologists journal = Journal l'Association canadienne des radiologistes. 2010 Feb;61(1):29-32; quiz 1-2. PubMed PMID: 19854608. Epub 2009/10/27. eng.