CLINICAL USE OF NEURO-IMAGING IN PSYCHIATRIC PATIENTS AT THE CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

By

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Declaration

I, Dr Bokang Lipuo Letlotlo, hereby declare that the work in this research paper is my own original work. I hereby declare that all sources used or referred to have been documented and recognised.

I declare that this research paper has not been previously submitted in full or partial fulfilment of the requirements for an equivalent or higher qualification at any other recognised education institution.

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Signed At Date

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Commissioner of Oaths

Dedication

This dissertation is dedicated to my father you challenged me to take on this masters degree. I made it! To my sister, none of my life achievements would have been possible without you. You complete me. My friends, Khosi and Rethabile, you persisted through the difficult times, always by my side. Thank you for your unconditional love.

Most importantly I dedicate this work to my son, Tankiso Moeketsane, thank you for your love.

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Abbreviations

AIDS	Acquired Immuno-deficiency Syndrome
CLP	Consultation Liaison Psychiatry
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CNS	Central Nervous System
CT	Computerized Tomography
CVA	Cerebro -vascular Accident
DSM-5	Diagnostic and Statistical Manual of Mental Disorders- Fifth Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (Text Revision)
FEP	First Episode Psychosis
GCS	Glasgow Coma Scale
HIV	Human Immuno-deficiency Virus
LOE	Late-Onset Epilepsy
LDL	Low-Density Lipoprotein
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MS	Multiple Sclerosis
NICE	National Institute for Health and Clinical Excellence.
MTS	Mesial Temporal Sclerosis
PET	Positron Emission Tomography
RPR	Rapid Plasma Reagin
SPECT	Single-Photon Emission Computed Tomography
TB	Tuberculosis
TPHA	Treponema Pallidum Hemagglutination Assay
VDRL	Venereal Disease Research Laboratory

Abstract

Background: The use of neuro-imaging tests such as Computerised Tomography and Magnetic Resonance Imaging in psychiatry have been largely evaluated as useful but not essential. Neuro-imaging has been said to play no major role in psychiatric diagnoses beyond ruling out medical conditions such as traumatic brain injuries, tumours, infections, infarctions and bleeds. Furthermore, the majority of studies in this field suggest that neuro-imaging may be over used in psychiatry. Thus there is a need for further research in the diagnostic yield of neuro-imaging in psychiatry in order to ensure that appropriate, cost-effective methods of diagnosis are adopted, especially in South Africa's under-resourced institutions.

Aim: This study aims to determine the clinical diagnostic value of neuro-imaging in psychiatric in-patients at the Charlotte Maxeke Johannesburg Academic Hospital during a two year period dating 1 January 2014 to 31 December 2015.

Methodology: A quantitative, retrospective record review of adult psychiatric in-patients was conducted at the aforementioned institution during a two-year study period. The inclusion criteria was all adult psychiatric in-patients that had brain Computerized Tomography and/or Magnetic Resonance scans performed and reported during the study period. The participants were investigated in terms of demographic characteristics, scan characteristics, DSM-IV-TR/5 diagnosis and medical diagnosis that may be associated with a positive scan result. Data analysis included descriptive statistics and a chi square analysis.

Ethical clearance was obtained from the Human Research Ethics Committee at the University of the Witwatersrand. Charlotte Maxeke Johannesburg Academic Hospital Chief Executive Officer permission to conduct the study was also obtained.

Results: Of the one thousand and fourty (n=1040) adult psychiatric patients' medical records reviewed for the time period between 1 January 2014 to 31 December 2015, two hundred and thirteen (n=213) adult psychiatric patients fit the inclusion criteria of documented CT brain scan or MRI results. In total, n=74, 34.7% of the neuro-images had abnormal reports recorded. There was no statistically significant difference between the normal and abnormal CT and/or MRI scan groups with regard to demographic characteristics (age and gender), scan characteristics (type, frequency and urgency of scan) and DSM-IV-TR/5 diagnosis. HIV has a statistically significant p-value of 0.04 to denote that abnormal neuro-imaging has clinical value in its diagnosis.

Conclusion: Diagnoses in psychiatry are based entirely on behavioural, not biological, criteria. As demonstrated in other studies, this study also came to the conclusion that structural neuro-imaging is not be the key diagnostic tool in psychiatry. However, neuro-imaging is essential in excluding medical conditions.

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

Neuro-imaging is fairly new to neuroscience and psychology. It is the use of various techniques to image the structure and function of the nervous system (Filler, 2009). The neuro-imaging techniques may be divided into two main groups, namely (Filler, 2009):

- **Structural imaging:** which assess the structurual anatomy of the brain; and
- **Functional imaging:** which, on a finer scale, assesses the physiological functioning of the brain such as in metabolic diseases. It may further assess intracranial lesions. It is extensively used for neurological and cognitive psychology research.

The guidelines for neuro-imaging indications vary internationally and locally, with no clear consensus. In 1996, an American survey attempted to refine indications for CT and MRI brain scans in psychiatric patients. The group of authors reported on a summary of the following indications for brain imaging in psychiatric patients (Hollister and Shah, 1996):

- New or unexplained focal neurologic signs,
- Confirming a clinical diagnosis of Alzheimer disease and
- First episode psychosis or personality change after the age of 50 years.

Recently, the South African Society of Psychiatrists (SASOP) 2013 guidelines recommend neuro-imaging for the following conditions:

- Schizophrenia: CT or MRI and EEG in first episode patients that present with atypical symptoms, or when there are abnormal clinical examination findings;
- Dementia: CT or MRI. Functional neuro-imaging recommended to clarify the diagnosis; and

- Bipolar Disorder I: MRI is recommended over CT, and maybe helpful if there is a suspected medical condition. The investigations are to assist with management, not diagnostic. (Emsley et. al., 2013).

Research recommends the use of functional neuro-imaging in psychiatry rather than the use of structural neuro-imaging. Although, the clinical value for functional neuro-imaging has not been demonstrated through research, it promises to highlight functional brain abnormalities, whilst it assists the clinician to measure the treatment response (Masdeu, 2011).

The place of structural neuro-imaging in psychiatry is unclear. Neuro-imaging has been shown to play no major role in psychiatric diagnoses beyond ruling out medical conditions such as traumatic brain injuries, tumours, infections, infarctions, bleeds (Khandanpour, Hoggard and Connolly, 2013; Chhagan and Burns, 2016). Furthermore, studies persistently report on inconclusive findings that question the value of performing these tests. The majority of studies have been against this practice and have reported on excessive use of neuro-imaging in psychiatry (Chhagan and Burns, 2016).

1.2 BACKGROUND

Literature is consistent on the lack of the clinical value of neuro-imaging in specific psychiatric illnesses such as psychoses. When neuro-imaging was done in these patients, the results did not offer assistance in the management of patients with psychosis (Strahl, Cheung and Stuckey, 2010; Khandanpour, Hoggard and Connolly, 2013).

Although, functional neuro-imaging assessments allow mapping of the physiology of the brain by various methods such as the measurement of blood flow and glucose metabolism (McGuire and Matsumoto, 2004), these techniques may be of benefit in disorders that are exceptionally difficult to diagnose on structural neuro-imaging such as mild TBI (Shenton et al., 2012). A review by Shenton et al. (2012), reported that additional advances in neuro-imaging methods, such as diffusion tensor imaging (DTI), make it possible to characterise brain abnormalities in mild TBI. The authors further reported that these developments could contribute to the identification of the biomarkers of injury, and therefore the ability to monitor these changes (Shenton et al., 2012).

CT brain scans reportedly show a lower yield of detecting pathology. This view was supported by the study by Chhagan and Burns (2016), that looked into the clinical value of brain CT use in Addington Hospital, Durban, South Africa; a general hospital offering psychiatric services. The authors found that abnormalities found on CT scans did not influence the overall management of 22 of their total 23 patients (Chhagan and Burns, 2016).

This poses a challenge in the South African public health setting, where CT scans are more accessible than MRI scans. Even when a more sensitive neuro-imaging modality such as an MRI is performed, the clinical significance of the results is not clear. MRI commonly detects incidental findings, the clinical relevance of these findings are unclear, therefore, the management thereof not clearly defined (Ebdrup et al., 2011). The study by Vernooij et al. (2007), reported a high MRI incidental findings in the non-psychiatric general population. The most frequent MRI brain incidental findings were; infarcts, aneurisms, and benign primary tumours. The recommendation from their study was to obtain further clinical information in order to determine the relevance of the incidental findings (Vernooij et al., 2007).

A small explorative study by Jeenah and Moosa (2007) reported a significant number of abnormalities on CT scans, especially in patients with FEP (First Episode Psychosis). The authors looked to determine the value of CT in the assessment of psychiatric patients, as is the aim of this study to determine whether neuro-imaging has a place in diagnosis of psychiatric patients. This study concluded that clinical abnormalities did not predict CT brain scan abnormalities.

1.3 LITERATURE REVIEW

1.3.1 Computerised Tomography Brain Scans

Progress in structural neuro-imaging started with the introduction of computed tomography (CT) (Krishnan, 2012). CT uses ionising radiation to produce multiple axial slices through the brain. The CT images can then be reconstructed into various planes (Krishnan, 2012).

After reviewing CT brain findings, Bennimahadeo and Maharajh (2016), developed guidelines for the use of CT brain scans in psychiatric patients. The authors recommended the use of CT screening only for patients with a clinical suspicion of intracranial pathology such as: localising signs, seizures, decrease in Glasgow Coma Scale (GCS), papilloedema and in patients where the onset of symptoms occurred at an age above 50 (Bennimahadeo and Maharajh, 2016).

Advantages of Computerised Tomography Brain Scans

CT has a few advantages: it is more accessible, non-invasive, and relatively cheaper and fast (Niogi and Mukherjee, 2010). According to the administrative department at the CMJAH, the cost for a CT is around R1 500 to R2 700 for a pre-contrast and post-contrast CT brain scans respectively, whilst the alternative to CT, the MRI is said to cost up to R7000.

Another advantage is that CT is better suited to imaging the unstable and agitated patient because of its speed, therefore quicker and easy to use in the acute setting. Furthermore, the CT environment is better equipped to accommodate life support equipment than the MRI, making its use preferred in the acute setting (Shenton et al., 2012).

Research has also reported a good comparison of the modern multi-slice CT to MRI when detecting global cortical atrophy and hippocampal atrophy (Korbo, Praestholm and Skot, 2002).

Disadvantages of Computerised Tomography Brain Scans

The use of ionizing radiation in CT scans can lead to detrimental side-effects that include: adverse reactions to the contrast, such as anaphylactic reactions and phlebitis have also been reported (Shenton et al., 2012).

A few studies also reported the risk of cancer associated with repeated CT ionizing radiation exposure. A greater number of studies dispute the carcinogenic consequences of ionizing radiation. McCollough et al. (2015), concluded that there is no evidence that CT scans increase cancer rates thus, only medically necessary CT scans must be ordered to decrease radiation dosage (McCollough et al., 2015).

1.3.2 Indications for Computerised Tomography Brain Scans

Differentiating between psychiatric manifestations of an underlying medical condition and a primary psychiatric disorder is crucial as management is not the same. The former is essentially managed by managing the medical condition.

It is not common practice in psychiatry to diagnose a psychiatric disorder based on neuro-imaging findings alone. Psychiatrists heavily rely on the history taking and clinical examination to form a comprehensive assessment of a patient. There are a number of identified medical and psychiatric indications for CT scans.

1.3.2.1 Psychiatric Indications for Computerised Tomography Brain Scans

Psychiatric indications for CT brain scans include: psychosis; mood disorder symptoms; anxiety disorder symptoms; dementia and intellectual disability (Emsley et. al., 2013).

a. Psychosis

The NICE 2008 guidelines define psychosis as a symptom of mental illness that is associated with delusions, hallucinations, and disordered thoughts. Those with psychotic symptoms may have impaired reality testing (National Institute for Health and Clinical Excellence, 2008). The time of the psychotic presentation may range from childhood to the elderly depending on the cause for psychosis (National Institute for Health and Clinical Excellence, 2008).

Psychosis is referred to as functional when it is associated with diagnoses such as schizophrenia or bipolar disorders. Functional psychoses are commonly diagnosed in young adults. Psychoses that are related to medical or surgical illnesses are referred to as organic psychoses. These commonly occur in the older people. Organic psychoses may be associated with the use of alcohol or illicit substances or with medical conditions such as intracranial lesions (tumour, cyst, etc.), stroke and head injury (National Institute for Health and Clinical Excellence, 2008).

FEP refers to the first presentation of psychotic symptoms. The NICE 2008 guidelines add that FEP includes those people who may have had psychosis for long periods without treatment intervention, and those whose symptoms persist despite treatment (National Institute for Health and Clinical Excellence, 2008). The NICE 2008 guidelines discourage routine structural neuro-imaging (CT/MRI) as part of the initial investigations for the management of FEP as the results do not influence clinical management. In their report, the NICE assessment group added that routine imaging of those with FEP did not show cost-effectiveness. Clinical management was affected in only a range of 0 % to 0.5 % of people with psychosis (National Institute for Health and Clinical Excellence, 2008).

A greater number of studies have similarly reported on the low yield of detecting pathology of structural neuro-imaging for psychosis. There are large reports of high yield of incidental findings in neuro-imaging results, hence the lack of cost-effectiveness.

A study by Khandanpour, Hoggard and Connolly (2013) reported that routine MRI or CT neuro-imaging was unlikely to significantly alter the course in management. The authors recommended against routine structural neuro-imaging of FEP in patients without focal neurological signs. In their study, they found no significant change in the management of these patients after the neuro-imaging scan results. Further, the study reported no significant differences between MRI and CT brain scans in their yield for detecting pathology, especially when the cause of FEP was HIV or a tumour. This retrospective study assessed whether imaging could identify the organic causes of FEP in three hundred and sixteen (n=316) scans. Two groups were assessed with either CT (n=204) or MRI (n=112) alone. The results showed a high number of incidental brain lesions for both MRI (62.5%) and CT (65.2%) scans. The incidental findings included cerebral atrophy, small vessel ischaemic changes and arachnoid cysts (Khandanpour, Hoggard and Connolly, 2013).

A study by Strahl, Cheung and Stuckey (2010), looked to assess the clinical efficacy of CT brain scans in patients presenting with FEP without neurological signs. This study did not find pathology that directly linked to the psychosis. The findings similar to the aforementioned study by Khandanpour, Hoggard and Connolly (2013), did not lead to a change in the clinical management (Strahl, Cheung and Stuckey, 2010).

A review of studies involving structural MRI techniques in patients with psychosis, published between 1976 and 2015, also reported on the low yield for pathology detection when structural neuro-imaging was used in patients with psychosis (Fusar-Poli and Meyer-Lindenberg, 2016).

A systematic review concluded in 2011, highlighted that there was no evidence in support of performing routine CT brain scans of FEP patients. The authors recommended that if intracranial pathology is suspected clinically, an MRI scan should rather be performed (Ebdrup et al., 2011).

Some studies have, however, reported on the significant findings of neuro-imaging in psychosis. A small study of 55 patients conducted at a tertiary referral hospital by Jeenah and Moosa (2007), reported that in a psychiatric population, CT investigations revealed a significant number of abnormalities, especially in patients with FEP (Jeenah and Moosa, 2007).

Even though research advocates for the employment of use of neuro-imaging techniques when a medical condition is suspected to be associated with psychosis, there is paucity of literature regarding the cost-effectiveness of diagnosing such organic illnesses using neuro-imaging. As medical practice guides, organic illnesses are diagnosed based on history taking and physical examination (Bennimahadeo and Maharajh, 2016), often aided by laboratory assessments.

b. Mood disorder symptoms

A mood disorder may present with mania, hypomania, depressive or a mixture of these symptoms. Either presentation could run an acute, gradual or a chronic course. The symptoms may qualify a primary mood disorder after the likely causal medical or substance use related factors have been excluded (American Psychiatric Association. Task Force on DSM-5, 2013). DSM-5 allows for a secondary diagnosis of a mood disorder, due to another medical condition (AMC) or due to a substance use (substance-induced mood disorder). The diagnoses of the mood disorders are based on the DSM-5 diagnostic criteria.

The morbidity and mortality rates for mood disorders is high, with depressive disorders the leading mood disorder diagnoses, making the reliable assessment and diagnosis of these disorders imperative (Ferrari et al., 2013; National Collaborating Centre for Mental Health, 2010).

Depressive disorders are the leading cause of disease burden globally. Major depressive disorder is the largest contributor of burden in suicide and ischemic heart disease (Ferrari et al., 2013). According to the Global Burden of Disease 2010, mental disorders accounted for the largest proportion of disability (56.7%), followed by neurological disorders (28.6%) and substance use disorders (14.7%) (Whiteford et al., 2015).

According to the NICE 2010 guidelines, depression affects 6% of adults yearly and contributes to the highest suicide rate annually. The depressive symptoms can be disabling, impacting on not only the individual patient but also on their families and the society at large (National Collaborating Centre for Mental Health, 2010).

A Korean study reported on depression as a significant burden on the society and the individual, leading to disability especially in terms of incapacity to work (Chang, Hong and Cho, 2012).

The use of rating scales to aid the diagnosis and to grade the severity is recommended in mood disorders. The rating scales may also be used to monitor treatment response in mood disorders. Different rating scales may be used for different population groups with reliable accuracy for diagnosing mood disorders (Emsley et. al, 2013; Costa et al., 2016).

These include the 17-item Hamilton Rating Scale for Depression (HDRS-17), the Patient Health Questionnaire-9 (PHQ-9) and the 15-item Geriatric Depression Scale (GDS-15) to diagnose major depressive episodes in older adults without neurocognitive disorders (Costa et al., 2016). The SASOP 2013 guidelines further include the primary care evaluation of mental disorders (PRIME-MD), the Hamilton Depression rating scale (HAM-D), the Montgomery-Asberg depression rating scale (MADRS), the structured clinical interview for the DSM-IV axis I disorders (SCID-I), young mania rating scale (YMRS) for mania, and bipolar depression rating scale (BDRS) for bipolar depression (Emsley et.al., 2013).

It is thus not common practice to diagnose a mood disorder on neuro-imaging. Neuro-imaging, however, may be used to confirm medical pathology that may be associated with a mood disorder. Therefore, an organic causal factor for the development of mood disorders may be identified on neuro-imaging, rather than basing the diagnoses on neuro-imaging (Klein, 2010).

The SASOP 2013 guidelines recommend that the use of neuro-imaging in bipolar disorder is indicated when an organic aetiology is suspected, in which case, the guidelines recommend for the use of an MRI (Emsley et. al., 2013). The guidelines do not make a reference to the use of neuro-imaging in depression.

The NICE guidelines recommend a full psychiatric assessment, including documenting a detailed history of mood and family history (National Institute for Health and Clinical Exellence, 2014).

When pathology is identified on neuro-imaging, cortical and/or white matter abnormalities that are not specific for a particular mental disorder may be found. Similar to previous studies, Barysheva et al. (2013), reported white matter abnormalities in the corpus callosum. The authors reported a link of the bipolar diagnosis with structural abnormalities of the tapetum, fornix and stria terminalis, a finding not exclusive to bipolar illness (Barysheva et al., 2013).

Further, the neuro-imaging findings of depression may be similar to those found in anxiety disorders, adding to the diagnostic uncertainty of neuro-imaging in these disorders. The findings of the study by Van Tol et al. (2010), reported on the reduced size of the anterior cingulate gyrus in both depression and anxiety disorders, independent of treatment use or demographics of the study sample (Van Tol et al., 2010).

A review by (Pandya et al., 2012) reported on the inconsistent findings regarding the areas involved in depression (Lim et al., 2012). Therefore, on-going research is necessary to answer the question of the value of neuro-imaging in mood disorders. First, clarification on the parts of the brain affected by mood disorders is needed. Price and Drevets (2010), reported on the links between the medial prefrontal cortex and the amygdala, the ventral striatum and pallidum, and the hypothalamus. After assessing the functioning of this system in monkeys, the authors reported that it may be this system that is primarily involved in mood disorders (Price and Drevets, 2010).

c. Anxiety Disorder symptoms

Anxiety involves physical and cognitive changes that are driven by a complex of neural mechanism (Grupe and Nitschke, 2013). This neural mechanism implicates amygdala connections to the hypothalamic–pituitary-adrenal (HPA) axis, the cingulate cortex and the pre-frontal cortex. At rest, people with high anxiety generally show a negatively correlated amygdala and ventral-medial pre-frontal cortex functional connectivity, while less anxious people show a positively correlated activity (Kim et al., 2011). Anxiety disorders show a close association with childhood life events and HPA abnormalities (Faravelli, 2012).

Similar to the diagnosis of mood disorders, the diagnosis anxiety disorders heavily relies on clinical judgement (Connor et al., 2001). As for mood disorders, the use of rating scales may add value to the diagnosis, measuring of severity, and monitoring of the treatment response (Emsley et. al., 2013), Connor et al., 2001)

The neuro-imaging findings in depression compare to those found in anxiety disorders, adding to the diagnostic uncertainty of neuro-imaging in these two disorders. The reduced size of the anterior cingulate gyrus in both depression and anxiety disorders has been a commonly reported neuro-imaging finding in both the disorders (Van Tol et al., 2010).

d. Dementia (Major Neurocognitive Disorder)

In the DSM-5, dementia is now named Major Neurocognitive Disorder (major NCD). It is defined as evidence of significant cognitive decline from a previous level of functioning in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) (American Psychiatric Association, 2013). Cognitive domains assessment is a clinical assessment.

The use of neuro-imaging in the assessment of dementia should be done with caution. Typically, when there are no obvious abnormalities detected on these scans, the scan is reported as normal, even though this may not rule-out dementia (Harper et al., 2014). In particular, structural neuro-imaging often shows cortical atrophy in demented patients. The correlation of atrophy with cognitive decline is diagnostic (Bonifacio and Zamboni, 2016), even though the absence of brain atrophy on neuro-imaging in clinically suspected dementia may not negate the diagnosis.

When neuro-imaging is indicated or used, functional techniques are rendered superior. However, these techniques should also be used and interpreted with caution and in the context of clinical history and examination.

Even though in their study, Bonifacio and Zamboni, showed that different MRI and PET imaging scans was able to detect unique abnormalities to the most common dementia syndromes, they found that neuro-imaging served a supportive role in addition to the clinical assessment. The authors also reported that the diagnoses could not be reached without a clinical assessment (Bonifacio and Zamboni, 2016).

If structural neuro-imaging is used, MRI is preferred. Some of the limitations of the structural MRI however, are that it takes time to change in relation to the disease process and does not provide information about function like the functional MRI. Also, structural MRI is not specific to the underlying pathology of dementing syndromes. A report of atrophy may be fitting to different diseases (Bonifacio and Zamboni, 2016).

An analysis into the appropriate use of neuro-imaging in the diagnostic work-up of dementia by Ontario (2014) found the clinical utility of structural neuro-imaging to be:

- High for patients with potentially mixed dementias than for those with vascular dementia. For those with vascular dementia, MRI compared to CT in picking up pathology;
- Low for patients with Alzheimer's disease (Ontario, 2014).

In this study, structural neuro-imaging showed low to moderate sensitivity in terms of diagnostic accuracy (Ontario, 2014). Medical factors resulting in the dementia may be apparent on neuro-imaging. For example: structural CT may detect a vascular infarct that may have resulted in dementia (Ontario, 2014).

e. Intellectual Disability

Formerly known as Mental retardation, DSM-5 has changed the term to Intellectual Developmental Disorder (IDD), commonly called Intellectual Disability (ID). ID is a disorder with onset during the developmental period that includes impairments in both intellectual (executive functioning and academic learning.) and adaptive functioning (conceptual, social, and practical) domains (American Psychiatric Association, 2013).

People with ID often have co-morbid medical and psychiatric disorders. A careful history and physical examination remain the most helpful tools for determining the aetiology and diagnosis of ID (Shea, 2012).

Medically, ID may present in association with genetic syndromes such as Down's syndrome and Turner's syndrome. Shea (2012) reported that genetic testing may reveal the aetiology of ID in only about 14% of children with non-diagnostic histories and physical examinations (Shea, 2012).

ID shares the highest co-morbidity with Epilepsy. A study by Arshad et al. (2011), reported a high incidence of severe ID and epilepsy co-morbidity (Arshad et al., 2011). Memisevic and Sinanovic (2009), also reported a high co-occurrence of epilepsy in children with ID (Memisevic and Sinanovic, 2009).

In psychiatry ID is often associated with Attention-Deficit/Hyperactivity disorder (ADHD) and Autism spectrum disorders (ASD) (Voigt et al., 2006; Lindsay et al., 2013; Faraone et al., 2017). A review by Tuchman, Cuccaro and Alessandri (2010), reported a strong association between ID, epilepsy and ASD (Tuchman, Cuccaro and Alessandri, 2010).

The use of neuro-imaging in ID is not routinely recommended. Studies have reported abnormal findings, commonly cortical atrophy, in people with ID without a clear clinical value. A study by Zhang et al. (2011), found that patients with ID had significantly reduced cortical thickness in multiple areas of the brain compared with a cohort. The regions affected included; bilateral fusiform gyri, bilateral parahippocampal gyri, the left inferior temporal gyrus, the orbitofrontal cortex, etc. Areas of cortical atrophy may explain the impaired intellectual, adaptive, and social functioning in patients with ID. However, the location of the atrophy or its severity may not correlate with the clinical findings (Zhang et al., 2011).

1.3.2.2 Medical indications for Computerised Tomography Brain Scans

Many medical conditions may give rise to psychiatric-like symptoms. Patients with these medical illnesses often end up on either side of the medical and/or psychiatric specialities.

The use of CT brain imaging in these patients has been reported. Some of the medical indications for CT brain scans that will be discussed include (Haydel et al., 2000; Runchey and McGee, 2010; Mitsunaga and Yoon, 2015; Gomolka et al., 2016):

- Brain Infections such as HIV, Tuberculosis (TB), Syphilis, etc.
- Focal neurological deficits (stroke and seizures) and
- Head injuries.

The use of CT imaging to assess the aetiology of delirium may be unnecessary (Theisen-Toupal et al., 2014; Vijayakrishnan, Ramasubramanian and Dhand, 2015). Delirium will also be discussed as a frequent medical condition seen in psychiatric referrals.

Because MRI has proven superior in its use in diagnosing CNS infections including HIV (Sarrazin, Bonneville and Martin-Blondel, 2012), the use of neuro-imaging in CNS infections will be discussed under MRI brain indications.

a. Stroke

Stroke or cerebrovascular accident is among the leading causes of death globally. The second National Burden of Disease Study looked at the mortality trends and differentials in South Africa from 1997 to 2012. The study indicated that in 2012, cerebrovascular disease (7.5%) was the second common cause of deaths after HIV/AIDS (29·1%) (Pillay-van Wyk et al., 2016).

HIV seems to be changing the field of the study in that the prevalence of strokes is increasing in younger people. HIV and associated infections are associated with chronic inflammation (Benjamin et al., 2012), which is one of the commonest causes of atherosclerosis. Atherosclerosis is an important risk factor for stroke. Also, although combination antiretroviral therapies for the treatment of HIV/AIDS are clearly beneficial, they have heavily been implicated in the aetiology of metabolic risk factors (such as hypertension, insulin resistance, and dyslipidaemia) further compounding the risk for strokes (Benjamin et al., 2012).

Even though the diagnosis of stroke is typically a clinical one, associated with focal neurological fallout, neuro-imaging is indicated to confirm the location and extent of the brain injury.

The most common ischaemic strokes seen affect the lacunar area. The neuropsychiatric sequelae of these kind of strokes include cognitive impairment and depressive disorder symptoms. A meta-analysis reported that cognitive impairment appeared to commonly follow lacunar strokes despite their small size. The authors reported a 20% new dementia diagnosis following a lacunar stroke (Makin et al., 2013).

A review by Sahathevan, Brodtmann and Donnan (2012) reported that the vascular risk factors appear to be independent risk factors in developing dementia (Sahathevan, Brodtmann and Donnan, 2012).

Depression affects most of the stroke patients and has a high risk of recurrence in the long term (Ayerbe et al., 2013). Hommel, Carey and Jaillard, reported a strong relation between depression and cognition characterized by executive function deficits and working memory dysfunction (Hommel, Carey and Jaillard, 2015).

Neuro-imaging is indicated and adds diagnostic value in the assessment of the stroke. An important indication of neuro-imaging is also to distinguish haemorrhagic from ischaemic strokes as there may not be adequate differentiating clinical signs.

A study that looked at the clinical findings to distinguish haemorrhagic stroke from ischaemic stroke found that in all patients with acute stroke, no finding or combination of findings was definitively diagnostic for haemorrhagic or ischaemic strokes. Therefore, neuro-imaging is indicated to differentiate haemorrhagic from ischaemic strokes (Runchey and McGee, 2010).

b. Seizures

The International League against Epilepsy defines a seizure as an occurrence of signs or symptoms due to an abnormal neuronal activity in the brain. During this time, there is abnormal firing by neurons (Fisher, Shafer, D'Souza, 2016). There are various causes for seizures, including epilepsy disorder.

Epilepsy is a common neurological disorder characterised by recurring seizures (National Institute for Health and Care Excellence, 2011). Epilepsy may have varying aetiologies associated with the blood brain barrier (BBB) dysfunction. The BBB is a specialized structure which functions to control the neuronal extracellular milieu. BBB dysfunction may be a result of medical conditions such as a stroke, traumatic brain injury, brain infections, tumour, etc. (Weissberg et al., 2011) which may result with ‘epilepsy’ or seizures. When neuro-imaging was used in late-onset epilepsy, the most common abnormalities reported were cerebral infarct and brain tumour (Owolabi et al., 2013).

One of the type of epilepsies that bear special interest in psychiatry is Temporal Lobe Epilepsy (TLE). TLE is the most common form of adult localization-related epilepsy (Weissberg et al., 2011; Tatum, 2012). People with TLE may present with a wide range of neuropsychiatric manifestations. Commonly seen are the cognitive impairments, specifically semantic memory impairments (Bonelli et al., 2010; Lambon Ralph et al., 2012). This may likely be due hippocampus sclerosis that shares a strong etiological association with TLE. Tatum (2012) reported that hippocampal sclerosis accounts for at least 80% of all temporal lobe seizures (Tatum, 2012).

MRI shows better sensitivity for the diagnosis of TLE. On coronal sections of the MRI, hippocampal sclerosis, also known as mesial temporal sclerosis, is reported a typical feature of TLE, usually missed on CT scans. Detecting mesial temporal sclerosis may also help by guiding the surgical intervention (Azab et al., 2015), in those with refractory TLE.

Another feature of mesial temporal sclerosis is hippocampal atrophy (Azab et al., 2015). Coan et al. (2014), reported on a high likelihood of detecting hippocampal sclerosis in people with TLE when 3T MRI was used (Coan et al., 2014).

For the diagnosis of other epilepsies, a clinical assessment that includes a neurological examination, together with a positive family history of epilepsy may suffice the diagnosis. An electroencephalogram (EEG) can be useful for diagnosis, management, and optimising treatment response in patients with seizures and status epilepticus (Foreman and Hirsch, 2012). According to the NICE 2012 guidelines, an EEG should only be used to support the diagnosis of epilepsy after a comprehensive history taking and clinical examination (National Institute for Health and Care Excellence, 2011).

Therefore, too much weight may not be placed on the diagnostic value of an EEG. Increasingly, literature suggests the use of video EEG, 24-hour EEG, etc.. Video-EEG monitoring make the seizure classification and the assessment of psychogenic non-epileptic seizures easier to assess (St. Louis and Cascino, 2016).

The use of neuro-imaging for the diagnosis of epilepsy may be warranted where a medical cause for a seizure is suspected, such as brain infections, trauma, tumour, etc. MRI is recommended over CT scan. In their study, St. Louis and Cascino (2016), found that MRI played an important role in the detection of the aetiology of the seizure disorder and in the localisation of the seizure (St. Louis and Cascino, 2016). Unfortunately, CT-scan remains a vital and available diagnostic tool for the epilepsy investigation in poor countries when MRI is not accessible (Moifo et al., 2014).

High MRI sensitivity was reported in detection of seizure aetiology in refractory epilepsy in a study by Nikodijevic et al. (2016), whereareas EEG was sensitive in localising the epileptogenic focus. The study aimed to correlate the imaging findings of EEG, MRI and CT scan in treatment-resistant epilepsies, and to assess their specificity in detecting the epileptogenic focus. Positive MRI findings were reported in 75.7 % patients, mostly with hippocampal sclerosis. The authors reported that, in detecting the epileptogenic focus, a significant difference ($p < 0.01$) was found in favour of MRI over CT scan, especially in patients with hippocampal sclerosis and cerebral malformations (Nikodijevic et al., 2016).

The NICE 2012 guidelines recommend the use of neuro-imaging in certain epilepsies only to identify the possible underlying structural pathology. The guidelines recommend the following indications for neuro-imaging in epilepsy:

- An MRI scan if epilepsy occurs before the age of 2 years; if epilepsy occurs in late adulthood; and if epilepsy occurs in the presence of focal neurology.
- Routinely when a diagnosis of idiopathic generalised epilepsy has been made.
- A CT scan if MRI is unavailable or contraindicated.
- A CT scan for children or young people who require the use of anaesthesia or sedation for an MRI.
- Lastly, a CT scan in an acute setting to identify acute causes such as an intracranial lesion, etc..

Epilepsy has serious neuropsychiatric manifestations in the long-term. These include affective and anxiety disorders, cognitive disorders, and rarely psychosis (Beghi et al., 2010; Vlooswijk et al., 2010; Smith and Puka, 2016). A study that looked at the neuropsychiatric morbidity in focal epilepsy found a significant association between the prevalence of depressive symptoms and non-lesional focal epilepsy (Adams et al., 2008). However, the diagnostic assessment of these neuropsychiatric manifestations does not require neuro-imaging.

c. Delirium

Delirium is a complex neuropsychiatric syndrome with fluctuation in cognition. Sleep-wake cycle disturbances often accompany the delirium (Jabbar et al., 2011). During a period of a delirium, patients may experience perceptual disturbances often in the form of visual hallucinations. The presentation may be that of hypo-active delirium, hyper-active delirium, or a mixture of the two types.

Psychiatric services are often required to assess and assist with the containment of the difficult behaviour of the delirious patient. In a retrospective study of all patients referred to the Helen Joseph Hospital (HJH) in Johannesburg, seen by the consultation-liaison psychiatry team over a 6-month period, Tema and Janse van Rensburg (2015) reported that the most common advanced reasons for referral were a request for assessment, which included assessing for capacity to consent for medical care. In their study, 10 % of cases consulted had diagnoses of delirium, dementia and/or a mood or psychotic disorder due to a general medical condition (Tema and Janse van Rensburg, 2015).

Paddick, Kalaria and Mukaetova-Ladinska (2015) reported high delirium rates in psychiatric patients (18.2%-29.9%) (Paddick, Kalaria and Mukaetova-Ladinska, 2015).

Those with dementia are reported to show higher vulnerability in acquiring delirium episodes. A cohort study of post-stroke patients by Melkas et al. (2012), found an association between dementia and delirium. The authors reported on the diagnosis of acute delirium for every one in five patients with dementia (Melkas et al., 2012).

A pilot study, conducted in intensive unit care survivors, looked to assess whether the duration of delirium could predict long-term cognitive impairment. In this study, delirium duration was associated with white matter abnormalities. White matter disruption was associated with worse cognitive scores. MRI was reportedly best suited to assess white matter abnormalities (Morandi et al., 2012).

Delirium is more common in the elderly, however, with the prevalence of HIV, more young people cases are reported (Paddick, Kalaria and Mukaetova-Ladinska, 2015). A study by Tema and Janse van Rensburg (2015), reported on a higher prevalence of delirium associated with HIV/AIDS in a demographic of female patients between 31 and 45 years of age (Tema and Janse van Rensburg, 2015).

Delirium is a clinical diagnosis encompassing a detailed history, clinical examination and usually a performance of laboratory investigations to confirm a suspected cause of the delirium. The use of neuro-imaging, therefore, may not be cost-effective. A study by Theisen-Toupal et al. (2014), looked at the diagnostic yield of CT for the medical patient with delirium and found that, the diagnostic yield of brain CT in determining the cause of delirium in that population was low. Of the 398 patients who underwent brain CT imaging, only 2.7 % had positive findings. A further 1.8 % had findings not related to the delirium. The study reported that brain imaging was found to be unnecessary in the majority of cases of delirium (Theisen-Toupal et al., 2014).

Vijayakrishnan, Ramasubramanian and Dhand (2015), reported acute changes on neuro-imaging in only four patients with delirium. The authors recommended that imaging should be considered only in cases of: head injury, history of anticoagulation, focal neurological signs, etc.(Vijayakrishnan, Ramasubramanian and Dhand, 2015).

However, there may be a group of high-risk individuals in which head imaging is indicated. Even though Theisen-Toupal et al. (2014), reported a low diagnostic yield of CT for their population of patients with delirium, the findings in those patients resulted in change in management. It is, however, unclear if the management of these patients may have changed in the absence of neuro-imaging (Theisen-Toupal et al., 2014).

Therefore, the development of more clear guidelines may be cost-effective and may assist with the reduction of the radiation exposure to the patients (Vijayakrishnan, Ramasubramanian and Dhand, 2015).

d. Head Injury

Head injury or Traumatic Brain Injury (TBI) is an acquired insult to the brain from an external mechanical force, possibly leading to permanent or temporary impairment of cognitive, physical, and psychosocial functions (Dawodu, 2011). TBI is a closed head injury, associated with a loss of consciousness (LOC) (Dawodu, 2011).

The duration of the LOC, duration of the post-traumatic amnesia and the Glascow Coma Score (GCS) may all be helpful in the grading of the TBI severity. The GCS of above 13 is reported as mild TBI, 9-12 is reported moderate TBI, and GCS of 3-8 reported severe TBI (Pearl Chung, 2013). The most common form of TBI is the mild TBI (mTBI), also known as post-concussion syndrome (Laskowski, Creed and Raghupathi, 2015).

TBI is reported to be amongst the most common causes of death and disability. There is paucity of data on TBIs in South Africa. Head injury was reportedly the leading cause of trauma-related deaths in a retrospective audit that was conducted by Moodley, Clarke and Aldous (2014), in an urban metropolitan complex in Kwa-Zulu Natal, Pietermaritzburg. The authors aimed to present a comprehensive overview of the forensic mortality data for trauma by reviewing all mortuary reports for the period 1 January 2010 to 31 December 2011. They reported death in a total of 1 105 trauma victims. The authors reported a higher male (84.2%) than female (15.8%) deaths. Of the deaths related to blunt trauma, road traffic collision (75.1%) accounted for more deaths than assault (24.9%). For penetrating trauma deaths; gunshot wounds accounted for more deaths than stab wounds. Stabbing was the most common cause of penetrating trauma. (Moodley, Clarke and Aldous, 2014).

The absence of an open head injury, or visible pathology on neuro-imaging does not exclude the possibility of a brain contusive injury as injury may occur at a microscopic and physiological level.

Obvious impairments from obvious open-brain injuries may be seen. More commonly, impairments from more subtle closed-brain injuries, such as mTBI, present. A detailed history, thorough clinical examination (including neurological examination), and neuro-imaging are mandatory.

Some of the TBI neuropsychiatric sequelae include mood and anxiety symptoms, commonly associated with mTBI. A review by Shenton et al. (2012), reported on the common presentation of PTSD, depression, and other co-morbid conditions in those suffering from mTBI (Shenton et al., 2012).

Cognitive disorders have also been reported in TBI (Niogi and Mukherjee, 2010). Some of the cognitive impairments include; impaired attention, memory, and/or executive functions (Laskowski, Creed and Raghupathi, 2015).

Neuropsychological battery of tests may be used to reliably localise the TBI lesion. The limitations of these tests are that they are expensive, time-consuming, and require a certain level of education and an understanding of the English language in most cases.

Neuro-imaging is indicated in TBI but the yield of diagnosis is low for structural neuro-imaging, especially in patients with mTBI. A review reported that the brain often appears quite normal on structural CT and MRI scans, making the diagnosis of mTBI controversial (Shenton et al., 2012). The use of especially CT scans for the assessment and diagnosis of TBI may therefore not be cost-effective. The study by Hinzpeter et al. (2017), in trauma patients found the use of repeated CT scans unnecessary. The authors further found that the radiation exposure to these patients may have been prevented, and that the use of CT scans was not cost-effective (Hinzpeter et al., 2017).

Newer and more advanced neuro-imaging techniques, such as MR spectroscopy and DTI, promise superior sensitivity in identifying areas of brain damage in mTBI (Kubal, 2012). These techniques are important for identification and localisation of pathology in mTBI, which is otherwise not easily detected by the older neuro-imaging techniques (Shenton et al., 2012).

Unlike CT or conventional MRI, the DTI advantage is its sensitivity to picking up axonal injuries, believed to result with persistent cognitive impairments and behavioural impairments seen in persons with mTBI (Niogi and Mukherjee, 2010).

1.3.3 MRI Brain scans

The study of neuro-anatomy using imaging has advanced valuable learning into how our brains function, more so under the influence of the changing environment and genes. Developments in magnetic resonance imaging (MRI) have been key to these advances (Lerch et al., 2017).

Since its introduction in the 1980's, MRI has rapidly become an essential diagnostic tool in modern medicine (Branco et al., 2014) and has become the most popular and versatile imaging method in psychiatric research (Derntl, Habel and Schneider, 2010). Since its inception, the rapid developments in MRI have paved way to interesting discoveries about the functioning of the brain (Krishnan, 2012).

MRI allows for the direct measurement of structures such as the thalamus, basal ganglia, limbic system (hippocampus, amygdala, cingulate cortex, hypothalamus etc.), structures of the posterior fossa and apical areas of the brain (Price and Drevets, 2010; Dannlowski et al., 2012; Goubran et al., 2016). The basic principle behind MRI is that radiofrequency pulses are used to excite the hydrogen nuclei (single proton) in water molecules in the human body, in this case the brain (Shenton et al., 2012).

MRI boasts a few important advantages over CT. It has no bone artefacts, therefore, the areas of injury around bone are easier to detect (Shenton et al., 2012). Magnetic resonance images can be manipulated to show contrast between grey and white matter (Ramsey., 2010), something not possible with CT images. Also MRI does not use ionizing radiation, as CT does (Giedd and Rapoport, 2010; Shenton et al., 2012), thereby reducing exposure to the toxic ionizing radiation effects. Further, MRI provides potential imaging in any plane (Shenton et al., 2012).

No structural imaging modality has full sensitivity and specificity for a given diagnosis. However, there may be a number of imaging characteristics unique to specific disorders/illnesses that may help narrow the differential diagnoses (Harper et al., 2014). MRI may have additional value to other diagnoses such as dementia, depression, schizophrenia, etc.

Harper et al. (2010), reported that, signal changes and cerebral atrophy visible on structural MRI could be used to identify diagnostically relevant imaging features, which provide support for clinical diagnosis of neurodegenerative dementias (Harper et al., 2014). Atrophy of medial temporal structures (such as the hippocampus) is now considered to be a valid diagnostic marker at the mild cognitive impairment stage (Frisoni et al., 2010). Structural neuro-imaging is also included in diagnostic criteria for the most prevalent non-Alzheimer dementias, therefore in these illnesses, structural neuro-imaging shows some value (Frisoni et al., 2010).

However, a study by Ramsey (2010), argued the difficulty in discriminating depression from schizophrenia as the two are sometimes difficult to distinguish on MRI imaging. Ramsey (2010) also argued that both schizophrenia and bipolar depression share decreased frontal cortex volume, suggesting some common denominator (Ramsey., 2010). Therefore, even the MRI findings can only be used as secondary after a good history taking and clinical examination.

MRI is not without limiting disadvantages. It is notoriously expensive, costing up to R 6 700 in our setting. MRI is also not readily available. In South Africa, MRI services are only available in tertiary hospitals with restricted access and long waiting periods. In our setting, the requisition for an MRI includes special motivation and discussion with a radiologist. A CT scan is a pre-requisite to the performance of an MRI. For those in-patients on the ‘urgent’ list for an MRI, there is about one week waiting period.

MRI is contraindicated in patients with pacemakers, implants, metallic foreign bodies and aneurism clips because of its magnetism.

Also, unfortunately, the increasing use of MRI for imaging of the brain in both research and clinical practice has led to an increased reports of incidental findings that have no clear implications. Even when healthy subjects undergo brain imaging, incidental findings are not rare (Borra and Sorensen, 2011; Cramer et al., 2011; Gupta, Gupta and White, 2016).

Studies persistently report that the intracranial incidental findings are generally of low clinical significance (Borra and Sorensen, 2011; Cramer et al., 2011; Thompson et al., 2011; Gupta, Gupta and White, 2016). A review on the spectrum of intracranial incidental findings on paediatric MRI reported a lack of a systematic approach to the interpretation these findings (Gupta, Gupta and White, 2016).

Borra and Sorensen (2011), reported on the incidental findings of 5%-20% of all examinations, whilst the percentage of clinically serious abnormalities was reported at only 0.3%-3.4% (Borra and Sorensen, 2011).

The incidental findings commonly reported are; enlarged ventricles, cysts, Virchow-Robin spaces, atrophy, etc. (Cramer et al., 2011).

Even though psychiatrists were generally reported to request the most MRI brain scans, the majority of them did not base psychiatric diagnoses on the result of these scans, but rather looked for an underlying medical cause. A study by Basto and Seixas (2009), measured the perceptions and expectations on brain imaging . Only 34 % of psychiatrists were reported to have expected to confirm their diagnostic hypothesis on brain MRI. Psychiatrists were the leading professionals (83 %) that only read the MRI report, compared to neurologists (36 %) and neurosurgeons (33 %) that also examined the MRI images. The neurologists had the least confidence in the MRI reports and the quality of images (Basto and Seixas., 2009; Branco et al., 2014). Psychiatrists were reported to be in the top 3 professionals that frequently request brain MRI (Basto and Seixas, 2009), yet only used these brain scans for confirmatory purposes.

MRI may not be the most cost-effective investigation in our clinical setting. However, the performance of MRI without having to perform a CT first may be cost-saving.

The clinical relevance of incidental findings should be interpreted within a given clinical context (Gupta, Gupta and White, 2016).

1.3.4 Indications for MRI Brain scans

Intracranial Infections (including HIV) and Brain Tumours will be discussed. Because of the impact of HIV in neuropsychiatry and its growing pandemic, HIV will be discussed under a heading of its own.

a. Human Immune-deficiency Virus

Human immune deficiency virus (HIV) belongs to a group of retroviruses called lentiviruses or slow viruses. There is an interval between the initial infection and the onset of symptoms. HIV infects blood cells (lymphocytes, monocytes and macrophages) by attaching to the CD4 on the membranes inside these cells. The most affected are the T-cell lymphocytes. Replication of the HIV inside these cells leads to the production of mature HIV (viremia). The more the T-cell lymphocytes become destroyed, the greater the vulnerability for opportunistic infections leading to the final stage of acquired immune deficiency syndrome, (AIDS).

HIV infection still accounts for about 1.5 million deaths annually, with sub-Saharan Africa mostly impacted by the pandemic (Chang et al., 2013). A high pandemic of HIV/AIDS in South Africa impacts on the health burden in our population. According to the second National Burden of Disease Study, in 2012, HIV/AIDS caused the most deaths in South Africa at 29.1% (Pillay-van Wyk et al., 2016). A study undertaken to provide a demographic and clinical profile of patients consulted by the consultation-liaison psychiatry service by Tema and Janse van Rensburg (2015), reported HIV to be the most common cause of illnesses (67.7 %) (Tema and Janse van Rensburg, 2015).

HIV and associated infections contribute to chronic inflammation (Benjamin et al., 2012). It is this inflammation, particularly in the brain, that results in detrimental neuropsychiatric sequelae. Although the combination antiretroviral therapies (ART) are clearly beneficial, they are associated with atherosclerosis. Atherosclerosis may lead to end-organ ischaemic injuries such as; strokes, cardiovascular events (e.g. myocardial infarction), nephropathies, etc. (Cysique et al., 2013).

Another challenge of ART is the prolongation of life, leading to an increase in an aging population with chronic atherosclerosis (Benjamin et al., 2012; Cysique et al., 2013).

The advent of ART has seen a significant decline in HIV-associated Dementia (HAD), but a rise in mild neurocognitive deficits. Clifford (2017), reported on worldwide poor outcomes on formal neurocognitive tests (Clifford, 2017), likely compounded by the prolongation of life by ART (Alfahad and Nath, 2013; Troncoso and Conterno, 2015). It is estimated that at least 40% of HIV-infected patients on ART continue to have cognitive impairments (Masters and Ances, 2014). Troncoso and Conterno (2015), reported a high prevalence of neurocognitive impairments according to the International HIV Dementia Scale. The high prevalence of neurocognitive impairments was associated with; female gender, low education level, and low CD4 level (Troncoso and Conterno, 2015).

HIV seems to share common biological characteristics with aging. Ances et al. (2012), reported on shared similarities between the brain functioning of HIV-positive people and that of older HIV-negative people. The authors measured brain functionality using functional MRI. The younger HIV-positive brain functioning compared to a 15-20 years older HIV-negative brain functioning (Ances et al., 2012).

A review reported that MRI and magnetic resonance spectroscopy studies performed in people in the pre-ART period and on those who were ART-naive suggested an accelerated aging process. Whilst those on ART showed age-inappropriate involutional changes (Holt, Kraft-Terry and Chang, 2012). With the early roll-out of ART, there is a large number of children entering adolescence and adulthood with a chronic infectious disease and therefore early neurocognitive impairments (Petersen et al., 2010). Mild neurocognitive and asymptomatic neurocognitive impairments are, therefore, more prevalent in the ART era (Liner, Ro and Robertson, 2010).

The most common neuropsychiatric sequelae of HIV is depression (Nakasujja et al., 2010; Nanni et al., 2015). Depression may occur at any time during the course of the HIV infection (Nanni et al., 2015). A review conducted in an Amsterdam outpatient clinic compared a cohort of 196 patients with HIV and mental health to HIV-positive patients in the general population, and to a control group of HIV-negative patients. The authors found that depressive disorders were the most commonly occurring diagnoses in the cohort. The common symptoms reported by HIV-positive patients included fear, anger and guilt. Those in the cohort were also significantly more suicidal than the control group (Schadé, van Grootheest and Smit, 2013).

In their study, Nakasujja et al. (2010), reported on a incidence of depression symptoms among the HIV-positive patients with cognitive impairment. The authors compared a cohort of HIV-positive people at risk of cognitive impairment who were being initiated on ART with a control group of HIV-negative people matched for age and education (Nakasujja et al., 2010).

The diagnosis of the HIV-related neuropsychiatric impairments rely heavily on thorough history taking, and on detailed, comprehensive, clinical examination including a neurological examination. A neuropsychological assessment is often indicated to detect even the most subtle of the neurocognitive impairments (Masters and Ances, 2014). The Montreal Cognitive Assessment (MOCA) scale is relatively quick and easy to perform with reliable sensitivity.

When structural neuro-imaging is used, MRI is the preferred modality of choice as it is superior to the CT scan in assessing the important subcortical brain structures, allowing for easier assessment of the white matter usually affected by HIV (Ances et al., 2012). The most commonly reported abnormalities on neuro-imaging in HIV/AIDS are cerebral atrophy and volumetric changes (Korbo, Praestholm and Skøt, 2002). In their study, Ances et al. (2012), reported on the size reductions associated with HIV in the subcortical structures such as the amygdala, caudate, and corpus callosum despite the use of ART. The authors further reported that a reduction in caudate size was associated with seroconversion (Ances et al., 2012).

HIV/AIDS, therefore, has great implications in psychiatry. The ability to measure brain functioning with functional neuro-imaging tools, even though may add value to the diagnosis, does not outweigh the clinical findings and therefore, the clinical opinion of the treating psychiatrist. Impressive as these tests may be, they may not be able to measure the extent of the brain dysfunction. For example, even functional neuro-imaging may not be able to measure the patient's judgment, planning skills, language abilities, etc.. Therefore, diagnosing the neuropsychiatric sequelae of HIV/AIDS still relies heavily on the opinion of the clinician after a comprehensive assessment. Neuro-imaging plays a supportive role.

b. Other Intracranial Infections

Intracranial infections are any infections that involve the brain and its parenchyma. These infections potentially have detrimental consequences to the brain.

The clinical picture may range from medical symptoms such as delirium, or neuropsychiatric presentations may ensue. The latter may present with mania-like, depressive and/or psychotic symptoms. There are increasing reports in literature about the high association between mood and psychotic disorders and chronic inflammation. Whether the chronic inflammation or the long-term symptoms begin first is currently controversial (Suvisaari and Mantere, 2013; Rosenblat et al., 2014).

Another study linked autoimmune diseases, infections, and mood disorders. Benros et al., (2013) aimed to measure the impact of autoimmune diseases and infections on the risk of developing a mood disorder. A third (32%) of the participants found to have a mood disorder had also been seen at the hospital for an infection prior (Benros et al., 2013).

Neurosyphilis, for example, is most commonly associated with symptoms likened to mania and psychosis. After the spirochetes cross the blood-brain-barrier, neurosyphilis develops. It is the tertiary manifestation of the syphilis infection in the brain. Syphilis is a chronic serological spirochete (treponema pallidum) infection acquired by means of sexual transmission (Sukthankar, 2010).

HIV heightens the vulnerability to the development of other intracranial infections. There is a high HIV prevalence in South Africa and HIV co-infection is common. A review reported on the five most common infections associated with HIV that contribute to a significant morbidity in HIV-infected patients globally. The common infections include: mycobacterium tuberculosis (TB), cryptococcus neoformans, hepatitis B virus, hepatitis C virus, and plasmodium falciparum (Chang et al., 2013).

Increasingly, studies report a particularly high incidence of syphilis in the recent times in those with co-existent HIV infection (Ghanem, 2010; Hook, 2017). In patients with syphilis, those who are HIV-positive tend to experience more aggressive symptoms and are at greater risk of developing neurological diseases such as dementia (McVey, Cameron and MacPherson, 2010).

Treating these infections should reverse the symptoms and result in their resolution. However, long-lasting irreversible impairments, such as neurosyphilitic dementia, may occur (Cysique et al., 2013).

After a clinical suspicion of neurosyphilis, cerebrospinal fluid analysis is diagnostic (Sarrazin, Bonneville and Martin-Blondel, 2012). Typically, in latent syphilis the infection becomes apparent only on serologic testing (Brown and Frank, 2003). Cerebrospinal fluid assessment should be performed in all persons with serologic evidence of syphilitic infection, measuring the rapid plasma reagin (RPR) titres, CSF pleocytosis and protein (Yu et al., 2010; Ghanem and Workowski, 2011).

Structural neuroimaging may confirm the presence of inflammation (acute or chronic) and lesions, unfortunately not specific to any infection. For example, a review reported on the two neuroimaging patterns suggestive of neurosyphilis; cerebral gummas – which may appear similar to meningiomas, tuberculomas, etc., and medial temporal lobe abnormalities that may appear similar to herpes encephalitis (Marra, 2015).

Another study reviewed the clinical presentations and MRI scans of six patients with general paresis due to neurosyphilis, and found differring results. Two patients had hyper-intense signal abnormalities in the anterior and mesial temporal lobe, while four patients were found on MRI to have cerebral atrophy. Three patients developed white matter lesions (Yu et al., 2010).

Therefore, the pattern of brain lesions may not be specific to a particular infection, and may not necessarily confirm the diagnosis in the absence of a clinical suspicion. The imaging findings should ideally be interpreted within the context of the clinical setting, more so in HIV-positive patients (Foerster et al., 2007).

c. Brain tumours

Generally, tumours of the brain are uncommon. A South African study looked at the cancer incidence rates and patterns, and did not report brain tumours as common. The study was based in a rural population, in the Eastern Cape Province for the period 1998 to 2002. The most common cancers reported were; cervical, oesophagus, and breast cancers for females, and oesophagus, lung and prostate cancers for the males (Somdyala et al., 2010).

The most common adult brain tumours are secondary (metastatic). Metastatic tumours are a collection of metastasised abnormal cells that have crossed the blood-brain-barrier from the other organs in the body. The commonest route of the metastasis is via the lymphatic system. The commonest metastases are from lung and breast cancers in males and females respectively (Butowski, 2015).

Primary brain tumours are most common in children, and originate from the brain. The most common primary tumours are gliomas followed by meningiomas. Meningiomas account for approximately one-third of all intracranial tumours (Butowski, 2015; Rapalino and Smirniotopoulos, 2016).

The neuropsychiatric sequelae of the brain tumours rely on the brain anatomical areas involved. The area involved, therefore, informs the clinical presentation. Presentations may include cognitive impairments, personality changes, mood, anxiety, ictal, psychotic symptoms, etc.. (Stretton and Thompson, 2012). The involvement of the temporal lobe is commonly associated with mood, anxiety, ictal and cognitive symptoms (Bonelli et al., 2010; Lambon Ralph et al., 2012; Thekkumpurath and Sharpe, 2009).

A review that looked into the common medical presentations of those with brain tumours reported on seizures, headache, and delirium as the most frequent (Butowski, 2015).

The diagnosis of intracranial tumours is most efficiently made by imaging, MRI is the preferred neuro-imaging modality as it renders superior to CT in the assessment of tumours (Butowski, 2015). MRI is particularly indicated for the assessment of the tumour characteristics and may help in the monitoring of the tumour progress (Maier, Sun and Mulkern, 2010).

CHAPTER 2: MOTIVATION, AIM AND OBJECTIVES

2.1 MOTIVATION FOR THE STUDY

Psychiatric diagnoses have been demonstrated to be heavily based on history and clinical examination (Chhagan and Burns, 2016). Neuro-imaging is an expensive tool and is not readily available in resource-limited health systems such as in South Africa (Chhagan and Burns, 2016). It however has value in the diagnosis of medical conditions such as traumatic brain injuries, tumours, infections, infarctions and bleeds (Khandanpour, Hoggard and Connolly, 2013; Chhagan and Burns, 2016). Neuro-imaging is also utilised as a tool to exclude life-threatening conditions affecting the brain (Khandanpour, Hoggard and Connolly, 2013; Chhagan and Burns, 2016). Klein (2010), recommends that in psychiatry neuro-images should be viewed to strengthen the available clinical evidence rather than be used as a confirmation of diagnosis.

Even though functional neuro-imaging is rendered superior to structural neuro-imaging, these techniques are not routinely available in the South African clinical setting. Furthermore, the most accessible forms of structural neuro-imaging in South Africa have restrictions (CT and MRI scans). The most accessible and cost-effective neuro-imaging modality in South Africa is the CT scan (Chhagan and Burns, 2016).

The purpose of the study is to evaluate the diagnostic yield of neuro-imaging in psychiatry in order to influence neuro-imaging management guidelines in resource constraint psychiatric services.

2.2 AIM OF THE STUDY

The aim of this study is to determine whether an abnormal result on neuro-imaging is a diagnostically useful tool in the discipline of psychiatry among adult psychiatric in-patients referred for neuro-imaging (CT and/or MRI scans) at CMJAH during the time period 1 January 2014 to 31 December 2015.

2.3 OBJECTIVES OF THE STUDY

1. To determine the proportion of abnormal findings on neuro-images conducted on adult psychiatric in-patients at CMJAH over a two-year period.

2. To determine whether demographic characteristics (age and gender) are associated with abnormal findings on scans amongst psychiatric in-patients at CMJAH.

3. To determine whether psychiatric DSM–IV Revised/5 diagnoses or medical diagnoses are associated with abnormal findings on neuro-images amongst psychiatric in-patients at CMJAH.

4. To determine whether scan characteristics (type of scan, urgency of scan and frequency of scan) are associated with abnormal findings on neuro-images amongst psychiatric in-patients at CMJAH.

CHAPTER 3: METHODS

In this Chapter, the methods used to conduct this study are described. Details are provided on the study setting, design, and the sampling strategy used. Furthermore, the collection of the data is described and the methods of data analysis and statistical testing are explained.

3.1 STUDY SETTING

This study was conducted at CMJAH's Psychiatric Department. CMJAH an academic hospital (level 1) situated in Johannesburg, South Africa. CMJAH caters for the population in the east and central parts of Johannesburg, with 1018 in-patients approved beds.

The Radiology Department is a twenty four hour imaging service (Lehohla, 2013). The neuroimaging modalities available include: MRI, CT and SPECT scans. The CMJAH radiology department has emergency and ASAP (as soon as possible) lists for the in-patients that are referred for neuro-imaging. The emergency scans are done on the same day and the scans on the ASAP list are done within two weeks of the request. All the requested MRI's must be discussed with the consultant radiologist on call. The scans are reviewed by the radiology registrar on duty and later reviewed by the consultant radiologist for errors in reporting.

The psychiatric services offered at CMJAH consist of the acute adult admissions unit and the Child, Adolescent and Family Unit (out-patient department). The practice at the CMJAH acute psychiatric unit is to request CT brain scans as a baseline for all admitted first presentations to psychiatry. The subsequent neuro-imaging scans are done as per medical indication.

3.2 STUDY DESIGN

This study was a quantitative retrospective record review. This study design method is best fit for health planning in initiation of hypothesis generation.

3.3 STUDY POPULATION

The population consisted of all adult psychiatric in-patients who had CT and/or MRI scans conducted during the period 1 January 2014 to 31 December 2015.

Inclusion criteria:

- All adult (patients aged above 18 years) psychiatric in-patients who had CT and/or MRI scans during the study period.

Exclusion criteria:

- All child (patients aged less than 18 years) psychiatric in-patients
- All adult psychiatric out patients
- All adult patients admitted in the medical wards referred for a psychiatric evaluation.

3.4 SAMPLE SIZE

One thousand and fourty (n=1040) adult psychiatric patients had been admitted during the selected study period of 1 January 2014 to 31 December 2015. The key selection criteria were adult psychiatric in-patients with referral for neuro-imaging (CT brain/MRI/both modalities). The performance level desired was 50% (worst case) with 5% precision, at the 95% confidence level. The sample required is 281.

Sample size for proportions was determined using the formula:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Where n = sample size:

Z = Z-statistic for the chosen level of confidence,

P = expected prevalence or proportion,

d = precision

TABLE 1: Sample size calculation

P	The percentage of cases for which you estimate the measure of quality will be present or absent	**0.5**
N	The number in the population which a clinical group wants to draw inferences from this sample to	**1040**
a	constant for a 95% level of confidence	**1.96**
d	Required range of accuracy	**5%**
	Required # of charts to be reviewed to determine performance level; sample size=	**281**

3.5 DATA COLLECTION METHOD AND INSTRUMENT

A retrospective record review was conducted using a data collection sheet developed from knowledge contained in literature concerning the diagnostic yield of neuro-imaging in psychiatry **(APPENDIX A)**. The questionnaire was written in the English language.

The clinical records kept in the CMJAH records filing system were retrieved manually from the list of patients identified to have been admitted in the adult psychiatric ward through discharge summaries accumulated during the study period. All the patients that were referred for CT and/or MRI scans were identified and their demographics, scan characteristics, psychiatric DSM-IV-TR/5 diagnoses and medical diagnoses captured on a Data Collection sheet **(APPENDIX A)**.

3.6 DATA MANAGEMENT AND ANLYSIS

Data from the clinical records were coded and captured onto Microsoft Excel 2013 spread sheets. All data were entered twice (double data verification). Double data entry was done in order to ensure data quality by checking for dataset entry variation and verifying entry errors. For the security of the database, the Excel data were immediately write-protected and stored on CD-ROM and dedicated memory stick. Copies of the original dataset were used in the analysis process. Summary data were examined for data errors. Following cleaning, variables were re-coded. The re-coded variables were then imported to the SPSS version 25 used to conduct the analysis.

Descriptive Analysis

Data analysis included descriptive statistics which involved calculations of proportions for binary variables. For all the continuous variables: frequency, mean and standard deviation was calculated provided the data were normally distributed; if not normally distributed the median and inter quartile ranges were used. Proportions and frequencies were calculated for categorical (binary) variables.

Chi Square Test

The research question that will be answered using a Chi-Square analysis would be: Is there a significant relationship between abnormal neuro-imaging results and demographic characteristics (age and gender), scan characteristics (type of scan, urgency of scan and frequency of scan), psychiatric DSM-5 diagnosis (psychotic disorders, mood disorders, anxiety disorders, eating disorders,

neurocognitive disorders and substance disorders) and medical diagnosis (hypertension, diabetes, HIV, neurological conditions, dyslipidaemia and infections).

The calculation of the Chi-Square statistic used is:

$$\chi^2 = \sum \frac{(f_o - f_e)^2}{f_e}$$

Where:

f_o= the observed frequency (the observed counts in the cells)
f_e= the expected frequency if NO relationship existed between the variables.

The formula thus depicts the Chi-Square statistic based on the difference between what is actually observed in the data and what would be expected if there was truly no relationship between the variables.

3.7 ETHICAL APPROVAL

3.7.1 Approval

Ethical approval to conduct the study was granted by the Human Research and Ethics Committee of the University of the Witwatersrand (Study number: M150809) **(APPENDIX B)** . Permission from the Department of Health to conduct the study was granted by the Chief Executive Officer (CEO) of CMJAH **(APPENDIX C).**

3.7.2 Informed consent

This is a retrospective study reviewing medical records, thus the Ethics Committee exempted the need for informed consent as data was to be de-identified.

3.7.3 Confidentiality

Each record was given a unique study number. No personal identifiers were used during capturing, analysis or discussion of data and no personal identifiers will be used in any reports or publications following from this study.

3.7.4 Justice

The results are reported in written format in the formal research report submitted to the Psychiatry Department at the University of the Witwatersrand. A written report will also be forwarded to the CMJAH Management.

CHAPTER 4: RESULTS

In this Chapter, the study findings are presented. Firstly, data collected for this study are presented on the descriptive characteristics of the study participants. Secondly, the factors associated with abnormal scan results amongst adult psychiatric in-patients at CMJAH are included.

4.1 DESCRIPTIVE STATISTICS FOR THE DATA

Of the one thousand and fourty (n=1040) adult psychiatric patients who had been admitted at CMJAH during the period 1 January 2014 to 31 December 2015, two hundred and thirteen (n=213) adult psychiatric patients fit the inclusion criteria of documented CT brain scan or MRI results. These 213 patients represented 20.5% of all adult admissions to the psychiatric unit.

4.1.1 PROPORTION OF ABNORMAL NEURO-IMAGING RESULTS

The majority of the reported neuro-imaging results were normal (n=139, 65.3%) **(Figure 1)**.

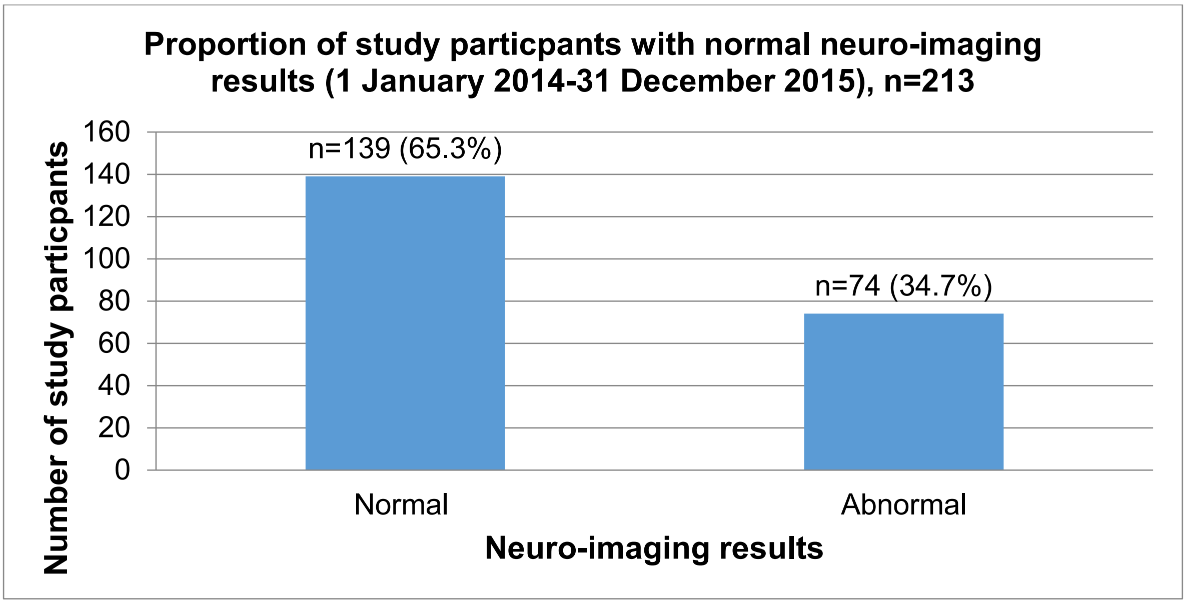

Figure 1: Proportion of study participants with normal neuro-imaging results (1 January 2014- 31 December 2015), n=213

4.1.2 DEMOGRAPHIC CHARACTERISTICS

4.1.2.1 Age

The age distribution of psychiatric in-patients whose records were included in the study ranged from 18 years to 88 years with a mean age of 38.8 years (SD 15.41). Overall, the highest proportion of adult psychiatric in-patients in the study fell in the 20-29 (n=61, 28.6%) year age category **(Figure 2)**.

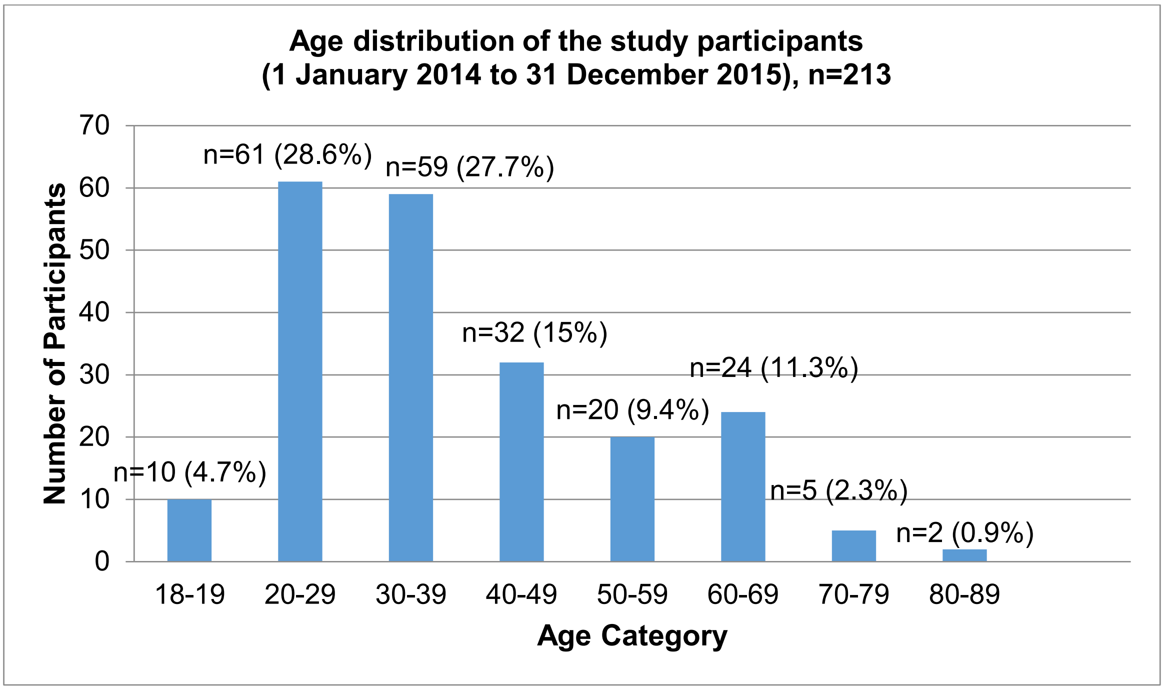

Figure 2: Age distribution of the study participants (1 January 2014- 31 December 2015), n=213

4.1.2.2 Gender

Out of the 213 psychiatric in-patient medical records reviewed, n=112 (52.6%) were male and n=100 (46.9%) were females. One of the medical records reviewed (n=1, 0.5%) had missing data for the gender of the in-patient. **(Figure 3)**.

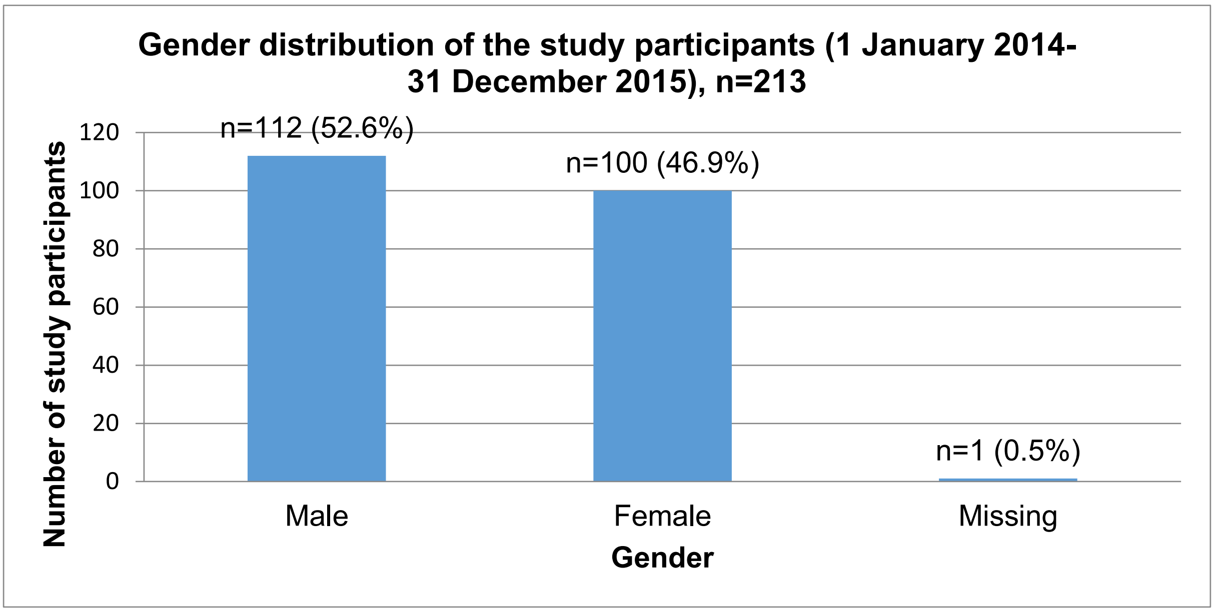

Figure 3: Gender distribution of the study participants (1 January 2014- 31 December 2015), n=213

4.1.3 SCAN CHARACTERISTICS

4.1.3.1 Type of scan (CT/ MRI/ Both)

The most frequently performed neuro-imaging modality for the time-period of this study was CT brain imaging with a total of one hundred and ninety eight (n=198, 93%) of the medical records reviewed reported that only CT brain scans had been conducted, while five (n=5, 2.3%) of the adult psychiatric in-patients were imaged using MRI scan only. Ten patients (n=10, 4.7%) had both forms of neuro-imaging modalities performed during the study period **(Figure 4)**.

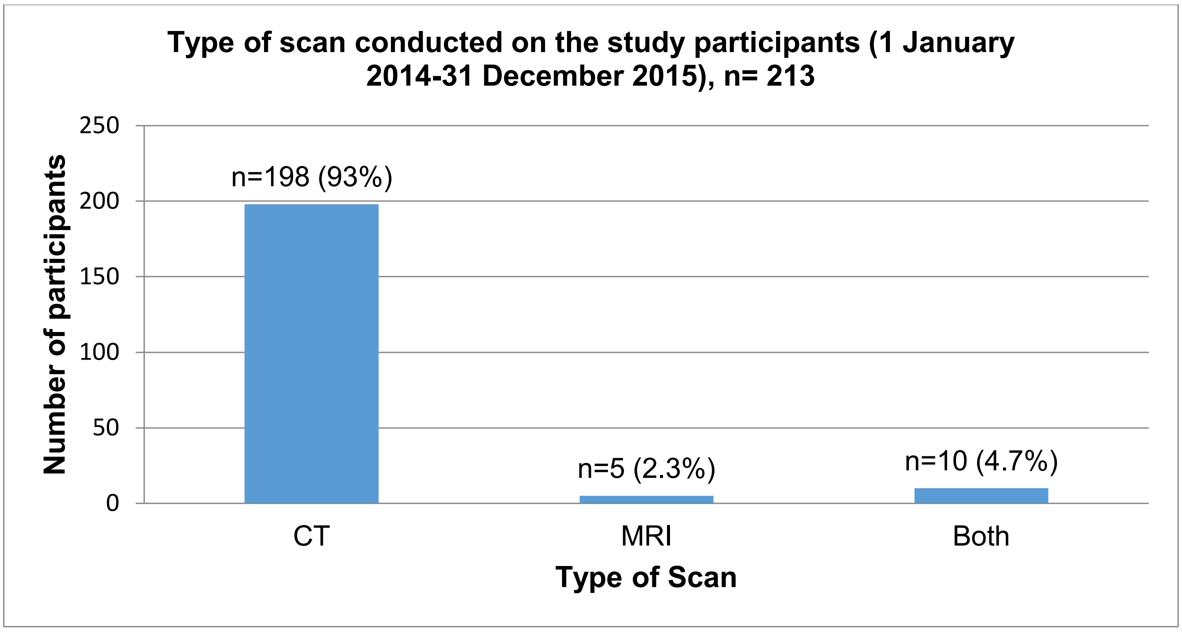

Figure 4: Type of scans performed on the study participants (1 January 2014- 31 December 2015), n=213

4.1.3.2 Urgency for scan

The neuro-imaging scans were either performed electively, as an emergency or the urgency was not stated (unknown). Of the two hundred and thirteen scans conducted, 6.1% (n=13) were elective, 8% (n=17) were emergency and the majority, 85.9% (n=183) were of unknown urgency **(Figure 5)**.

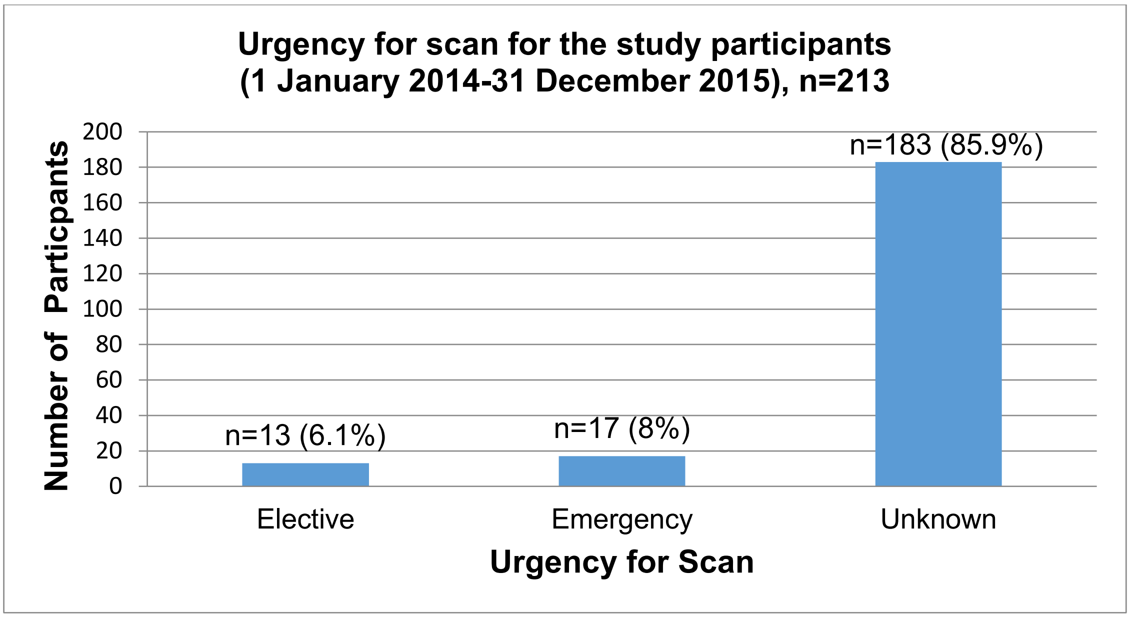

Figure 5: Urgency for scan the study participants (1 January 2014- 31 December 2015), n=213

4.1.3.3 Frequency of scans

Of the two hundred and thirteen records reviewed, n=11, 5.2% included scan results of in-patients that had neuro-imaging prior to the study period and a repeat scan during the study period. Their scans were included in the study as repeat scans **(Figure 6)**.

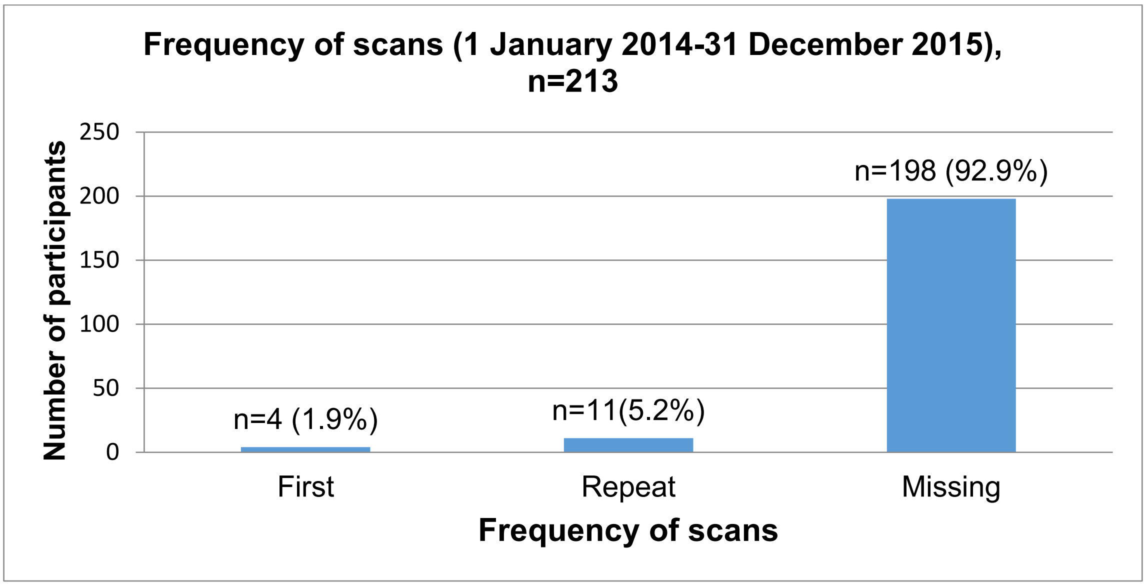

Figure 6: Frequency of scans performed on the study participants (1 January 2014- 31 December 2015), n=213

4.1.4 NUMBER OF PSYCHIATRIC ADMISSIONS

The distribution between in-patients that were index patients and those who had been admitted previously was 46.9% (n=100) and 44.6% (n=95) respectively. Twelve (n=18, 8.5%) of the medical records reviewed had missing data for the number of psychiatric admissions. **(Figure 7)**.

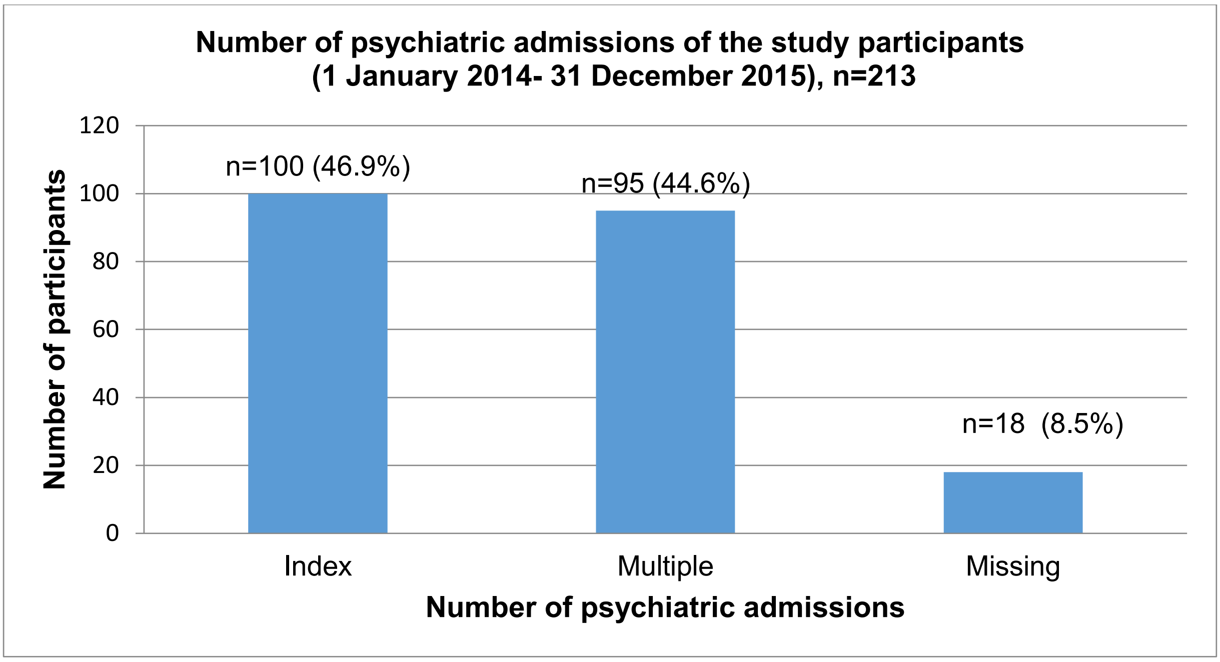

Figure 7: Number of psychiatric admissions of the study participants (1 January 2014- 31 December 2015), n=213

4.1.5 DSM - 5 DIAGNOSES

The majority of patients, n=137, 64.3%, had more than one DSM-IV-TR/5 diagnosis. The four commonest grouped primary DSM-IV-TR/5 diagnoses were: Psychotic Disorders (n=134, 33%); Mood Disorders (n=88, 22%); Neurocognitive Disorders (NCD) (n=82, 20%); and Substance-related and Addictive disorders (n=66, 16%) respectively **(Figure 8)**.

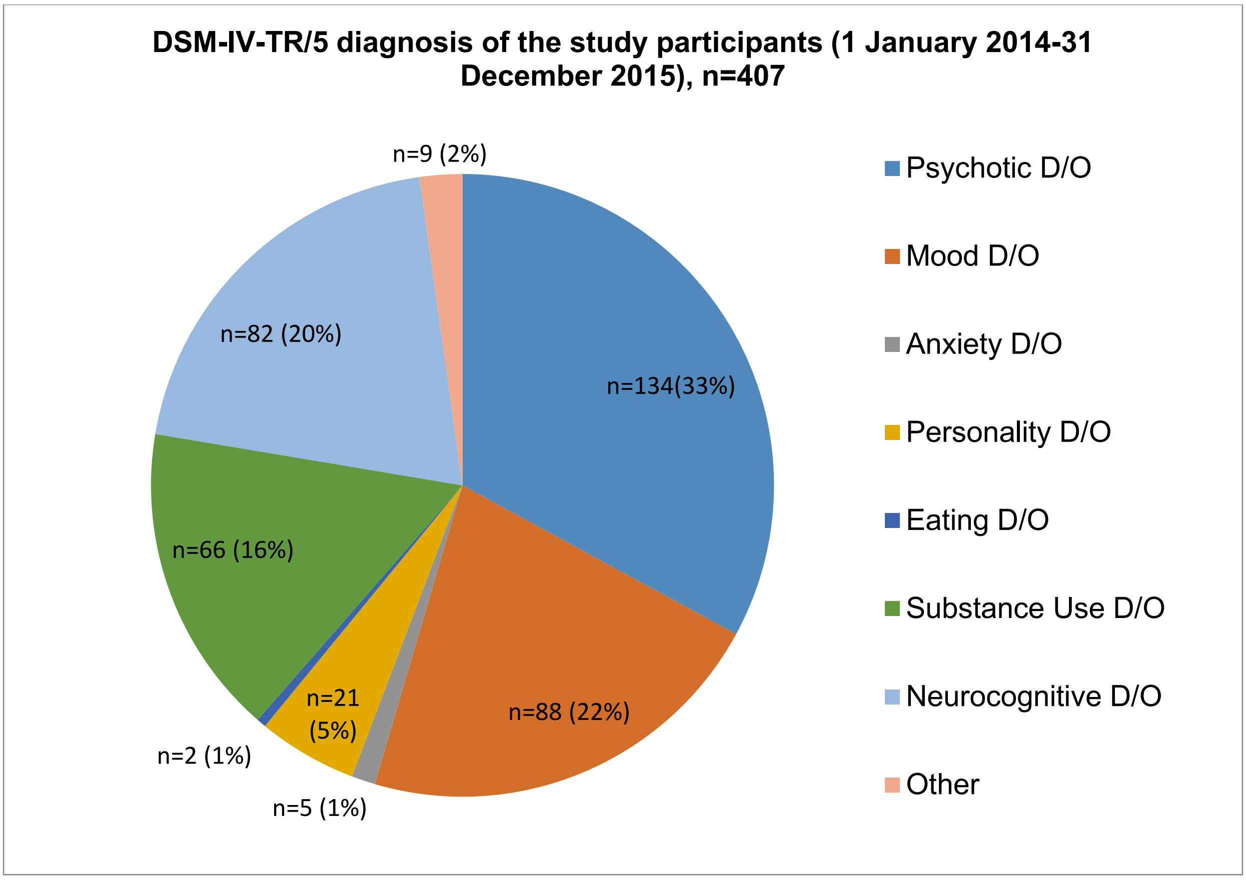

Figure 8: DSM-IV-TR/5 diagnosis of the study participants (1 January 2014- 31 December 2015), n=407

Of the one hundred and thirty four (n=134) psychotic disorders diagnosis, the most frequently diagnosed psychotic disorders were due to a medical condition (AMC), n=44, 32.5% and chronic psychotic disorders, n=41, 30.4% respectively.

Over half of those diagnosed with mood disorders as the first diagnosis were either reported to have substance use disorders (n=29, 32.6%) or had NCD (n=21, 23.6%).

4.1.6 MEDICAL DIAGNOSIS

Over three quarters of the study participants had underlying medical conditions (n=150, 70.4%) **(Figure 9)**. Of the one hundred and fifty study participants with underlying medical diagnosis, n=32, 21.3% had multiple medical diagnoses. The medical conditions diagnosed in the study participants included: HIV (n=52, 28.4%), neurological illnesses (n=49, 26.8%), infections (n=41, 22.4%), hypertension (n=28, 15.3%), diabetes (n=7, 3.8%) and dyslipideamia (n=6, 3.3%) **(Figure 10)**.

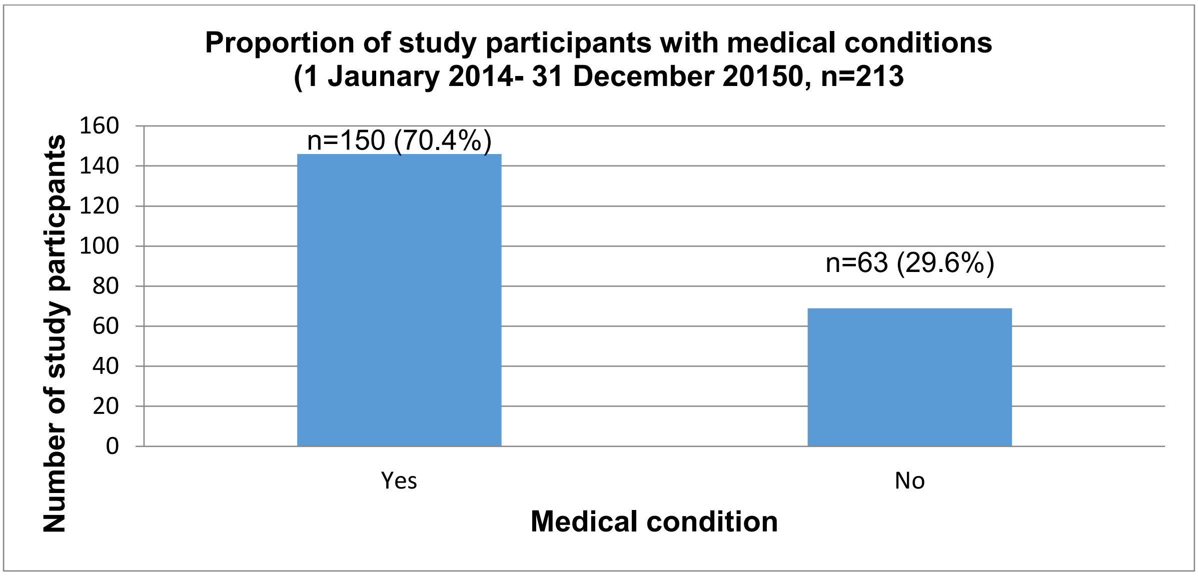

Figure 9: Proportion of study participants with medical conditions (1 January 2014- 31 December 2015), n=213

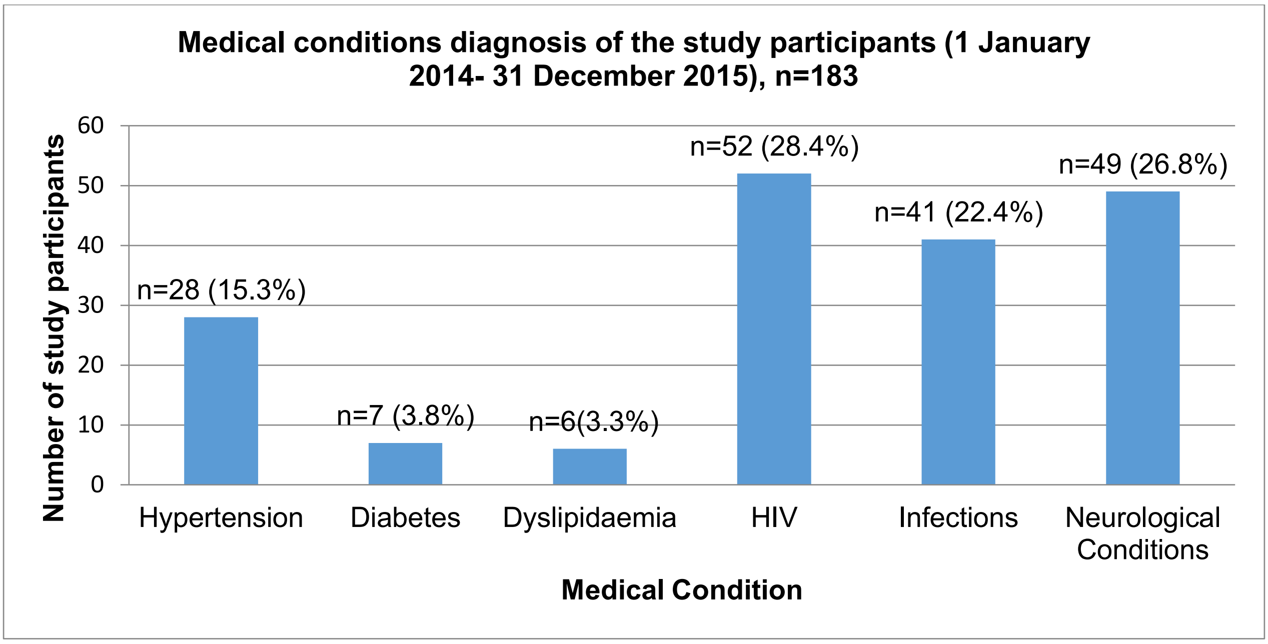

Figure 10: Medical conditions diagnosis of the study participants (1 January 2014- 31 December 2015), n=183

4.1.6 NEURO-IMAGING RESULTS

The most frequently reported pathology on the neuro-images included: other lesions (n=18, %), other results (n=10, %) and atrophy (n=22, %) **(Figure 11)**.

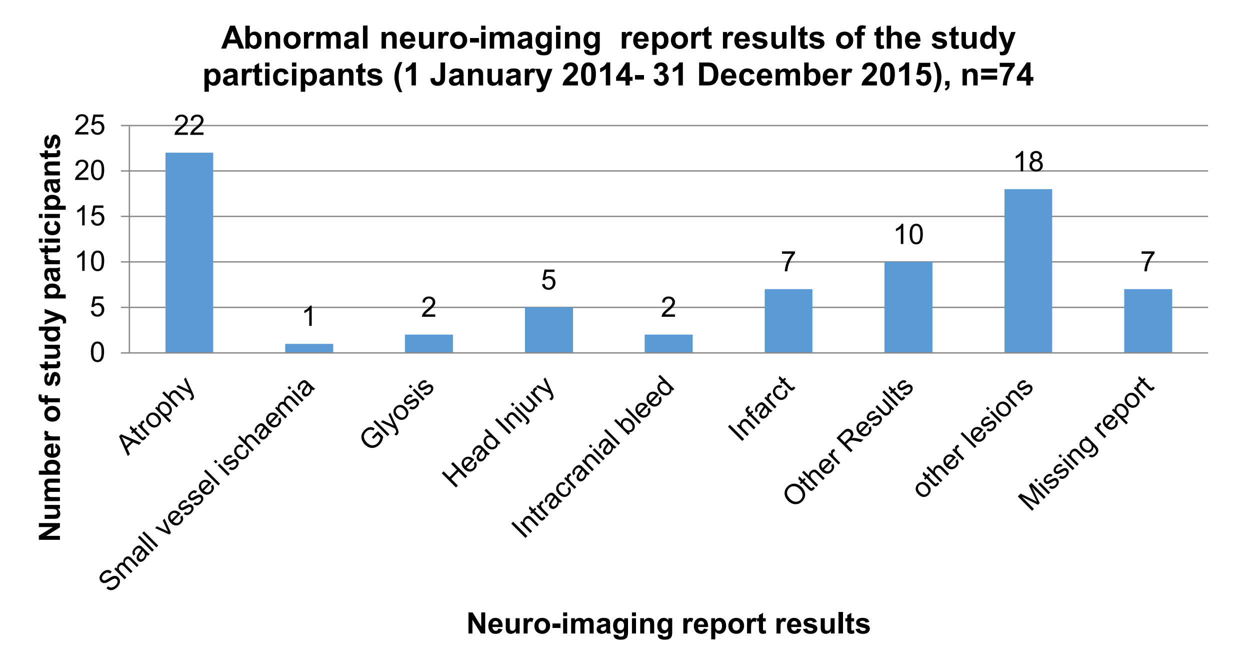

Figure 11: Abnormal neuro-imaging report results of the study participants (1 January 2014- 31 December 2015), n=213

4.2 CHI SQUARE STATISTIC

These neuro-imaging were enumerated and correlated with demographic characteristics, scan characteristics, psychiatric diagnosis and medical diagnosis in each psychiatric in-patient **(Table 2)**.

Variable	Total (%)	Abnormal Neuro-imaging (%)	Chi-square	p-value	Odds ratio (95% CI)
Age					
18-19 years	10 (4.7)	4 (5.4)	3.5	0.8	*
20-29 years	61 (28.6)	20 (27)			
30-39 years	59 (27.7)	20 (27)			
40-49 years	32 (15)	10 (13.5)			
50-59 years	20 (9.4)	8 (10.8)			
60-69 years	24 (11.3)	11 (14.9)			
70-79 years	5 (2.3)	1 (1.4)			
80-89 years	2 (0.9)	0 (0.0)			

Gender					
Female	100 (46.9)	38 (51.4)	1.3	0.5	*
Male	112 (52.6)	36 (48.6)			
Unknown	1 (0.5)	0 (0.0)			
Type of scan					
CT	198 (93.0)	68 (91.9)	1.5	0.5	*
MRI	5 (2.3)	1 (1.4)			
Both	10 (4.7)	5 (6.8)			
Urgency of scan					
Elective	13 (6.1)	6 (8.1)	3.7	0.2	*
Emergency	17 (8.0)	9 (12.2)			
Unknown	183 (85.9)	59 (79.7)			
Frequency of scan					
First	4 (1.9)	1 (1.4)	2.1	0.3	*
Repeat	11 (5.2)	6 (8.1)			
Unknown	198 (93)	67 (90.5)			

Psychotic disorders					
Yes	134 (62.9)	45 (60.8)	0.2	0.6	0.95 (0.8-1.2)
No	79 (37.1)	29 (39.2)			
Mood disorders					
Yes	88 (41.3)	27 (36.5)	1.1	0.3	1.4 (0.8-2.4)
No	125 (58.7)	47 (63.5)			
Anxiety disorders					
Yes	5 (2.3)	0 (0.0)	2.7	0.1	1.0 (1.04-1.01)
No	208 (97.7)	74 (100.0)			
Personality disorders					
Yes	21 (9.9)	4 (5.4)	2.5	0.1	2.4 (0.8-7.5)
No	192 (90.1)	70 (94.6)			
Eating disorders					
Yes	2 (0.9)	1 (1.4)	0.2	0.6	0.5 (0.03-8.6)
No	211 (99.1)	73 (98.6)			
Substance disorders					
Yes	66 (31.0)	17 (23.0)	3.4	0.07	1.8 (0.96-3.5)

No	147 (69.0)	57 (77.0)			
Neurocognitive disorders					
Yes	82 (38.5)	30 (40.5)	0.2	0.7	0.9 (0.5-1.6)
No	131 (61.5)	44 (59.5)			
Hypertension					
Yes	28 (13.1)	10 (13.5)	0.01	0.9	1.0 (0.4-2.2)
No	185 (86.9)	64 (86.5)			
Diabetes					
Yes	7 (3.3)	2 (2.7)	0.1	0.7	1.3 (0.3-7.1)
No	206 (96.7)	72 (97.3)			
HIV					
Positive	52 (24.4)	12 (16.2)	4.1	0.04**	2.1 (1.0-4.3)
Negative	161 (75.6)	62 (83.8)			
Infections					
Yes	41 (19.2)	15 (20.3)	0.1	0.8	0.9 (0.4- 1.8)
No	172 (80.8)	59 (79.7)			
Neurological Conditions					
Yes	49 (23.0)	22 (29.7)	2.9	0.09	0.6 (0.3-1.1)

No	164 (77.0)	52 (70.3)			
Dyslipidaemia					
Yes	6 (2.8)	3 (4.1)	0.6	0.4	0.5 (0.1-2.7)
No	207 (97.2)	71 (95.9)			

CHAPTER 5: DISCUSSION OF FINDINGS AND LIMITATIONS

In the previous chapter, the results of the study were summarised. This chapter will focus on the discussion of the analysis of the study data obtained and interpret these results in light of other published studies.

5.1 DISCUSSION OF FINDINGS

5.1.1 Proportion of abnormal neuro-imaging results

The reported rates for abnormal neuro-imaging results do not vary widely among countries: this study found that n=74 (34.7%) psychiatric patients admitted at the acute psychiatric ward at CMJAH, during the two year period dated 1 January 2014 to 31 December 2015 have abnormal neuro-imaging results. Other studies have demonstrated similar abnormal neuro-imaging results prevalence rates between 11% and 32%% (Sommer et al., 2013 & Mona et al., 2018).

5.1.2 Demographic characteristics

The majority of the study participants with abnormal neuro-imaging results were evenly distributed between the age groups of 20-29 years (n=20, 27%) and 30-39 (n=20, 27%). In the 2018 findings of a study conducted by Mona et al., patients younger than 20 years of age were found to have abnormal findings at the rate of 7%. The Mona et al. (2018) study also demonstrated 21% rate of abnormal findings in the 20-65 years age group whereas Illes et al. (2004), reported a prevalence of 15% in 151 apparently normal adult control participants.

Slightly more females (n=38, 51.4%) who participated in this study had abnormal neuro-imaging results reported than males (n=36, 48.6%). The prevalence of abnormal neuro-imaging results among the genders was similar in the study conducted by Jahanshad & Thompson (2017) which demonstrated that sex differences in brain abnormalities detected with structural neuro-imaging was less common than initially believed.

5.1.3 Scan characteristics

The current neuro-imaging guidelines at CMJAH recommend that the clinician's first neuro-imaging investigation is a CT brain scan. MRI requires clinical motivation and are thus requested only when the CT brain scan did not provide sufficient information and/or when more clinical information is required for diagnosis. It is thus not surprising that in this study the majority of neuro-images were CT brain scans (n=198, 93%).

The low frequency of abnormal CT scans (n=68, 34.3%) and low frequency of abnormal MRI scans found in this study (n=1, 1.4%), highlight the need for Dougherty et al., (2004) recommendations to be followed when deciding on which neuro-imaging modality to use in psychiatry. Doughery et al., (2004), suggests that the indication for the neuro-image should be the guide for either requesting a CT brain scan or MRI. The study also suggests that CT is useful for the diagnosis of acute trauma in the emergency setting (Dougherty et al., 2004). In contrast the aforementioned study recommends the use of MRI in psychiatry when ruling out white matter lesions, infarcts, contusion, infection, and new onset psychiatric symptoms in subacute settings (Dougherty et al., 2004).

5.1.4 Psychiatric diagnosis

From the n=74, 34.7% psychiatric in-patients with abnormal neuro-imaging results reported, one hundred and thirty one (n=131, 43.1%) DSM-5 diagnoses were made. Even though existing neuro-imaging research on psychiatric diagnoses have identified patterns of neural structure that differentiates pathology from non-pathology (Gillihan and Parens, 2011), this research has not been able to identify biology unique to psychiatric illnesses (Gillihan and Parens, 2011). Studies by Bennimahadeo and Maharajh (2016); Khandanpour, Hoggard, and Connolly (2013); and Strahl and Stuckey also did not demonstrate neuro-imaging findings that led to significant changes in management either (Bennimahadeo P, Maharajh J, 2016; Strahl, Cheung and Stuckey, 2010; Khandanpour, Hoggard and Connolly, 2013). In particular, the study by Bennimahadeo and Maharajh (2016) looked at 507 psychiatric patients that received screening CT brains. Only one (n=1) patient required intervention. This patient presented with focal neurology. CT brain showed extradural hematoma that required neurosurgical intervention (Bennimahadeo P, Maharajh J, 2016).

In those that used substances, cannabis was commonly associated with more psychotic than mood symptoms and alcohol use was commonly associated with more mood and anxiety symptoms than psychotic symptoms. This compares to the studies by Wilkinson, Radhakrishnan and D'Souza (2014) and Bolton, Robinson and Sareen (2009), that respectively reported on a link between cannabis use and psychosis; and the use of alcohol in those with anxiety and mood symptoms (Bolton, Robinson and Sareen, 2009; Wilkinson, Radhakrishnan and D'Souza, 2014). Also, similar to our study, Skalisky et al., (2017), reported on a high co-morbid use of alcohol and other illicit drugs in those that used cannabis. Out of their total submitted samples of 2834, 27% were positive for cannabis. Cannabis users were 2.2 times more likely to submit an alcohol-positive sample (Skalisky et al., 2017). In this study, substance use disorders accounted for 31% (n=66).

Atrophy (n=23, 31.1%) was the most commonly diagnosed lesion on these neuro-images. In some studies, atrophy has been shown to be associated with psychosis (Van Lutterveld eta al., 2014). While atrophy in several cortical regions (e.g. cingulum, prefrontal and temporal) has also been demonstrated in patients with depression (Ribeiz et al., 2013 and Mackin et al., 2013).

5.1.5 Medical diagnosis

Most of the psychiatric patients in this study, n=150 (70.4%) had a medical condition. Furthermore, of those who had medical conditions, n=56 (37.3%) had abnormal scans.

Of those with abnormal scans, n=23, 41.1% have a neurological condition, n=13, 23.2% are HIV positive and n=5, 8.9% are epileptic.

CT brain scan are commonly performed to diagnose acute altered mental statuses, however, negative CT results are common, which results in unnecessary CT use (Shin et al., 2018). Furthermore, CT scans have some limitations when used to diagnose non-intracranial pathology-related to acute mental status, thus it is important for clinicians to consider the neurologic examination findings which include; the presence of focal neurologic deficit, a low Glasgow Coma Scale, as well as elevated infection markers in order to avoid and reduce the unnecessary use of brain CT in psychiatry (Shin et al., 2018) .

5.1.6 Chi Square Statistics

The chi-square test for independence was carried out in SPSS in order to determine whether there is a significant association between abnormal neuro-imaging results and demographic characteristics, scan characteristics, psychiatric DSM-5 diagnosis and medical diagnosis.

The null hypotheses are given below:

Hypothesis 1: there is a positive relationship between demographic characteristics (age and gender) and abnormal neuro-imaging results.

Hypothesis 2: there is a positive relationship between scan characteristics (type of scan, urgency of scan and frequency of scan) and abnormal neuro-imaging results.

Hypothesis 3: there is a positive relationship between psychiatric DSM diagnoses (psychotic disorders, mood disorders, anxiety disorders, eating disorders, neurocognitive disorders and substance disorders) and abnormal neuro-imaging results.

Hypothesis 4: there is a positive relationship between medical diagnosis (hypertension, diabetes, HIV, neurological conditions, dyslipidaemia and infections) and abnormal neuro-imaging results.

The chi-square test for independence indicated significant association between abnormal neuro-imaging results and HIV:

$$\chi^2\ (1,\ n = 52) = 4.1,\ \ p = 0.04$$

From **Table 2** above, we see that the value of the chi-square test statistic is 4.1 and its corresponding p-value is 0.04. Since the p-value of the test statistic is less than 0.05, there is sufficient evidence to conclude that there is a significant association between abnormal neuro-imaging results and HIV.

HIV does not infect the neurons directly, it is believed that viral proteins released by infected macrophages and microglia leads to neural cell death and persistent intracranial inflammation, which contribute to the development of HIV-1-associated atrophy, which increases the rate of abnormal neuro-imaging results (Kaul et al. 2005).

5.2 LIMITATIONS

5.2.1 Bias

Systematic error that results in an incorrect estimate of association between exposure and outcome may have occurred in this study. The two categories of bias that may have arisen include:

5.2.1.1 Selection bias

This type of bias may have occured due to the convenience sampling method used to select all of the consecutive cases within a given time frame. This sampling method may distort the measure of association. It is noteworthy that an important group of patients admitted from emergency department wait to occupy a psychiatric bed in the emergency department ‘overflow’ ward. Some psychiatric in-patients may have had neuro-imaging tests performed whilst in this ward and subsequently discharged before reaching the acute in-patient ward. Records of these patients may have also been missed and this population group could have also added value to the factors associated with abnormal neuro-imaging in psychiatric patients. Medical records of patients who had neuro-imaging within the selected study period but no report were also excluded and could have also added value to the study outcome.

5.2.1.2 Information bias

Information bias may have resulted in systematic inaccuracies during the measurement and analysis of data. Missing information can lead to non-response bias in the results, in that subjects with missing information may differ systematically from the others. Typical with retrospective studies, partial information in medical records to complete absence of entire medical records occured. The neuro-images were reported by medical practitioners with varying skills. Although they may be validated by a specialist Radiologist, the reporting of the pathology on the neuro-images has the potential to introduce information bias.

5.2.2 Use of medical records

Medical records are easily available at no cost to the Principal Investigator. The challenges encountered when using medical records as a primary source of data was the incompleteness of the records. Missing data was accounted for as ‘unknown’ on the data collection sheet.

The filing system may have also been an important limiting factor that may have contributed to some data being missed: prior to March 2015, all the discharge summaries were filed at the psychiatric outpatient department at the CMJAH, together with the outpatient files of the patients that may have not had admissions to the hospital, mixed together with inpatient files. When patients were discharged from the acute psychiatric unit, they were either referred to the outpatient psychiatric clinic at the CMJAH or were down-referred to local clinics. A new system to file the discharge summaries was implemented in April of 2014. Since then, discharge summaries are filled alphabetically at the time of discharge in the different alphabetically-labelled files.

These files are kept in the acute in-patient ward. The old-filing system made it difficult to locate the discharge summaries relevant to the study.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

6.1 CONCLUSION

The study has explored the clinical value of neuro-imaging in psychiatry. The study demonstrated that structural neuro-imaging played a limited role in excluding medical conditions such as HIV encephalopathy and therefore neuro-imaging may not be the key diagnostic tool in psychiatry. Neuro-imaging was found to have a low yield in detecting pathology in psychiatric illnesses and disorders.

The art of modern psychiatry is a mainly symptom-focused and a clinical diagnostic process. In resource constraint settings such as in South Africa, this study has highlighted the need to intensify the development of clear indications and clinical guidelines to be used in order to justify the cost incurred by neuro-imaging studies in the field of psychiatry.

6.2 RECOMMENDATIONS

From these results it is recommended that:

1. Psychiatric academia in South Africa should develop protocols to guide the criteria for psychiatric patient eligibility for neuro-imaging.

6.3 FURTHER AREAS OF RESEARCH

The findings of this study suggest that future researchers could investigate the following:

1. Health economic evaluations to cost neuro-imaging in psychiatric resource constraint settings need to be conducted.

2. Further research be conducted to define the clinical role for structural neuro-imaging in diagnoses, monitoring disease progression and predicting prognoses.

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APPENDIX A: DATA COLLECTION SHEET

DEMOGRAPHIC CHARACTERISTICS			
Gender	MALE	FEMALE	
Age	YEARS		
SCAN CHARACTERISTICS			
Urgency of scan	ELECTIVE	EMERGENCY (PROVIDE REASON)	
Scan frequency	FIRST	REPEAT	
Type of scan	CT /MRI	BOTH (REASON)	
NUMBER OF PSYCHIATRIC ADMISSIONS			
Psychiatric admissions	INDEX EPISODE	MULTIPLE	
DSM-IV-TR/5 DIAGNOSES	**YES**		**ELABORATE**
Psychotic disorders			
Mood disorders			
Anxiety disorders			
Personality disorders			
Eating disorders			
Substance-related and Addictive disorders			
Neurocognitive disorders			
Other mental disorders			
MEDICAL DIAGNOSES	**YES**		**ELABORATE**
Metabolic syndrome (HT, DM, obesity, dyslipidaemia)			
HIV			
Infections e.g. Tuberculosis			
Neurological conditions e.g. Epilepsy			
Other medical illnesses			
None			

Unknown			

SCAN RESULTS	YES	LOCATION	DESCRIBE
Brain atrophy/involutional changes-age (in)appropriate]			
Small vessel ischaemic changes			
Gliosis/evidence of previous injury			
Aneurism			
Intracranial bleed/infarct			
Cavernoma, arachnoid, or other cysts			
Tumour/malignancy (specify type) OR other lesions			
Other			
Not stated/unknown			

APPENDIX B: LETTER OF APPROVAL- WITS ETHICS COMMITTEE

R14/49 Dr Bokang Lipuo Letlotlo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150809

NAME: (Principal Investigator)	Dr Bokang Lipuo Letlotlo
DEPARTMENT:	Psychiatry Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Clinical Use of Neuro-Imaging in Psychiatric Patients at the Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	28/08/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Lavinia Lumu
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	02/09/2015

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 research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature ____________ Date ____________

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX C: LETTER OF APPROVAL- CMJAH CEO

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Dr. M. Mofokeng
Office of the Clinical Director
Tell: (011): 488-3365
Email: Mamorena.Mofokeng@gauteng.gov.za
18 September 2015

Dear Dr. L. Letlotlo

STUDY TITLE: Clinical Use of Neuro-Imaging in Psychiatric Patients at the Charlotte Maxeke Johannesburg Academic Hospital.

Permission is granted for you to conduct the above recruitment activities as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not anyway incur or inherit costs as result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported / not supported

Dr. M.I. Mofokeng
Clinical Director
DATE: 18/09/2015

Approved/~~not approved~~

Ms. G. Bogoshi
Chief Executive Officer
Date: 18/09/2015

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