Cognitive outcomes in adults with HIV-associated Tuberculous Meningitis

by

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DECLARATION

I, Christine Albertyn, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abbreviations

ADLs	activities of daily living
AES-I	Marin's Apathy Evaluation Scale - Informant version
ANI	asymptomatic neurocognitive impairment
ART	antiretroviral therapy
AUDIT	Alcohol Use Disorders Identification Test
BDI-II	Beck's depression inventory version II
BMRC	British Medical Research Council
BVMT-R	The Brief Visuospatial Memory Test-revised
CLAT	Cryptococcal Latex Antigen Test
CNS	central nervous system
CRF	case report form
CSF	cerebrospinal fluid
CT	computed tomography
CTT I	Color Trail Test I
CTT II	Color Trial Test II
CXR	chest x-ray
DARTEL	Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra
DECO	Deterioration Cognitive Observee
DoH	Department of Health
DTI	Diffusion Tensor Imaging
Extra-CNS TB	Tuberculosis outside of the central nervous system
FTA	fluorescent treponemal antibody
GCS	Glasgow Coma Scale
GDS	Global Deficit Score

HAD	HIV-associated dementia
HAND	HIV-associated neurocognitive disorder
Hb	haemoglobin
HIV	human immunodeficiency virus
HVLT-R	The Hopkins Verbal Learning Test revised
IADL	Lawton instrumental activities of daily living scale
IHDS	international HIV dementia scale
IQ	intelligence quotient
IQR	interquartile range
IRIS	immune reconstitution inflammatory syndrome
JLOT	Judgement of Line Orientation test
LP	lumbar puncture
MAT	Mental Alternation Test
MDR TB	multi-drug resistant tuberculosis
MMSE	Mini Mental State Exam
MND	mild neurocognitive disorder
MRI	magnetic resonance imaging
MRS	Modified Rankin Scale
NHLS	National Health Laboratory Services
PAOFI	Patient's Assessment of Own Functioning Inventory
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form
QOL	quality of life
RPR	rapid plasma reagin

SCWT	Stroop Color Word Test
SD	standard deviation
TB	tuberculosis
TBM	tuberculous meningitis
TMT A	Trail making Test A
UCT	University of Cape Town
VBM	voxel-based morphometry
VDRL	venereal disease research laboratory
WAIS III	Wechsler Adult Intelligence Scale, 3rd Edition

Chapter 1: Introduction and review of the literature

1.1 Introduction

Tuberculous meningitis (TBM) is a common cause of meningitis in adults in South Africa (1-3), second only to cryptococcal meningitis in studies of microbiologically confirmed meningitis, and accounting for 28% of cases in one (1). Conventional diagnostic tests for TBM are, however, relatively insensitive, and the true incidence is likely to be underreported. When both microbiological and clinical diagnostic criteria (4) are used in the same setting, the incidence of TBM rose to 57% (3), emerging as the most common cause of meningitis in adults in a district level hospital in the Western Cape. In the setting of high human immunodeficiency virus (HIV) and tuberculosis (TB) prevalence, approximately 88% of patients with definite or probable TBM are co-infected with HIV (3, 5) and six-month mortality in this group approaches 50% (3). Survivors may be left with long-term disability secondary to hydrocephalus, cranial neuropathies, seizures and strokes (6).

1.2 Cognitive impairment associated with TBM

The impact of TBM on cognition is not clear. A few long-term follow-up studies of childhood TBM patients have been carried out in South Africa (7-9). The first study from 1997 assessed 19 children at a median follow-up period of three years after TBM diagnosis (7). The Herbst test, a culturally appropriate developmental assessment tool developed in South Africa (10), was used for cognitive testing. The Herbst test assesses 10 aspects of neurodevelopment, including concepts of direction, form, colour and number, analysis and synthesis, and picture perception. In this study by Schoeman *et al.* cognitive development was scored and expressed as percentages of those expected for normal children of similar age and background. Median cognitive development in the children with TBM was 66.9% (95% CI 59.1 - 73.2). The degree of impairment was similar for all 10 cognitive functions tested, ranging from 61.8% to 70.4%.

The second study described a paediatric cohort of 76 children who were followed up at a median period of 6.5 years after TBM diagnosis and used intelligence quotient (IQ) testing as a measure of cognition (8). Detailed IQ testing, using the Weschler Intelligence Scale for Children, found performances suggestive of cognitive impairment in 80% of children; and in the majority of these children it was considered likely to be severe enough to affect scholastic performance. Interestingly, poor scholastic performance was the presenting complaint from only 7% of parents, whereas 22% voiced concern about their children's behaviour, which was in fact the most common presenting complaint.

A third retrospective cohort study was performed, spanning 20 years of paediatric TBM in the Western Cape (9). Five hundred and fifty-four children were followed up at six months after TB treatment and IQ testing was performed using the Bayley test, Griffiths test, or Junior South African Individual Scale, depending on the age of the child. Patients were grouped as "normal" (IQ: > 80), "mild intellectual impairment" (IQ: 50–80), or "severe intellectual impairment" (IQ: < 50). In this large study, it was found that 77% of children had IQ scores suggestive of cognitive impairment. This cognitive impairment was mild in 58% and severe in 19% of children.

Data regarding neuropsychological outcomes after TBM in adults are scarce and there is a dearth of published information. A retrospective folder review from Auckland City hospital in New Zealand reported cognitive impairment to be present in 12% of adult TBM patients who completed TBM treatment at a median follow-up period of 18 months (range 1–197 months), but it is unclear how cognition was assessed (11). In two cohort studies from India, patients were evaluated at six months (12) and one year (13) after TBM diagnosis, respectively, using the Mini Mental State Exam (MMSE) (14). Cut-off MMSE scores were applied, ranging from 22 to 29, depending on years of education. Approximately half of these patients (54% and 55% respectively) were then found to be impaired.

More recently, the effect of TBM on long-term cognition was studied by Lin *et al*. HIV negative adults with previous TBM underwent Diffusion Tensor Imaging (DTI) (15). Nineteen TBM patients were tested at a median of 81 months post-TBM diagnosis and compared with 32 healthy controls. TBM patients performed significantly worse than controls on tests of executive function (Digit symbol coding, similarity and picture arrangement from the WAIS-III) and visuo-construction function (Picture Complete and block design, also from the WAIS-III). Worse neuropsychological performance directly correlated with poorer parameters on DTI indices with changes of white matter integrity in the anterior cingulate gyrus, the parahippocampal gyrus and globus pallidus. A further study by the same group used Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) voxel-based morphometry (VBM) to assess the integrity of grey matter in these same TBM patients (16). Patients were assessed cognitively using the full scale IQ measure from the Chinese version of the WAIS-III. Patients with TBM performed significantly poorer on the digit symbol, similarities, block design, matrix reasoning, and letter-number sequencing subtests of the WAIS compared to healthy adults. These TBM patients were therefore impaired on the indices of verbal comprehension, perceptual organisation (non-verbal reasoning and structuring of a visual scene), and working memory. These changes correlated with smaller grey matter volumes in the right thalamus, right superior temporal gyrus, right precuneus, right middle temporal gyrus, left putamen, right caudate nucleus, and right middle temporal gyrus. Overall this study suggested cortical as well as subcortical (deep grey matter) involvement in TBM.

The pathogenesis of cognitive impairment in TBM is unclear and is probably multifactorial. Important mechanisms are likely to be secondary vascular disease as well as hydrocephalus. Encephalitis may result when the basal inflammatory process extends into the parenchyma (17).

Small and medium vessel vasculitis is prominent in the pathology of TBM, and may result in ischaemia or infarction, particularly in the territory of the perforating branches of the middle cerebral artery (18). A focal clinical

neurological deficit in TBM can occur in up to 20% of patients (19). However, computed tomography (CT) and magnetic resonance imaging (MRI) may reveal cerebral infarctions in a larger proportion of patients, up to 35% and 57% respectively, rates that are similar to autopsy findings of infarction in up to 56% of patients (20). Strokes are often unnoticed clinically for many reasons: firstly, the patient may already have an altered level of consciousness so that new deficits are not recognised; secondly, co-existent arachnoiditis with myelo- or polyradiculopathies may confuse the clinical picture; and thirdly, the stroke may be in a clinically silent region of the brain. Basal ganglia infarctions are the most common and result from involvement of the small perforating arteries, specifically the lenticulostriate arteries. A “tubercular zone” has been described with infarction involving the head of the caudate nucleus, anteromedial thalami and anterior limb and genu of internal capsule. Up to 75% of patients with a basal ganglia infarct have an infarct in this region (18).

In addition to vascular changes, hydrocephalus secondary to TBM may impact on cognition. The development of hydrocephalus is more common in children than adults with TBM, with a CT study finding that 12% of adults had severe hydrocephalus, contrasting with 87% of children (21). A recent American study found that 8.4% of adult patients with TBM required ventriculoperitoneal shunting for hydrocephalus (22). The thick inflammatory exudate in the subarachnoid space impairs cerebrospinal fluid (CSF) drainage, particularly around the basal cisterns, leading to communicating hydrocephalus (23). It has been suggested that the presence of hydrocephalus may be associated with worse outcomes (death or significant disability) at one year and with higher risk of strokes (24). Cognitive outcomes in hydrocephalus primarily relate to the underlying etiology, but in paediatric studies visuospatial difficulty and motor dysfunction have been found regardless of the cause (25). Adults with normal pressure hydrocephalus may have impairment in multiple cognitive domains, particularly memory and learning; dexterity; reaction time; and executive functions; and it is plausible that chronic hydrocephalus post-TBM may cause similar dysfunction (26).

1.3 Cognitive impairment associated with HIV

Approximately 50% of HIV-infected patients will also present with HIV-associated neurocognitive disorder (HAND) (27) and this will undoubtedly impact on the cognitive profile of patients co-infected with HIV and TB. The Frascati criteria for HAND defines three subgroups: asymptomatic neurocognitive impairment (ANI), which is characterised by mild cognitive impairment (scoring between one and two standard deviations [SDs] below the mean in at least two cognitive domains) in the absence of functional impairment; mild neurocognitive disorder (MND), with a similar level of cognitive impairment but additional functional impairment; and HIV-associated dementia (HAD), with more severe cognitive impairment (more than two SDs below the mean in at least two cognitive domains) with significant functional decline (28).

The neurocognitive profile of HAND has evolved as treatment of HIV-infected patients improved. In the era before antiretroviral therapy (ART), slowing of motor and cognitive processing; impaired fluency; learning; and abstraction was found (29, 30). In the modern ART era, more frequent impairment in verbal memory (learning) and complex attention has been described (31, 32). Additional cortical deficits over and above the subcortical features have been suggested, but HAND test batteries have not been designed to test language and visuospatial skills sufficiently (31). Because individuals with HIV are now living a near normal life span, the effects of aging also need to be considered. It has been hypothesised that the increased prevalence of co-existing neurodegenerative processes in older individuals add to the risk cognitive decline (33). Supporting this theory, a study by Valcour *et al*. (34) has demonstrated the independent risk of HAD relating to apolipoprotein E4 in older participants but not in younger participants.

In the developed world in the era of ART, severe forms of HAND (i.e. HAD) have become rare, documented in only about two percent of patients (27) compared to 10-15% of patients with HAD in the pre-ART era (35). However, milder forms of HAND persist and about half of all treated patients with HIV

still demonstrate cognitive impairment, as evidenced largely by studies from developed countries (27, 36).

However, in developing countries the prevalence of HAD is likely to be higher, although varying results have been reported from African countries: 31% of HIV-infected patients from Kampala in Uganda were diagnosed with HAD (using the Memorial Sloan-Kettering [MSK] severity score) (37), while a Malawian study reported lower rates of 3% when applying the Frascati criteria (38). In Botswana, the international HIV dementia scale (IHDS) was used with a cut-off score of 9.5 to indicate possible HAD, and found that 38% of patients were at risk (39). In South Africa, rates of HAD of up to 25% have been reported in an ART naive cohort (40).

When one looks at all classes of HAND (and not just HAD) in South Africa, the prevalence data varies depending on the cohort studied (e.g. ART usage; outpatient or hospital setting) and the testing employed to diagnose or screen for HAND (eg. detailed neuropsychological testing, IHDS). Subsequently, the incidence of HAND varies widely from 23.5% to 76.5% (40-42). A study performed in the Western Cape by *Joska et al.* using detailed neuropsychological testing found a high rate of HAND in 76.5% of ART naïve patients attending a primary health care clinic (40). Of these patients with HAND, 25% were severely affected with HAD. If this is reflective of the larger population of people living with HIV in South Africa, then well over a million people may be at risk for HAD (43).

In studies of HAND in South Africa, the prominent domains affected are similar to other descriptions: learning, motor processing speed and executive functioning (40, 44). This pattern of impairment may be explained by neurotoxic effects of HIV, which are most prominent in frontal-subcortical structures. The basal ganglia; the caudate in particular (45); as well as the frontal neocortex and the white matter tracts connecting these regions, have been shown to be affected by HIV (46). Another region shown to be involved, using DTI, is the corpus callosum (47). Splenium abnormalities were

associated with dementia severity and psychomotor slowing, while genu abnormalities were associated with visual memory dysfunction.

Advancing age (34), lower nadir CD4 lymphocyte count (48), alcohol use (49) and lower levels of education (50) are associated with neurocognitive impairment.

1.4 Cognitive impairment associated with HIV-associated TBM

There are no published studies of cognitive outcomes in HIV-associated TBM. Based on our review of the literature, similar subcortical structures may be affected in both HAND and TBM. This may compound the individual risk of cognitive impairment or may worsen the degree thereof. Although additional cortical involvement may be seen in HAND in the first world in the ART era, this has not been described in South Africa. It has been suggested by the small studies referenced above (15, 16), that visuospatial deficits may be seen in TBM over and above the subcortical picture.

A pathologic study of alterations of astrocytes and microglia in postmortem human brains compared TBM only, HIV only, and TBM and HIV co-infection (51). In TBM alone, there is activation of microglia and astrocytes with hypertrophy and hyperplasia, aggregating in the subpial zone and around granulomas. However, in TBM and HIV co-infection there was a muted glial and microglial response. The microglial and astroglial response in the central nervous system (CNS) may act two-fold: as a direct effector of infection-related damage and, on the other hand, as a neuroprotectant. An alteration of the immune response in TBM in association with HIV infection was thus demonstrated, although the nature of neuronal-astroglial-microglial interaction and its impact should be studied further.

Ongoing neural injury in HIV may be driven by chronic inflammation in the ART era. This may be facilitated by low-level viral replication in the CNS or abnormal immune activation triggered by HIV (46). Alarmingly, this chronic inflammation may even persist despite good virologic control and is a possible

explanation for the high prevalence of HAND in the ART era (32). Neural injury may be exacerbated by cofactors such as substance abuse, co-infections (e.g., hepatitis C) (52, 53), and aging (33). Based on this evidence, one might hypothesise that systemic inflammation, as driven by chronic TB infection, may also contribute to worsening neuronal functioning.

There is no direct evidence to confirm or reject the hypothesis that HIV worsens the effect of TBM on cognition, as it has not been studied systematically. However, the interaction between HIV infection and tuberculous meningitis has been studied in Vietnam by Thwaites *et al*. (54), looking at the effect of HIV on clinical presentation, response to treatment, and outcome. They found a detrimental effect of HIV infection on survival (relative risk of death at nine months from any cause, 2.91 [95% confidence interval, 2.14–3.96]). However, there were no significant differences between the incidence of severe disability (as defined by scores of 3, 4, or 5 on the modified Rankin scale or functional dependance on the “simple questions” score) between the HIV-infected and HIV-uninfected survivors after nine months of treatment. This finding was confirmed in a recent retrospective study in America, where TBM patients with HIV infection were found to *not* be at increased risk of complications (strokes, seizures, hydrocephalus, visual or hearing impairment) as compared to patients without HIV infection (22).

1.5 Summary

HIV is highly prevalent, as is TB. Both of these infectious diseases may lead to neuropsychological impairment and it is reasonable to expect that TB and HIV together may have compounding effects on cognition. In our setting of high HIV/TB co-infection there is a need for a systematic study of cognitive performance of HIV-infected TBM patients. We need to identify the risk and quantify the burden of this form of disability as a consequence of TBM. The impact of cognitive impairment on the daily functioning of these patients may have important socio-economic implications.

Chapter 2: Aims and hypotheses

2.1 Purpose of the Study

The purpose of our study is to measure and describe cognitive functioning in adult HIV-infected patients with TBM.

2.2 Aims

2.2.1 Primary aim

To determine the cognitive outcome of adult patients with HIV-associated TBM compared to HIV-infected patients with TB infection outside of the CNS compartment (hereafter referred to as extra-CNS TB), at six months after TB treatment initiation.

2.2.2 Secondary aims

1. To assess cognition in conjunction with its impact on daily functioning;
2. To describe the pattern (neuropsychological profile) of cognitive impairment for the two patient groups; and highlight the cognitive performance in patients with an impaired global deficit score (GDS);
3. To identify predictors of poor cognitive outcome; and
4. To assess the impact on quality of life and employment status in TBM patients at six months after TB treatment initiation.

In order to address these aims, specific hypotheses were drafted.

2.3 Hypotheses

2.3.1 Primary hypothesis

HIV-associated TBM patients will have a more severe degree of cognitive impairment as measured by the continuous GDS (55) than patients with extra-CNS TB; and the proportion of patients with cognitive impairment will be

larger for TBM patients than extra-CNS TB patients as measured by a GDS of ≥ 0.5; at six months after TB treatment initiation.

2.3.2 Secondary hypotheses

1. The Frascati criteria for HAND (28) incorporate daily functioning into its classification of patients, as discussed in Chapter 1. We hypothesise that TBM patients will have more functional decline as measured by: the Lawton instrumental activities of daily living scale (IADL), modified for South Africa (56, 57); the Patient's Assessment of Own Functioning Inventory (PAOFI) (58); and the Deterioration Cognitive Observee (DECO) (59); as compared to extra-CNS TB patients. This functional decline, alongside cognitive impairment, will lead to worse grades of HAND by Frascati criteria in TBM patients.
2. The pattern of neuropsychological impairment in TBM is likely to be of a subcortical nature. Similar frontostriatal structures, and the white matter tracts connecting these regions, have been implicated in both HIV (33, 46) and TBM (12, 18). In TBM patients, there are two possible additional manifestations: cortical deficits due to larger arterial strokes (18) and visuospatial impairment based on previous studies (15, 16).
3. The following variables will be associated with worse cognitive outcome at six months:
    3.1. In *both groups*: older age; female gender; lower level of education; smoking; alcohol use; the presence of traditional vascular risk factors; lower CD4 lymphocyte count at diagnosis; not being on ART at time of diagnosis; and shorter duration on ART at six months follow-up. Although the presence of strokes is a likely predictor of poorer outcome, the observational design of this study does not lend itself to standardised neuroimaging and was therefore not included as a predictor.
    3.2. In the *TBM group*: a diagnosis of TBM-immune reconstitution inflammatory syndrome (IRIS); and more severe TBM disease grading at diagnosis, as defined by Grade II or III on the modified British Medical Research Council (BMRC) scales (60).

3.3. In the *extra-CNS TB group*: the presence of disseminated TB as opposed to single-site TB.

4. Patients with TBM will have poorer quality of life (QOL), as assessed by the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF) (61) and are more likely to be unemployed than extra-CNS TB patients.

Chapter 3: Methods

3.1 Design

This was a prospective, observational, cohort study. The cohort consisted of HIV-infected adults. The exposed group is defined as having TBM and the non-exposed group as having extra-CNS TB. The outcome of interest was the presence of cognitive impairment at six months after TB diagnosis as measured by the GDS (see Figure 3.1).

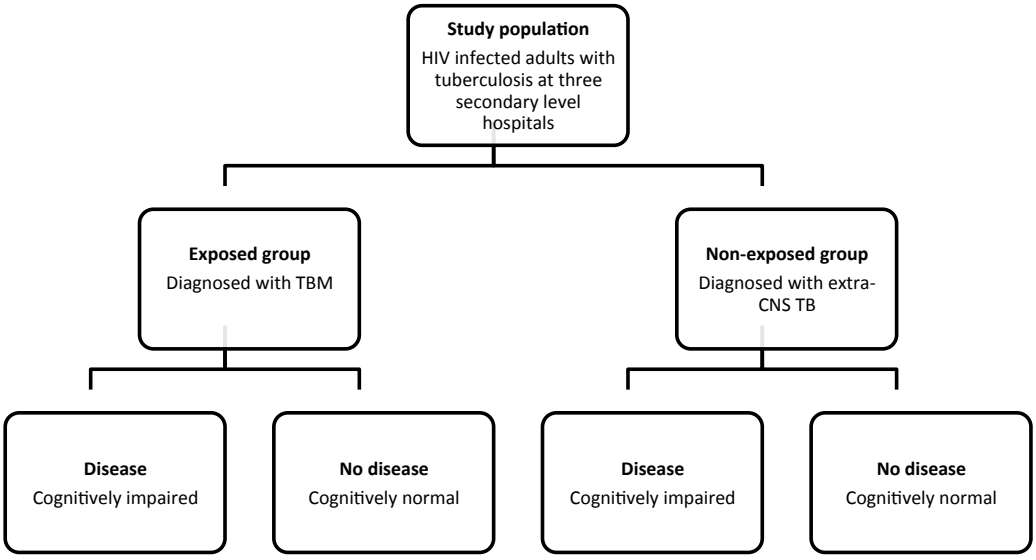

Figure 3.1: Our cohort study design

3.2 Sample size power calculation

This was a pilot study as there is scant data on cognitive outcomes in adults with TBM and no data in HIV-infected adult TBM patients. Based on studies in HIV-uninfected adults, Kalita *et al.* found cognitive impairment as assessed by the MMSE in 36/65 (55%) patients at one year follow-up (13). Ranjan *et al.* found similar rates of impairment as assessed by the MMSE at six months follow-up: 13/24 (54%) patients were affected (12).

Our sample size estimation was as follows: This data indicated that the probability of the outcome (cognitive impairment) among exposed individuals would approximate 0.5. If we recruited 60 exposed (TBM patients) and 60

non-exposed subjects (extra-CNS TB patients), we would be able to detect true probabilities of the outcome (cognitive impairment) among cases of 0.254 or 0.746 with probability (power) = 0.8. The Type I error probability associated with this test of the null hypothesis that the outcome rates for case and controls are equal is 0.05.

3.3 Ethics

The study was approved by the University of Cape Town (UCT) Faculty of Health Sciences Human Research Ethics Committee (HREC 565/2014) as well as the Western Cape Health Research Committee (WC_2014RP4_14 METRO). All aspects of the study complied with the Declaration of Helsinki (62).

3.4 Setting

We recruited patients from three secondary level hospitals in the Cape Town Metropolitan district in the Western Cape Province: New Somerset Regional Hospital, Khayelitsha District Hospital and Mitchell's Plain District hospital. These hospitals predominantly serve patients with a low income from densely populated areas. The majority of patients presenting to these referral centers speak isiXhosa as a first language with Afrikaans and English being the home language in smaller proportions (63). The Cape Town Metro district accounts for approximately 66% of the population of the Western Cape province. Migration stream from outlying provinces is a factor in the province's population growth with a total population gain of 94,600 for the period 2006-2011 (64).

Antenatal HIV-seroprevalence rates in the province are estimated at 18.5% (64). The HIV epidemic is currently driving the TB epidemic with more than 70% of TB patients also living with HIV (65). In 2015 the incidence of TB cases in South Africa was 834 per 100 000 population, of which 258 000 were HIV-related. This equates to similar rates in the Western Cape in 2010 when

the incidence rate of all TB cases was 885 per 100 000, one of the highest incidences for all smear positive cases of TB in South Africa (64).

3.5 Recruitment of participants

3.5.1 Inclusion/exclusion criteria

Inclusion and exclusion criteria are set out in Table 3.1 and Table 3.2 below.

Table 3.1: Inclusion criteria

Inclusion criteria	
Applicable to both TBM and extra-CNS TB patients • Adults (age 18-65 years) • HIV-infected • Diagnosed with TB in past 10 days	
TBM patients	**Extra-CNS TB patients**
Definite or probable TBM diagnosis[1]	Extra-CNS TB based on clinical features compatible with TB plus at least one of the following: 1. acid fast bacilli seen on microscopy, 2. Xpert MTB/RIF positivity, 3. *Mycobacterium tuberculosis* culture positivity, 4. supportive histological findings, 5. supportive radiological findings, or 6. based on treating physician's discretion[2]

[1]TBM diagnosis as defined by clinical research criteria (4)

[2]This group of patients will be reviewed individually and included based on consensus opinion amongst the study team.

Abbreviations: Extra-CNS TB = Tuberculosis outside of the nervous system; HIV = Human immunodeficiency virus; TB = Tuberculosis; TBM = Tuberculous meningitis.

Table 3.2: Exclusion criteria

<table>
<tr><th colspan="2">Exclusion criteria</th></tr>
<tr><td colspan="2">Applicable to both TBM and extra-CNS TB patients:
Significant CNS disease including previous stroke, previous CNS opportunistic infection (e.g. cryptococcal meningitis, neurosyphilis, TBM)
Known prior cognitive impairment or dementia as defined by a known diagnosis of dementia, or HAND, or a referral to a specialist clinic with a concern regarding cognitive impairment
Illegal substance use and/or high level drinking or dependance in the preceding six months as defined by the Alcohol Use Disorders Identification Test (AUDIT, score ≥ 16) (66, 67)
Poor socio-economic support that would make return to follow-up appointment non-feasible[1]
Multi-drug resistant TB[2]</td></tr>
<tr><th>TBM patients</th><th>Extra-CNS TB patients</th></tr>
<tr><td>Any other cause for CNS symptoms identified after enrollment e.g. cryptococcal meningitis, neurosyphilis</td><td>Symptoms and signs suggestive of TBM[3]
Investigations, such as lumbar puncture, performed at the discretion of the treating physician that are suggestive of TBM or any other cause of CNS disease in addition to extra-CNS TB.</td></tr>
</table>

[1]These included patients who do not have a fixed abode, no telephonic contact details and no family member/ friend/carer with telephonic contact details. In such patients we would have been unable to perform a telephonic interview at two months and it is very unlikely that these patients would have returned for a follow-up visit in six months' time, hence the reason for their exclusion.

[2]Patients with MDR TB were excluded as non-standard drug regimes may be a confounder of cognitive outcomes.

[3]Symptoms include headache, irritability, vomiting (not related to gastro-enteritis), neck stiffness, convulsions, focal neurological deficits, and altered consciousness as outlined in research criteria (4)

Abbreviations: CNS = Central nervous system; Extra-CNS TB = Tuberculosis outside of the nervous system; HAND = Human immunodeficiency virus-associated neurocognitive disorder; HIV = Human immunodeficiency virus; TB = Tuberculosis; TBM = Tuberculous meningitis.

3.5.2 Recruitment procedures

All treating physicians were informed of our study by way of a presentation at a local academic meeting where referral of potential patients was invited. Further paper advertisements were posted in doctors' offices in the medical wards and casualty departments. Additionally, we accessed the National Health Laboratory Services (NHLS) web-based reporting system to identify possible TBM cases admitted to either of the three secondary level hospitals where our study was conducted, by screening for markedly abnormal CSF examinations using previous TBM study criteria (one of the following criteria present: neutrophils > 5 cells x 10^6/L, lymphocytes> 20 cells x 10^6/L, protein >1 g/L, and glucose <2.2 mmol/L) (3). The medical wards and casualty departments were visited twice weekly to screen patient folders for eligible patients. Such patients were then approached and invited to participate.

3.5.3 Informed consent

3.5.3.1 Capacity to consent

The majority of patients with TBM will have an altered level of consciousness. This confusional state that results from the meningitic process renders these patients unable to give valid informed consent. The legal issues around the use of proxy consents in South Africa are unresolved (68, 69). Despite the absence of clear law regarding substitute decision-making in research in South Africa, both Pope and Roux argue that proxy consent in line with Section 7(1) of the Health Act 2003 should be permissible. Such a position is in line with the Medical Research Council and the Department of Health (DoH) Research Ethics Guidelines, both of which allow for proxy consent to be used in research involving people unable to consent. The DoH Ethics Guidelines stipulate that proxy consent should only be permissible where research does not pose additional risks to research participants, and where consent is sought from participants as soon as possible after they regain decisional capacity.

Our study was primarily observational in nature and did not expose research participants to more than minimal risk. We also sought consent from the participants before they were discharged from the hospital if they regained decisional capacity. If at any time-point participants refused consent, we destroyed all data collected.

With regard to determining suitable proxies, we followed Section 7(1) of the National Health Act of 2003, that stipulates “a health service may not be delivered unless the user is unable to give informed consent and no person is mandated or authorised to give such consent, and the consent is given by the spouse or partner of the user or, in the absence of such spouse or partner, a parent, grandparent, an adult child or a brother or a sister of the user, in the specific order as listed”. Therefore, we sought consent from a spouse or partner in the first instance, or parent/child/sibling if spouse/partner was not available.

In cases where no family member was contactable and given the patient didn’t decline assent, we enrolled the patient and continued to seek contact with relatives. Furthermore, delayed consent was sought from patients as they regained decision-making capacity.

3.5.3.2 Consent and assent forms

All consent forms were translated into isiXhosa. We outlined the study requirements separately in the informed consent form and incorporated checkboxes at the end of the consent form for each separate aspect:
a) the neurological examination and Case Report Form (CRF);
b) the two-month telephone call;
c) the six-month visit for neuropsychological testing.

Using this outline, we could obtain consent for each aspect separately in a chronological fashion as it became pertinent to the study.

3.6 Research procedures

3.6.1 Baseline procedures at TB diagnosis

Following informed consent, suitable patients were enrolled. A medical history was taken from patients and/or family. For patients who were disorientated or lacked clarity regarding their symptoms, collateral history was taken from family members where possible. The medical notes of admitting doctors were also reviewed for additional information regarding details of the presenting complaint. For patients without family members present, we aimed to obtain a history during the time of admission by contacting family members telephonically or by personal interview. Patients underwent a neurological examination, which allowed determination of the level of consciousness and the presence or absence of focal neurological signs by assessing cranial nerves, the motor, sensory and cerebellar systems. This allowed grading of TBM severity using the modified BMRC grading (60) where patients with grade I disease have a Glasgow Coma Scale (GCS) score of 15 with no focal neurologic signs; patients with grade II either have a GCS score of 11 to 14, or have a GCS score of 15 with focal neurologic signs; and patients with grade III have a GCS score of 10 or less, regardless of the presence/absence of focal neurological signs.

The following data was documented on a standardised CRF:

1. Demographic details (including age, gender, substance use [including completion of the AUDIT questionnaire], level of education, and employment status)
2. Medical comorbidities and medication use previously and during hospitalisation e.g. ART and steroid therapy
3. History of clinical presentation
4. A neurological examination including the TBM severity grade using the modified BMRC grading (60)
5. Tests performed as part of routine medical care e.g. CD4 lymphocyte count, full blood count, electrolytes, cerebrospinal fluid findings, radiological investigations, and any additional special investigations pertaining to TB and/or HIV.

6. Neuroimaging findings (CT and/or MRI if performed)

To minimise loss to follow-up, we recorded multiple phone numbers (especially land line telephone numbers) for both patients and for multiple contacts at enrolment. We documented addresses for patients and contacts. We also documented the patient's primary health care clinic details so as to reach a patient here by liaising with clinic staff. For patients who were re-admitted following diagnosis, the medical folder was reviewed to document hospital outcome.

3.6.2 Two-months follow-up

At two months following initiation of TB treatment, patients were contacted telephonically to enquire regarding compliance with TB drug therapy and whether ART had been initiated or is being continued. Patients were also asked regarding any serious intercurrent illnesses or additional admission to hospital. If so, hospital records were reviewed to ascertain the nature of the illness, e.g. an IRIS.

3.6.3 Six-months follow-up

At six months following TB diagnosis, patients were assessed using a detailed validated neuropsychological battery (see Section 3.7 below) as well as patient and carer questionnaires (see Section 3.8 below). This face-to-face interview took place either at Groote Schuur Hospital or Khayelitsha District Hospital in a quiet, private room. All testing for English- and Afrikaans-speaking patients was performed by the investigator herself following neuropsychological training. A research assistant, trained in administration of the tests (including practice sessions with non-study participants), performed the testing for all Xhosa-speaking patients under the supervision of the investigator.

3.6.4 Reimbursement for Participation

Patients were reimbursed for their time and transport cost to the amount of R150 in cash.

3.7 Neuropsychological battery

The cognitive battery included tests validated in HAND studies in South Africa in the past (40, 44); for which normative data (obtained from 103 patients) was available; and which had been forward- and back-translated into isiXhosa. We also added three tests for which normative data was obtained: Judgement of Line Orientation test (JLOT) (70); action fluency (71); and the CLOX test (72). These norms were obtained from a local isiXhosa speaking population in Khayelitsha, Western Cape, as a nested study within a larger norming study (Gouse *et al*., Human Research Ethics Committee Reference number: 596/2014). This study enrolled 114 healthy controls. The battery that we performed spans eight cognitive domains with at least two tests per domain (see Table 3.3). The neuropsychological battery took approximately two hours to administer. Patients were given a tea break halfway through to prevent fatigue.

Table 3.3: Cognitive battery listing domains and subtests within each domain

[1]Neuropsychological Tests according to Domain	What the test entails
Motor skills	
Grooved Pegboard Test (73)	Timed test consisting of pegboard with 25 holes with randomly positioned slots. Pegs with a key on one side must be rotated to match the hole before they can be inserted. Test of dexterity and motor speed; performed with the dominant and non-dominant hand once only
Finger Tapping Test	Timed test in which the tip of the thumb must be tapped against the tip of each other finger on the hand in sequence. This task must be performed five times, with the dominant and non-dominant hand in turn.
Memory (learning, recall)	
The Hopkins Verbal Learning Test revised (HVLT-R) (74, 75)	A list of words is read to the participant. These words must be immediately repeated (three trials are allowed, with a rereading of the list in between). This creates the learning score. The words must then be recalled after 20 minutes, and also be recognised from a longer list of words with other distracter words. These tasks create the recall score.
The Brief Visuospatial Memory Test-revised (BVMT-R) (76)	Participants view 6 geometric figures laid out in a 2x3 array on a page for 10 seconds. They must then reproduce this as closely as possible from memory. Three learning attempts are required. 25 minutes later the test is repeated. At this stage the participants are also requested to identify the 6 figures from a list of 12 similar figures.
Psychomotor processing speed	
Trail making Test A (TMT A) (77)	Timed test in which circled numbers must be connected in ascending sequence.
Color Trail Test I (CTT 1) (78)	Timed test in which circled numbers must be connected in ascending sequence. (The colour of the circled numbers alternates as the numbers ascend, but there is only one of each number.)

Wechsler Adult Intelligence Scale, 3rd Edition – WAIS III (Digit symbol coding and symbol search) (79)	In digit symbol coding, the participant is presented with digit-symbol pairs. They are then subsequently required to write the appropriate symbol next to a list of digits, as quickly as possible. Symbol search requires correctly identifying given symbols from a list of similar symbols, under time pressure.
Attention (and working memory)	
Wechsler Memory Scale—III (Digit span) (80)	For the forward digit span, participants are asked to repeat a string of numbers which increase in length. For the backward digit span participants are required to repeat a digit string in the reverse order. This digit string also becomes progressively longer.
Wechsler Memory Scale III (Mental control) (80)	The participants are required to recite known sequences, such as numbers from 1-20, the alphabet, days of the week and months of the year. With the exception of the alphabet, these tasks are then repeated in reverse (i.e. counting 20-1, days' order backwards etc). Finally the participant needs to say the days of the week sequentially, alternating each day with an increasing number of 6 added (i.e. 0 Sunday, 6 Monday, 12 Tuesday etc). All these tasks are done under time pressure.
Mental Alternation Test (MAT) (81)	Participants initially count to twenty, then recite the alphabet, then do both at the same time, alternating numbers and letters in ascending sequence. This is done under time pressure.
Executive Function	
Stroop Color Word Test (SCWT) (82)	In this task, the participant is asked to recognise colours, then read the names of colours in black and white print, before being shown a sheet with the names of colours, printed in another colour (e.g. RED written in blue ink). Here, they are required to say the colour that they see and not read the word printed. This test is timed.
Color Trial Test II (CTT II) (78)	Timed test in which circled numbers must be connected in ascending sequence, alternating

	between two different colours of circle. (The correct colour must be chosen each time – each number appears in both colours).
Verbal fluency (and executive functioning)	
Category Fluency Test (Animals & Fruit/Vegetables) (83)	Participants must name as many animals (or fruits and vegetables) as possible within one minute.
Action Fluency (71)	Participants must name as many verbs as possible within one minute. They are told: "I would like you to tell me as many different things as you can think of that people do"
Visuospatial skills	
Judgement of Line Orientation Test (JLOT) (70)	Participants are asked to match two angled lines to a set of 11 lines that are arranged in a semicircle and separated 18 degrees from each other on a multiple choice response card.
CLOX test (72)	Participants are asked to draw a clock displaying a certain time (unprompted task, CLOX 1). In the second part of this test they observe the examiner drawing a similar clock and are asked to copy this (copying task, CLOX 2).

[1]**Partly reproduced with permission from: Cross, HM, Combrinck MI. "HIV-Associated Neurocognitive Disorders: Biomarkers and the Response to Antiretroviral Therapy". MSc, University of Cape Town, 2012 (84)**

The neuropsychological battery was largely based on strong evidence of a subcortical pattern of cognitive impairment in HIV. The predominantly affected ability domains include: learning of new information; attention; and speed of information processing. Furthermore, the nature of memory deficits in HIV has been shown to be due to subcortical retrieval difficulty, rather than hippocampal pathology (85). We used a similar ability domain classification as proposed in the Frascati classification of HAND (28) and by Carey *et al.* in developing the GDS score (55). In addition to these seven suggested domain abilities, we added a visuospatial domain based on the suggestion of visuospatial difficulty in TBM patients (15, 16).

3.8 Questionnaires

3.8.1 Patient administered questionnaires

Questionnaires assessing quality of life, apathy, mood, motor functioning and activities of daily living were administered to patients. They were given a break prior to this part of the session. These took approximately 30-45 minutes to administer:

1. The PAOFI (58), assessing the patient's sense of functional capacity validated in populations with cognitive or psychiatric impairment (86, 87). This scale has been widely used in South African based studies of HAND (42).
2. The Q-LES-Q-SF (61). This scale has been used in general psychiatric settings (88) as well as South African studies relating to HAND (40, 42).
3. The modified Rankin Scale (mRS) as a measure of motor outcome. This is a well-known measure of motor disability, frequently used in TBM trials (60, 89).
4. Beck's depression inventory II (BDI II), widely validated in developed and developing countries (90, 91). Standard cut-off scores (91) to delineate mild (14-19), moderate (20-28) or severe (29-63) depression were applied.
5. The IADL - modified for South Africa (56, 57).

3.8.2 Carer/ family member administered scales

The following two scales were completed by a family member or carer (either personally if accompanying the patient or by telephonic interview):

1. Marin's Apathy Evaluation Scale - Informant version (AES-I) (92), used in the Groote Schuur Hospital Memory clinic and in imaging studies of HIV-infected patients with HAND in South Africa (93). A cut-off score of 34 or more was used to delineate significant apathy as based on norms from a healthy population with ages ranging from 20-65 years (94).
2. The DECO scale, that compares current cognitive functioning with status one year prior (59). This observer questionnaire has been used in a heterogenous elderly population in South Africa (95) and is also used in the Groote Schuur Hospital Memory clinic.

We sought participation from family members/carers who fulfilled the following inclusion criteria:

a) Should have known patient for six months prior to patient presenting with TB to ensure premorbid knowledge of patient.

b) Should either have lived with patient or have at least had weekly interaction (personally or telephonically) with preference given to participants living with the patient.

An exclusion criterion was significant CNS disease in the participant that would have rendered him/her unable to recall and/or relay details regarding the functioning of the patient (e.g. significant head injury, known diagnosis of dementia, known psychiatric disease).

For all participating family members or carers, the patient's HIV status was not disclosed unless the participant volunteered knowledge thereof. Therefore references to HIV were omitted in the informed consent form for carers.

3.9 Privacy and Confidentiality

Study data was and will continue to be stored in a locked cabinet in a limited access office in the Neurology Department at Groote Schuur Hospital. The patient's name was recorded once, together with a study number, on a list kept separately from the patient CRFs and thereafter all study data was labeled with the study number and not the name to maintain confidentiality of patient identity. Only the study team has access to this data.

3.10 Collation of data

Data was collected on an anonymised CRF and transferred electronically to an Excel (Microsoft® Excel® for Mac 2011) database. Patient identifiers were kept in a locked filing cabinet in a locked office.

3.11 Assessment of raw data

3.11.1 Determination of neurocognitive function

3.11.1.1 Global deficit score

For the primary outcome the GDS was used as a binary outcome measure with a GDS < 0.50 being normal and a GDS of ≥ 0.50 indicating cognitive impairment (55).

The recognised way to obtain a GDS is as follows:

1. *Calculate a Z score*.

A Z score is derived as follows:

$$\mathbf{z = (X - \mu) / \sigma}$$

where: **z** is the Z-score, **X** is the patient's raw score, **μ** is the sample population mean raw score, and **σ** is the standard deviation of the population.

2. *Calculate a T score*.

To transform a Z score to a T score:

$$\mathbf{t = (10 \times z) + 50}$$

where: **t** is the T-score, **z** is the Z-score.

The T-score for each test in a cognitive domain is added up and divided by the number of tests for that domain (ranging from two to four tests in our study). An overall T score for each cognitive ability domain is hereby rendered. See illustrating Figure 3.2. This is a slight modification of the method described by Carey *et al*. (55), where each neuropsychological test is assigned a T-score, which is then converted to a deficit score, after which all the deficit scores are averaged to yield a GDS. Our method of calculating a domain summary T-score, which is then converted to a deficit score, has been used in other studies of HIV cognition in developed and developing countries (96, 97). Our cognitive battery spans eight cognitive domains and each domain does not include the same number of tests (e.g. speed of information processing was assessed by four tests whereas executive functioning was assessed by two tests). We therefore chose the domain-averaging method to

prevent bias brought about by over- or under-emphasis of domain-specific impairment. The potential misclassification of a patient as cognitively impaired, due to overrepresentation of a domain with a higher number of neuropsychological tests assigned to it, may hereby be lessened.

For each cognitive test, the primary raw score is generally used to generate the T-score (e.g. when using the HVLT as a test of verbal memory, the delayed recall score is used rather than a percentage retained score or recognition score).

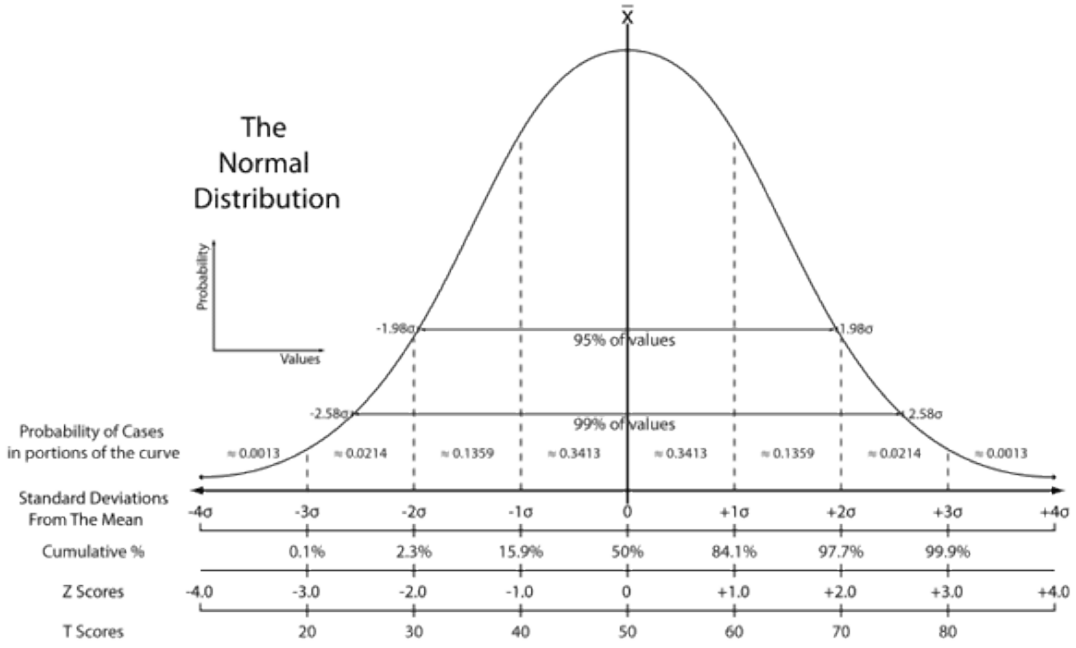

Figure 3.2: The normal distribution curve

From https://commons.wikimedia.org/wiki/File:The_Normal_Distribution.svg. (Accessed 12/08/2017)

3. *Calculate a deficit score*.

The T score for each cognitive ability domain is then assigned a deficit score, according to the schema devised by Carey *et al.* (55), and is shown in Figure 3.3.

T-scores	Deficit score	Impairment descriptor
≥ 40	0	Normal
39-35	1	Mild
34-30	2	Mild to moderate
29-25	3	Moderate
24-20	4	Moderate to severe
≤19	5	Severe

Figure 3.3: A Conversion Table for Transforming T Scores into Deficit Scores

From Carey *et al* 2004: "Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection", J Clin Exp Neuropsychol. 2004 (55)

Adding the Deficit Scores from each cognitive domain, and dividing this by the total number of domains, calculates the GDS. T scores of 40 or more (which indicate performance within normal limits) are assigned a deficit score of 0, whilst T scores in the impaired range are assigned progressively higher scores. This method of summarising the results emphasises poorer performance, whereas performances in the normal range will not be distinguished from those performances above average. This allows for the detection of more subtle impairment, which may otherwise be lost in simple mean calculations across test results.

A cut point (for determination of global impairment) of ≥ 0.50 has been shown to have good diagnostic power: sensitivity: 0.77, specificity: 0.92, positive predictive power: 0.88, negative predictive power: 0.83. The overall diagnostic accuracy rate, when compared to clinical ratings by experienced neuropsychologists, was previously reported as 0.85 (55). In the study by Carey *et al*, it was further shown that 93% of the participants who had a GDS of ≥ 0.50, also had impairment in at least two ability domains as determined by clinical ratings (55). This is important, as the diagnostic criteria for HAND require diagnosis of impairment in at least two ability domains.

The GDS approach has a further advantage in that it provides a continuous measure of impairment in addition to a categorical measure.

3.11.1.2 Classification of HAND

In 2007 the research criteria for diagnosis of HAND was updated (28). The so-called Frascati criteria for HAND defines three subgroups:

1. ANI, which is characterised by mild cognitive impairment (scoring between one and two standard deviations below the mean in at least two cognitive domains) in the absence of functional impairment.
2. MND with a similar level of cognitive impairment as the ANI group but additional functional impairment.
3. HAD with more severe cognitive impairment (more than two standard deviations below the mean in at least two cognitive domains) with significant functional decline.

When assigning Frascati criteria, the Woods criteria are used for guidance (98). Here it states:

"*If Learning and Memory are the only two domain ratings greater than or equal to five, then carefully re-examine the percent retained (i.e., secondary) scores before assigning a global rating.*

i. *If the memory impairment is primarily attributable to poor learning, then do not double penalize the participant when assigning a global rating (i.e., do not factor in the Memory domain rating when assigning the global rating).*
ii. *However, if there is evidence for deficits in both learning and retention, then the global rating should reflect the impairment in both of these domains*" (98)

With this in mind, the results of all patients with impaired Z scores in only the domains of learning and memory were further scrutinised by calculating a Z-score for the percentage of visual or verbal material retained. If the Z-score for the percentage retained was less than one standard deviation below the mean the patient was not assigned as having cognitive impairment (effectively only one domain impaired). Conversely, if the Z-score for the percentage retained was greater than one standard deviation below the mean, this suggested that memory was impaired in addition to poor learning and the

patient was assigned with mild or severe impairment (depending on the Z-scores for these domains).

3.11.1.3 Determination of Neuropsychological impairment

When grading functional impairment as none, mild or severe impairment, we were guided by the following from the Frascati group (28):

1) "*Self report of increased assistance with at least two instrumental activities of daily living (IADLs).*" We measured this with the IADL- modified for South Africa (56, 57). A score of 14 out of 16 indicated mild impairment while a score of 13 or less indicated severe impairment.

2) "*Inability to perform some aspects of a previous job*, *not ascribed to physical difficulty.*" If a patient could still return to work but some adjustments were necessary or more difficulty was experienced, we assigned this as mild functional impairment. If a patient was unable to return to work at all, this was rated as severe impairment.

3) "*Increased difficulty with aspects of cognition in daily life*." These included difficulties with memory for recent events; understanding conversations or reading materials; word finding; planning activities; problem solving; concentrating; thinking clearly or logically; finding his or her way about; calculating; or following directions or instructions. The scale used to measure this was the PAOFI (58). This 33-item questionnaire uses a Likert scale and higher scores indicate greater impairment while a score of zero indicates normal functioning. A score of two or three was assigned mild impairment (provided that the difficulty was in two or more cognitive domains) while a score of four or more was assigned severe impairment (provided that the difficulty was in four or more cognitive domains). In the presence of significant depression (Beck Depression Inventory score ≥ 20) (91), symptom reporting may be biased and in such cases we sought informant report of similar difficulties. If there were no corroborated reports we did not assign the patient with functional impairment, as symptoms of cognitive impairment may be overestimated in patients with depression (87).

The scale administered for the purpose of informant report of cognitive decline was the DECO scale which compares current cognitive functioning with status one year before (59). It spans multiple areas of cognitive functioning. The 19 questions can be answered as no change (score 2), not as well (score 1) or much worse (score 0). Therefore lower scores equate to greater impairment. Mild impairment was assigned to scores of 31 through 36. Severe impairment was assigned to scores of 30 or less (providing the response was much worse and occurred in four or more cognitive domains).

Patient self-report was combined with informant reports to assign a final functional impairment grading. This meant that a patient who denied any functional impairment might still be classified as impaired based on informant reports of such decline.

3.12 Statistical analysis

The difference between the cognitive outcomes for two groups was analysed in three ways: for our primary hypothesis, we employed a dichotomous outcome for the presence or absence of cognitive impairment using the validated cutoff of the GDS of 0.5. For this, a Fisher's exact test was employed. Secondly, the GDS can be used as a continuous variable to grade severity of cognitive impairment. The GDS is not normally distributed, and therefore a Mann-Whitney U test was used. Lastly, the Frascati/AAN categories of HAND are a useful measure to estimate differences between groups especially as it incorporates level of functioning. The Fisher's exact test was used for this analysis.

For predictors of cognitive outcome, we used the Mann-Whitney U test for non-parametric variables (age, level of education, CD4 lymphocyte count, duration of ART use). Fisher's exact test was used for categorical variables (gender, smoking, alcohol, ART usage, BMRC severity grading, presence of TBM-IRIS).

Spearman's Rho statistic was used to test the association between QOL and the GDS. The asymptotic Kruskal-Wallis Test was used to test how well the Frascati criteria correlated with the GDS.

Cohen's D (Hedges G adjustment was made for small sample size) was applied to calculate an effect size for differences between groups in Z-scores across cognitive domains. The Mann-Whitney test was used to generate a p-value for these Z-scores.

I performed the descriptive statistics, calculation of norming study means and standard deviations (SDs), calculation of the GDS, and classification of Frascati criteria myself. Dr Reshma Kassanjee (UCT Dept of Statistical Sciences) assisted with univariate analysis of baseline measures and Dr Jonathan Ipser (UCT Dept of Psychiatry, National Research foundation fellow) assisted with analysis of cognitive data.

Chapter 4: Results

This chapter will commence with a description of the study population followed by the results of the primary and secondary aims.

4.1 Description of the study cohort

We recruited patients from three district level hospitals in Cape Town. The flowchart of patients enrolled and patients who followed up six months after TB diagnosis is shown in Figure 4.1.

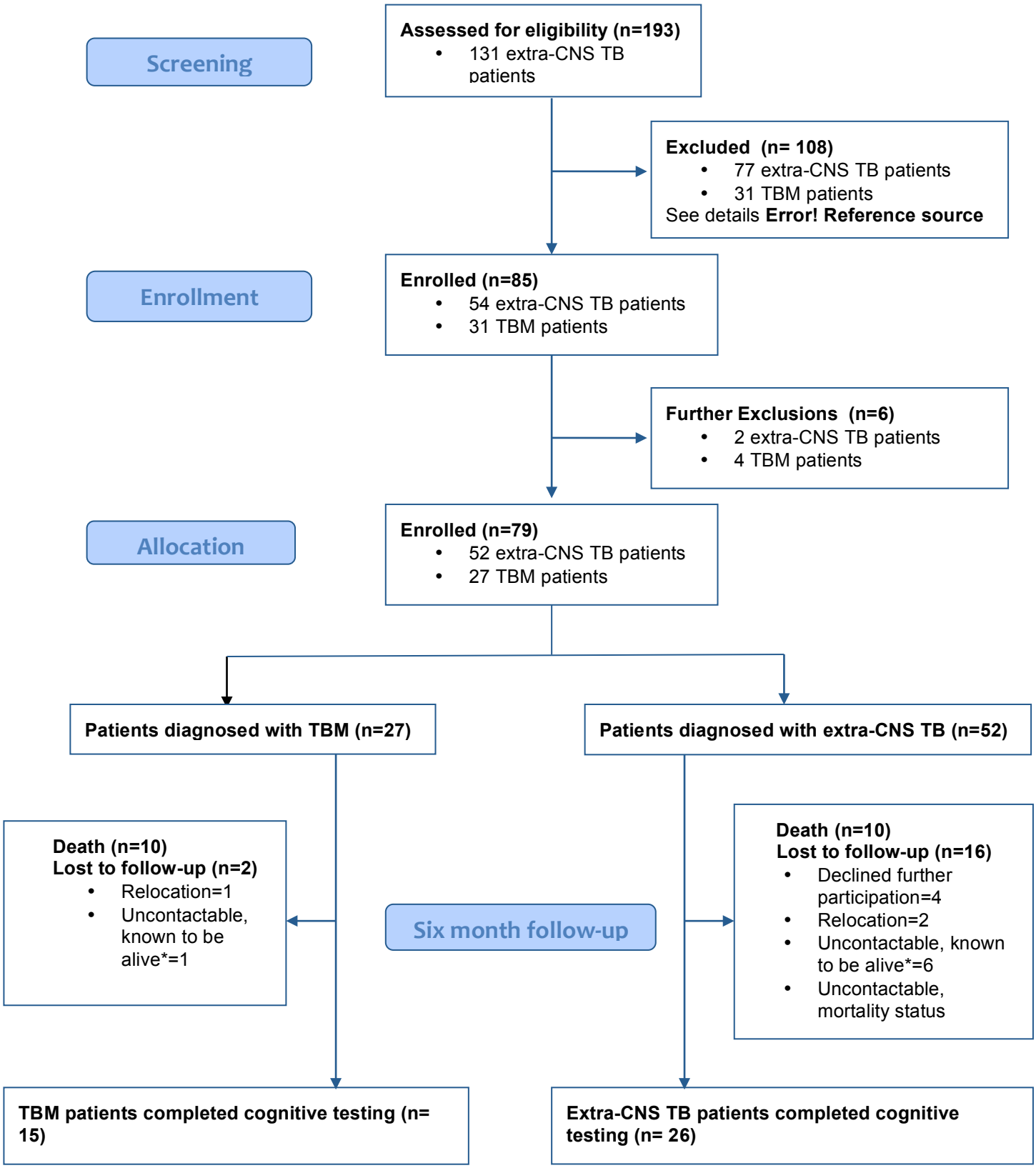

Figure 4.1: Flowchart for screening, recruitment and final cognitive analysis of exposed (TBM) and non-exposed (extra-CNS TB) patients

***Patients known to be alive as evidenced by active patient records on the National Health Laboratory Services (NHLS) web-based reporting system at or after the six-month follow-up date.**

A total of 108/193 patients screened were not suitable for enrollment. The reasons for exclusion from the TBM group is shown in Figure 4.2, and exclusion from the extra-CNS TB group are shown in Figure 4.3.

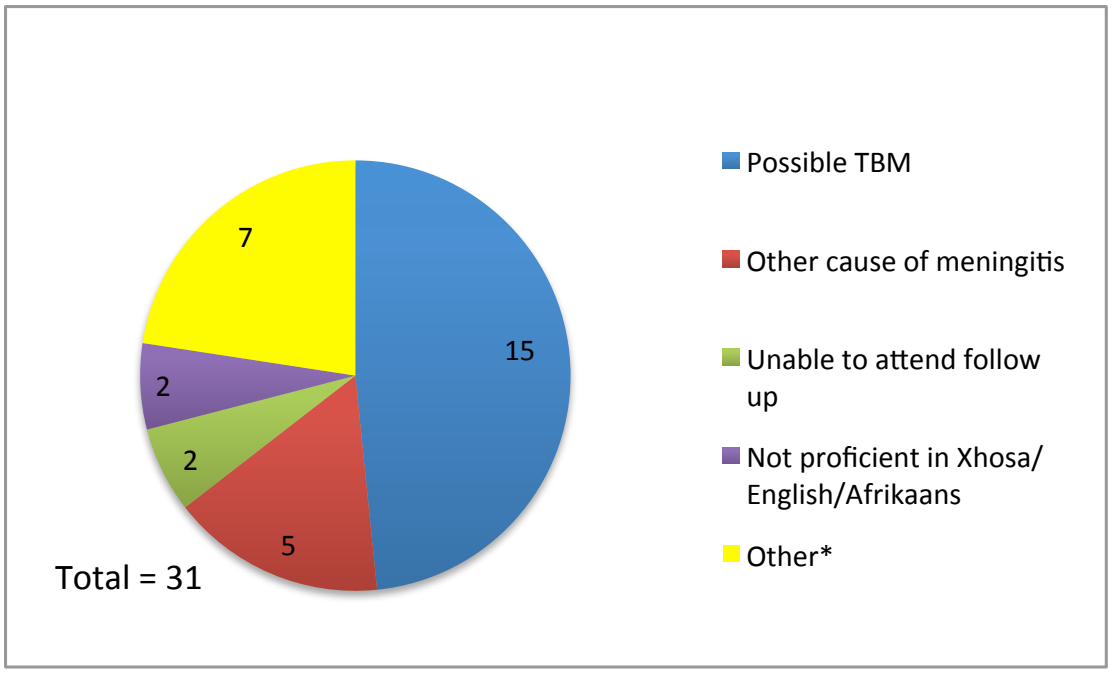

Figure 4.2: Reasons for exclusion from the TBM group amongst patients screened

Only definite and probable TBM patients were included, possible TBM patients were excluded as they did not meet clinical research criteria for higher grades of diagnostic certainty.

***Other reasons include: Multi-drug resistant TB, level of education less than Grade 7, substance abuse, previous CNS Toxoplasmosis, previous traumatic brain injury, declined HIV test, on TB treatment for more than 10 days.**

Abbreviations: CNS = Central nervous system; extra-CNS TB = Tuberculosis outside of the central nervous system; HIV = Human immunodeficiency virus; TB = tuberculosis.

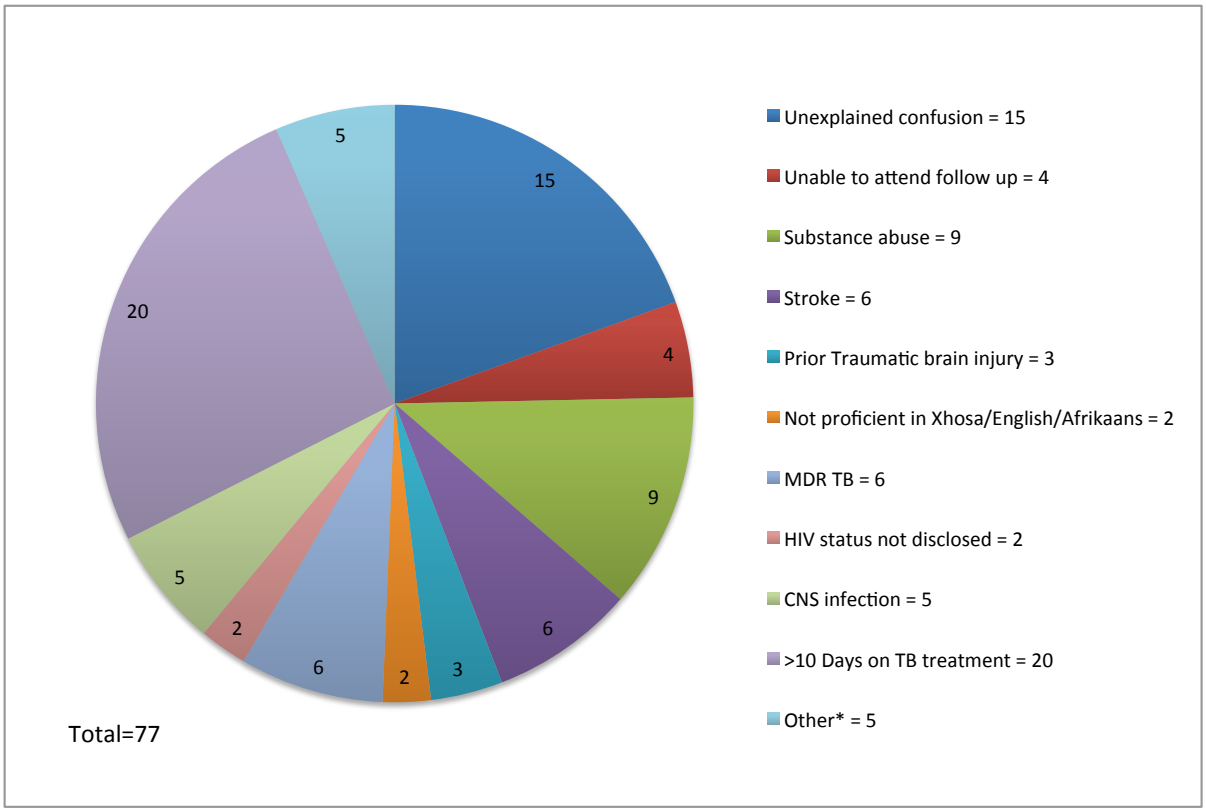

Figure 4.3: Reasons for exclusion from the extra-CNS TB group amongst patients screened

***Other reasons include: Prior HIV dementia, non-standard TB drug regime, level of education < Grade 7, headache, withheld consent.**

Abbreviations: CNS = Central nervous system; extra-CNS TB = Tuberculosis outside of the central nervous system; HIV = Human immunodeficiency virus; MDR TB = Multi-drug resistant tuberculosis.

There were six further exclusions from the group of 85 patients who were initially enrolled. Two extra-CNS TB patients were excluded: one patient had non-tuberculous mycobacterium cultured while the other patient had multi-drug resistant (MDR)-TB. Four TBM patients were excluded: three with MDR-TB and one patient with only possible TBM rather than probable TBM (this transpired on review of symptom duration).

The final group of patients enrolled consisted of 79 patients: 27 (34.2%) with TBM and 52 (65.8%) with extra-CNS TB.

The baseline socio-demographic characteristics (Table 4.1) and clinical symptoms (Table 4.2) of these 79 patients are tabulated. There were slightly

more females. The median age of all participants was 35 years (interquartile range [IQR] 29-40) and ranged from 19 to 65 years. The average time of schooling was 10 years. Forty-five (57.0%) of the patients were not on ART at the time of enrollment. This includes patients who were ART naive as well as patients who defaulted treatment. Patients presented with acute symptoms (relating to the system involved, i.e. coughing in an extra-CNS TB patient or headache in a TBM patient) of on average a week duration on a background of approximately one month’s systemic/constitutional TB symptoms.

Table 4.1: Socio-demographic details for the enrolled cohort

	TBM group (n=27)		Extra-CNS TB group (n=52)	
	Median (IQR) or N (%)	Range	Median (IQR) or N (%)	Range
Age (years)	35 (28-40)	20-65	34 (30-38)	19-58
Sex (female)	17 (63)	-	27 (52)	-
Level of education (years)	10[1] (10-11)	7-16	10 (9-11)	7-14
Employed (yes)	10/24[2] (42)	-	21 (40)	-
Smoking (yes)	6/24[3] (25)	-	14 (27)	-
Alcohol use (yes)	4/23[4] (17)	-	18 (35)	-
AUDIT score	6 (3-9)	1-10	7 (3-10)	1-18[5]
On ART (yes)	9 (33)	-	25 (48)	-
Duration of ART (weeks)	23 (14-63)	2-287	6 (4-27)	2-1036

[1]Level of education unknown for eight of the TBM patients.

[2]Employment status unknown for three of the TBM patients.

[3]Smoking status unknown for three of the TBM patients.

[4]Alcohol use unknown for four of the TBM patients.

[5]One patient reported alcohol use initially with an AUDIT score of 16 but subsequently on review six months later admitted higher intake with an AUDIT score of 18. He was not excluded but the AUDIT scores between groups were analysed.

Abbreviations: ART = Anti-retroviral therapy; AUDIT = Alcohol use disorders identification test; Extra-CNS TB = Tuberculosis outside of the central nervous system; IQR = Interquartile range; TBM = Tuberculous meningitis.

Table 4.2: Clinical symptomatology for the enrolled cohort

	TBM group (n=27)		Extra-CNS TB group (n=52)	
	Median (IQR) or N (%)	Range	Median (IQR) or N (%)	Range
Duration acute symptoms (in days)	7 (7-13)	1-23	7 (5-14)	1-96
Duration systemic symptoms (in days)	30 (19-49)	10-63	30 (21-61)	14-151
Systemic symptoms	12/27 (44)		21/52 (40)	
Loss of weight	17 (63)	-	43 (83)	-
Night sweats	12 (44)	-	26 (50)	-
Respiratory	14 (52)	-	45 (87)	-
Gastro-intestinal	3 (11)	-	29 (56)	-
Acute (neurological) symptoms in TBM				
Headache	25 (93)	-	-	-
Vomiting	12 (44)	-	-	-
Confusion	17 (63)	-	-	-
Neck pain	21 (78)	-	-	-
Seizures	4 (15)	-	-	-
Photophobia	9 (33)	-	-	-

Abbreviations: Extra-CNS TB = Tuberculosis outside of the central nervous system; IQR = Interquartile range; TBM = Tuberculous meningitis.

Amongst the 52 extra-CNS TB patients, the presenting complaint was respiratory in nature in most patients (87%). There were no focal neurological signs or meningism in this patient group. Three patients had mild disorientation to the date: this was ascribed to hyponatremia and urinary tract infection in one; hypoxia and fever of 40° Celsius in another; and hypoxia in the last patient (who also had a normal lumbar puncture). The site of TB was

confirmed to be pulmonary in 51 patients, with additional sites including abdominal (n=16), adenitis (n=2), haematological (n=2), cardiac (n=6), genito-urinary (n=3), and miliary (n=4).

The clinical signs are summarised in Table 4.3. Most patients presented with tachycardia, but high-grade fever was unusual. Twenty-four TBM patients (89%) had meningism and seven patients (26%) had focal neurological signs. These focal signs included cranial neuropathies in two patients, hemiparesis in five patients and cerebellar signs in two patients. According to the BMRC TBM disease severity grading (60), the majority of patients were classified as grade two. No patients met grade three classification.

Table 4.3: Clinical signs in the enrolled patients

	TBM group (n=27)		**Extra-CNS TB group (n=52)**	
	Median (IQR) or N (%)	Range	Median (IQR) or N (%)	Range
Pulse	115 (98-126)	72-153	121 (107-132)	79-164
Temperature	36.6 (36.4-37.5)	36-40	36.5 (36.2- 37.1)	35.4-39.3
Meningism in TBM patients (yes)	24 (89)	-	-	-
GCS	14 (13-15)	11-15	15 (15-15)	14[1]-15
Focal signs (yes)	7 (26)	-	0 (0)	-
BMRC grading (for TBM patients)[2]				
Grade 1	7 (26)	-	-	-
Grade 2	20 (74)	-	-	-

[1] Three extra-CNS TB patients had mild disorientation to the date. See text for details.

[2] No patient had a BMRC grading of three.

Abbreviations: BMRC = British medical research council; Extra-CNS TB = Tuberculosis outside of the central nervous system; GCS = Glasgow coma scale; IQR = Interquartile range; TBM = Tuberculous meningitis.

Laboratory results are shown in Table 4.4. All patients had full blood count and renal function tests. All but one patient had a chest x-ray (CXR). Anemia and hyponatremia was common, but a peripheral blood leucocytosis, renal failure and significant liver enzyme abnormalities were rare.

Table 4.4: Laboratory and radiological investigations for the enrolled patients

	TBM group (n=27)		Extra-CNS TB group (n=52)	
	Median (IQR) or N (%)	Range	Median (IQR) or N (%)	Range
CD4 lymphocyte count, cells/µL	80 (44-152)	2-281	60 (20-119)	1-402
Hb, g/dL	11 (9.7-12.2)	6.4-14.6	8.9 (7.5-10.4)	2.8-14.3
White cell count, x10^9/L	5.9 (4.3-6.7)	2.9-9.7	8.3 (5.7-10.8)	2.3-23.4
Urea, mmol/L	3.5 (3.0-5.1)	1.8-13.6	5.4 (3.3-7.9)	1-71.3
Creatinine, µmol/L	58 (51-67)	35-219	76 (54-116)	33-795
Sodium, mmol/L	128 (121-133)	114-139	130 (125-132)	117-137
Alanine transferase, U/L[1]	36 (21-61)	10-479	29 (20-57)	9-272
Alkaline phosphatase, U/L[2]	125 (75-179)	53-883	112 (72-198)	38-512
CSF[3,4]				
Lymphocytes, x10^6/L	89 (23-177)	0-1113	0 (0-0)	0-0
Neutrophils, x10^6/L	13 (0-36)	0-133	0 (0-0)	0-0
Glucose, mmol/L	1.7 (1.2-2.6)	0.5-8.8	3.5 (3.2-4.0)	2.4-5.3
Protein, g/L	2.68 (1.64-4.93)	0.28-35.00	0.24 (0.22-0.26)	<0.1-0.36
Radiological investigation (Nr abnormal /nr performed)				
CXR	23/27 (85)	-	49/51 (96)	-
Abdominal ultrasound	6/10 (60)	-	15/24 (63)	-
Echocardiogram	1/2 (50)	-	6/12 (50)	-
CT Brain	5/8 (63)	-	-	-

[1]Performed in 47/52 extra-CNS TB patients and in 23/27 TBM patients.

[2]Performed in 27/52 extra-CNS TB patients and in 14/27 TBM patients.

[3]A lumbar puncture was performed in seven patients with extra-CNS TB.

[4]A lumbar puncture was performed in all TBM patients.

Abbreviations: CSF = Cerebrospinal fluid; CT = Computed Tomography; CXR = Chest X-ray; Extra-CNS TB = Tuberculosis outside of the central nervous system; Hb = Haemoglobin; IQR = Interquartile range; Nr = Number; TBM = Tuberculous meningitis.

The TB diagnoses for each group are shown in Table 4.5. For the TBM group, definite TBM was diagnosed in 12 patients with the remaining 15 patients having probable TBM, as defined by clinical research criteria (4). The CSF findings were as expected: a lymphocytic-predominant meningitis with raised protein and low glucose levels. Eight patients had a CT brain scan performed: five (63%) of these patients had findings supportive of TBM as outlined in the clinical research criteria (4); one patient had changes suggestive of either progressive multifocal leucoencephalopathy or HIV encephalitis; the other two patients had a normal scan. It is noteworthy that five out of the eight patients who had a CT brain scan performed died prior to the six-month follow-up point. TB was proven outside of the CNS compartment in 23 (85%) patients: all these patients had respiratory involvement (either sputa or suggestive CXR) with additional sites including abdominal (n=8), miliary (n=7), adenitis (n=1), cardiac (n=1), and genito-urinary tract (n=1). Of note, all of the patients classified as definite TB also had evidence of TB elsewhere. There were therefore four probable TBM patients who did not have TB proven elsewhere. The first patient had a suggestive CSF picture and a contrasted CT Brain scan suggestive of TBM with a tuberculoma, basal meningeal enhancement and cerebral oedema. The other three patients had no other systems involved but scored 10 on the TBM research criteria (six points for symptoms, four points for CSF findings). Two of the patients without extra-CNS involvement did not have any sputum samples sent for testing while the other two had sputum tested for GeneXpert analysis but not for microscopy or culture. All but one patient were prescribed steroid treatment together with their TB treatment upon discharge.

Table 4.5: TB diagnoses for enrolled patients

	TBM group (n=27)		Extra-CNS TB group (n=52)	
	Median (IQR) or N (%)	Range	Median (IQR) or N (%)	Range
TBM classification				
Definite	12 (44)	_	-	-
Probable	15 (56)	-	-	-
TB outside of CNS for TBM patients (yes)	23 (85)	-	-	-
TB classification for extra-CNS TB patients				
Single-site	-	-	32 (62)	-
Disseminated	-	-	20 (38)	_
TB site in extra-CNS TB patients				
Pulmonary	_	_	51 (98)	_
Abdominal	-	-	16 (31)	_
Adenitis	-	-	2 (4)	_
Haematological	-	-	2 (4)	_
Cardiac	-	-	6 (12)	_
Genito-urinary	-	-	3 (6)	_
Miliary	-	-	4 (8)	_
Steroids prescribed at discharge (yes)	26 (96)	-	3 (6)	-

Abbreviations: CNS = Central nervous system; CSF = Cerebrospinal fluid; CT = Computed Tomography; CXR = Chest X-ray; Extra-CNS TB = Tuberculosis outside of the central nervous system; Hb = Haemoglobin; IQR = Interquartile range; TBM = Tuberculous meningitis.

Regarding the extra-CNS TB group, the number of patients with disseminated TB was 20 (38%) vs 32 (62%) patients with single-site TB. Forty-two patients had definite TB with the remaining ten patients having probable extra-CNS TB. Three patients were prescribed steroid treatment upon discharge: two for suspected Pneumocystis jiroveci pneumonia and one for TB pericarditis. Seven patients had a lumbar puncture (LP) performed and the CSF results were all normal. Reasons for LP included: positive serum Cryptococcal Latex Antigen Test (CLAT) in which case the CSF CLAT was negative; sepsis screen; and as part of a further search for TB.

Investigations of alternative diagnoses for TBM and potential confounders of cognitive performance are summarised in Table 4.6. A minority of patients had Vitamin B12 or thyroid function tests. Roughly half the patients had some form of syphilis testing. One TBM patient had a weak positive CSF Fluorescent Treponemal Antibody (FTA), but CSF Venereal disease research laboratory (VDRL) testing was negative as was serum FTA and VDRL. This patient tested positive on a CSF TB GeneXpert test. A few patients tested positive for serum FTA: seven extra-CNS TB patients and one TBM patient. In six of these patients, the serum VDRL and/or Rapid plasma reagin (RPR) was negative. The remaining two patients (both with extra-CNS TB) had low VDRL titres of one and two respectively. All but two TBM patients had CSF CLAT testing performed. All patients had CSF sent for bacterial culture and these were all negative.

Table 4.6: Further special investigations performed which may have an impact on cognitive outcomes

	TBM patients (N=27)		Extra-CNS TB patients (N=52)	
	Nr/ nr performed	%	Nr/ nr performed	%
Vitamin B12 (low)	0/5	0	0/16	0
s-RPR or VDRL (positive)	0/13	0	2/29[1]	7
s-FTA (positive)	1/12	8	7/25	28
TSH (abnormal)	0/7	0	0/5	0
CSF FTA (positive)	1/15[2]	7	0/4	0
CSF RPR and/or VDRL (positive)	0/5	0	0/3	0
CSF CLAT (positive)	0/25	0	0/6	0

[1]Weak titres of 1 and 2 respectively.

[2]Weak positive.

Abbreviations: CLAT = Cryptococcal latex antigen test; CNS = Central nervous system; CSF = Cerebrospinal fluid; Extra-CNS TB = Tuberculosis outside of the central nervous system; FTA = Fluorescent Treponemal antibody; Nr = number; RPR = Rapid plasma reagin; s = serum; TBM = Tuberculous meningitis; TSH = Thyroid stimulating hormone; VDRL = Venereal disease research laboratory.

Following enrollment, eighteen patients were lost to follow-up (see Figure 4.1). Ten TBM and 10 extra-CNS TB patients died, that is, almost double the

number of TBM compared to extra-CNS TB (37% vs. 20.8%) patients. Despite the clinical significance of this finding, the trend to higher mortality in the TBM group did not reach statistical significance (p-value = 0.175).

Regarding time to death, the exact date of death was known for the majority of patients, but in the two patients where this was not known, the date of death was taken as the date of the two-month follow-up phone call. Fourteen out of the 20 patients died within the first two months after enrollment with an equal distribution of seven patients in each group. In the TBM group, half of the patient deaths (5 patients) occurred within the first week, contrasting with no deaths in the first week in the extra-CNS TB group. The remaining six patients (three in each group) died after two months but prior to the six-month follow-up period.

The median time to death in the TBM group was 33 days (IQR 4-82). In the extra-CNS TB group the median time to death was 42 days (IQR 26-78). This trend of earlier deaths in the TBM group is further demonstrated in the cumulative survival graph in Figure 4.4.

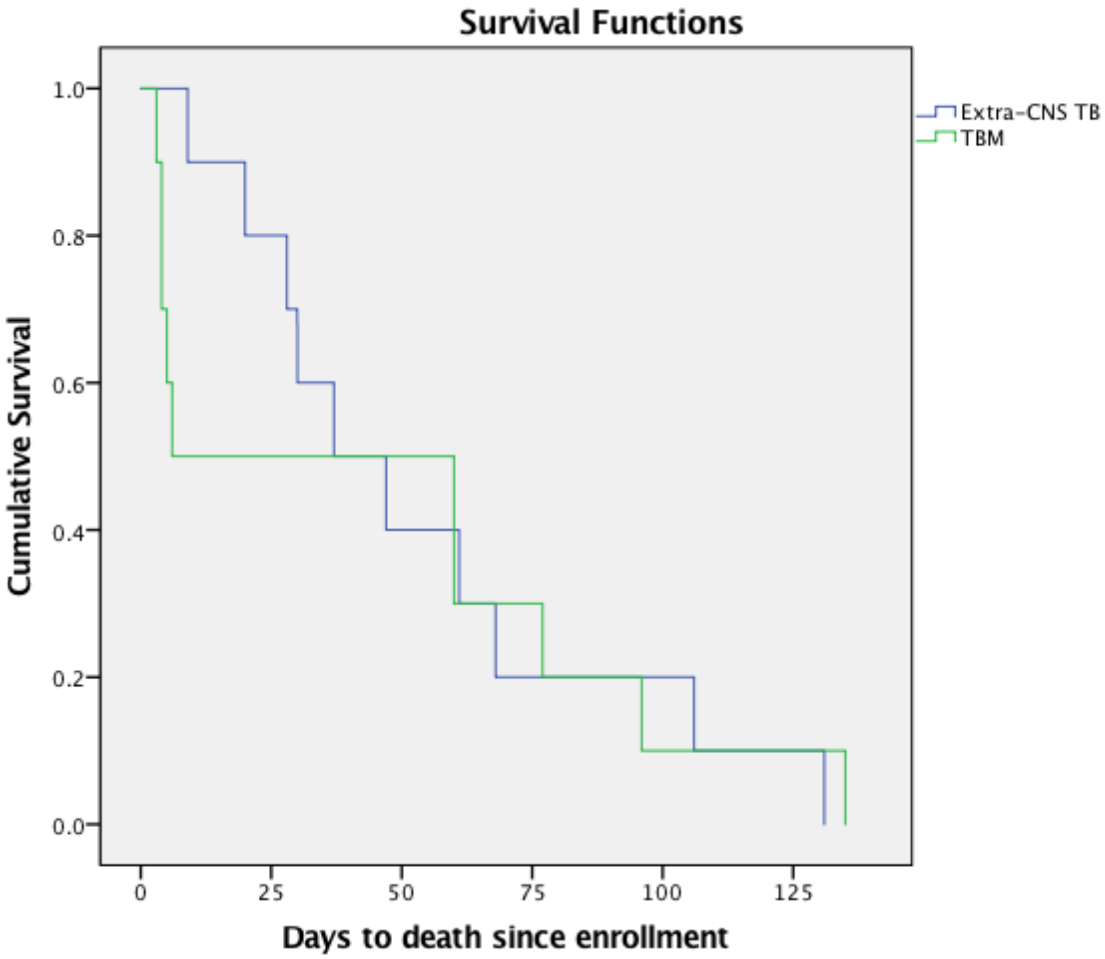

Figure 4.4: Graph of cumulative survival in both groups

Abbreviations: Extra-CNS TB = Tuberculosis outside of the central nervous system; TBM = Tuberculous meningitis.

Because a relatively large number of patients died (and disproportionately so between the two groups), this is potentially an important confounder of predictors of poor cognitive outcomes in the patients who survived. In other words, it is possible that the patients who died would have performed worse cognitively, had they survived. We therefore looked for significant differences in baseline measures for patients who died and those who survived in each group. The comparison of the TBM group and extra-CNS TB group are shown in Table 4.7 and Table 4.8 respectively.

Table 4.7: Comparison of baseline measures in TBM patients who survived and those who died

	Survivors (N = 16) Median (IQR)	Range	Deaths (N = 10) Median (IQR)	Range	P-Value
Age (years)	35 (25-38)	20-46	38 (34-43)	29-65	0.083
Sex (female)	11, 65%	-	6, 60%	-	1.000
Level of education (years)	10 (10-11)[1]	7-16	8 (8-9)[2]	7-10	0.038*
CD4 lymphocyte count (cells/μL)	103 (61-170)	25-281	46 (35-75)	2-163	0.014*
ART duration (weeks)	33 (15-59)	13-152	23 (13-155)	2-287	1.000
On ART (yes)	6, 35%	-	3, 30%	-	1.000
Alcohol use (yes)	3, 18%	-	1/6[3], 17%	-	1.000
Smoking (yes)	4, 24%	-	2/7[4], 29%	-	1.000

The one patient whose mortality status was unknown is not included in this analysis.

[1]LoE unknown for one patient.

[2]LoE unknown for seven patients.

[3]Alcohol use unknown for four patients.

[4]Smoking status unknown for three patients.

*P-Value < 0.05

Abbreviations: ART = Anti-retroviral therapy. IQR = Interquartile range.

There were two significant differences between the TBM patients who survived and those who died: level of education and CD4 lymphocyte count. The lower level of education in patients who died should be interpreted with caution, as this information was only known for three of the patients who died. Patients who died had a lower mean CD4 lymphocyte count. Furthermore, there was a trend for older age to be associated with death, but this did not reach significance.

Table 4.8: Comparison of baseline measures in extra-CNS TB patients who survived and those who died

	Survivors (N = 38)		Deaths (N = 10)		P-Value
	Median (IQR) or N (%)	**Range**	**Median (IQR) or N (%)**	**Range**	
Age (years)	35 (28-38)	19-50	35 (32-43)	24-58	0.286
Sex (female)	21 (55)	-	5 (50)	-	1.000
Education (years)	10 (9-11)	7-14	10 (9-11)	7-12	0.381
CD4 lymphocyte count (cells/μL)	68 (23-128)	1-402	76 (23-128)	9-348	0.639
ART duration at enrollment (weeks)	7 (4-21)	2-1036[1]	4 (4-5)	2-171	0.374
On ART (yes)	19 (50)	-	5 (50)	-	1.00
Alcohol use (yes)	14 (37)	-	2 (20)	-	0.460
Smoking (yes)	12 (32)	-	2 (20)	-	0.701

The four patients whose mortality status was unknown were not included in this analysis.

[1]Patient with vertical transmission of HIV, on ART from neonatal period.

Abbreviations: ART = anti-retroviral therapy; IQR = Interquartile range.

There were no significant differences between extra-CNS TB patients who survived and those who died.

A total of 41 patients (26 [63%] patients with extra-CNS TB and 15 [37%] patients with TBM) were therefore seen at six months after enrollment for comprehensive cognitive testing. The demographic and clinical variables were compared (see Table 4.9).

Table 4.9: Comparison of demographic and clinical measures in the two groups of patients who followed up at six months after TB diagnosis

	TBM (N = 15)		Extra-CNS TB (N = 26)		P-Value
	Median (IQR) or N (%)	Range	Median (IQR) or N (%)	Range	
Age (years)	28 (25-40)	20-46	35 (30-41)	19-50	0.212
Sex (female)	10 (67)	-	11 (42)	-	0.197
Education (years)	10 (10-11)	7-16	10 (9-11)	7-14	0.944
CD4 lymphocyte count (cells/μL)	103 (61-194)	25-281	74 (28-112)	1-402	0.078
On ART (yes)	5 (33)	-	16 (62)	-	0.111
ART duration in weeks[1]	48 (15-107)	13-152	7 (3-24)	2-1036[2]	0.069
Alcohol use (yes)	3 (20)	-	10 (38)	-	0.305
AUDIT score ≥ 8	1 (7)	-	6 (23)	-	0.232
Smokers (yes)	4 (27)	-	10 (38)	-	0.512

[1]ART duration in weeks at enrollment.

[2]Duration = 20.4 years in a patient with vertical transmission of HIV.

Abbreviations: ART = Anti-retroviral therapy; AUDIT = Alcohol Use Disorders Test; Extra-CNS TB = Tuberculosis outside of the central nervous system; IQR = Interquartile range; TBM = Tuberculous menigitis.

There were no significant differences between the two groups on any of the measures reported. Patients were slightly older in the extra-CNS TB group and included a slightly lower proportion of females. There was a trend to significance for the difference in CD4 lymphocyte count with a lower CD4 lymphocyte count in the extra-CNS TB group. This finding may partly be explained by the fact that TBM patients with low CD4 lymphocyte counts were significantly more likely to die as shown in Table 4.7. The TBM group had a lower proportion of patients on ART at enrollment, but for the TBM patients who were on ART, the duration was longer than for the extra-CNS TB patients. We looked at the difference between groups relating to alcohol use (yes or no) but also at differences on the scores of the AUDIT questionnaire. A cut-off score of ≥ 8 on this measure indicates potentially hazardous or harmful drinking (medium level drinking). We excluded all patients with high level drinking or dependence (score ≥ 16). There were more patients who consumed alcohol in the extra-CNS TB group and also more patients with an

AUDIT score of ≥ 8 in this group. The difference was not statistically significant. There was a similar discrepancy between groups relating to smoking: a higher proportion of patients in the extra-CNS TB group smoked, but this did not reach statistical significance.

At six-months follow-up, we also looked at measures of depression and apathy that might impact on cognition and confound performance (see Table 4.10).

Table 4.10: Depression and apathy questionnaire scores

	TBM (N=15)		Extra-CNS TB (N=26)		P-Value
	Median (IQR)	Range	Median (IQR)	Range	
BDI-II	8 (4.5-12.5)	2-37	6.5 (3-14.25)	0-33	0.464
AES-I	28 (24-35)	20-57	25 (24-28.8)	19-69	0.288

Abbreviations: AES-I = Apathy evaluation scale, informant version; BDI = Beck Depression Inventory scale, version II; Extra-CNS TB = Tuberculosis outside of the central nervous system; IQR = Interquartile range; TBM = Tuberculous menigitis.

There was no significant difference on apathy scores between the two groups when analysed as a continuous variable. We also analysed the AES-I score as a binary measure (normal or impaired), using a cut-off score of ≥ 34 to delineate apathy as based on norms from a healthy population (94). There were five patients (33%) who were apathetic in the TBM group compared to three (12%) in the extra-CNS TB group (p-value 0.12). Two of the three (67%) apathetic patients in the extra-CNS group were impaired on the GDS. In contrast, only two of the five (40%) apathetic patients in the TBM group were impaired on the GDS. Two TBM patients who were apathetic were also depressed as scored by the BDI. One extra-CNS TB patient who was apathetic was also depressed.

There was no significant difference on depression scores (as a continuous variable) between the two groups. Looking at the scores on the BDI-II as a categorical measure, standard cut-off scores (91) to delineate mild (14-19),

moderate (20-28) or severe (29-63) depression were applied. For patients who were moderately or severely depressed, three (20%) TBM patients and two (8%) extra-CNS TB patients fell into this category. This difference was not statistically significant. One patient from each group was also impaired on the GDS.

Functional impairment was subjectively measured using the modified IADL scale and PAOFI, or using collateral information from the DECO questionnaire. Results are shown in Table 4.11.

Table 4.11: Questionnaires assessing functional impairment

	TBM (N=15)		Extra-CNS TB (N=26)		P-Value
	Median (IQR)	Range	Median (IQR)	Range	
IADL	16 (15.5-16)	2-16	16 (16-16)	13-16	0.501
DECO	38 (31.5-38)	0-38	38 (38-38)	16-38	0.273
PAOFI	0 (0-1.5)	0-30	0 (0-0)	0-10	0.258

Abbreviations: DECO = Deterioration in cognitive observee; Extra-CNS TB = Tuberculosis outside of the central nervous system; IADL = Instrumental activities of daily living, modified for South Africa; IQR = Interquartile range; PAOFI = Patient assessment of functional impairment; TBM = Tuberculous menigitis.

The scores on the modified IADL were comparable between the groups. There was a non-significant trend towards TBM patients having more impairment on DECO and PAOFI questionnaires.

The mRS scores were different between the groups with a median score of 0 (IQR 0-1; range 0-2) for the extra-CNS TB group and 1 (IQR 0-2; range 0-4) for the TBM group. This difference rendered a near-significant p-value of 0.06.

4.2 Primary Aim

Our primary aim was to determine the cognitive outcome of TBM patients compared to extra-CNS TB patients at six months after TB treatment initiation. We hypothesised that TBM patients will have a more severe degree of cognitive impairment as measured by the continuous GDS than patients with

extra-CNS TB and that the proportion of patients with cognitive impairment will be larger for the TBM patients than extra-CNS TB patients as measured by the binary GDS with a cutoff of ≥ 0.5.

4.2.1 Continuous GDS analysis

The mean GDS for the entire cohort was 0.34 (SD 0.69) with a range of 0 - 2.625. The median for the group was 0 (IQR 0- 0.188). The histogram of the GDS for the study cohort is shown in Figure 4.5 and demonstrates the skew distribution with the majority of patients having a score of 0.

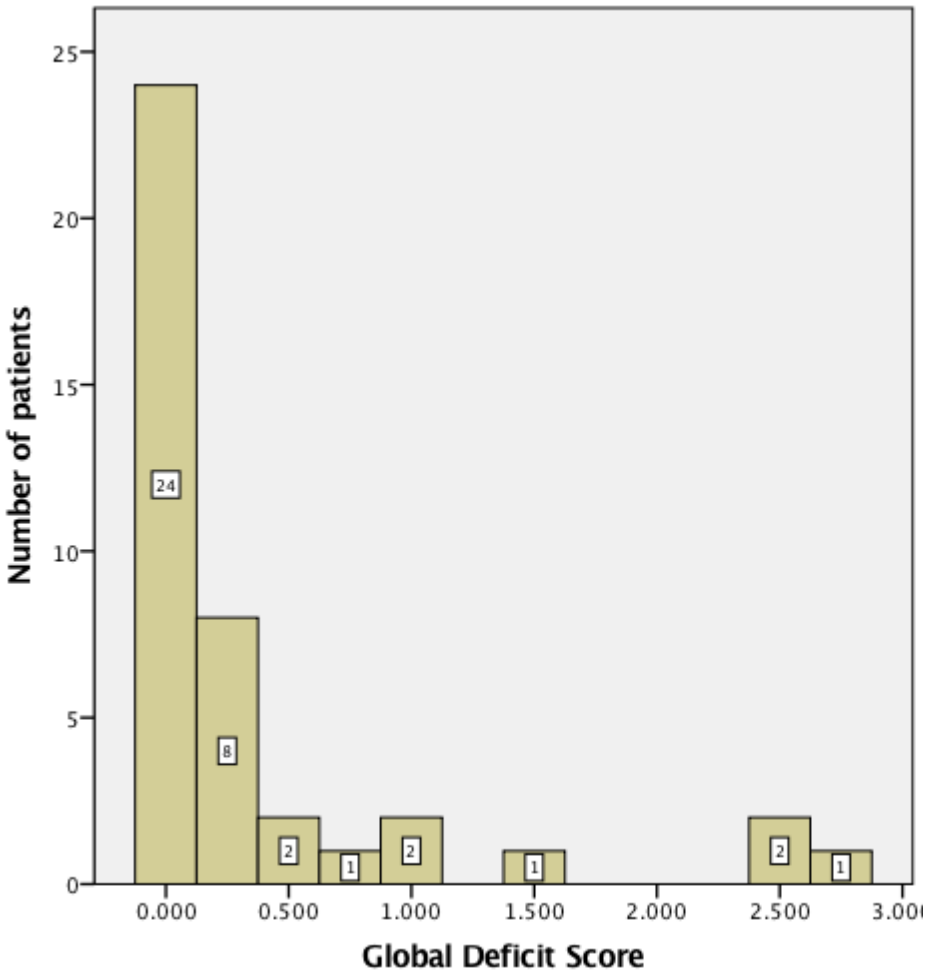

Figure 4.5: Histogram of the GDS for all patients

GDS = Global deficit score

Continuous GDS analysis for each group was performed. The histogram for the GDS of the TBM patients is shown in Figure 4.6 and for the extra-CNS TB patients in Figure 4.7.

The extra-CNS TB patients had a median score of 0 with an IQR of 0 - 0.125. Scores ranged from 0 - 2.375. The TBM patients had a median score of 0 as well, but with an IQR of 0 – 0.5, thereby designating all patients in the fourth quartile to the impaired range of ≥ 0.5. Scores ranged from 0 - 2.625.

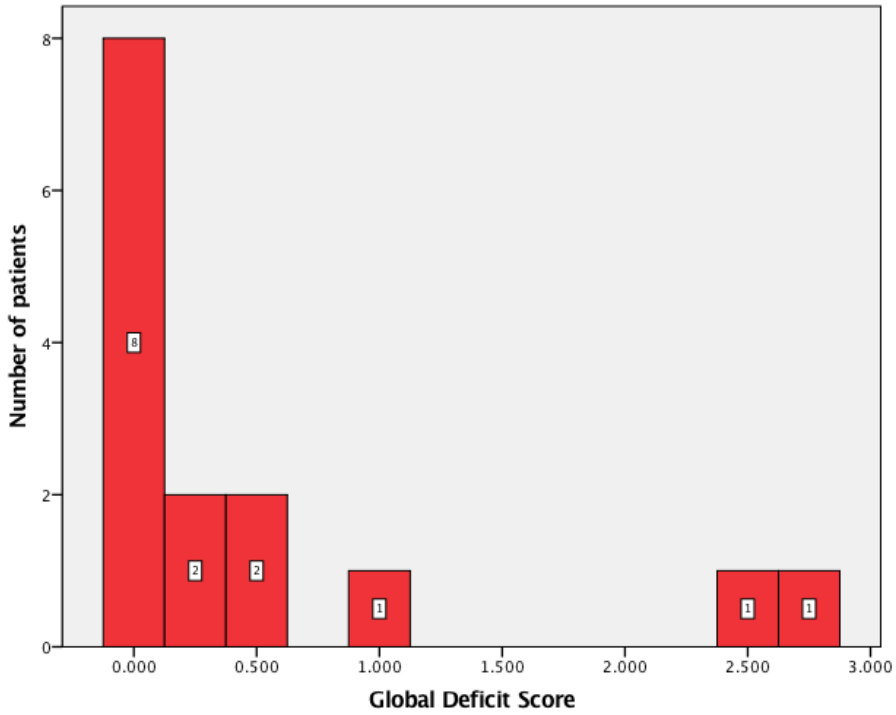

Figure 4.6: Histogram of the GDS for the TBM patients

Abbreviations: GDS = Global deficit score. TBM = Tuberculous meningitis.

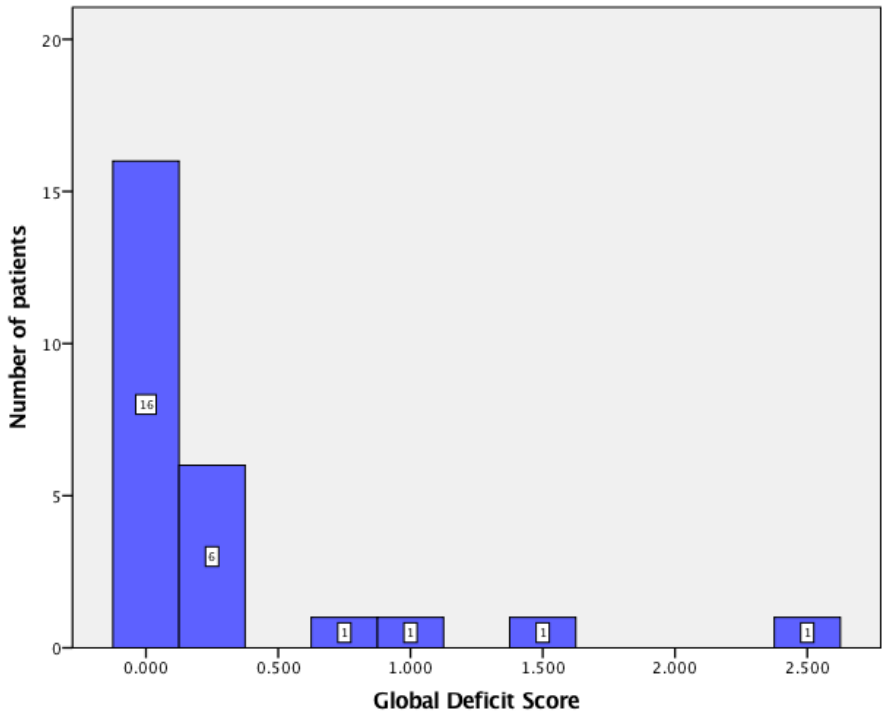

Figure 4.7: Histogram of the GDS for the extra-CNS TB patients.

Abbreviations: extra-CNS TB = Tuberculosis outside of the central nervous system. GDS = Global deficit score.

The boxplot of the GDS distribution amongst the two cohorts is shown in Figure 4.8. This again demonstrates the wider spread of interquartile range scores for the TBM group extending into the impaired GDS range.

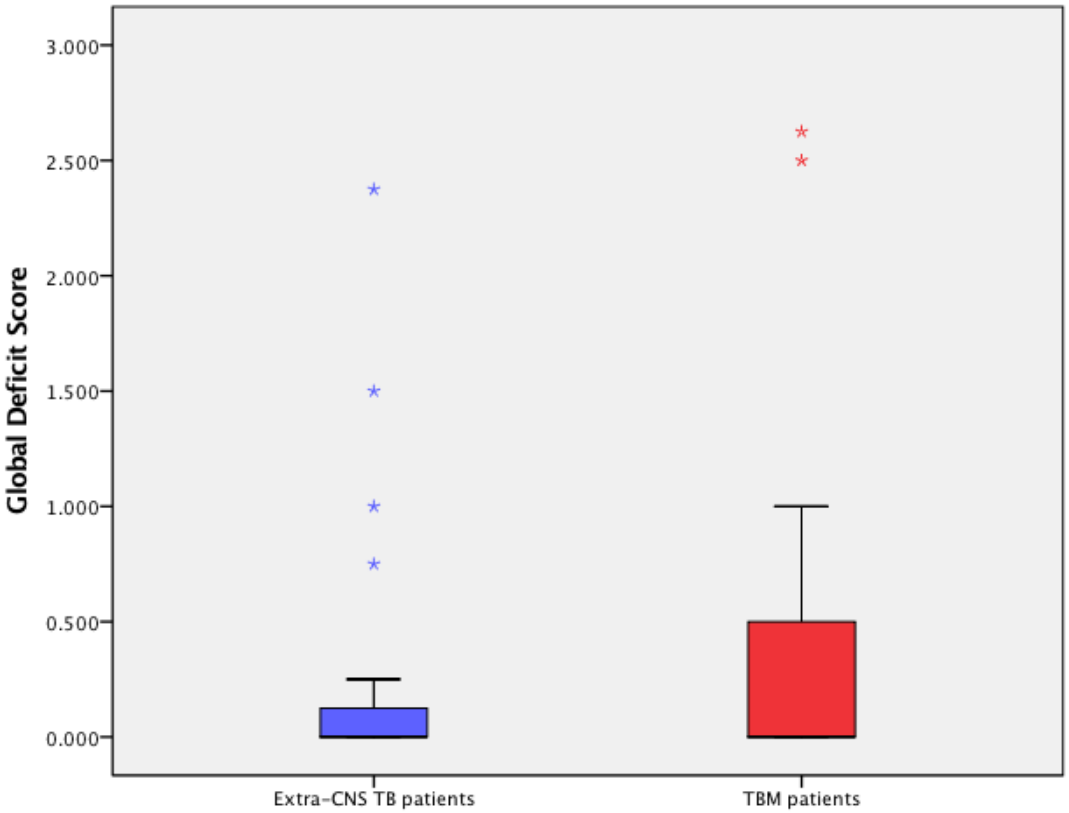

Figure 4.8: Boxplot of the GDS for TBM and extra-CNS TB patients

The boundaries of the box are Tukey's hinges. A line inside the box identifies the median. The length of the box is the interquartile range (IQR) computed from Tukey's hinges. Values more than three IQR's from the end of a box are labeled as extreme, denoted with an asterisk (*).

Abbreviations: Extra-CNS TB = Tuberculosis outside of the central nervous system; GDS = Global deficit score; IQR = Interquarile range; TBM = Tuberculous meningitis.

The difference between the groups' continuous GDS was not significant with a p-value of 0.439.

4.2.2 Binary GDS analysis

Other than the degree of impairment as measured by the GDS, we also wanted to quantify the absolute number of patients who were impaired. For this purpose we used the recognised GDS cutoff of ≥ 0.50. Across groups, nine (22%) patients were cognitively impaired. Five patients were from the TBM group and four patients were from the extra-CNS TB group. Therefore, 33% of the TBM patients were impaired compared to 15% of the extra-CNS TB patients. Despite double the proportion of affected patients in the TBM

group, this clinically significant difference did not reach statistical significance (p=0.248).

To assess the effect of biased patient deaths (with a higher proportion of deaths in the TBM group) on cognitive outcomes, we also looked at whether TBM exposure status correlated with GDS classification and death. There was no significant association between TBM exposure and GDS classification or death (p = 0.285).

4.3 Secondary Aims

4.3.1 Cognitive outcomes by Frascati criteria

Our first secondary aim was to classify patients into HAND categories: normal; ANI; MND; or HAD. Definitions for these classifications have been discussed in Chapter 2. Across groups, eight (20%) patients were impaired, with four patients in each group, which equates to 27% of TBM patients and 15% of extra-CNS TB patients. Three patients were classified as ANI (7%), two (5%) as MND and three (7%) as HAD. The distribution of these classifications by TBM exposure is shown in Table 4.12. To assess whether patients who were exposed to TBM performed worse than extra-CNS TB patients by Frascati criteria, we drew up a contingency table (see Table 4.12).

Table 4.12: Contingency table of TBM exposure status and Frascati classification

		Normal	ANI	MND	HAD	p-Value
TBM patients	Number (%)	11 (73%)	1 (7%)	1 (7%)	2 (13%)	
Extra-CNS TB patients	Number (%)	22 (85%)	2 (8%)	1 (4%)	1 (4%)	0.685

Abbreviations: ANI = asymptomatic neurocognitive impairment; Extra-CNS TB = Tuberculosis outside of the central nervous system; HAD = HIV-associated dementia; MND = mild neurocognitive disorder; TBM = Tuberculous meningitis

There was no significant difference in cognitive performance by Frascati criteria for the two TB groups.

To assess cognitive impairment and associated impact on functional status, we further divided patients into two groups based on the Frascati criteria as follows: patients with normal cognitive performance and asymptomatic neurocognitive impairment in the first group; and patients with mild neurocognitive disorder and HIV associated dementia in the second group. This dichotomised classification has real-life meaning, as the first group, by definition, has normal daily functioning, whereas the second group is functionally impaired (albeit to mild degrees for MND and severely for HAD).

Only five patients (12.2%) had functional impairment (classification of functional impairment has been outlined in Chapter 3): two (8%) patients in the extra-CNS TB group and three (20%) in the TBM group. This difference was not statistically significant (p-value = 0.336). Three of these five patients had severe functional impairment while the remaining two patients had mild functional impairment. These five patients all had a GDS of ≥ 1. This leaves three patients with impaired cognition but normal functioning. These three patients had mildly impaired cognition by Frascati criteria and were thus classified as ANI.

There was one patient with a GDS of 0.5 who was not rated as impaired by Frascati criteria. This patient (number 90) is discussed in further detail below in section 4.3.2.1. There were no patients who were impaired by Frascati criteria and had a normal GDS.

There were eight patients who were functionally impaired but performed normally on cognitive tests. Four of these patients had mild functional impairment and four had severe functional impairment. Looking at the four patients with severe functional impairment: one patient had significant depression and apathy as measured by the BDI-II and AES-I questionnaires respectively. The second patient was not depressed but was markedly apathetic (highest score of the entire cohort). The third and fourth patients were mildly depressed but not significantly apathetic.

To assess how well the Frascati criteria correlated with the GDS, we ran the asymptotic Kruskal-Wallis Test. There was a highly significant increase of GDS across HAND groups, indicating a very good correlation between these two measures of cognitive impairment (p-value <0.001).

4.3.2 Description of cognitive impairment by domains

We assessed whether there were differences in performance across domains between the two groups. We grouped the 21 cognitive tests into eight cognitive domains as discussed in Chapter 3. Performance by domain is shown in Table 4.13. The Z-scores were derived from local norms as discussed in Chapter 3.

Table 4.13: Performance scores in the eight cognitive domains, for the entire cohort and across groups

Domains	Entire cohort (N=41) Mean Z-score (SD)	Extra-CNS TB (N = 26) Mean Z-score (SD)	TBM (N = 15) Mean Z-score (SD)	Cohen's D (95% CI)[1]	P-Value
Motor	-0.21 (0.57)	-0.15 (0.44)	-0.31 (0.75)	0.27 (-0.39, 0.93)	0.685
Learning	-0.05 (1.13)	0.04 (1.22)	-0.20 (0.97)	0.21 (-0.45, 0.87)	0.401
Memory	-0.06 (1.17)	-0.01 (1.12)	-0.14 (1.30)	0.11 (-0.55, 0.76)	0.957
Information processing speed	-0.44(0.92)	-0.32 (0.83)	-0.65 (1.07)	0.35 (-0.31, 1.01)	0.449
Attention/ Working memory	-0.52 (0.56)	-0.44 (0.58)	-0.67 (0.50)	0.41 (-0.25, 1.08)	0.267
Executive function	-0.55 (0.82)	-0.45 (0.64)	-0.73 (1.07)	0.33 (-0.33, 0.99)	0.715
Fluency	-0.11 (0.86)	-0.05 (0.81)	-0.23 (0.97)	0.20 (-0.46, 0.86)	0.516
Visuospatial	-0.18 (1.01)	-0.06 (0.98)	-0.38 (1.06)	0.31 (-0.35, 0.97)	0.176

[1]Hedges G correction was used due to small sample sizes.

Abbreviations: Extra-CNS TB = Tuberculosis outside of the central nervous system; SD = Standard deviation; TBM = Tuberculous meningitis.

Looking at the cohort as a whole, the most impaired domains were that of information processing speed; attention and working memory; and executive function. The same applies to each group individually with the three lowest mean Z-scores being in those specific domains. The effect sizes for the differences between groups were small to medium (Cohen's D between 0.2 and 0.5) for all domains except memory. For memory performance, the effect size of the difference between groups was negligible. If we examine the p-values, the strongest trend towards significant differences between groups was in the visuospatial domain (p=0.176). In this domain, the TBM patients performed worse with a mean Z-score of -0.38 (SD=1.06) contrasting with a near-normal performance in the extra-CNS TB group with a mean Z-score of -0.06 (SD 0.98).

A description of the performance on subtests within each cognitive domain is shown in Table 4.14.

Table 4.14: Performance on subtests for each cognitive domain, across groups

Cognitive test	TBM Mean Z-score[1] (SD)	Extra-CNS TB Mean Z-score[1] (SD)	Cohen's D (95% CI)*	P-Value
Motor speed				
Grooved pegboard				
Dominant	-0.67 (1.23)	-0.24 (0.53)	-0.50 (-1.18, 0.18)	0.303
Non-dominant	-0.25 (0.57)	0.01 (0.21)	-0.69 (-1.42, 0.03)	0.318
Finger tapping				
Dominant	0.31 (0.88)	-0.53 (0.87)	0.06 (-0.61, 0.73)	0.837
Non-dominant	0.15 (0.88)	-0.31 (0.74)	-0.08 (-0.76, 0.61)	0.829
Learning				
HVLT-R trials 1-3	-0.76 (1.31)	-0.47 (1.28)	0.22 (-0.45, 0.9)	0.597
BVMT-R trials 1-3	0.36 (0.92)	0.55(1.52)	0.14 (-0.53, 0.82)	0.766
Memory				
HVLT-R delayed	-0.5 (1.52)	-0.44 (1.31)	0.04 (-0.63, 0.71)	0.923
BVMT-R delayed	0.21 (1.27)	0.41 (1.37)	0.15 (-0.52, 0.82)	0.595
Information processing speed				
TMT A	-0.53 (1.66)	-0.01 (1.02)	-0.40 (-1.07, 0.28)	0.755
CTT I	-0.72 (1.20)	-0.27 (1.22)	-0.36 (-1.04, 0.32)	0.223
Digit symbol coding	-0.69 (1.02)	-0.69 (0.93)	0.00 (-0.67, 0.67)	0.745
Symbol search	-0.68 (0.86)	-0.33 (0.8)	0.42 (-0.26, 1.10)	0.101
Attention/ Working memory				
Digit span forward	-0.24 (0.74)	-0.18 (1.09)	0.05 (-0.62, 0.73)	0.976
Digit span backward	-0.58 (1.02)	-0.05 (0.96)	0.52 (-0.16, 1.21)	0.136
Mental control	-0.99 (0.69)	-0.91 (0.80)	0.10 (-0.58, 0.77)	0.860
Mental alternation test	-0.56 (0.54)	-0.26 (0.57)	0.53 (-0.15, 1.22)	0.156
Executive function				
SCWT	-0.80 (0.81)	-0.58 (0.58)	0,32 (-0.36, 1.00)	0.296
CTT II	-0.66 (1.52)	-0.32 (0.90)	-0.28 (-0.96, 0.39)	0.818
Fluency				
Category fluency (animals)	-0.31 (1.16)	0.04 (1.00)	0.32 (-0.35, 1.00)	0.301
Category fluency (fruit & veg)	-0.04 (1.16)	0.02 (0.81)	0.06 (-0.61, 0.73)	0.567
Action fluency	-0.33 (1.20)	-0.20 (0.97)	0.12 (-0.55, 0.79)	0.664
Visuospatial				
JLOT	-0.05 (1.24)	0.20 (1.14)	0.20 (-0.47, 0.88)	0.439
CLOX	-0.70 (1.30)	-0.31 (1.05)	0.33 (-0.34, 1.01)	0.361
CLOX 1	-0.51 (1.12)	-0.08 (0.97)	0.41 (-1.05, 0.23)	0.170
CLOX 2	-0.42 (1.34)	-0.28 (1.04)	0.12 (-0.52, 0.75)	0.898

[1]The mean Z-score for each test is reported using patient raw scores compared to local normative data.

Abbreviations: BVMT-R = Brief visuospatial memory test – revised; CTT I = Color trails test I; CTT II = Color trails test II; Extra-CNS TB = Tuberculosis outside of the central nervous system. HVLT-R = Hopkins verbal learning test – revised; JLOT = Judgement of line orientation test; SCWT = Stroop Color Word Test; SD = Standard deviation; TBM = Tuberculous menigitis; TMT A = Trail making test A.

There were no large effect sizes noted for the subtests of each cognitive domain. There were moderate effect sizes for the following tests: the dominant and non-dominant hand Grooved Pegboard test with the TBM patients performing slower; the backward digit span with the TBM patients having a shorter span; and the mental alternation test with TBM completing fewer correct number-letter sequences in the allocated time.

4.3.2.1 Description of patients with impaired cognition

The performance of the nine patients who were impaired by the GDS will now be further discussed. It warrants stating that because a fixed research protocol is followed, an accurate description of these patients' neurocognitive deficit is not always possible. A qualitative impression by taking a more extensive history is lost in the research setting and further probing of areas of impairment is not supported in this context. Also, this battery does not assess language to a sufficient extent. With these caveats in mind, a vignette for each of the nine cognitively impaired patients is created. Z-scores within one SD of the mean is taken as a normal performance; between one and two SD below the mean as mild impairment; more than two SD below the mean as moderate to severe.

1. Patient number 23, TBM patient, GDS = 2.5

She is a 29-year-old lady who was ART naive when she was diagnosed with definite TBM based on symptoms and CSF TB GeneXpert positivity. She was started on TB treatment and high dose oral Prednisone in hospital and on ART six weeks after diagnosis. She re-presented to hospital two months after diagnosis with worsening headache and a CSF protein of 13.8g/L (compared to a level of 1.6g/L at diagnosis) and an increasing CSF lymphocyte count. Her CT Brain was unremarkable. She was diagnosed with TBM-IRIS and treated with high dose Prednisone. Three months later, she presented again, with confusion and leg weakness and was assessed as having TBM-IRIS with myelo-meningo-radiculopathy and given another course of oral Prednisone. She was transferred to a rehabilitation facility. She was cognitively assessed at this facility at six months after TBM diagnosis.

She denied any impairment in her IADLs but complained of mild memory difficulty. Her husband reported a definite decline in cognition since time of TBM diagnosis. She was not apathetic or depressed.

Her **motor speed** was slow for finger tapping and the grooved pegboard test with a summary Z-score of -1.6.

Her **verbal learning** on the HVLT was impaired: she recalled four, six and seven words for the three learning trials respectively (Z-score -1.8). Her **verbal memory** was very poor as she could only recall four out of the 12 words after a delay, giving her a Z-score of -2.2. Her verbal percentage retained score generates a slightly better Z-score of -1.7. She did much better, however, on the **recognition** task where she correctly identified 11/12 words with no false positive responses.

In terms of **visual learning** on the BVMT, she scored two, four and three out of 12 for the three respective trials (Z-score -0.7). Her **visual memory** was very poor, however, as she could not correctly reproduce any of the six figures after a delay. With prompting she had four true positive responses and two false positive responses. This translates to a very poor Z-score of -3.8 for **visual recognition** memory.

On tests of **information processing speed** she performed poorly: more than two standard deviations below the norm for TMT A, CTT 1 and digit symbol coding. She performed slightly better on the Symbol Search test (see Figure 4.9), but still had a summary Z-score for this domain of -2.2.

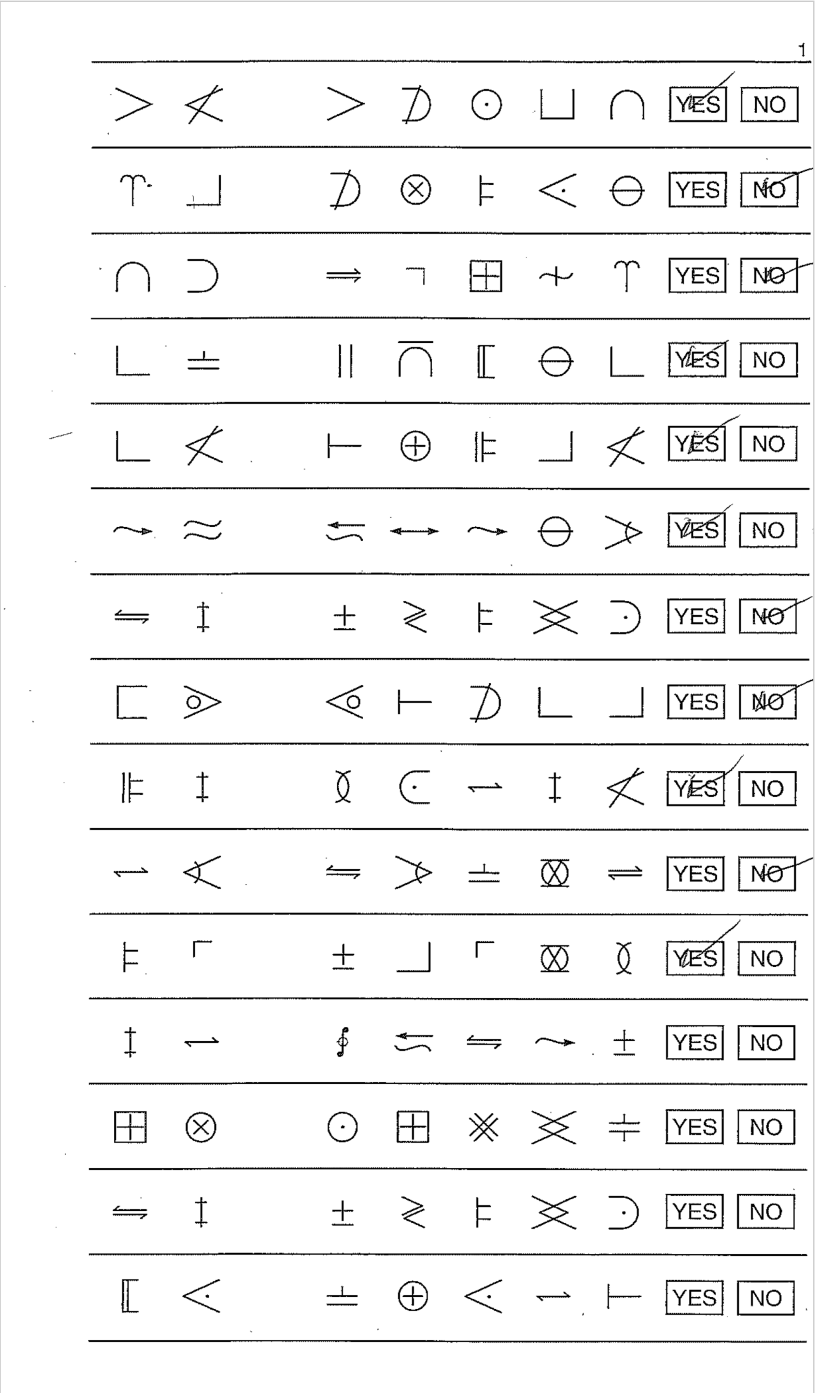

Figure 4.9: Symbol Search test for patient number 23

Symbol search requires correctly identifying the presence of target symbols on the right from either of the two symbols on the left, under time pressure. Slow processing speed is demonstrated with eleven responses in two minutes.

Regarding **attention**, her forward digit span was within normal limits with her correctly repeating a number string of five once. **Working memory** was within normal limits on the backward digit span test where she could muster a string of three numbers. She had somewhat impaired performances on the mental

alternation test and mental control. Overall, her summary Z-score for the domain of attention and working memory was -1.3.

Testing of her **executive functioning** revealed impaired performance. On the SCWT, she gave just 17 responses in 45 seconds, giving her a Z-score of -1.7. On CTT 2, she took just over 4 minutes to complete the task (compared to a mean time of 116 seconds for the sample population). Her summary Z-score for this domain was -2.3.

Performance on the two category and single action **fluency** tasks was clearly impaired with all her scores more than two SDs below the mean. She generated six words for the fruit and vegetable category compared with the population mean of 14. She could only generate one verb in one minute (population mean 10.4). Her summary Z-score for fluency was -2.3.

In terms of **visuospatial** functioning, she performed very poorly on the JLOT with only one correct response (correctly identifying the orientation of the two paired lines, Z-score -3.1). Her performance on the CLOX was also impaired with a score of 8/15 (Z-score -1.7) for the spontaneous drawing (see Figure 4.10) and 11/15 (Z-score -3.4) for the copy (see Figure 4.11). Her unprompted drawing showed a concrete approach with the watchstraps drawn, poor planning and incorrect placement of the hands. Her copy again showed poor planning and crowding of numbers on the right half of the clock face. This total score of 19 is well below the norm (25) and generates a Z-score of -2.3. Her summary score for the visuospatial domain is -2.7.

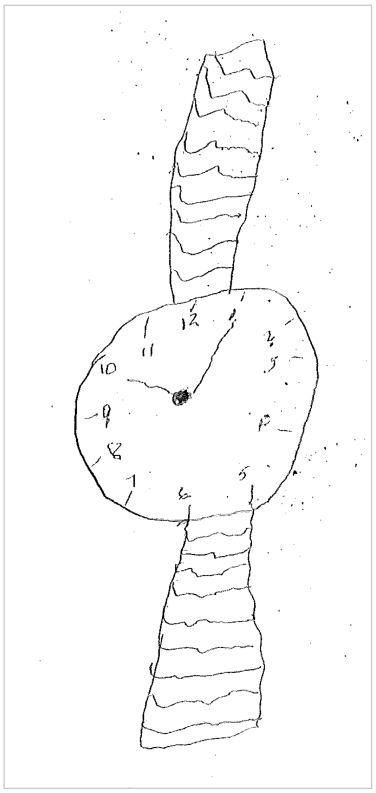

Figure 4.10: Clock drawing on CLOX 1 task for patient number 23

Patient was asked to draw a clock that says 1:45. Image not to scale.

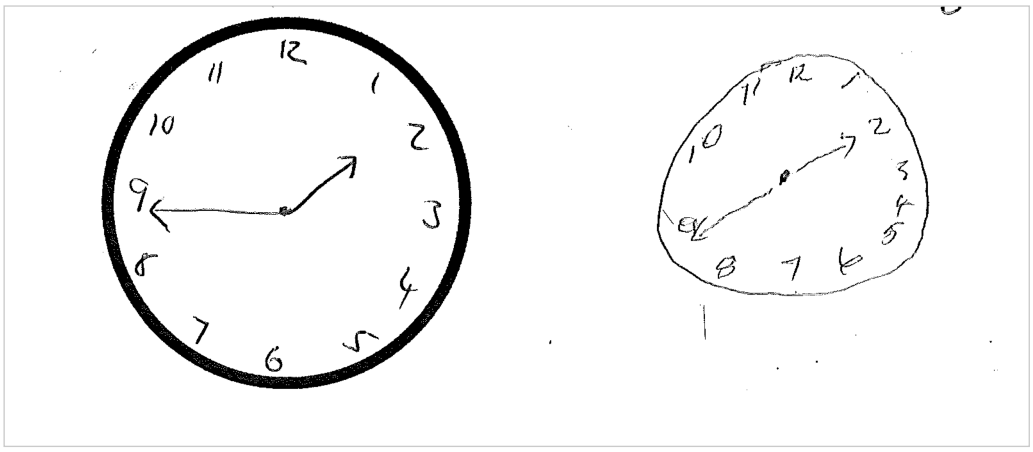

Figure 4.11: Clock copy on CLOX 2 task for patient number 23

Patient was asked to copy examiner's clock as shown on the left. Image not to scale.

In summary, this patient attended well and was motivated. She was impaired in all eight domains tested. She had impaired verbal learning and poor retention of both the verbal and visual material that she had learnt. For the verbal material, she clearly benefitted from prompting, but this was less striking for visual material. In addition, she had slow motor and mental processing speed; poor executive functioning; poor generativity and poor

visuospatial skills. Although one could argue that the spontaneous drawing on the CLOX 1 task is loaded on both an executive and visuospatial basis, her performance on the copying task was also very impaired, suggesting additional visuospatial impairment. This is in keeping with her performance on the JLOT, which was the worst of all 41 patients tested. The above picture would suggest a frontal-subcortical process with additional visuospatial impairment.

2. Patient number 33, TBM patient, GDS = 1

This 36-year-old lady was ART naive when she presented with meningitic symptoms and signs. She was diagnosed with definite TBM based on a positive CSF TB culture.

She had no intercurrent hospital admissions and was tested six months after diagnosis. She reported normal daily functioning although her sister reported mild cognitive deterioration. She was not depressed or apathetic.

Her **motor speed** was normal.

Verbal learning was mildly impaired (Z-score -1.1) while **visual learning** was normal (Z-score - 0.8). An example of her learning of the third trial of the BVMT is shown in Figure 4.12. Note the impaired accuracy of the figures as well as poor placement and poor spacial use of the page.

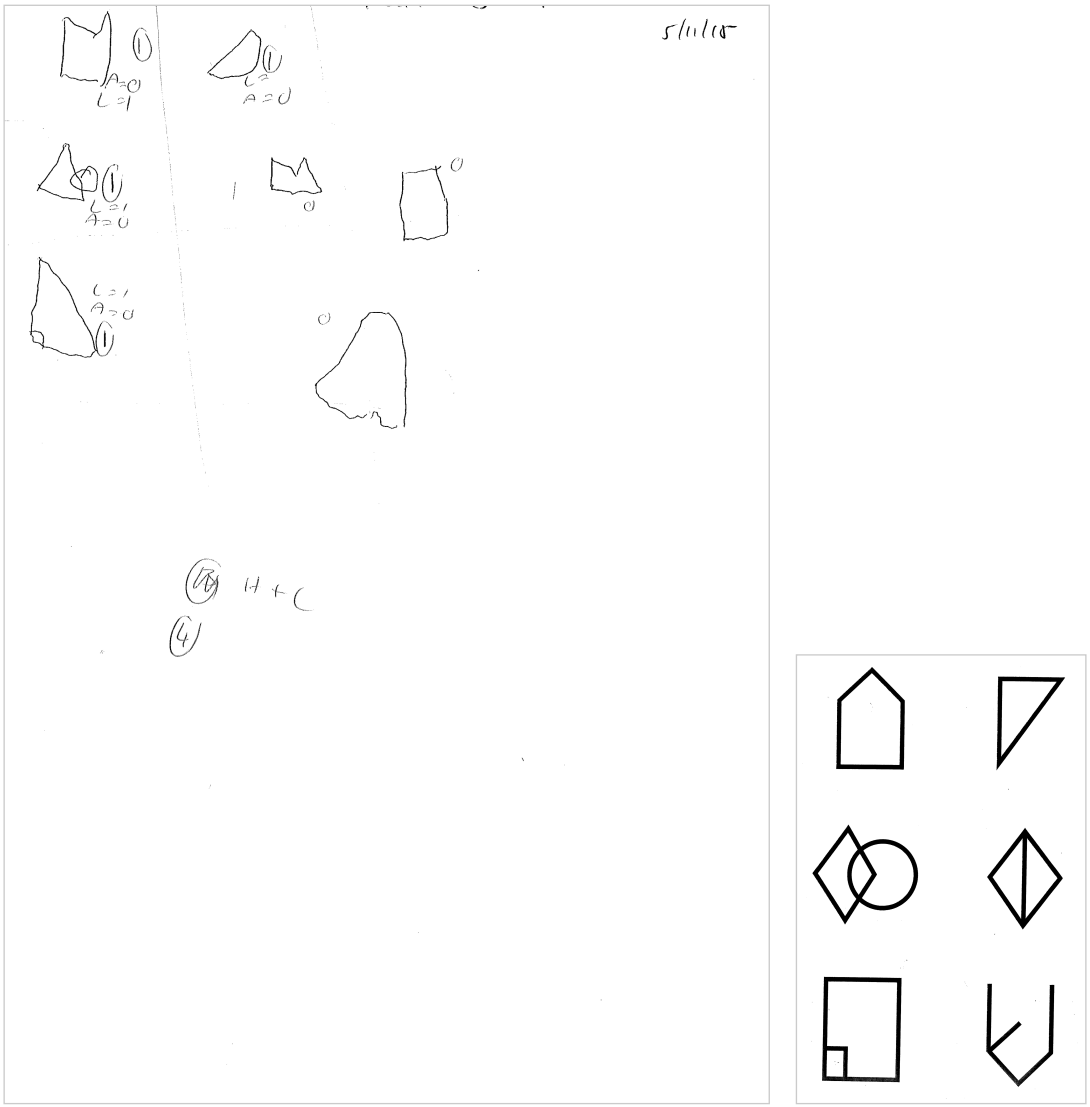

Figure 4.12: Third learning trial on the BVMT for patient number 33

Note examiner scoring marks on the sheet: L=location, A= accuracy. The patient scored 4 for this attempt. The target figures shown to patient for 10 seconds prior to her drawing are shown in the lower right corner. Image not to scale.

BVMT = Brief visuospatial memory test.

Her **verbal and visual memory** was normal and she retained all of the words she learnt on the HVLT and retained 75% of the visual material.

Speed of information processing was impaired: TMT A took 76 seconds to complete (Z-score -2.2), while she scored between one and two standard deviations below the mean for the other three tests. This gave her a summary Z-score of -1.7.

In terms of **attention**, her forward digit span was borderline impaired at four

digits (Z-score -1.0). Her **working memory** was much more impaired, however, with a backward digit span of two words on one trial only (Z-score -2.1). Performance on mental control and mental alternation tests were also impaired, with a summary score for attention and working memory of -1.4.

On tests of **executive functioning**, her performance on the SCWT was normal. She was very slow to complete CTT 2 at 221 seconds compared to the population mean of 116 (Z-score -2.2). Her summary Z-score for this domain was -1.6.

For **fluency** she was mildly impaired on both semantic categories, but performed in the normal range for action fluency. Interestingly, her verb generation in one minute (10 words) was better than her animal generation (7 words), whereas the population shows an opposite trend (more words generated for semantic categories than for verbs). Her summary Z-score for fluency was -1.1.

Regarding **visuospatial** functioning, her JLOT was impaired with only 10/30 pairs identified correctly (Z-score -1.3). Her unprompted clock drawing on the CLOX 1 task (see Figure 4.13) showed a disorganised approach and switching of numbers 6 and 12. There was also incorrect placement of the hands (Z-score -1.7).

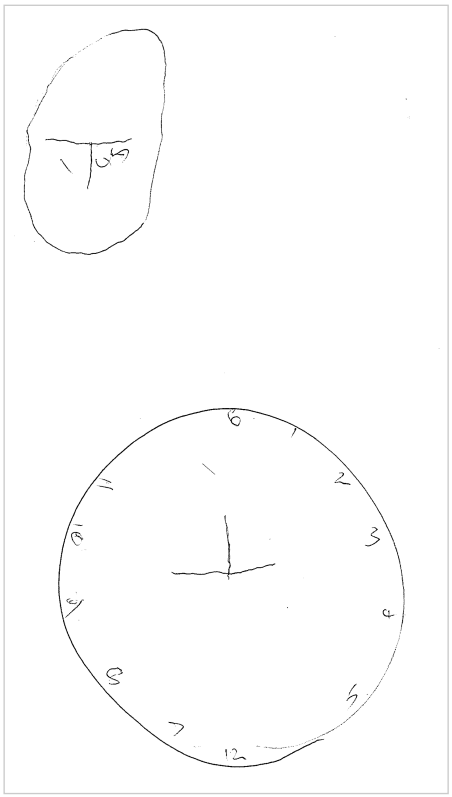

Figure 4.13: Clock drawing on CLOX 1 task for patient number 33

Patient was asked to draw a clock that says 1:45. Image not to scale.

On her copying of the clock, (see Figure 4.14) however, the circular outline was distorted, as was the number spacing. An impression of a rushed approach was noted and planning was again poor (Z-score for CLOX 2 task -3.4). Her visuospatial summary Z-score is -1.8.

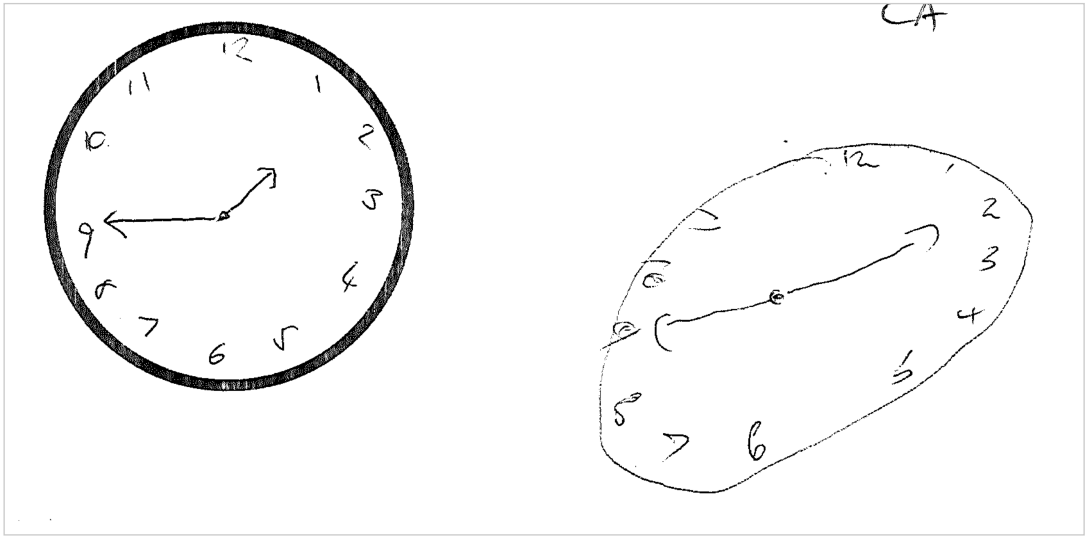

Figure 4.14: Clock copy on CLOX 2 task for patient number 3

Image not to scale

Overall, her impairments were mild and in the domains of information processing speed, working memory, executive functioning, and visuospatial functioning. A frontal-subcortical process is likely and may be impacting on her performance on the visuospatial tests, but seperate pathology impacting visuospatial processing cannot be ruled out.

3. *Patient number 52, extra-CNS TB patient, GDS=1*

This 37-year-old man, on ART for seven years, was diagnosed with pulmonary TB based on symptoms and a suggestive CXR. He had no further hospital admissions and was assessed at six months. The patient had a slight stammer and this may have hampered his performance on verbal timed tasks (e,g, mental alternation test).

Neither the patient nor his father reported any functional impairment. He was not apathetic or depressed.

His **motor speed** was normal.

In terms of **verbal learning**, he recalled six, four and seven words on the three trials of the HVLT respectively (Z-score -1.8). For **verbal memory** he recalled six words, which is slightly impaired (Z-score -1.3). However, his retention memory of 85% was normal and he correctly **recognised** 10/12 words.

For **visual learning**, his figure reproduction was poor with scores of zero, one and three for the three trials of the BVMT respectively (Z-score -1.5). His third learning trial is shown in Figure 4.15.

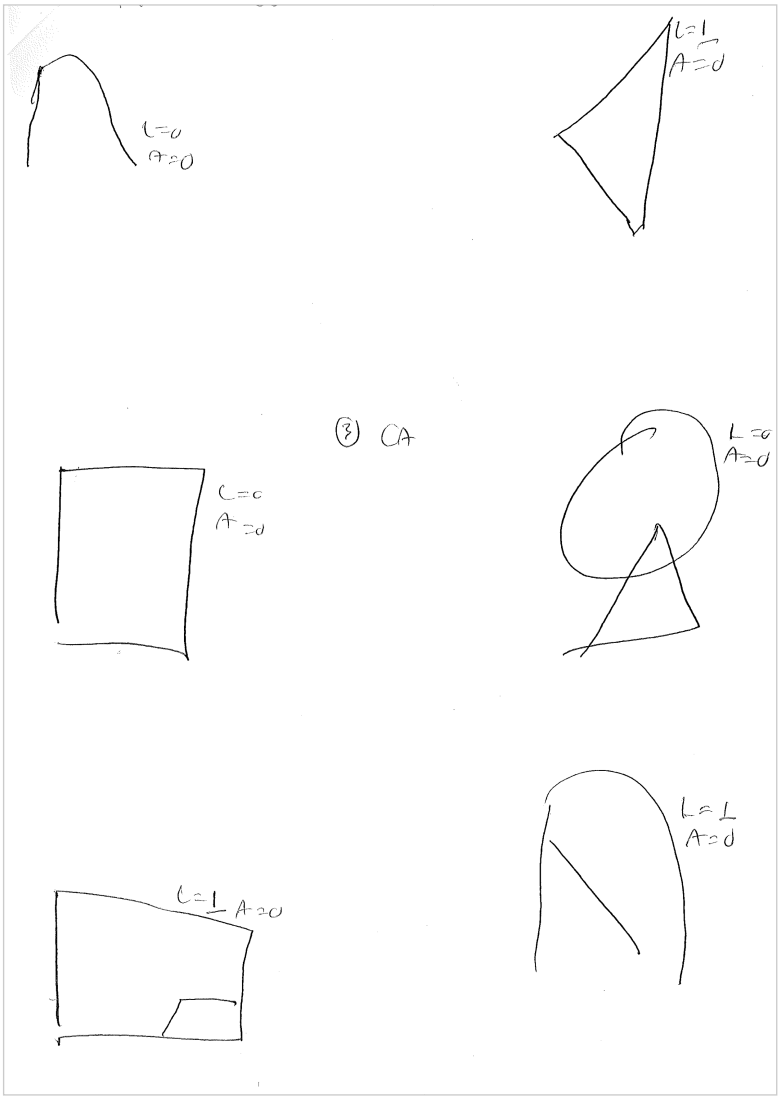

Figure 4.15: Learning trial 3 of the BVMT for patient number 52

Annotation by examiner: L= Location; A= Accuracy. Image not to scale.

BVMT = Brief visuospatial memory test.

For **visual memory** after a delay, he scored three, which paralleled his best learning performance, thereby retaining 100% of information learnt. This image is shown in Figure 4.16. He correctly **recognised** five out of the six true positive shapes.

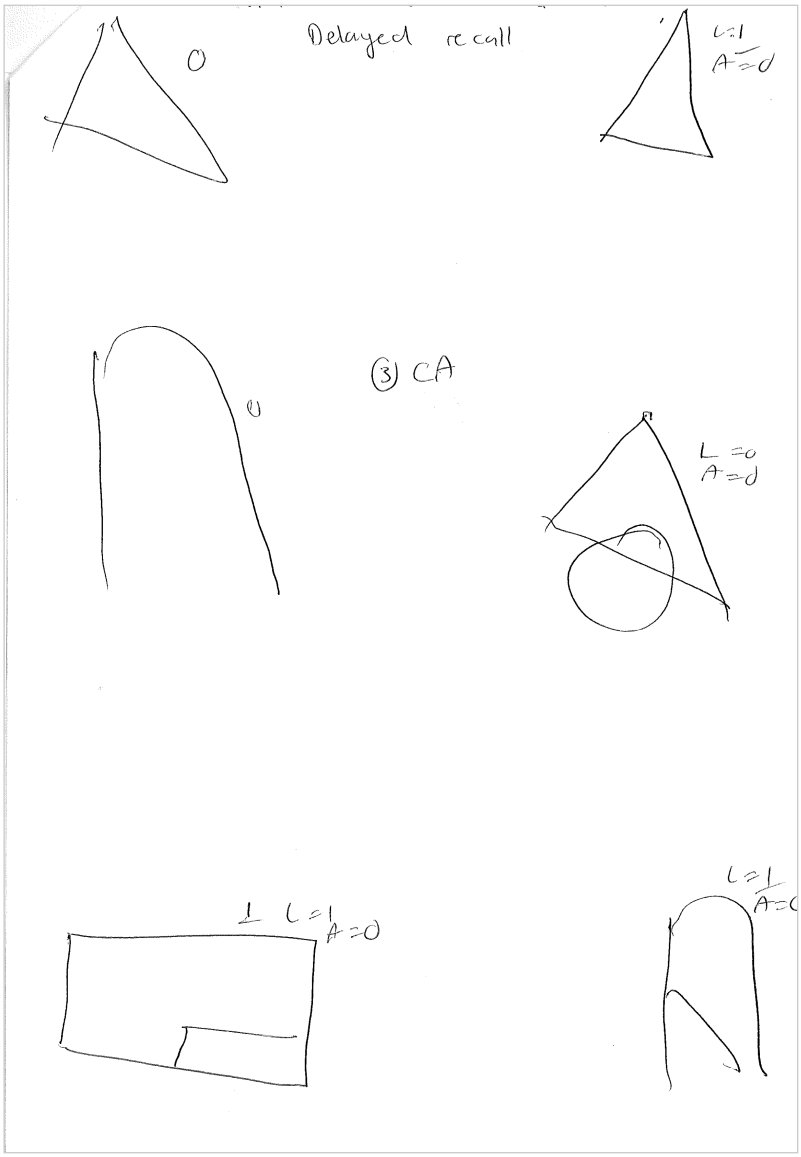

Figure 4.16: Delayed recall of visual stimulus from the BVMT for patient number 52

Annotation by examiner: L= Location; A= Accuracy. Image not to scale.

BVMT = Brief visuospatial memory test.

On **speed of information processing**, he was slightly slow on the CTT 1, digit symbol coding and symbol search tasks with a normal TMT A performance. A summary Z-score for this domain was -1.4.

His test of **attention** was poor, with a forward digit span of three only (Z-score -2.2). His **working memory** was normal with a backward digit span of three. His performance on the mental control task was impaired with a Z-score of -2.2, but he performed normally on the mental alternation task. His summary Z-score for this domain was -1.4.

For tasks tapping into **executive functioning**, he was mildly impaired on the SCWT and the CTT 2. This rendered a summary Z-score of -1.6.

For the **fluency** tasks, he was mildy impaired for both semantic categories but performed normally on the action fluency task by generating seven verbs. A summary Z-score of -1.2 was rendered.

For **visuospatial testing**, he performed well on the JLOT, correctly identifying 22 pairs (population mean 16). His CLOX drawing and copy was slightly rushed and not detailed, but placement of the hands and numbers were reasonable. He scored 24/30. This normal performance was reflected in a summary Z-score of 0.3.

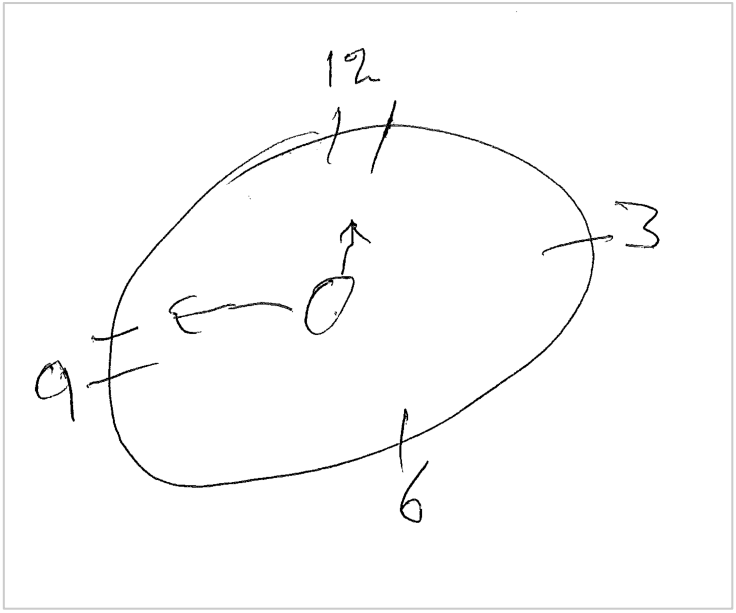

Figure 4.17: Clock drawing on CLOX 1 task for patient number 52

Patient was asked to draw a clock that says 1:45. Image not to scale.

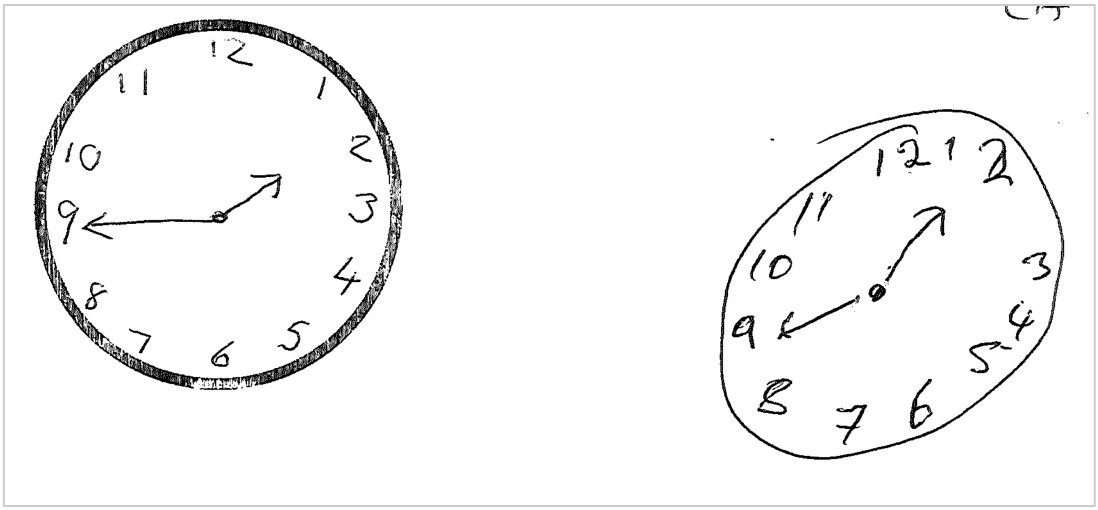

Figure 4.18: Clock copy on the CLOX 2 task for patient number 52

Image not to scale.

In summary, this patient's performance was characterised poor attention and working memory, which likely impacted on his ability to learn. His memory of the material that he learnt, however, was good. He further had mildly impaired information processing speed, executive functioning and semantic fluency. This picture would be compatible with a mild frontal-subcortical process.

4. *Patient number 74, TBM patient, GDS = 2.625*

This 44-year-old man, ART naive, presented with a six week history of confusion and not reporting to work. He had night sweats and back pain during this time with difficulty walking. He then developed headache and cough with hemoptysis, which prompted admission to hospital. He was diagnosed with probable TBM based on symptoms and a suggestive CSF. He did not have evidence of TB elsewhere. Testing for neurosyphilis and cryptococcal meningitis was negative. Vitamin B12 levels and thyroid function tests were normal. He was discharged on TB treatment and oral steroids and ART was initiated a month later. He improved initially, but four months after diagnosis he re-presented to hospital with psychotic behaviour. Repeat CSF testing showed improvement in CSF parameters and a contrasted CT Brain revealed bilateral periventricular and subcortical white matter disease, early hydrocephalus and mild brain atrophy. Differential diagnoses considered included Efavirenz or Isoniazid induced psychosis; psychosis secondary to TBM; or HIV associated neurocognitive disorder. His ART and TB drug

regime was adjusted to allow cessation of Efavirenz and Isoniazid. He was assessed at a psychiatric inpatient facility seven months after TBM diagnosis. Of note, the patient was on psychotropic drugs (Lithium and Haloperidol) at time of testing. He had pressure of speech and was disinhibited.

Both self-reported and informant-reported questionnaires of functioning revealed marked perceived impairment. He scored in the moderate range for depression and was deemed markedly apathetic on the AES-I.

Motor speed was slow, with his grooved pegboard times being the slowest of the entire cohort (dominant hand Z-score -4.5). He performed better on finger tapping tests. His summary Z-score was -1.8.

Verbal learning was very poor with six, four and four words recalled for the three respective trials of the HVLT (Z-score -2.6). After a delay, he could not recall one word from the list, giving him a Z-score of -4.2 for **verbal memory**. On the test of **recognition** memory he identified 9/12 true positives, which is also impaired (Z-score -2.7, population mean is 11.5/12), but did indicate a benefit from prompting.

In contrast to verbal learning, his **visual learning** was normal (three, two and four points for the three learning trials of the BVMT respectively). See Figure 4.19 for his third trial drawing. However, after a **delay**, he could not recall any figures correctly, yielding a Z-score of -2.1. His delayed drawing attempt was interesting for some perseverative features and is shown in Figure 4.20. For the recognition memory task, he gave 5/6 true positive responses (Z-score -1.7), which again was not normal but much better than spontaneous recall of these figures.

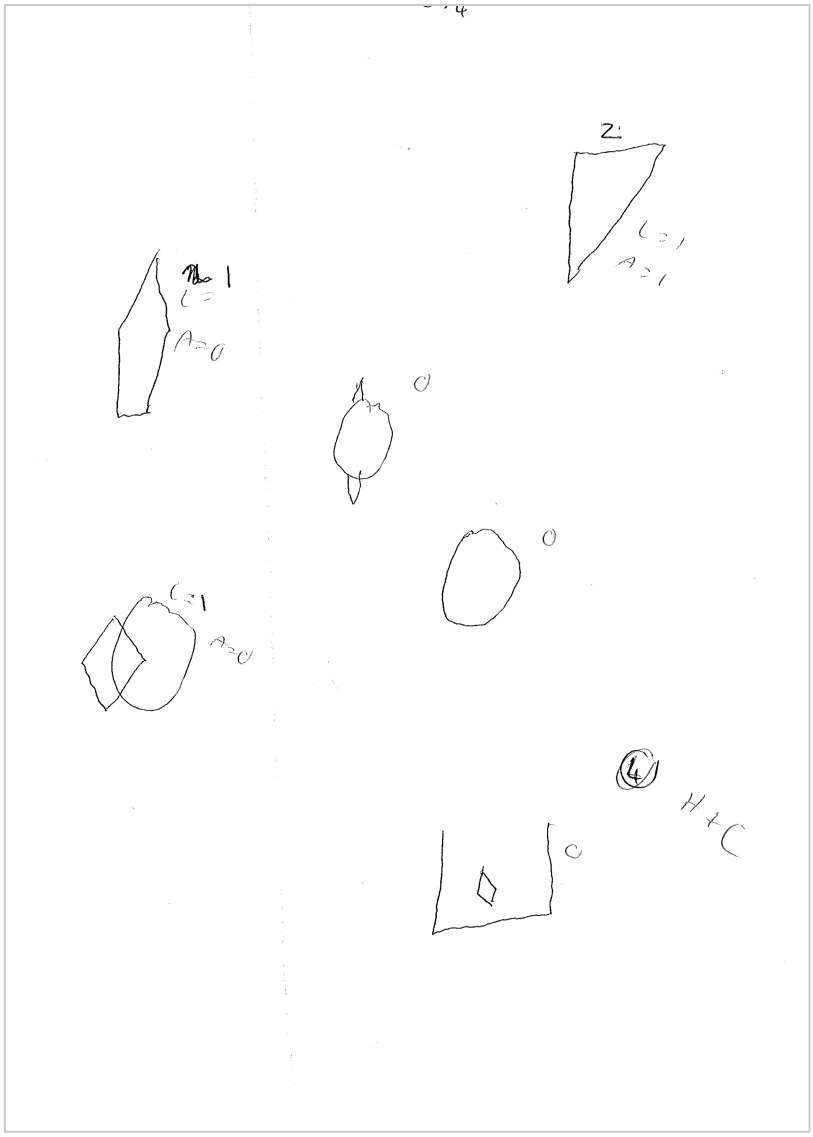

Figure 4.19: Drawing of trial three of the BVMT for patient number 74

Annotation by examiner: L= Location; A= Accuracy. Image not to scale.

BVMT = Brief visuospatial memory test.

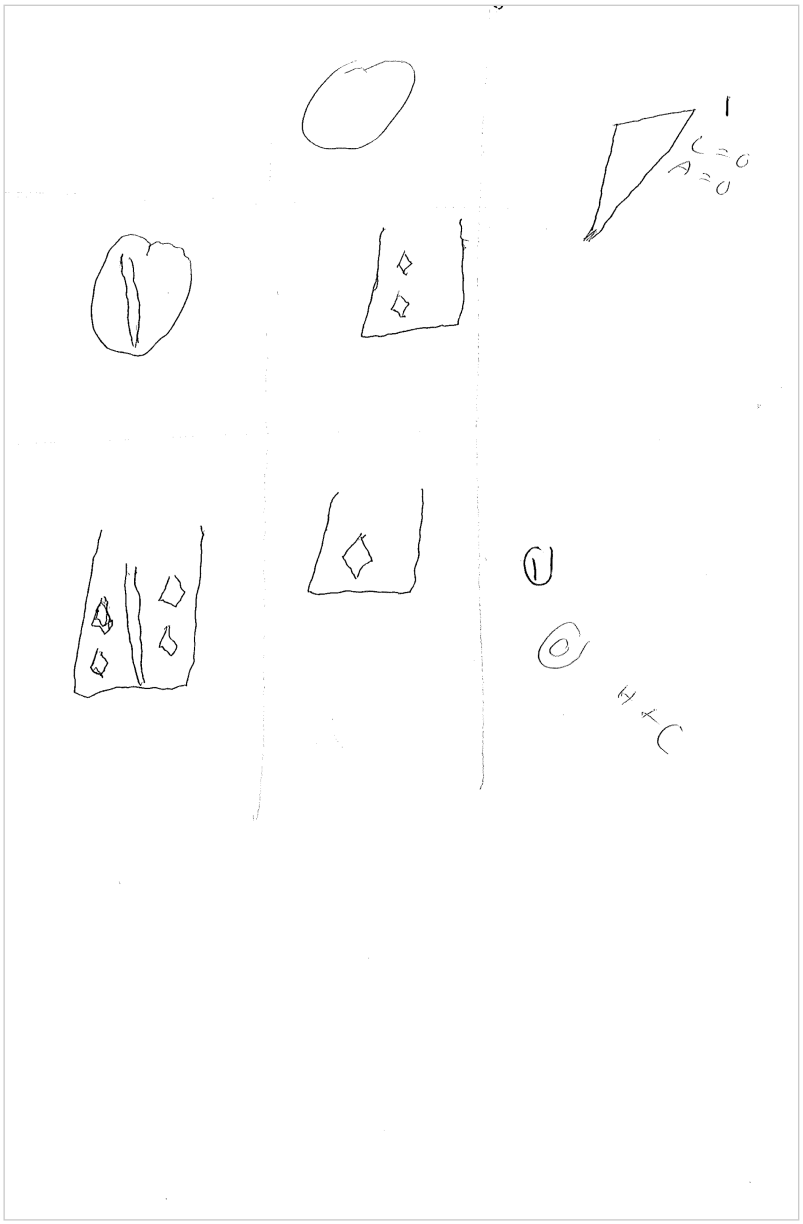

Figure 4.20: Delayed recall drawing of the BVMT for patient number 74

Note perseveration of the diamond shape. Annotation by examiner: L= Location; A= Accuracy. Image not to scale.

BVMT = Brief visuospatial memory test.

On tests of **speed of information processing** this patient was drastically impaired. He took 121 seconds to complete the TMT A (contrast with population mean of 41 seconds, yielding a Z-score of -5.1). His CTT 1 took double the time of the population mean while his digit symbol coding and symbol search were also impaired. His symbol search is shown in Figure 4.21. His summary score for this domain was -3.0.

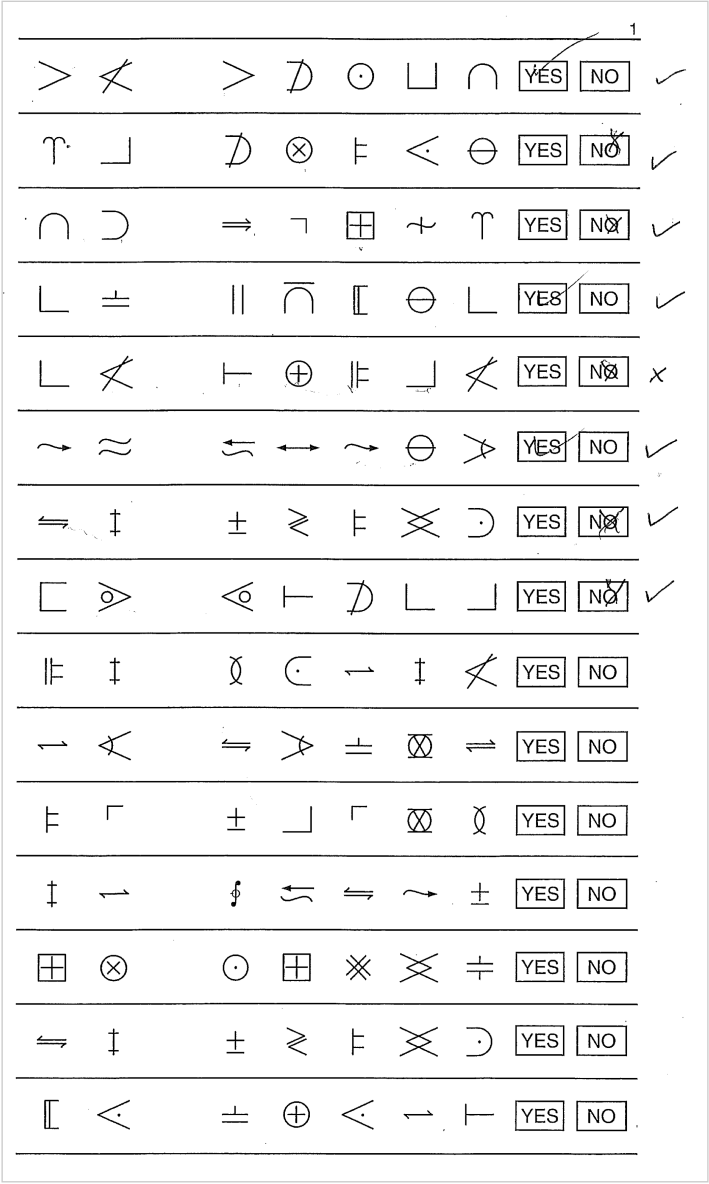

Figure 4.21: Symbol Search test for patient number 74

Symbol search requires correctly identifying the presence of target symbols on the right from either of the two symbols on the left, under time pressure. Patient had only seven correct responses in two minutes.

His **attention** was assessed by his forwards digit span and this was five (Z-score 0.2). His **working memory** as assessed by backwards digit span was two (Z-score -1.5). Mental alternation and mental control tests were also impaired between one and two SDs below the mean. His summary score for this domain was -1.4.

Tests of **executive functioning** highlighted marked difficulty. On the SCWT he correctly read out only 13 words in the allocated 45 seconds. For the CT 2,

he took nearly six minutes to complete this compared with the population mean of under two minutes. The summary Z-score for this domain was -3.5.

On tests of **fluency**, he could name eight animals, 12 fruit and vegetables, and six verbs. This yielded a summary Z-score of -1.2.

On **visuospatial** tests, he performed within the normal range for both JLOT and CLOX tests with a summary Z-score of -0.9. His CLOX 1 drawing is shown in Figure 4.22, which demonstrates the disorganised and perseverative numbering and asymmetric spacing of the numbers. On the copying task in Figure 4.23, some minor errors with minute and hour hands persist, but shows improvement on his CLOX 1 drawing.

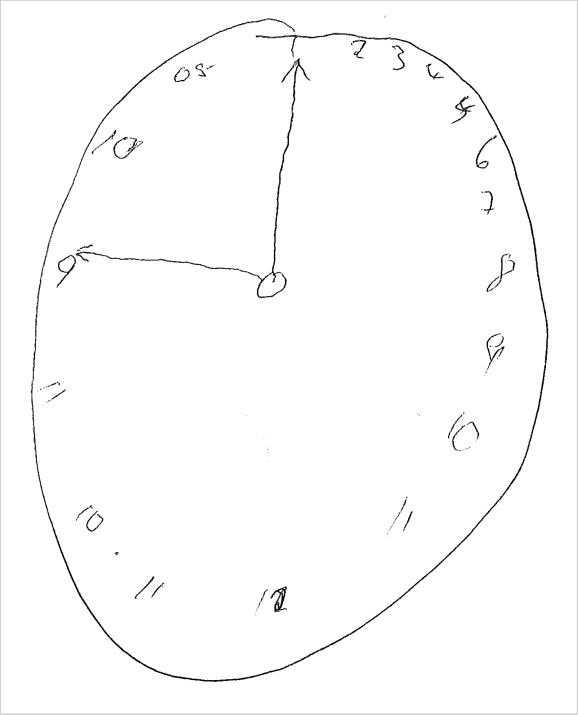

Figure 4.22: Clock drawing on CLOX 1 task for patient number 74

Patient was asked to draw a clock that says 1:45. Image not to scale.

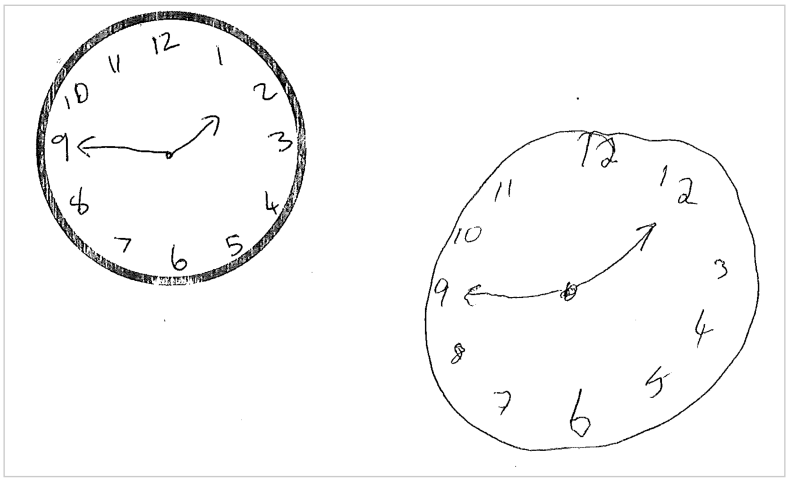

Figure 4.23: Clock copy on CLOX 2 for patient number 74

Image not to scale.

In summary, this patient's performance has to be assessed in the context of a psychotic state and the presence of neuroleptic drugs. The first standout feature of his performance is marked slowing (mental processing speed to a greater extent than motor speed); which may in part by accounted for by extrapyramidal side-effects of anti-psychotic drugs. His attention was normal, although some fluctuation of attention cannot be ruled out. He had poor verbal learning and poor verbal and visual memory which both demonstrated some benefit from prompting. Furthermore, he demonstrates a marked dysexecutive syndrome. Generativity/fluency and visuospatial skills were relatively spared. These features would be compatible with severe white matter/subcortical and frontal pathology.

5. *Patient number 19, extra-CNS TB, GDS = 2.375*

This 51-year-old lady, ART naive, presented with diarrhoea, vomiting and fever. She was diagnosed with pulmonary TB based on sputum GeneXpert positivity and a suggestive CXR. She was started on TB treatment and ART was initiated a month after diagnosis. She was assessed at six months after diagnosis.

She reported some difficulty managing her finances, but was otherwise independent in her activities of daily living (ADLs). She had mild visual

complaints on the PAOFI. Her daugther denied significant changes in her cognition and she was not deemed apathetic or depressed.

Her **motor speed** was slightly slowed for her dominant hand, but normal for her non-dominant hand, rendering a normal summary score.

Her **verbal learning** was impaired, with four, five and seven words learnt on the three learning trials of the HVLT (Z-score -2.1). She **recalled** three words after a delay, thereby retaining less than half of what she learnt. Her verbal memory Z-score was -2.7. On the **recognition** task, she gave 10/12 true positive responses with one false positive response. This generates a Z-score of -1.6 for recognition memory.

Her **visual learning** was somewhat better with two, two and three points respectively for the three learning trials of the BVMT (Z-score -1.0). Her third learning trial is shown in Figure 4.24. This demonstrates a poor learning curve, but because the population mean learning score for the three trials is 12.9 (SD 5.9), she was only bordeline impaired.

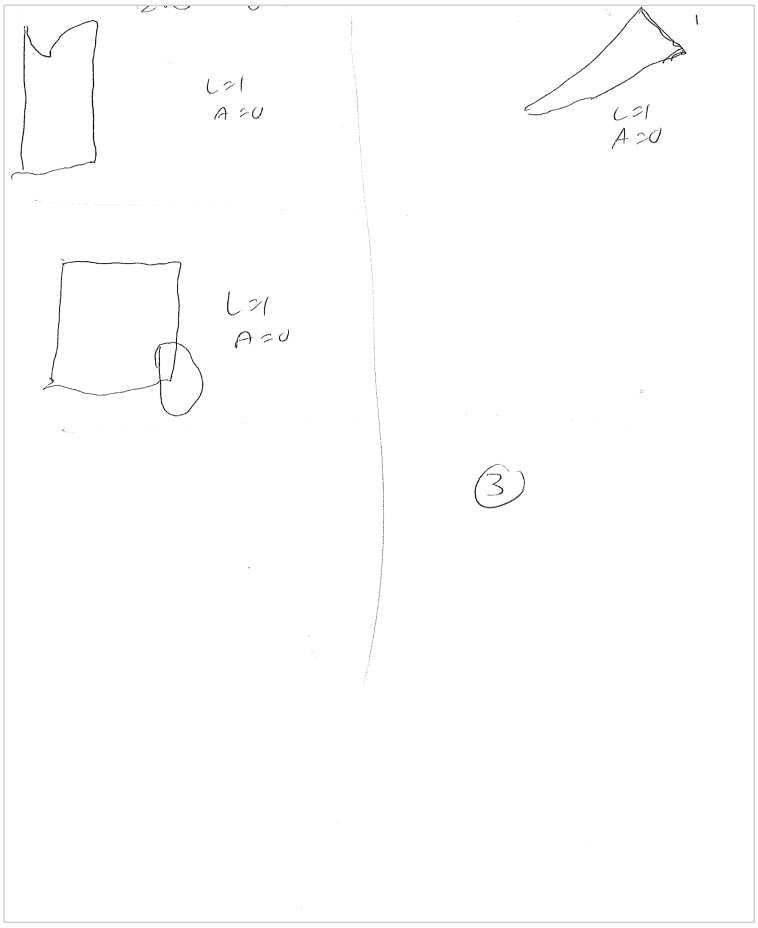

Figure 4.24: Drawing of the third learning trial of the BVMT for patient number 19

Annotation by examiner: L= Location; A= Accuracy. Image not to scale.

BVMT = Brief visuospatial memory test.

Her **delayed recall** of the BVMT is shown in Figure 4.25, demonstrating good retention of the little that she learnt. The score of three renders a Z-score of -0.9. On the test of visual **recognition** memory, she correctly identified 5/6 figures but also gave two false positive answers. This was impaired compared with the population mean.

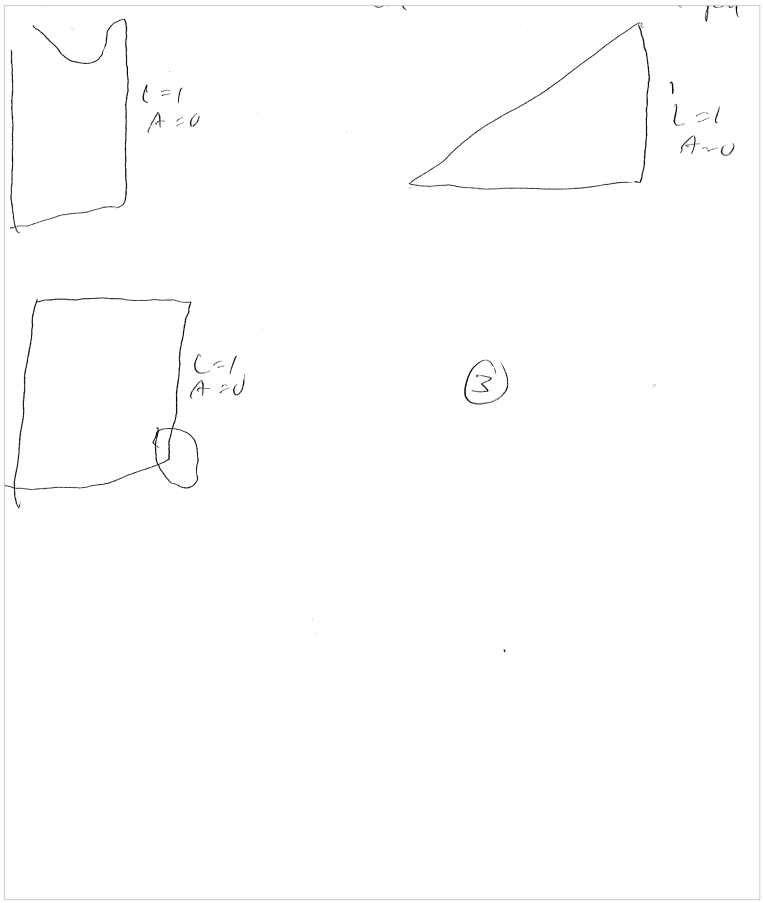

Figure 4.25: Delayed recall drawing of the BVMT for patient number 19

Annotation by examiner: L= Location; A= Accuracy. Image not to scale.

BVMT = Brief visuospatial memory test.

Speed of information processing was markedly impaired. For both TMT A and CTT 1 she had a very slow performance with a Z-score of between three and four SDs below the mean. For digit symbol coding and symbol search tests, she scored between two and three SD below the mean. Her summary Z-score for this domain was -2.7.

Her **attention** was normal as assessed by a forward digit span of five (Z-score -0.4). Her **working memory** was tested by her backward digit span which was only two (Z-score -1.5), as well as tests of mental alternation and mental control which were similarly impaired, rendering a summary Z-score of -1.5.

Testing of **executive function** yielded a slightly impaired performance on the SCWT but a markedly slow completion of the CTT 2 at 276 seconds (Z-score -3.3). Her summary Z-score was -2.5.

On the **fluency** tasks, she generated the names of six animals, eight fruit and vegetables and seven verbs. This was somewhat impaired with a Z-score of -1.6 overall.

Visuospatial functioning was impaired to a great extent. She could only correctly identify four line pairs on the JLOT (Z-score -2.5). On the CLOX 1 task she scored extremely poorly (Z-score -3.6), her drawing is shown in Figure 4.26. There was no clear concept of the numbering or hands of the clock. There were six annotations/marks on the right side of the clock correlating with placement for six numbers but on the left side of the clock the markings do not correspond with standard numbering. The copy of the clock as shown in Figure 4.27 is much better but the number spacing is not symmetrical, minute and hour hand placement incorrect, and planning was again poor (12, 6, 3 and 9 not placed first), yielding a Z-score of -3.4. Her summary score for the visuospatial domain is -3.1.

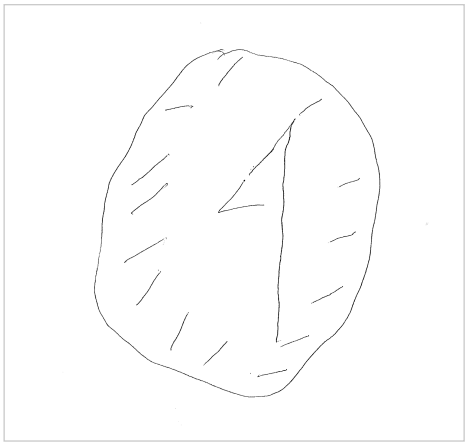

Figure 4.26: Clock drawing on the CLOX 1 task for patient number 19

Patient was asked to draw a clock that says 1:45. Image not to scale.

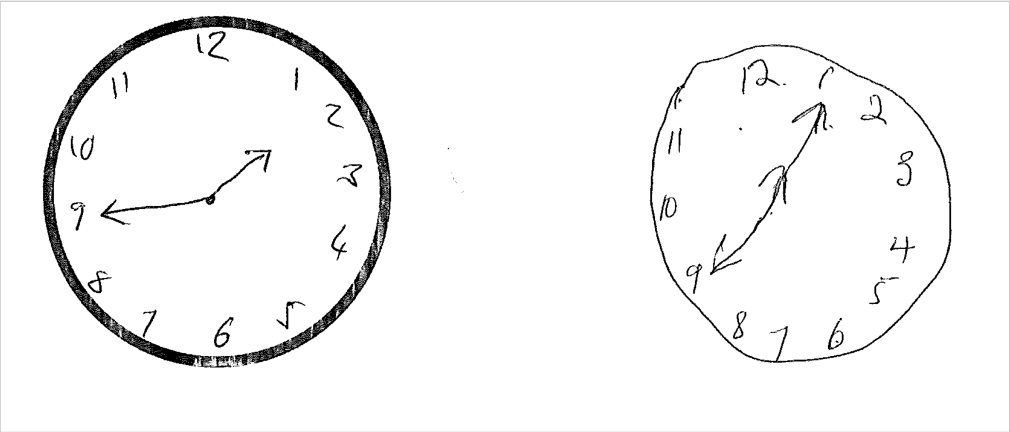

Figure 4.27: Clock copy on the CLOX 2 task for patient number 19

Image not to scale.

Overall, the areas of moderate to severe impairment were speed of information processing, executive functioning and visuospatial functioning. She had poor working memory, which might have impacted on verbal learning, which was poor. Her verbal memory was also poor, but did benefit from prompting. Her memory performance and some aspects of the clock drawing supported a dysexecutive syndrome. However, the very poor performance on the JLOT task argues for some visuospatial difficulty in addition to the marked frontal-subcortical syndrome.

6. *Patient number 22, extra-CNS TB, GDS = 0.75*

This 35-year-old man was started on ART two weeks prior to presenting with a cough. He was diagnosed with disseminated TB-IRIS based on a suggestive CXR and abdominal ultrasound, and a positive sputum GeneXpert test. His CD4 lymphocyte count was 7 cells/μL. He was discharged on TB treatment and improved. He did not have any intercurrent admissions and was able to return to work as a labourer.

The patient and his brother denied any difficulty with ADLs or cognition. He was not depressed or apathetic.

His **motor speed** was within normal limits.

His **verbal learning** was impaired with three, six and seven words learnt on the three trials of the HVLT (Z-score -2.1). His **delayed recall** was five, thereby retaining 71% of what he learnt. His **recognition** memory was poor, with only 8/12 true positives identified and one false positive response. This is very impaired compared to the population mean of 11.5 true positives and rendered a Z-score of -3.8, but was nonetheless an improvement on his spontaneous recall.

His **visual learning** was also impaired with two, one and two points respectively for the figure reproduction on the three learning trials of the BVMT (Z-score -1.3). The third trial drawing is shown in Figure 4.28. For his **delayed recall** of the figures (see Figure 4.29), he scored 2 out of a possible 12, thereby retaining the little that he had learnt. His Z-score for **visual memory** was -1.3. During the **recognition** task, he positively identified 4 figures correctly, with one false positive. This poor recognition contrasted with the population mean of 5.8 true positives, but was also an improvement on his spontaneous recall.

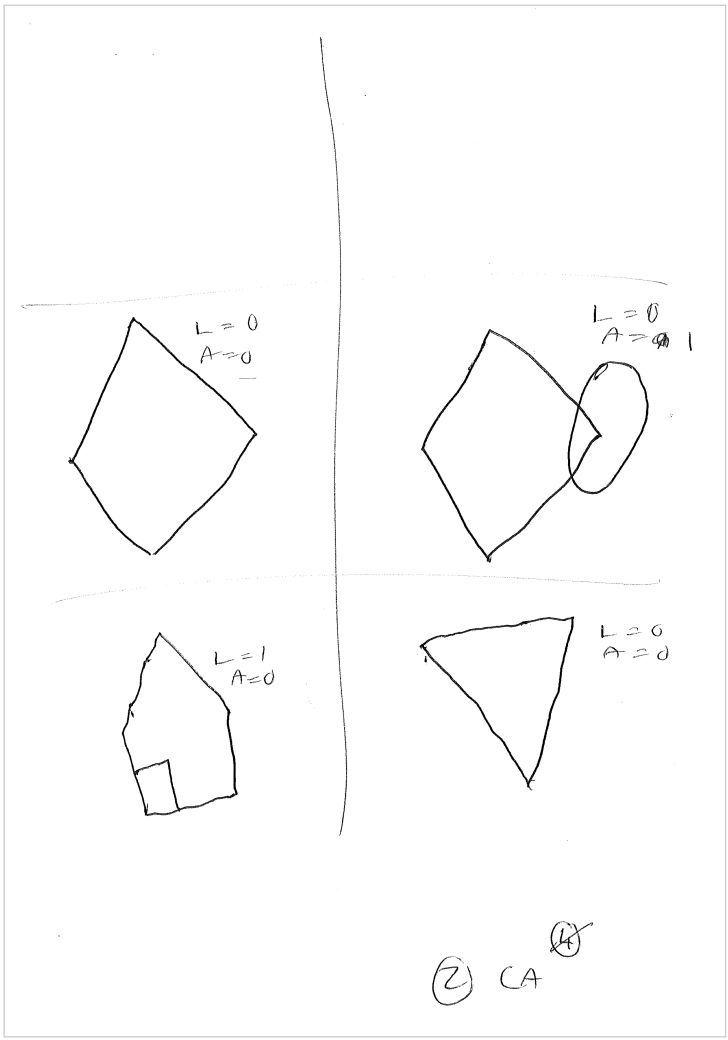

Figure 4.28: Drawing of the third trial of the BVMT for patient number 22

Annotation by examiner: L= Location; A= Accuracy. Image not to scale.

BVMT = Brief visuospatial memory test.

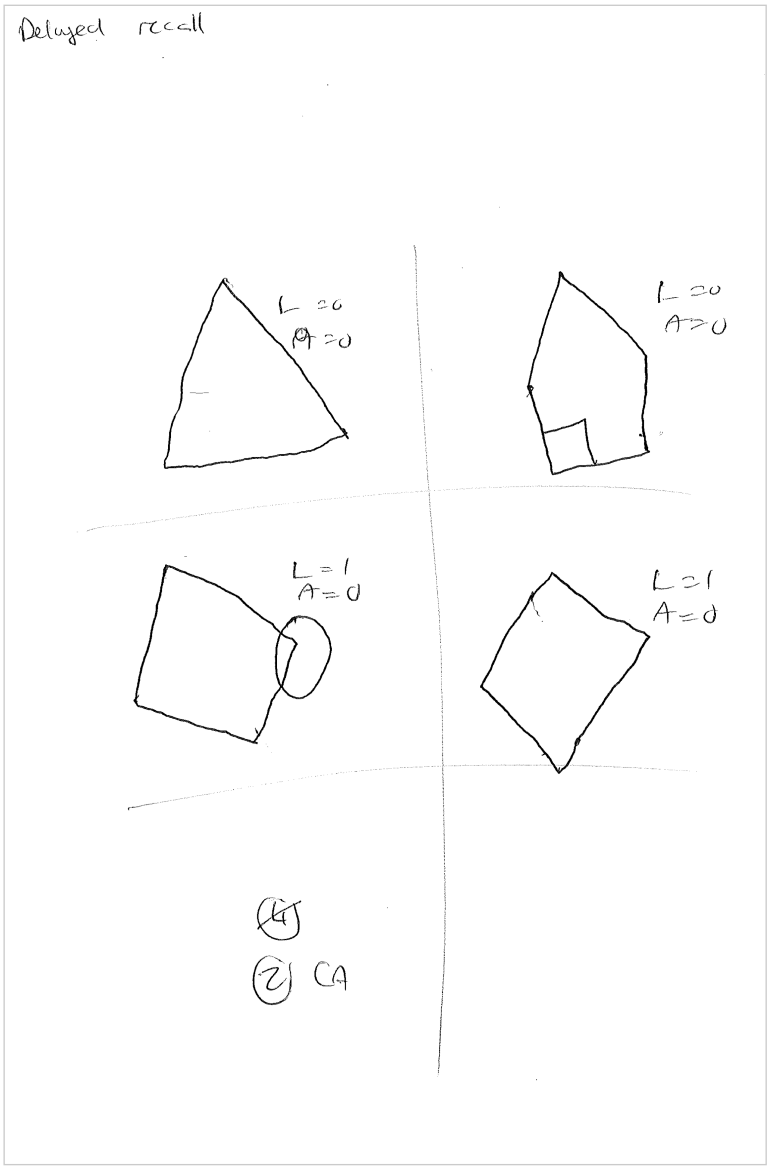

Figure 4.29: Delayed recall drawing on the BVMT for patient number 22

Annotation by examiner: L= Location; A= Accuracy. Image not to scale

BVMT = Brief visuospatial memory test.

Tests of **speed of information processing** were largely intact with a summary Z-score of -0.7.

During testing of **attention**, his digit span forward was intact for a number string of four (Z-score -1.0). His **working memory** revealed a normal backward digit span of three on one trial. Mental alternation and mental control tests were borderline impaired. The summary Z-score was -1.1.

Regarding **executive functioning**, he performed in the mildly impaired range on the SCWT but performed better than the mean on the CTT 2, thereby yielding a normal summary score for this domain.

For **fluency**, he generated 10 animal names, eight fruit and vegetables and six verbs. This gave a summary Z-score of -1.3.

His performance on **visuospatial** tasks approximated the population mean scores and his summary Z-score was -0.1. His clock drawing and clock copy are shown in Figure 4.30 and Figure 4.31 respectively. Although his clock drawing wasn't accurate in terms of hand placement and symmetry, his copy was near normal, except that he didn't place the 12, 6, 3 and 9 first.

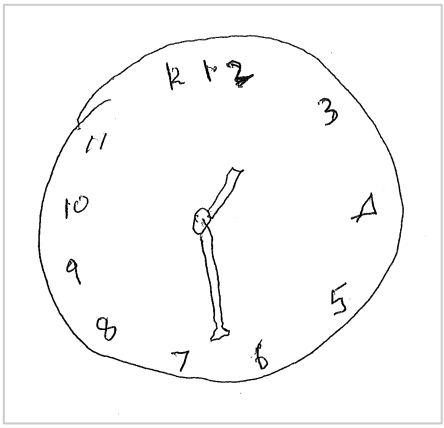

Figure 4.30: Clock drawing on CLOX 1 task for patient number 22

Patient was asked to draw a clock that says 1:45. Image not to scale.

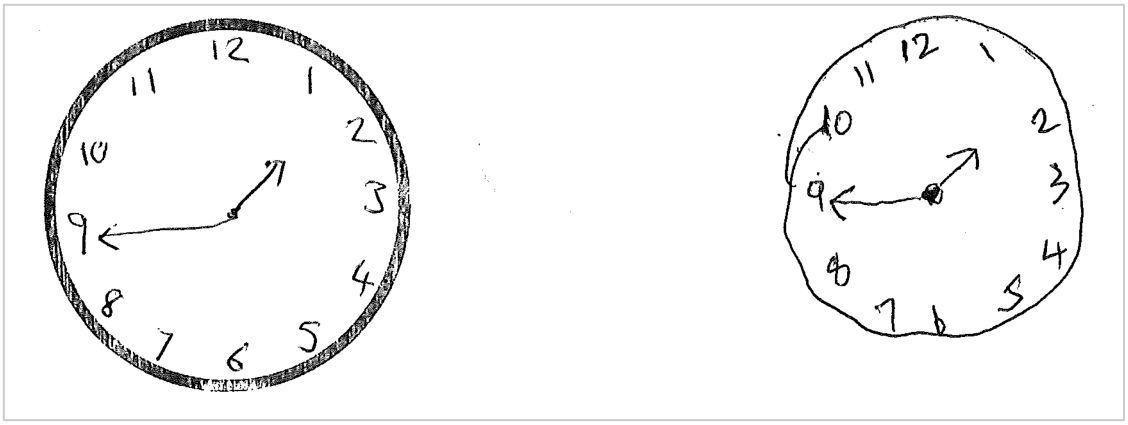

Figure 4.31: Clock copy on CLOX 2 task for patient number 22

Image not to scale.

Overall, this patient performed in the impaired range of the GDS largely due to poor learning and memory. His verbal and visual learning was poor, but he retained 71% of the verbal and 100% of the visual matter that he learnt. Based on how the GDS is calculated though (absolute score on recall, not the percentage retained), he was "penalised" on memory scores as well as learning. In his case visual and verbal recognition memory was also sub-par, but he recognised more material than he recalled spontaneously. This would support a mixed picture of impaired encoding and retrieval. Furthermore, he had borderline impaired performances on attention/working memory and fluency domains, which lends further weight to common frontostriatal pathology contributing to the final impaired GDS score.

7. Patient number 90, TBM patient, GDS = 0.5

This 36-year-old man; not on ART at time of hospitalisation as he had defaulted treatment two years prior; presented with headache, neck pain, confusion and a flaccid paraparesis. He was diagnosed with probable TBM based on symptoms, a suggestive CSF profile, an abnormal CXR and a supportive CT Brain scan (basal meningeal contrast enhancement). He was started on TB treatment and high dose steroids and was transferred to a rehabilitation facility because of leg weakness. He re-presented three months later with headache and worsening leg weakness. His repeat CSF showed an increase in protein and lymphocyte counts. He was diagnosed with TBM-IRIS and steroid therapy was reinstated. He improved and was discharged from the rehabilitation hospital five months after diagnosis. He was assessed at 6.5 months after diagnosis. His limb strength had improved to normal.

There was no self-reported or informant-reported impairment in daily functioning or decline in cognitive skills. He was not apathetic or depressed.

His **motor speed** was normal.

His **verbal learning** was very poor with three, four and five words respectively recalled on the three learning trials of the HVLT (Z-score -3.0). His **delayed**

recall was three (Z-score -2.3), thereby retaining 60% of what he learnt, which was also impaired. His **recognition memory** was impaired with 9/12 true positive responses, but did show an improvement compared to spontaneous recall. The Z-score generated hereby was -2.7.

For **visual learning** he scored one, three and five respectively for the three learning trials on the BVMT, giving him a total learning score of nine, which was within normal limits. On the **delayed recall** task he scored four, thereby retaining 80% of what he learnt. Both the absolute recall score and percentage-retained score were within normal range. On the **visual recognition** task, he gave 5/6 true positive responses.

Overall, verbal learning and memory were therefore clearly impaired with near-normal scores for visual learning and memory.

His **information processing speed** was normal for all four tasks undertaken.

Regarding **attention**, his forward digit span was five, but he had impaired **working memory** with a backward digit span of two only. On tasks of mental alternation and mental control his performance was borderline. However, his summary Z-score for the domain was still within normal at -0.9.

For tests of **executive functioning**, he was mildly impaired on the SCWT (Z-score -1.3) but this was countered by a better-than-normal performance on the CTT 2 task. His summary score was normal.

On tests of **fluency**, he gave a normal performance by generating 14 animals, 11 fruit and vegetables, and nine verbs.

On tests of **visuospatial** functioning he performed very well with the joint highest score on the JLOT of 24 (Z-score 1.5) and CLOX score of 28 (Z-score 1.0). His CLOX 1 task is shown in Figure 4.32 and his CLOX 2 task in Figure 4.33.

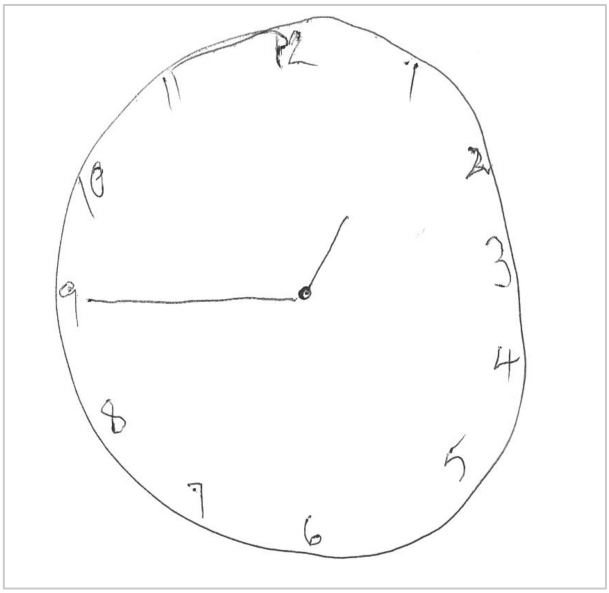

Figure 4.32: CLOX 1 drawing task for patient number 90

Patient was asked to draw a clock that says 1:45. Image not to scale.

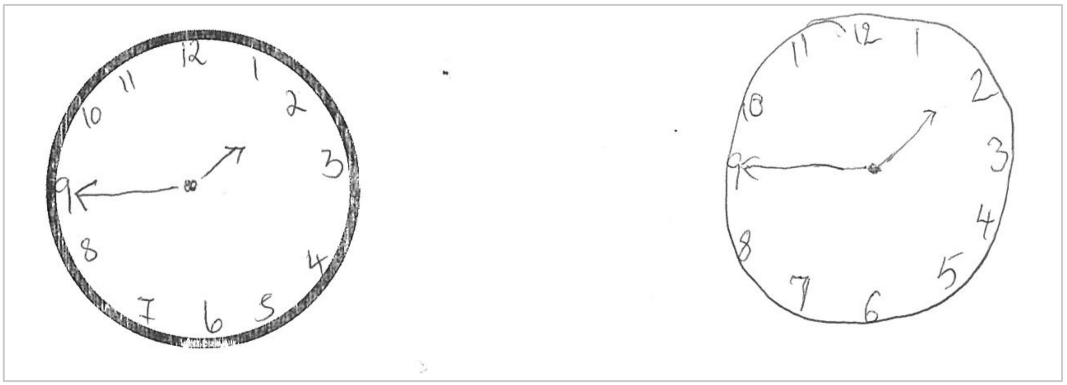

Figure 4.33: CLOX 2 copying task for patient number 90

Image not to scale.

Overall, this patient performed very poorly on tasks of verbal learning and memory. He performed in the normal range for all other domains. It is interesting to note that his visual learning and memory was normal, suggesting some laterality with impairment in the dominant hemisphere. His verbal memory deficit did show benefit from prompting (recall of three words, recognition of 9/12 words) but his percentage-retained score was still below normal. This pattern could be described as a mixture of encoding and retrieval difficulty. A more pervasive dysexecutive syndrome was not seen.

This patient was not rated as impaired by the Frascati HAND criteria as two or more domains have to be involved and if those two domains are learning and

memory the secondary scores of percentages retained are used instead. In this case our patient had a Z-score for verbal and visual memory (using percentage retained) of -0.9. Hereby, he was impaired only in the single domain of learning.

8. *Patient number 6, extra-CNS TB patient, GDS = 1.5*

This 30-year-old lady presented on ART, which was reinstated after her defaulting treatment the previous year. She was diagnosed with disseminated TB based on symptoms, a positive sputum GeneXpert result, radiological abdominal TB features, and a pericardial effusion on echocardiogram. She was treated with TB treatment and oral prednisone for the pericardial effusion.

Both the patient and her mother reported a decline in daily functioning and cognitive skills. She was also deemed apathetic on the AES-I with a high score of 59 (second highest of the entire cohort) and was moderately depressed.

During the assessment, she struck me as apathetic and unmotivated.

Her **motor speed** was slightly impaired with a Z-score of -1.2.

Verbal learning was very poor with one, three and eight words recalled on the three respective learning trials of the HVLT (Z-score -3.0). Her **delayed recall** was three words, rendering low scores for absolute number of words recalled (Z-score -2.7) as well as the percentage retained (Z-score -2.9). Her **recognition memory** was much better with 11/12 true positive responses and one false positive response.

Visual learning was also impaired with no correct figures reproduced in the first two learning trials of the BVMT and three points for the third trial (Z-score -1.7). This is shown in Figure 4.34. A slightly careless, unmotivated and disorganised approach is demonstrated. On the **delayed recall** task, she did not attempt any drawing (Z-score -2.1). On the **recognition** task, she had 4/6 true positive responses, yielding a Z-score of -3.8.

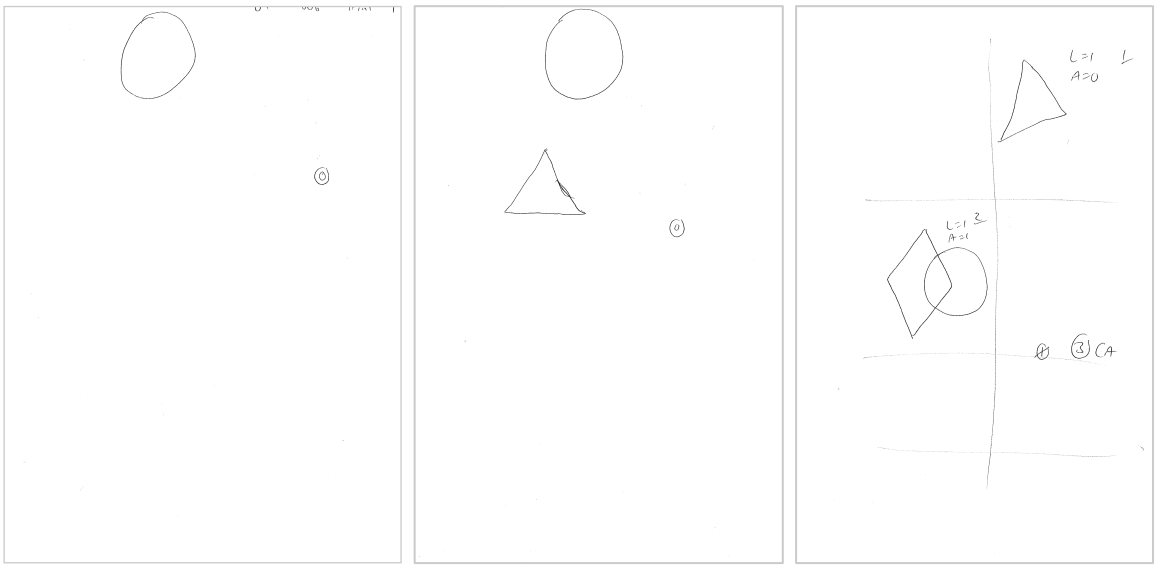

Figure 4.34: Learning trials 1, 2 and 3 (from left to right) on the BVMT for patient number 6

Images not to scale.

BVMT = Brief visuospatial memory test.

On tests of **speed of information processing**, she was impaired on the digit symbol coding test where she only completed 17 items and these included five errors. However, she performed within normal limits for the CTT 1, TMT A and digit symbol search to generate a normal summary Z-score for this domain of -0.9.

Attention was impaired: she could repeat a string of four numbers forwards once. For **working memory**, her backward digit span was three. Tests of mental control and mental alternation were marginally impaired. Her summary Z-score was thus -1.3.

Executive functioning was normal on the SCWT and slightly impaired on the CTT 2, yielding a normal summary Z-score.

On tests of **fluency** she was marginally impaired for animal and fruit and vegetable fluency where she generated 10 and 11 words respectively. However, she had very diminished action fluency and could only name three verbs (population mean is 10). This led to a summary Z-score of -1.3.

She performed poorly on tasks of **visuospatial** functioning: she could only correctly identify 3/30 line pairs on the JLOT (Z-score -2.7). For her CLOX tasks she averaged with Z-score of -1.6. Her spontaneous drawing of the clock showed poor planning, poor symmetry and poor self-monitoring. The patient then self-initiated a second clock with better number spacing but incorrect hand placement (Figure 4.35). Her copy was rushed and included some sectoring/tic marks (Figure 4.36). Her summary Z-score for this domain was -2.1.

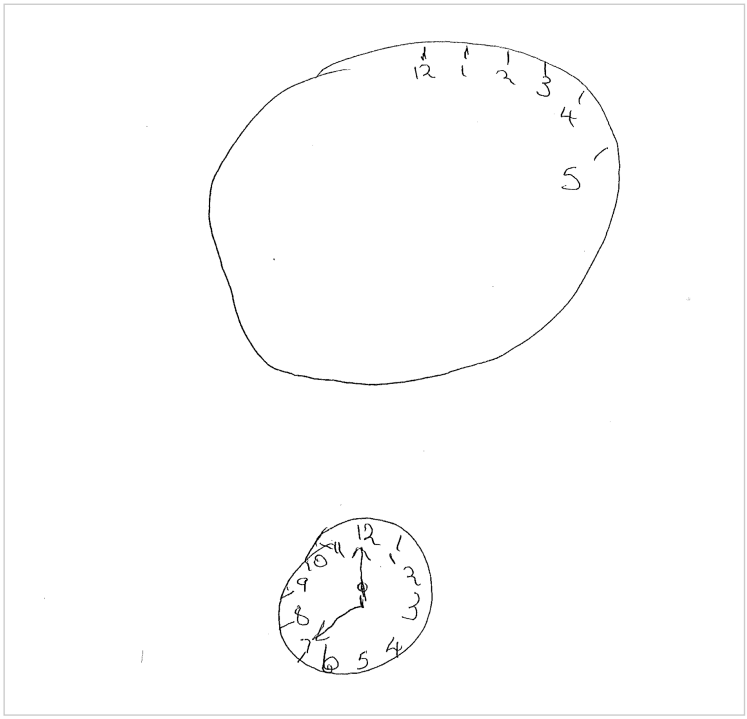

Figure 4.35: CLOX 1 drawing task for patient number 6

Patient was asked to draw a clock that says 1:45. The patient self-initiated the second drawing below her first attempt. Image not to scale.

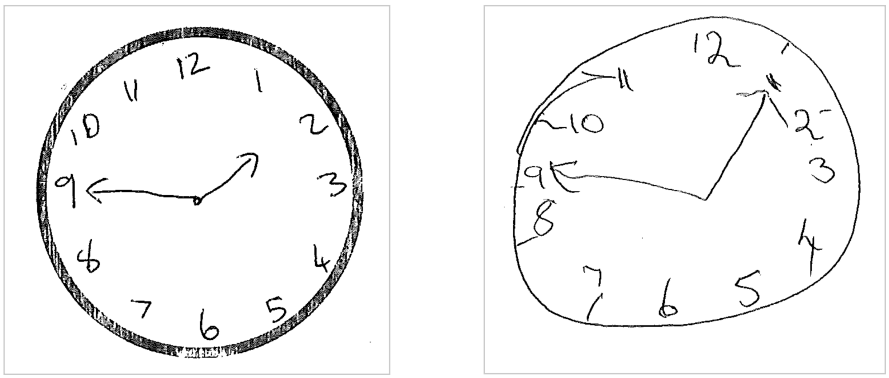

Figure 4.36: CLOX 2 copying task for patient number 6

Image not to scale.

In summary, this patient had a neurobehavioural syndrome characterised by marked apathy and globally impaired neuropsychological performance. She performed poorly in the domains of learning, memory and visuospatial functioning. Her learning and memory performance was characterised by impaired immediate and delayed free recall in the setting of relatively better recognition performance for both verbal and visual domains. Visuospatial functioning (as judged by her performance on the JLOT and some aspects of the CLOX tasks) was clearly impaired. Furthermore, she had milder impairment in the domains of motor speed, attention/working memory and fluency. The picture is compatible with a frontal-subcortical process with additional visuospatial impairment. The marked apathy may be explained by involvement of medial frontal-anterior cingulate circuitry (99).

9. *Patient number 68, TBM, GDS = 0.5*

This 40-year-old man presented with headache, vomiting and hiccups. He was not on ART after defaulting three years prior. He was diagnosed with probable TBM based on symptoms and a very suggestive CSF: protein 11.83g/L, lymphocyte count 1113 $x10^6$/L and glucose 0.7mmol/l. He was started on TB treatment and oral steroids, which was weaned after six weeks. He then re-presented a week after steroid treatment was stopped with ataxia and seizures. A CT Brain scan demonstrated basal and cortical leptomeningeal enhancement and vasogenic oedema. TBM-IRIS was diagnosed and steroid treatment was reinstated. Two weeks after this second course of steroids was weaned he again relapsed with worsening ataxia and limb weakness. A second CT Brain scan showed multiple tuberculomas. Toxoplasmosis and cryptococcal disease were excluded and TBM-IRIS was again diagnosed. He was restarted on oral steroids after which he improved. He was assessed in a rehabilitation facility at six months after enrollment. He was able to walk with a crutch and had a mild left hemiparesis and ataxia.

Neither the patient nor his mother reported functional impairment or a decline in cognition. He was not depressed or apathetic.

On tests of **motor speed**, he was marginally impaired with a summary Z-score of -1.0.

For **verbal learning**, he recalled three, six and six words respectively on the three HVLT learning trials. This was impaired with a Z-score of -2.3. His **delayed recall** was good with nine words recalled (Z-score 0.2). He identified 10/12 true positive stimuli on the **recognition** memory task.

For **visual learning**, he showed a good learning curve with one, five and nine points scored on the three respective learning trials of the BVMT (Z-score 0.3). This is shown in Figure 4.37. On the **delayed recall** task, he scored seven, which was better than the norm of 5.3. For the **recognition** task, he identified 5/6 objects as true positives.

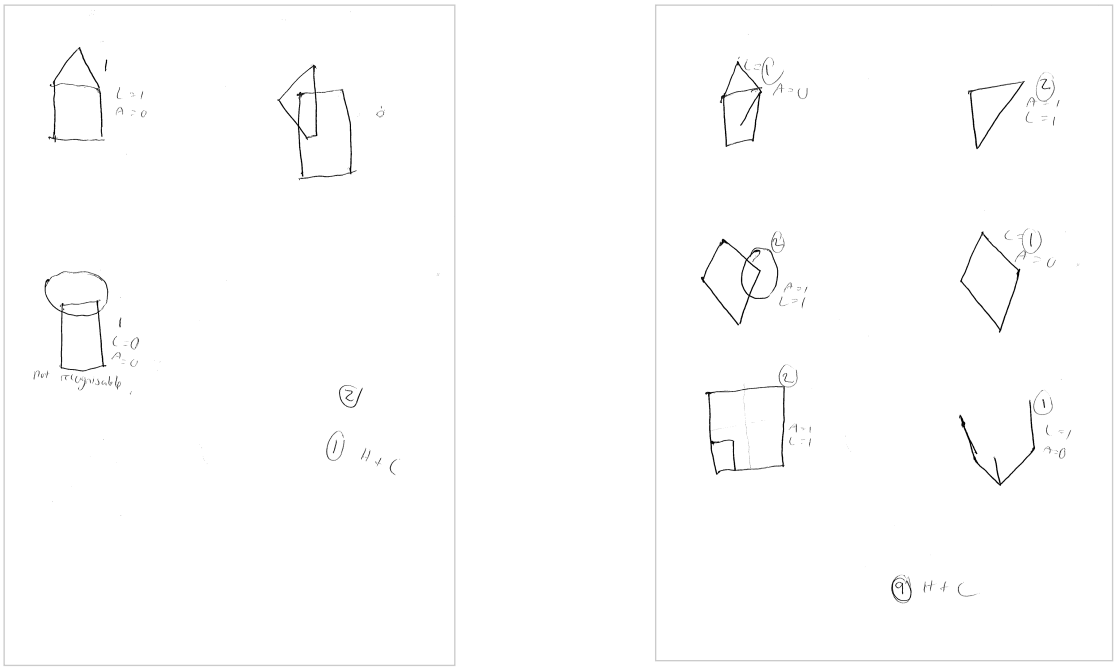

Figure 4.37: First learning trial (shown on the left) and third learning trial (shown on the right) of the BVMT for patient number 68

Images not to scale.

BVMT = Brief visuospatial memory test.

On the tests of **information processing speed**, he was marginally impaired for CTT 1, TMT A and Digit Symbol Search. For digit symbol coding he scored more than two SD below the mean by only completing 16 correct digit-symbol pairs in the allocated time. His summary Z-score for this domain was -1.4.

For **attention** as tested by the digits forward test, he could repeat a string of four digits on one occasion (Z-score -1.6). For **working memory**, he could repeat only two digits backwards (Z-score -1.5). He was slightly impaired on the mental control task but normal on the mental alternation task. His average Z-score for this domain was -1.1.

Testing **executive functioning** revealed some difficulty with the SCWT where only 16 words were read in the allocated time (Z-score -1.9). His performance on the CTT 2 was normal. A summary Z-score of -1.3 was obtained.

His **fluency** was normal with 12 animals, 13 fruit and vegetables and 11 verbs generated.

On testing **visuospatial** functioning, he performed better than the mean on the JLOT. For the CLOX task he fell within normal limits. His summary Z-score for this domain was -0.2.

In summary, this patient's neuropsychological profile is of mild impairment in motor and information processing speed, executive functioning, and attention and working memory. This is compatible with a mild frontal-subcortical process.

4.3.2.2 Summary of cognitive performance in patients with an abnormal GDS

The domain of attention and working memory was most commonly affected (in all but one patient), albeit to a mild extent only. Learning, memory, and fluency were impaired in all but two patients. The details of impaired cognitive domains (stratified by severity) for both groups are shown in Table 4.15.

Table 4.15: Breakdown of impairment by cognitive domain for the nine patients with a GDS ≥ 0.5

Cognitive Domain	All n=9	TBM n=5			Extra-CNS TB n=4		
	Total	Total			Total		
		Mild	Mod	Severe	Mild	Mod	Severe
Motor speed	**4**	**3**			**1**		
		3	0	0	1	0	0
Learning	**7**	**3**			**4**		
		3	0	0	3	1	0
Memory	**7**	**3**			**4**		
		1	1	1	3	1	0
Speed of information processing	**6**	**4**			**2**		
		2	1	1	1	1	0
Attention & working memory	**8**	**4**			**4**		
		4	0	0	4	0	0
Executive functioning	**6**	**4**			**2**		
		2	1	1	1	1	0
Fluency	**7**	**3**			**4**		
		2	1	0	4	0	0
Visuospatial skills	**4**	**2**			**2**		
		1	1	0	0	1	1

Mild impairment if Z-score between one and two standard deviations below the mean; moderate impairment if Z-score between two and three standard deviations below the mean; severe impairment if more than three standard deviations below the mean.

Abbreviations: Extra-CNS TB = Tuberculosis outside of the central nervous system; GDS = Global deficit score; Mod = Moderate; TBM = Tuberculous menigitis.

The most common neuropsychological pattern of impairment was a frontal-subcortical picture. This was seen in eight of the nine patients. However, in four of these patients (50%), there was additional visuospatial impairment. The one patient who did not have a frontal-subcortical picture had an isolated deficit of verbal learning and memory only. Fluency was often impaired, usually only to a mild extent. We saw the pattern of worse action fluency compared to category fluency, as described in HAND literature (100), in one patient only. Interestingly, the converse was true for three patients with better action fluency than category fluency.

4.3.3 Predictors of poor cognitive outcome

4.3.3.1 Predictors of poor outcome in both groups

In both cases and controls we postulated that higher age, female gender, smoking, alcohol use, lower level of education, lower CD4 lymphocyte count, shorter duration of ART at six months, and not being on ART at enrolment, would be predictors of worse outcome. Although we hypothesised that the presence of traditional vascular risk factors would predict worse cognitive outcome, only one patient was hypertensive and none of the patients were known to be diabetic or hypercholesterolaemic. This may be a reflection of a younger population with low prevalence of these risk factors or may be due to infrequent screening for these chronic illnesses at a primary care level. Therefore, due to the low prevalence of this risk factor in our cohort, this was not analysed.

We analysed age, level of education, CD4 lymphocyte count, and duration of ART in two ways. Firstly as categorical variables with a binary split around the median (see Table 4.16) and subsequently as continuous variables (see Table 4.17). Gender, smoking, alcohol use, and ART use at enrolment, were analysed as categorical variables and results are shown in Table 4.16.

Table 4.16: Predictors of cognitive outcome in both groups for categorical variables

			GDS Impaired	p-Value
Age (years)	<35	Count	2	
		%	10.5%	
	≥35	Count	7	
		%	31.8%	0.140
Sex (female)	Yes	Count	4	
		%	19.0%	
	No	Count	5	
		%	25.0%	0.719
Alcohol use	No	Count	6	
		%	21.4%	
	Yes	Count	3	
		%	23.1%	1.000
Smoking	No	Count	5	
		%	17.9%	
	Yes	Count	4	
		%	30.8%	0.429
Level of education (years)	≤10	Count	7	
		%	28.0%	
	>10	Count	2	
		%	12.5%	0.441
CD4 lymphocyte count (cells/μL)	<60	Count	3	
		%	21.4%	
	≥60	Count	6	
		%	22.2%	1.000
Duration of ART (days)	<200	Count	6	
		%	35.3%	
	≥200	Count	3	
		%	12.5%	0.128
On ART at enrollment	No	Count	6	
		%	30%	
	Yes	Count	3	
		%	14.3%	0.277

Abbreviations: ART = Anti-retroviral therapy; GDS = Global deficit score.

There is a trend for older age and shorter duration on ART (< 200 days) at six months follow-up to cause more impairment on the GDS, but this did not

reach statistical significance. The scatterplot of ART duration against GDS is shown in Figure 4.38.

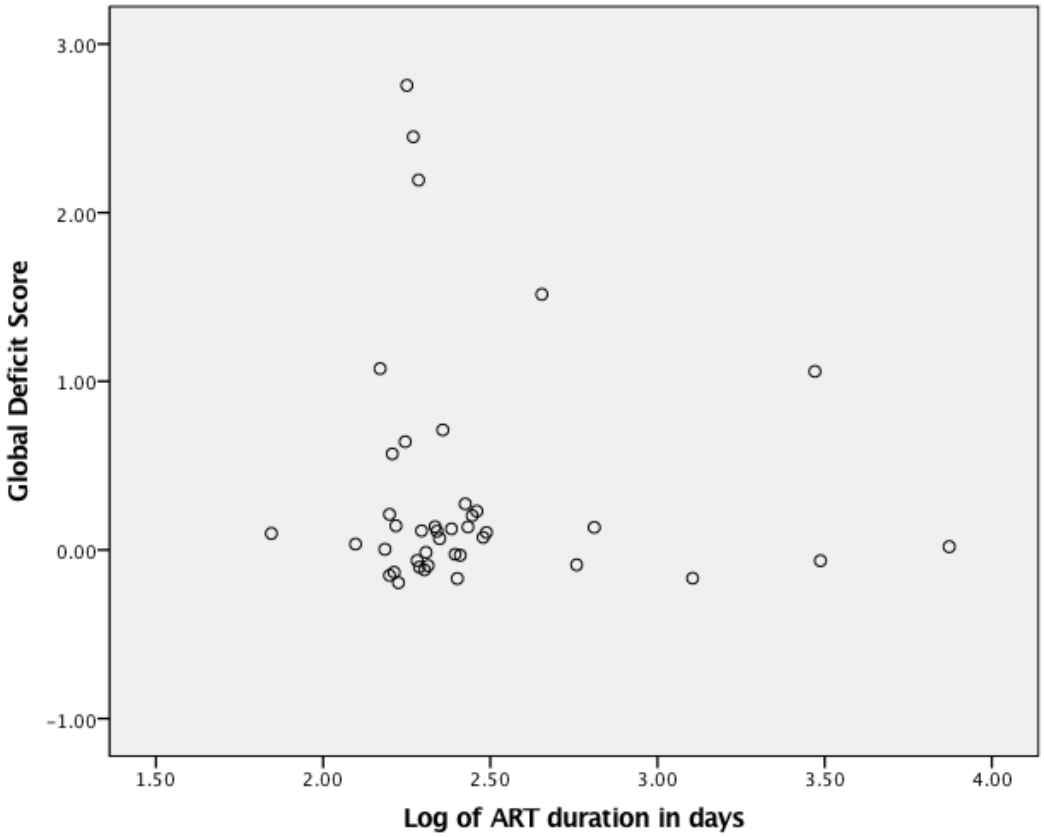

Figure 4.38: Scatterplot of the log of ART duration in days (at six months follow-up) against the GDS

Abbreviations: ART = Anti-retroviral therapy; GDS = Global deficit score.

Roughly double the proportion of patients who were not on ART at the time of enrolment were impaired on the GDS compared to those patients who were already on treatment. This difference did not, however, reach statistical significance.

Table 4.17: Predictors of cognitive outcomes in both groups for continuous variables

Continuous variable	**Association with binary GDS P-value**
Age (years)	0.18
Level of education (years)	0.248
CD4 lymphocyte count (cells/μL)	0.498
Duration of ART (at six months follow-up)	0.345

Abbreviations: ART = Anti-retroviral therapy

The continuous variables were analysed for an association with cognitive outcome, as shown in Table 4.17. There was again a trend for older age to be associated with worse cognitive outcome. The CD4 lymphocyte count was not significantly associated with cognitive outcomes. However, if one looks at the proportion of patients with a normal GDS vs impaired GDS vs patients who died, the results (Table 4.18) show a trend towards significance (p-value 0.18) with a lower CD4 lymphocyte count accounting for a higher proportion of patients who died.

Table 4.18: Association of CD4 lymphocyte count (<60 vs ≥60 cells/μL) with GDS status or death

			GDS classification and death			p-Value
			Normal	Impaired	Died	
CD4 lymphocyte count (cells/μL)	<60	Count	11	3	12	
		%	42.3%	11.5%	46.2%	
	≥60	Count	21	6	8	
		%	60.0%	17.1%	22.9%	0.18

Abbreviations: GDS = Global deficit score.

4.3.3.2 Predictors of poor outcome in TBM patients

Both TBM-IRIS and a higher BMRC severity grading were postulated to predict a worse cognitive outcome. Results are shown in Table 4.19.

Table 4.19: GDS classification for TBM patients, stratified by TBM-IRIS status and BMRC severity grading

			GDS impaired	p-Value
TBM-IRIS	No	Count	2	
		%	20%	
	Yes	Count	3	
		%	60%	0.251
BMRC severity grading[1]	1	Count	2	
		%	33.3%	
	2	Count	3	
		%	33.3%	1.000

Abbreviations: BMRC = British medical research council; GDS = Global deficit score; TBM = Tuberculous menigitis; IRIS = Immune reconstitution inflammatory syndrome.

Five patients developed TBM-IRIS. Four patients developed IRIS within the first 2 months while the other patient presented approximately 11 weeks after TBM diagnosis. Although not statistically significant, it is interesting to note that 60% of patients with TBM-IRIS were impaired by the GDS while only 20% of patients without TBM-IRIS were impaired. The patient with the second most impaired cognition (as reflected in a GDS of 2.5) across the entire cohort had an IRIS phenomenon. The median GDS score for the TBM-IRIS patients was 0.5 (SD 1.02). This is in contrast to the median GDS score for the non-TBM-IRIS patients of 0 (SD 0.85).

The proportion of patients with an impaired GDS was identical for both BMRC severity grades. However, if one analyses the BMRC grading against the outcomes of GDS classification and death, there is an almost significant difference (p=0.059) between patients with a higher BMRC grading and GDS classification or death. All of the TBM patient deaths occurred in patients with a BMRC grading of 2 while all of the patients with a BMRC grading of 1 survived.

4.3.3.3 Predictors of poor outcome in extra-CNS TB patients

We postulated that patients with disseminated TB would perform worse on cognitive testing by the GDS compared to patients with single-site TB.

Two patients (14.3%) were impaired by the GDS in the single-site TB group compared with two patients (16.7%) in the disseminated TB group (p-value 1.00). There was also no difference between groups when looking at GDS classification or death.

4.3.4 Quality of life and employment status

4.3.4.1 Quality of life

We postulated that patients with TBM would have poorer QOL as measured by the Q-LES-Q-SF (61). This questionnaire has a range from 16-80 with higher scores indicating a better quality of life.

The median QOL score for TBM patients was 64 (IQR 56-70) with a range from 27 to 77. The median QOL score for extra-CNS TB patients was 66 (IQR 55-74) with a range from 35 to 79. The box-and-whiskers plots illustrate these descriptive statistics for the two groups in Figure 4.39.

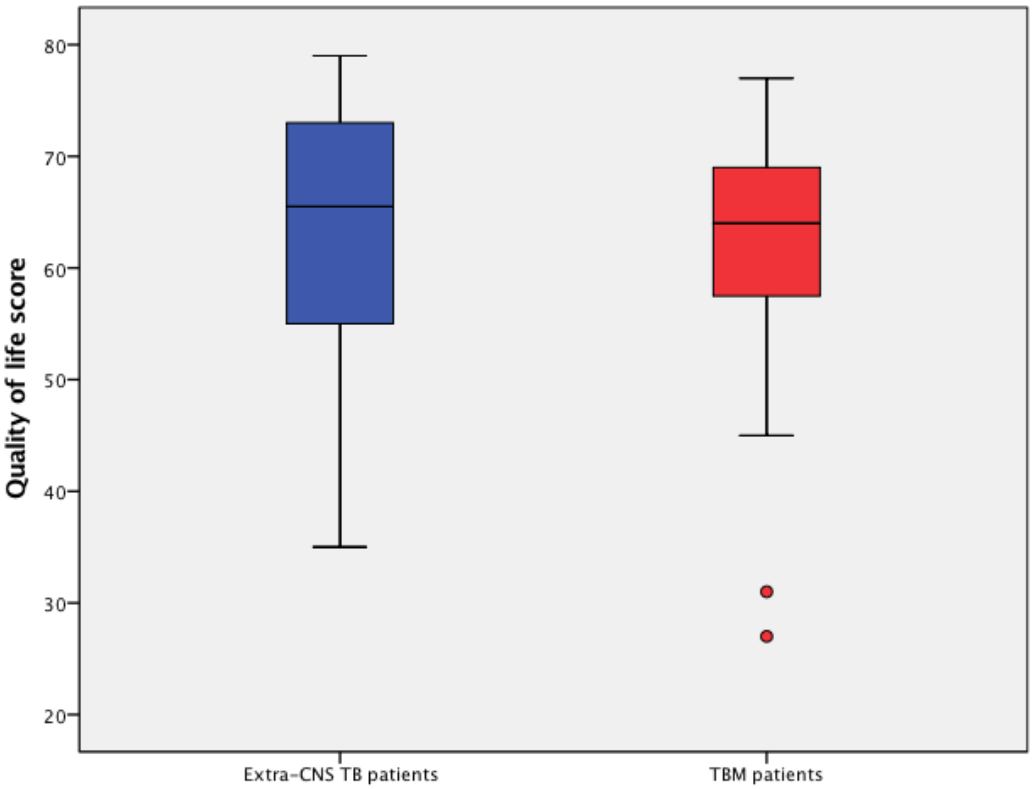

Figure 4.39: Box and whiskers plot of quality of life scores amongst TBM and extra-CNS TB patients

The boundaries of the box are Tukey's hinges. The median is identified by a line inside the box. The length of the box is the interquartile range (IQR) computed from Tukey's hinges. Values more than 1.5 IQR's but less than 3 IQR's from the end of the box are labeled as outliers (o).

Abbreviations: Extra-CNS TB = Tuberculosis outside of the central nervous system; TBM = Tuberculous menigitis.

The statistical test of a relationship between TBM and quality of life rendered a non-significant p-value of 0.565.

From Figure 4.39 one can see that two patients in the TBM group had outlying low QOL scores of 27 and 31. It is interesting to note that these two patients had the two highest GDS scores (2.625 and 2.5 respectively) of the entire cohort. When one looks at the extra-CNS TB group, the lowest QOL score is

35. This patient had a GDS of 1.5, which is the second lowest GDS for the extra-CNS TB group and the fourth lowest GDS score overall. This would suggest that patients who perform very poorly on cognitive tests may have a poorer quality of life. Based on this trend, we investigated whether there was an association between QOL and cognitive performance. This scatterplot is shown in Figure 4.40.

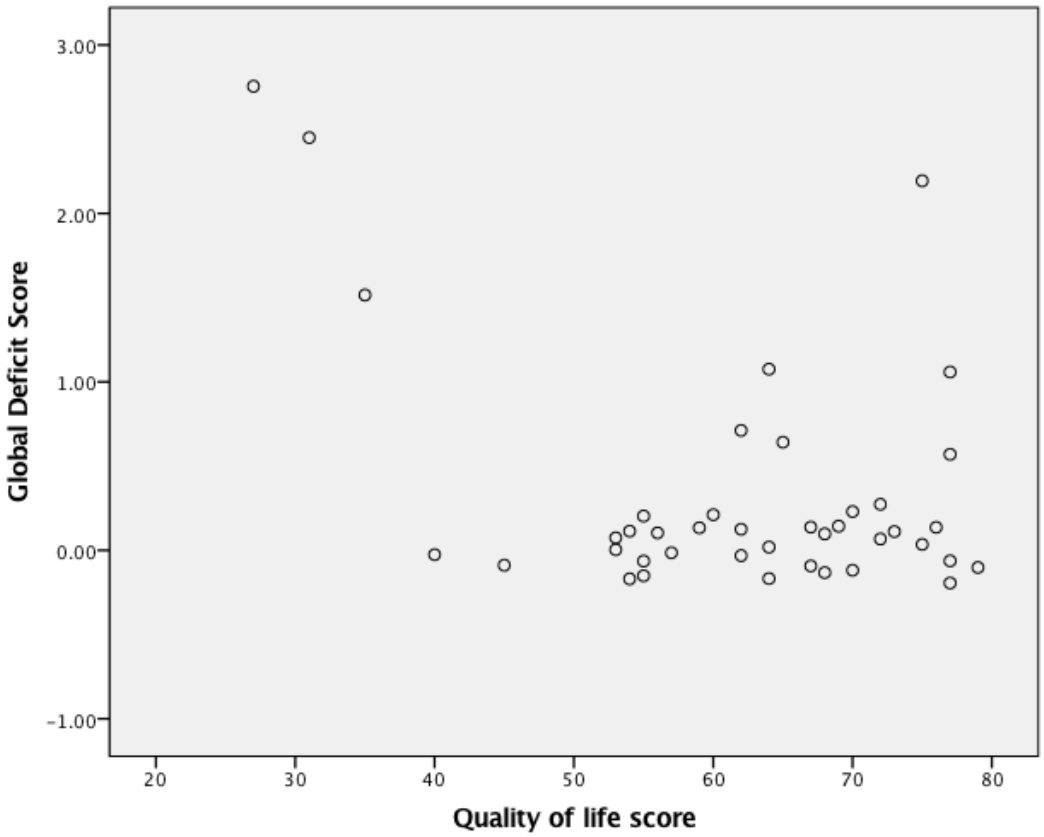

Figure 4.40: Scatterplot of quality of life against the GDS

GDS = Global deficit score.

As seen from the scatterplot in Figure 4.40, only four patients had a GDS of greater than one. Of these four patients, three had the lowest three QOL scores. However, the other patient with a GDS of 2.375 had a good QOL score of 75. To test the association between QOL and GDS, a Spearman's rho test was performed. This did not support an association (p-value = 0.859) with a very weak correlation coefficient of -0.029.

4.3.4.2 *Employment status*

We hypothesised that a greater proportion of patients in the TBM group would lose employment compared to extra-CNS TB patients. Employment status data is tabulated in Table 4.20.

Table 4.20: Employment status stratified by TBM exposure

		Employment status			
		Remain unemployed	**Remain employed**	**Loss of employment**	**Gain of employment**
TBM patients	Count	7	2	6	0
	%	46.7%	13.3%	40%	0%
Extra-CNS TB patients	Count	10	8	7	1
	%	38.5%	30.8%	26.9%	3.8%

Abbreviations: Extra-CNS TB = Tuberculosis outside of the central nervous system; TBM = Tuberculous menigitis.

For analysis, we looked at the proportion of patients who lost employment over the six-month period following TB diagnosis (see Table 4.20). Note that patients were classified as “no loss of employment” if they remained employed or if they were not employed at enrollment to start with. Or conversely seen, patients were classified as “loss of employment” only if they were employed at enrollment and subsequently lost their job in the intervening six months before follow-up.

Six (40%) patients with TBM lost employment over the six-month period following TB diagnosis compared with seven (26.9%) patients in the extra-CNS TB group. The difference was not statistically significant (p-value 0.492).

Chapter 5: Discussion

5.1 Characteristics of the study population

The two groups of patients in this cohort study were well matched with no significant differences in factors (other than their disease status) that may impact on cognition. The cohort is characterised by young to middle aged patients from a poor socio-economic background with advanced immunosuppression (median CD4 lymphocyte counts below 100 cells/μL for both groups) and the majority were not on ART at the time of enrollment.

Both patient groups were exposed to HIV, to the same TB treatment regime (although this would extend for a longer period in TBM patients, at the six-month follow-up timepoint treatment duration was equivalent) and to ART. All patients were on ART at the time of cognitive testing, albeit for different lengths of time. For the patients who were not on ART at diagnosis, this was instated between two and six weeks after the TB diagnosis for the vast majority of patients.

In the TBM group, there was a trend to a higher CD4 lymphocyte count and longer duration of ART for those patients who were on ART at time of enrollment. About a third of patients in the TBM group were on ART at diagnosis compared to about half of the extra-CNS TB patients. The difference in CD4 lymphocyte count is partly explained by the fact that the TBM patients who died had a median CD4 lymphocyte count of 46 cells/μL (IQR 35-75) compared with a median lymphocyte count of 103 cells/μL (IQR 61-170) in the patients who survived. This contrasts with a CD4 lymphocyte count in the extra-CNS TB group that was similar for patients who survived or died.

Neither group was extensively worked up for other potential causes of cognitive impairment, but it is noteworthy that none of the patients who did have tests for Vitamin B12 deficiency (n=21), thyroid dysfunction (n=12) and/or neurosyphilis (n=19) had abnormal or positive results. Screening for

Hepatitis C infection was infrequently undertaken although it has been reported to contribute to cognitive impairment (52).

A higher proportion of patients died in the TBM group (37%) than in the extra-CNS TB group (21%). The mortality rate in the TBM group is slightly lower than previous reports of 48% mortality at six months after diagnosis in the same province (3). There are a few possible reasons for this. Firstly, early deaths in patients with severe TBM may have been missed as our study enrolled patients up to 10 days after presentation. Secondly, the original study was performed in 2009 compared to ours during 2014-2015: practice in ART initiation changed during this time with treatment being started at higher CD4 lymphocyte counts (<350 cells/μL) compared with CD4 lymphocyte counts of <200 cells/μL (101). This may have contributed to better outcomes.

The neurobevioural features of apathy and depression were assessed by the AES and BDI-II respectively. These neurobehavioural features are both reported to be more common in HIV-infected patients and to impact on functioning (102). There was a trend for a higher proportion of patients in the TBM group than the extra-CNS TB group to have clinically significant apathy, as defined by a score of ≥ 34 on the AES-i (p-value 0.12). This is important as this lack of drive/self-initiation impacts not only on cognitive and instrumental functioning, but also interpersonal relationships. In our TBM cohort, three out of five patients with significant apathy had a normal GDS. This has been reported in the literature of HIV-infected patients, where apathy was found to correlate with white matter changes even in the absence of cognitive impairment or depression (93). On the other hand, apathy has also been reported to correlate with executive dysfunction and a common frontal-subcortical process has been suggested, thereby impacting both on executive and neuropsychiatric functioning (103). The rates of moderate to severe depression was slightly higher in the TBM group, but did not reach significance.

There was a near-significant difference (p-value 0.06) between the mRS scores for the two groups. The more frequent motor disability in TBM patients is not unexpected given the burden of TB on the brain, spinal cord and lumbosacral roots, in our cohort of TBM patients.

5.2 Primary aim

Our primary aim was to assess cognitive outcomes in the TBM patient group compared to the extra-CNS TB patient group. Our hypothesis was that the TBM group would perform worse.

The extra-CNS TB patients had a median GDS of 0 (IQR 0-0.125) whereas the TBM group had the same median score of 0 but an IQR of 0-0.5, thereby extending into the impaired range.

As measured by the binary GDS, there was a greater proportion of impaired patients in the TBM group (33%) compared to the extra-CNS TB group (15%). This clinically significant difference did not, however, reach statistical significance (p-value 0.248). The most likely reason for this is the small sample size, which was not adequately powered to detect a significant difference.

Another potential reason for the non-significance of this difference is that some patients who were classified as having extra-CNS TB, may have also had TBM. Care was taken to avoid this misclassification as a careful search for symptoms and signs of TBM was performed, but this clinical method is not infallible. Mild disorientation may incorrectly have been ascribed to delirium. However, in patients with mild disorientation to the date, this resolved rapidly following treatment of the underlying cause (e.g. correction of electrolyte disturbance, treatment of urinary tract infection) and was therefore unlikely to be due to TBM. Not all patients had a lumbar puncture performed and even if they did, normal CSF findings do not rule out TBM. A normal CSF profile has been described in HIV-associated TBM in between 13% to 21% of patients, especially in the context of advanced immunosuppression (104-106).

However, if one considers a normal CSF profile together with the absence of clinical symptoms and signs of TBM, a diagnosis of TBM becomes unlikely.

A further possible explanation for the non-significant difference in cognitive outcomes between the two groups is that the frequency or severity of HAND may differ between the groups. The known risk factors for the development of HAND include lower CD4 lymphocyte count (48), advancing age (34), lower levels of education (50), and drug and alcohol abuse (49). In our study, the extra-CNS TB patients who came to testing had a lower CD4 lymphocyte count, older age and more alcohol use. Although none of these differences alone were significant, it may be that cumulatively it impacted on HAND frequency or severity in the extra-CNS TB group. This in turn may serve to dilute the differences in cognitive performance between groups.

5.3 Secondary aims

5.3.1 Cognitive outcomes by Frascati criteria

The Frascati criteria (28) are important cognitive measures, as it incorporates functioning and therefore has real life consequences for patients receiving such a diagnosis. It has been noted that measurement of functional impairment can be complex and influenced by cultural and demographic factors (36). For example, in our setting of high unemployment, subtle difficulties in executive functioning or memory may go unnoticed when a profession does not demand it. In other studies of HAND in South Africa, self-reported ART adherence rates are also used in defining functional impairment (107). Some groups propose more objective assessment of functional impairment e.g. the Columbia medication management test or the San Diego finances test (108). Such a tool has not yet been validated in South Africa.

With these limitations in mind, our study was designed to be relatively sensitive to functional decline by using two patient-reported measures (modified-IADL and PAOFI) and a relative/carer account (DECO). A patient could be rated as impaired by any or all of these three measures.

There were eight patients who were impaired by Frascati criteria: four in each group. Of these eight patients, only five had functional impairment (two with mild impairment, three with severe impairment). There were no differences between the two groups when this classification was used.

It is noteworthy that amongst the 13 patients (32% of the entire cohort) with functional impairment, more patients had a normal cognitive performance (eight patients, 20%) than patients with impaired cognition (five patients, 12%). Taken together, we can conclude that although poor insight might lead to underestimation of cognitive difficulty, all our patients with severe cognitive impairment by Frascati criteria (i.e. ≥ 2 SDs below the mean in two or more cognitive domains) did have measurable functional impairment. This may be due to the fact that proxy report of functional impairment was also incorporated in our study design. The converse was seen in our study: more patients had functional impairment in the cognitively normal group than in the cognitively impaired group. This may be due to the recognised influence of affective disturbances (depression in particular) leading to an overestimation of cognitive symptoms (87, 109). On the other hand, it may also mean that the cognitive battery we used is not sensitive in detecting subtle cognitive difficulty that translates to impaired daily functioning.

5.3.2 Description of cognitive impairment by domains

The domains that were the most impaired were the same for the two groups: information processing speed; attention and working memory; and executive functioning. The degree of impairment was worse in the TBM group across all three domains. This pattern of neuropsychological impairment is in keeping with a frontal-subcortical picture and has been well described in HAND (85). There have also been reports of poor learning, subcortical memory impairment, and reduced verbal fluency in the context of HIV (46), but these were not a prominent finding in our cohort as a whole. These domains were, however, frequently impaired in the nine patients who had cognitive impairment (see Section 5.3.2.1 below).

In summary, these findings support a *qualitatively* similar pattern in both groups, but a *quantitatively* worse outcome in the TBM group. This may be due to more severe or widespread frontal-subcortical involvement in the TBM group. One could hypothesise that a combined/dual effect of TBM and HIV on subcortical structures could lead to such pathology, albeit via different mechanisms. In TBM, this would be expected to be largely due to an arteritis, resulting in ischaemia (with or without infarction) in the tubercular zone (affecting the caudate, anterior thalamus, and internal capsule) whereas in HIV, neurotoxicity in similar striatal and white matter structures has been postulated (33).

It is interesting to note that the most discrepant scores were in the domain of visuospatial functioning (p-value 0.176) where the extra-CNS TB group had a near-normal mean Z-score of 0.06 (SD 0.98) compared with the TBM group Z-score of -0.38 (SD 1.06). When one scrutinises the subtests for this domain, it seems plausible that this difference is largely accounted for by the difference in CLOX 1 scores. This unprompted clock drawing task taps into a wide range of cognitive functions: in addition to visuoperceptual and visuoconstructional praxis, executive functioning (planning, organisation, inhibition and self-monitoring) is also assessed by this task (72, 110). When one takes this into account, we should investigate the CLOX 2 performances (copying task) as a more pure test of visuoperception or visuoconstructive praxis. There was no difference between the two groups on the CLOX 2 task. Furthermore, the difference on the JLOT scores; which is a relatively pure test of visuospatial functioning; was small. One would therefore caution against over-interpreting the domain summary score as an indicator of visuospatial skill when it may be reflecting executive dysfunction. However, in the context of reports of visuospatial impairment in TBM (15, 16), this is an area that warrants further discussion.

Studies in chronic TBM patients have demonstrated impairment in the index of perceptual organisation (significantly impaired performance on block design and picture completion tests) in a DTI study (16) and a voxel based morphometry study (15). Visuospatial impairment has not been widely

described in HIV when one compares it with the multitude of reports of frontal subcortical involvement (46). However, there has been a MRI cortical thickness mapping study in HIV-infected adults demonstrating thinning of the parietal cortex (111). The parietal and prefrontal thinning correlated with motor and cognitive impairment. A study investigating the relation of numerical and spatial cognition in asymptomatic HIV-infected individuals has been reported (112). Participants were given tasks of mental number line bisection, physical line bisection, and physical number line orientation. The HIV-infected group was significantly slower and made more errors on visuospatial and number processing tasks than the HIV-uninfected group. These findings were held to provide evidence for disruption of frontostriatal circuits and their parietal projections. In another DTI study, reduced integrity of the centrum semi-ovale was correlated with visuoconstruction and verbal memory impairments (113). A study of mental rotation and hierarchical pattern perception in HIV-infected men showed impairment in both these visuospatial tasks (114). The authors postulated involvement of the inferior parietal cortex to account for these visuospatial impairments. But it remains difficult to disentangle the role of the frontostriatal structures connected to these cortical areas (46) and further studies are needed elucidate the mechanism and neuropathological localisation of visuospatial impairment in the context of HIV.

5.3.2.1 Description of patients with impaired cognition

The nine patients (five with TBM, four with extra-CNS TB) who had a GDS score of ≥ 0.5 were studied in more detail.

The most commonly impaired domain was that of attention and working memory (albeit to a mild extent only). The second most commonly affected domains were those of learning, memory and verbal fluency. Impaired immediate and delayed free recall in the setting of relatively better recognition performance was typical.

Qualitatively, a frontal-subcortical picture was seen in all but one patient (who had selective impairment of verbal learning and memory). The frontal-

subcortical picture was not isolated in half of these patients by virtue of additional visuospatial impairment. In all four these patients, the impression of visuospatial impairment was based on poor performances of the JLOT task as well as the copying task of the CLOX 2 (thereby not relying only on the more executively loaded CLOX 1 task).

As discussed above in section 5.3.2, the presence of visuospatial impairment does not necessarily equate to cortical parietal pathology and may equally be due to involvement of frontostriatal pathways connecting to this cortical region. The classical division of visuospatial functioning into a ventral ("what", relating to object vision) and dorsal ("where", relating to spatial vision) stream still holds true. But knowledge in this area is expanding and is likely to evolve (115). The anatomical pathways have also been elucidated. Initially, the ventral stream was described as running through the occipitotemporal cortex to its anterior temporal destination, and the dorsal stream as coursing through the occipitoparietal cortex to the inferior parietal lobule. It has recently been shown that these streams extend further into the prefrontal cortex: from the anterior temporal lobe into the ventrolateral prefrontal cortex for the ventral stream; and from the inferior parietal lobe into the dorsolateral prefrontal cortex for the dorsal stream. See Figure 5.1 as reproduced from Kravitz *et al.* (115).

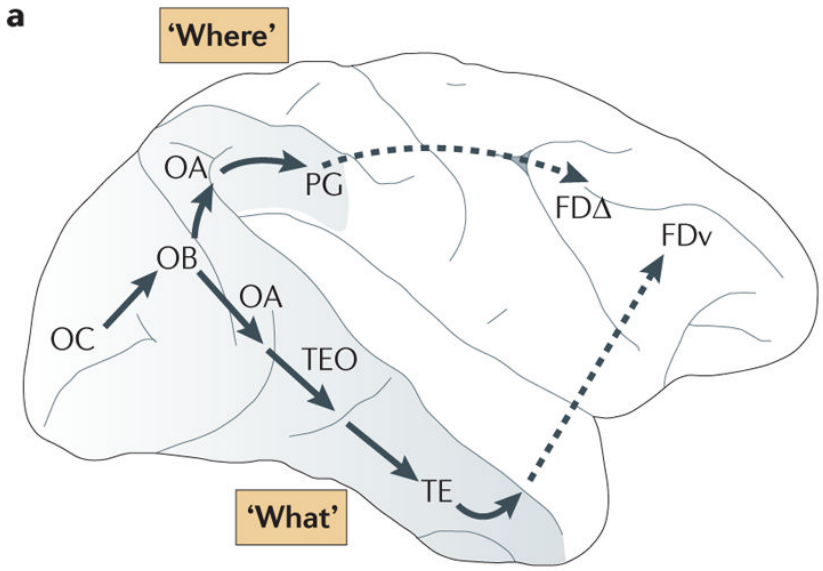

Figure 5.1: Frameworks of visual processing

From Dwight J. Kravitz, Kadharbatcha S. Saleem, Chris I. Baker, Mortimer Mishkin. "A new neural framework for visuospatial processing". Nat Rev Neurosci. 2011 April ; 12(4): 217–230. doi:10.1038/nrn3008. Accessed 12/08/2017.

Abbreviations: OC = striate cortex, OB = Visual area 2, OA = Visual area 4, PG = inferior parietal lobule, TEO = posterior inferior temporal cortex, TE = rostral inferior temporal cortex, FDΔ = dorsolateral prefrontal region, FDv = ventral prefrontal region.

The JLOT, used in our battery, has been shown to be a good test of the dorsal ("where") stream. A study using a MRI lesion-deficit mapping technique found that impairment on the JLOT was most strongly associated with damage to the right posterior parietal region (116). In our patients, we can infer pathology either in this region *or* along the white matter pathways that connect this area with the dorsolateral prefrontal cortex (115). Taking into account the circumstantial evidence of other frontal-subcortical involvement in our patients and the absence of isolated visuospatial impairment, the latter would seem the more likely explanation in our affected patients.

Impaired action fluency compared to semantic fluency has been reported in patients with HAND (117, 118). This may be due to the fact that the action fluency task taps into frontal systems, executive functioning, and motor planning. This is contrasted with semantic (category) fluency, which relies primarily on temporo-parietal networks and semantic memory stores (119). When looking at the nine impaired patients in our cohort, they did not bear out this discrepancy. In fact, there were more patients with impaired semantic

fluency compared to action fluency. This may be due to the heterogenous nature of our cohort with TBM causing involvement of more diverse subcortical structures or perhaps more temporal cortical involvement.

5.3.3 Predictors of poor cognitive outcome

5.3.3.1 Predictors of poor cognitive outcome in both groups

None of the factors investigated showed a significant association with cognitive outcomes. There was a weak trend however for older age and ART duration of less than 200 days to associate with poor cognitive outcomes as measured by a GDS of ≥ 0.5. These findings are in keeping with published literature. Older age is recognised to associate with worse cognitive performance in studies of HAND (34). A systematic review of the effect of ART on neurocognition has been conducted by Joska *et al*. (57) and they found that ART does improve cognitive functioning in HIV-infected individuals, although it does not cause complete resolution of impairments.

Looking at cognitive outcomes and deaths, there was a weak trend for a positive association between a CD4 lymphocyte count of less than 60 cells/μL and this combined outcome. This finding of an association between advanced immunosuppression and death is not surprising.

5.3.3.2 Predictors of poor cognitive outcome in TBM group

Although not reaching statistical significance, the presence of TBM-IRIS was associated with cognitive impairment in 60% of patients contrasting with cognitive impairment in only 20% of non-TBM-IRIS patients. This finding has clinical significance, as the risk of cognitive impairment may be higher in the context of TBM-IRIS as opposed to TBM without an IRIS phenomenon. This gives further impetus to ongoing studies on ways to prevent TBM-IRIS in high-risk patients.

There was no association between BMRC disease severity grading and GDS classification. However, there was a near-significant association between

BMRC grading and GDS classification or death, with all patient deaths occurring in patients with a Grade 2 classification. This is consistent with reports of poorer outcomes in patients with higher BMRC disease severity grades (120, 121).

5.3.3.3 Predictors of poor cognitive outcome in extra-CNS TB group

There was no difference in cognitive outcomes between patients with single-site TB or disseminated TB. A potential confounder is the fact that treating physicians may not pursue an extensive search for TB in other sites once it has been proven in one (e.g. after receiving a positive sputum result for TB, abdominal ultrasound may not be deemed necessary as it would not change treatment in that particular patient). Therefore, it is possible that a proportion of patients with single-site TB in fact did have undocumented disseminated TB.

5.3.4 Quality of life and employment status

5.3.4.1 Quality of life

There was no significant difference between the QOL scores for the two patient groups. It was interesting to note that the patients with the three lowest QOL scores all had significant cognitive impairment (their scores were amongst the four lowest scores overall). There was no association overall though for QOL and GDS, suggesting that this association of poor QOL with cognitive impairment apply to the outlying patients only.

5.3.4.2 Employment status

There was no significant difference between the loss of employment rates for the two patient groups. The relatively small number of patients who were employed at enrollment (about half of the TBM group, about 60% of the extra-CNS TB group) is likely to contribute to weak power to detect a significant difference. It is disconcerting that 40% of TBM patients and 27% of extra-CNS TB patients lost their job in the six months following their TB diagnosis.

5.4 Strenghts and limitations

5.4.1 Strenghts

As far as we know, this is the first study of cognitive outcomes in HIV-infected adult patients with TBM. The two study groups were well matched in terms of CD4 lymphocyte count, exposure to ART, and TB treatment duration. This was a cohort of vulnerable patients with advanced immunosuppression from a poor socio-economic background. The cognitive battery was detailed, spanning eight cognitive domains, and included measures of visuospatial functioning (which is not routinely included in tests of HAND). Cognitive tests were always administered in the patients' first language with the aid of an isiXhosa translator. All the cognitive tests were administered by the investigator herself, which ensured continuity and limited the confounding effects of inter-rater variability. It also gave her a qualitative impression of cognitive performance and features that may impact on performance (e.g. lack of motivation, poor concentration, anxiety). This was a highly enjoyable aspect of the study, and patients overall perceived it as a positive experience too. The use of a locally derived normative sample (n=114) for cognitive tests is a further strength of the study. This data will also be useful for future cognitive studies in this population. The measurement of functional impairment was assessed in detail (both patient and proxy reports of functioning were taken into account) and this helps to translate findings of cognitive impairment into real life meaning for the study participants. Additionally, neurobehavioural features of depression and apathy were assessed as important potential confounders of cognitive performance.

5.4.2 Limitations

Our study had several limitations. The most important limitation is the small sample size and this is the most likely reason for the non-significance of the between-group differences. The first reason for the small sample size is limited resources (manpower, study duration, and costs involved) as well as a high loss to follow-up rate in the extra-CNS TB patient group. Reasons for the loss to follow-up included patients relocating to other provinces (in most

instances these were patients who returned to their province of birth following their illness), patients declining further participation (mostly applicable to working patients who were hesitant to lose a day of employment), and patients not having a fixed dwelling and/or contact number or losing a mobile phone if they had one. Unconfirmed death is also a possibility, although this could account for loss to follow-up of four patients only. The disproportionate loss to follow-up in the extra-CNS TB group creates a potential bias for cognitive outcomes.

The next limitation is the presence of a major risk factor (HIV) for the outcome of interest (cognitive impairment) in both patient groups. However, an HIV and TB co-infected control group was chosen for two reasons: Firstly, the burden of HIV and TB co-infection in South Africa is large and devastating and therefore warrants description. In theory, by having HIV present in both cohorts the additional effect of TBM on cognition could still be analysed. Furthermore, if one were to compare HIV-infected adults with TBM with patients with HIV only, there would be more between-group differences than these imposed by our study design: differential TB drug effects on the CNS; chronic inflammation due to TB, with chronic inflammation having been shown to affect neurodegeneration (122, 123); and degree of immunosuppression; all of these would have been likely confounders. Secondly, although a third control group consisting of HIV-uninfected adults with TBM was considered, only 12% of adult TBM cases are HIV-uninfected in our setting (3) and it would have been difficult to recruit an adequate number of patients to generate sufficient statistical power.

A challenge in the design of our study is that the presence of TBM in patients assigned to the non-exposed (extra-CNS TB) group cannot be ruled out altogether. We relied on the absence of clinical symptoms and signs of TBM (4), but this is not infallible. A retrospective study of HIV-infected adults with TBM from Brazil found that only 15% of patients presented with the classical triad of fever, headache, and meningeal signs simultaneously (105). On the other hand, a large prospective comparison study in Vietnam by Thwaites *et al.* (54) looked at the influence of HIV infection on clinical presentation of TBM

in adults. They did not find significant differences between how HIV-infected and HIV uninfected patients presented. In our study, it may be that subtle confusion due to TBM may have been incorrectly judged to be due to delirium, of which there are many potential causes in this setting (e.g. hyponatremia, hypoxia, sepsis, drug effects). Arguing against this is the fact that the few patients who had mild disorientation to the date, all improved rapidly following correction of the underlying cause of delirium. To further complicate this matter, the presence of a normal CSF profile does not rule out TBM, especially in patients with low CD4 lymphocyte counts (124) and it has been shown that patients with HIV infection are more likely to present with normal protein or an acellular CSF (106). We did keep these limitations in mind, and took care to minimise the misclassification of TB patients as far as possible.

Our study was observational in nature, and therefore neuroimaging was not routinely performed in this cohort of patients. In fact, the secondary level hospital from which most patients were recruited, does not have a CT scanner on site. Patients have to be referred to a tertiary level hospital for this, which brings about its own logistical challenges and makes clinicians reluctant to request this test unless there is a strong clinical indication. We were therefore unable to draw any for clinico-radiological conclusions.

The follow-up time point for cognitive testing was chosen to be six months, as this allowed a similar duration of exposure to TB drugs for both groups (treatment would be extended to nine months in total for TBM patients, whilst for most extra-CNS TB patients, treatment would be stopped after six months). This is important, as the anti-tuberculous drug, Isoniazid, is known to be a potential cause of CNS toxicity (125) and can lead to psychosis, seizures or encephalopathy (126). One could argue that the six-month time point was too early and that a full treatment course for TBM should have been completed prior to cognitive testing. However, testing patients at different time points such as at completion of TB treatment (six months for extra-CNS TB patients and nine months for TBM patients), or at nine months in both groups, would both have introduced its own confounders. From a HAND point of view, there may have been a benefit in extending the follow-up period, as some

patients were only started on ART after enrollment (usually two to six weeks after TB treatment was initiated). This means that these patients would have been on ART for shorter than six months at the time of cognitive testing. In a review of studies of the effectiveness of ART on neurocognitive function (57), the duration of ART use ranged from 8 weeks to 2 years, but most studies employed an average study period of 6 months. It has been shown that clinically meaningful neuropsychological improvement peaks around six to nine after ART was initiated (127). However, our two patient groups did not show significant differences in terms of duration of ART at follow-up, so the inadequate effects of ART would be similar across groups.

We did not exclude patients who drank alcohol, but instead used the AUDIT scale to assist in stratifying use. Patients with high level drinking or dependence in the preceding six months, as defined by the AUDIT score ≥ 16, were excluded. Alcohol use is a potential confounder of cognitive impairment and one could argue that a more stringent cut-off could have been used. However, there was no significant difference in alcohol use between groups. Furthermore, when stratifying patients with an AUDIT score ≥ 8, there was still no significant difference between groups. Due to resource constraints, we did not perform urine toxicology screening on our patients, but relied instead on self-report of substance use. This is a limitation as patients may underreport use of illicit substances.

Chapter 6: Conclusion and recommendations

To our knowledge, this is the first study of cognitive outcomes in HIV-infected adults with TBM. It adds value to the description of patients with HIV and TB co-infection, which is a common and devastating scenario in South Africa. Although limited by small numbers and our inability to reveal statistically significant differences between groups, there were trends towards more frequent and more severe cognitive impairment in patients with TBM compared to patients with extra-CNS TB, at six months after TB diagnosis.

The majority of cognitively impaired TBM patients had TBM-IRIS.

The neuropsychological picture was similar between groups, supportive of a frontal-subcortical process, and characterised by slowed information processing speed; impaired attention and working memory; and executive dysfunction. Additionally, there was a non-significant trend towards more visuospatial impairment in the TBM group.

Future studies in TBM patients with HIV infection are needed to confirm whether this trend towards more cognitive impairment in TBM patients is borne out. The design of future studies should include a larger sample size and may include a third control group of HIV-uninfected patients with TBM. The addition of neuroimaging at diagnosis or shortly thereafter would aid in elucidating clinico-radiological associations. Furthermore, the follow-up period for cognitive testing may be extended to two time points: at six and 12 months, thereby allowing for completion of TBM treatment and for optimal effect of ART to take place. The cognitive battery may include more detailed visuospatial testing and tests of language, in addition to the domains tested in our study.

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