Executive Function Deficits in HIV-Associated Neurocognitive Decline

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ABSTRACT

People with HIV infection are living longer as a result of advances in combination antiretroviral therapy. This increase in lifespan has been coupled with an increase in the prevalence of HIV associated neurocognitive decline (HAND). A central feature of this presentation is the impairment of executive functioning, and the aim of this study was to explore whether there is general impairment of this domain or whether there is an executive function profile (of *deficits* versus relatively *preserved* aspects of function) in people with HAND.

Sixteen participants with HAND (mean age = 49.25 years, range 23 to 72 years) were recruited from an inpatient HIV-rehabilitation unit, and completed cognitive and executive function batteries.

The executive function profile obtained at group level suggested impairments in working memory, verbal initiation, verbal inhibition, rule induction, and processing speed abilities. In contrast letter fluency and visuo-spatial switching scores were less affected.

Case series analyses indicated that cognitive and executive functioning varied widely within the participant sample. However verbal initiation and inhibition were impaired in all profiles, indicating these impairments are prominent in the early stages of disease.

The findings of this study indicate that it may be beneficial for clinicians to use executive function batteries when assessing for HAND, since a thorough assessment of this multi-faceted cognitive domain can support more informed clinical decision-making. Further, the study suggests which tests may be clinically useful in detecting executive function deficits in HAND.

1. INTRODUCTION

Literature databases (PsychInfo, Pubmed and Science Direct) were searched for articles containing key terms relevant to the topic under investigation (e.g. ‘HIV’, ‘cognitive impairment’, ‘executive functioning’). Abstracts from the results of these searches were screened and, where appropriate, full articles obtained. Chapters of relevant books were also screened. Finally, authors featuring prominently in the first two search phases were then used as search terms to elicit any further useful material.

1.1 Epidemiology

Human Immunodeficiency Virus (HIV) infection results in progressive decline of the body’s natural immune responses, thus leading to increased susceptibility to opportunistic infections and diseases. Advanced stages of decline are associated with Acquired Immunodeficiency syndrome (AIDS).

1.1.1 Worldwide Prevalence

The United Nations Programme on HIV/AIDS (UNAIDS, 2013) estimated that there are 35.3 million people globally living with HIV, and that there were 2.3 million new infections in 2012. Because many people live for some time without knowing they are infected, other authors have given much higher figures of prevalence. For example Ellis, Langford, and Masliah (2007) put the figure of those infected at over 40 million, whilst Sharp and Hahn (2011) suggest 60 million. The UNAIDS (2013) highlights that since the start of the epidemic in the early 1980s approximately 70 million people have been infected in total. Kumar and Clark (2012) note that since the first description of AIDS in 1981, and the identification of the causative organism, HIV, in 1983, more than 30 million people are thought to have died.

Prevalence figures appear to vary significantly between different countries. It is believed that HIV originated in Sub-Saharan Africa, and this region is still the most affected by the disease today; 1 in 20 adults in this area has HIV and it

accounts for 69% of the total worldwide prevalence. Interestingly there has been a 42% decline in new infections in the Caribbean (the second most affected region in the world; UNAIDS, 2013). However Kumar and Clark (2012) note that it is Eastern Europe and parts of central Asia where infection rates have been rising sharply in more recent years. The authors also note the societal and economic costs are great, and that 33% of 15-year olds in countries with high prevalence and incidence rates will ultimately die of the infection.

1.1.2 UK Prevalence

It is estimated that over 96,000 people are infected with the disease in the UK (Health Protection Agency, 2012), however Kumar and Clark (2012) note that approximately one quarter of those infected are unaware, thus contributing to further onwards transmissions and poor clinical outcomes (with late diagnosis the most common cause of HIV-related morbidity and mortality). Kumar and Clark (2012) further note that in Western countries such as the UK, with falling death rates and continued new infections, prevalence may continue to increase though incidence rates may stay stable or fall.

1.1.3 Transmission

Kumar and Clarke (2012) note that heterosexual intercourse (vaginal and anal) accounts for the largest proportion of new infections globally. They also note that transfer of HIV appears to be more proficient when passed from male partners to female partners, and to the receptive partner in anal intercourse. In the UK homosexual transfer and heterosexual transfer account for new infections equally, however in Africa and Asia new infections are principally accounted for by heterosexual intercourse.

Other significant modes of transmission include mother-to-child transfer, with up to 40% of children born to HIV-infected mothers also acquiring the virus without intervention (Kumar & Clarke, 2012); transmission may occur in utero, however it is more likely to occur peri-natally, with breast feeding being shown to double the risk of vertical transmission. Finally needle stick injuries and intravenous drug use with contaminated needles also contribute to the spread of infection.

1.1.4 History of HIV

Sharp and Hahn (2011) note that AIDS was first discovered in 1981, following a period when large numbers of young homosexual men were observed to be dying of unusual opportunistic infections and tumours. A retrovirus (a type of virus which inserts its DNA into the host cell in order to replicate) now known to be HIV was identified in 1983 as the causal vehicle.

Kumar and Clark (2012) note that there are two types of the virus, HIV-1 and HIV-2, with the former occurring more frequently. HIV-1 appears to have evolved from the simian immunodeficiency virus found in chimpanzees and reportedly has three strains – the first and most prominent is the M (main) strain. It is believed to make up 90% of all infections worldwide. Sharp and Hahn (2011) note that since it's first identification over 30 years ago, the M group has infected 60 million people and resulted in more than 25 million deaths. (The other strains – 'O' and 'N' are less studied due to their relatively smaller distribution).

HIV-2 appears to have evolved from sooty mangabey monkeys and is reportedly not as virulent as HIV-1. It is principally found in West Africa, France, and Portugal. Kumar and Clarke (2012) note that HIV-2 is only 40% structurally similar to HIV-1, and although also associated with immunosuppression, it appears to be less malignant. Neither virus is pathogenic in its natural host (Sharp & Hahn, 2011).

It is believed that HIV originated in sub-Saharan Africa (Gabon, Equatorial Guinea, Cameroon, and the Republic of Congo) in non-human primates and was transferred to humans in the late 19th or early 20th century (WHO, 2007). There are a number of theories explaining the transfer of the virus to humans. For example Hahn, Shaw, de Cook, and Sharp (2000) report evidence to suggest that humans may have been infected as early as the 1930s, after being exposed to animal blood and secretions during hunting, or by consuming contaminated meat. The AIDS epidemic did not occur until the end of the twentieth century, and Hahn et al. (2000) cite a number of social, economic, and behavioural factors which provided optimal conditions for the virus to reach epidemic proportions including social disruption, urbanisation, slavery, and prostitution. Others have

highlighted the roles of stigma and discrimination (UNAIDS, 2013), lack of education, and misconceptions about HIV (Leclerc-Madlala, Simbayi & Cloete, 2009) as influential in facilitating the spread of the virus.

Edward Hooper (1999) also attempted to account for cross-species contamination and, therefore, the spread of HIV. He hypothesised that vaccination trials containing chimpanzee and sooty mangebey kidneys carried out in the Belgian Congo in the late 1950s played a central role. However, Hahn et al. (2000) note that this hypothesis is not consistent with a stronger body of evidence indicating that certain strains of the virus originated 50 years before the trials were conducted.

Finally the Duesberg hypothesis, a fundamental driver behind the 'AIDS Denialism' movement, (Duesberg, 1998) states that various non-infectious causes such as pharmaceutical and recreational drug use are the cause of AIDS, and that HIV only serves as a passenger virus. However this controversial claim is thought to have lead to some devastating outcomes; in 2006 as a result of these ideas, Thebo Mbeki, a former South African Health Minister, promoted natural remedies such as garlic over the use of anti-retroviral medication. Chigwedere, Seage, Gruskin, Lee, and Essex (2006) estimate that this resulted in 365,000 deaths at the time. Consequently the Duesberg Hypothesis, which was never widely received, has been largely discredited by the scientific community.

1.1.5 Natural History of HIV

Classification systems attempt to track the progression of diseases from the point of exposure to the causal agent. The WHO (2007) classified the progression of HIV into the following three stages (please see Appendix A for fuller descriptions):

i. *Acute Infection Phase*

Approximately 2-4 weeks after exposure to the virus, 40-90% of individuals will experience extreme flu-like symptoms. These symptoms are often mistakenly attributed to other causes.

ii. *Asymptomatic HIV Infection/Clinical Latency*

Infected individuals can remain asymptomatic for long periods. During this phase HIV infection reproduces at relatively low levels, and individuals are able to remain well without the use of medications.

iii. *HIV Disease & AIDS*

If untreated, HIV will develop into AIDS. In this phase immunity is severely impaired and there is a high risk of developing infections and tumours. These diseases can be fatal and life expectancy can be as little as one year.

1.2 HIV Pathology

It is thought that HIV attacks the central nervous system thus leading to, among other diseases, HIV associated neurocognitive decline (HAND). Masliah, DeTeresa, Mallory, and Hansen (2000) suggest that the brain is the second most frequently infected organ after the lungs. Fischer-Smith and Rappaport (2005) report that approximately 60% of individuals infected by HIV become neurologically impaired with causes including toxoplasmosis, opportunistic infections and neurologic disorders (e.g. tumours and strokes). These individuals often present with symptoms indicating neurotoxicity, neurodegeneration, inflammation, and consequently cognitive changes. McArthur et al. (2003) note that HAD, the severest form of HAND, is currently the most common form of dementia in those under the age of 60.

Hult, Chana, Masliah, and Everall (2008) argue that in non-pathological circumstances CD4 +T lymphocyte cells, macrophages, and monocyte cells maintain immunity of the CNS. HIV infection attacks these cells and either destroys them or alters their functioning, thus leading to a gradual deterioration in immunity and, consequently, development of opportunistic infections and cancers (McArthur, Steiner, Sacktor & Nath, 2010). Further, since it is a retrovirus it is able to replicate itself, and Kumar and Clarke (2012) note that HIV is also a

lentivirus since there is often a delay in the onset of symptoms after the acquisition of infection.

The blood brain barrier is highly selective however the Trojan Horse Hypothesis (Liu et al., 2002) suggests that HIV is able to infiltrate the barrier by targeting and corrupting immunity cells, and acting as a passenger being carried into the brain. This results in the blood brain barrier becoming inflamed and, consequently, functionally and structurally impaired. Macrophages have many important roles including ridding the body of dead cells and playing a crucial role in initiating the body's immune response. It is thought that in the case of HIV infection, macrophages not only become infected, but also become reservoirs of on-going virus replication.

Microglia, cells specifically involved in supporting immunity of the brain, are thought to become infected through contact with infected macrophage cells and are also targeted by HIV as sites of replication. Hult et al. (2008) note that HIV infected migroglia produce neurotoxic substances which result in dendric damage and neuronal injury.

Lindl, Marks, Kolson and Jordan-Sciutto (2010) note that these processes demonstrate the 'direct' mode of action that HIV employs. The authors argue that this process is also coupled with an 'indirect' mode of impact; direct injury leads to further inflammation as the immune system stimulates uninfected microglia in an attempt to curb additional injury. In support of this, Anthony and Bell (2008) note that HIV associated dementia appears to correlate with extent of neuro-inflammation rather than with viral load or HIV encephalitis.

Hult et al. (2008) note that damage to the CNS may be characterised into primary and secondary pathologies. Primary pathologies are thought to be those caused directly by the presence of the virus and have been explored above. The authors note that primary HIV neuropathology has been linked to a triad of impairments comprising cognitive, motor, and behavioural deficits. Secondary pathologies are those occurring due to the immunosuppression resulting from HIV acquisition and

are termed ‘opportunistic infections’ e.g. lymphomas, Cryptococcus infections and progressive multifocal leukoencephalophy.

It is worthy of note that the account provided above is not unproblematic since not all those infected with HIV show reproductive infection at autopsy. This has led some to hypothesize that reproduction of the virus may occur not in the CNS, but in the bone marrow where CD14+ CD16+ monocyte cells are produced (Ellis et al., 2007). Anthony and Bell (2008) note that since there has been limited opportunity to study the brain in the early stages of disease, there is still no conclusive evidence as to which cells harbour HIV at the stage of disease acquisition. However what is agreed is that, as the disease progresses, HIV encephalitis (HIVE) and opportunistic infections start to present. These conditions are associated with activated or infected microglia and microphage cells that release toxins, which in turn damage neurons and synapses. Ellis et al. (2007) note that these toxins target the frontal cortex, the basal ganglia, the hippocampus and the white matter.

Further, Lentz, Kim, and Lee (2009) note that neuroimaging has demonstrated that subcortical brain areas are targeted in the early stages while cortical areas affected later. A number of authors have reported reduced volume of the basal ganglia in people with HIV infection (Berger & Arendt, 2000; Jernigan et al., 1993). In support of these findings Thomson et al. (2005) found strong patterns of neurotoxic impact resulting from high levels of nacetylasperate (a key indicator of neuroaxonal damage) in the basal ganglia, but they also reported evidence of damage in the frontal neocortex and the white matter tracts connecting these regions - the fronto-striato-thalamo-cortical loops; this neurotoxicity was associated with cognitive impairment in their study.

Woods, Moore, Weber, and Grant (2009) note that the virus may also impact other structures and neural systems. The authors suggest that this is because once it has crossed the BBB, the virus can affect synaptodenric injury through direct and indirect (neuroinflammatory) mechanisms (thus resulting in wide-ranging damage as also concluded by Lindl et al., 2010). They further note that

the degeneration of the fronto-striatal loops impacts broader neural networks and thus results in the manifestation of cognitive deficits.

1.3 Treatment

Reportedly only one adult has ever been 'cured' of the infection (Hutter et al., 2009). Another study in the New England Journal of Medicine (Persaud et al., 2013) discusses the case of a baby who was treated with antiretroviral therapy 30 hours after birth following exposure to the virus. The child at 30 months of age is reported to be virus free.

In spite of these two cases, there is strong consensus within the medical community that there is currently no cure for HIV infection. The introduction of antiretroviral therapy (ART) in 1987 appeared to change the prognosis of those with HIV, however it was quickly realised that single-drug therapy was unable to supress viral mutation, and thus often failed to result in longer-term benefits (Ellis et al., 2007).

It was discovered that for treatment to be effective (i.e. to prevent virus mutation and therefore the development of drug resistant strains) more than one antiretroviral drug needed to be taken. Consequently in 1996 combination antiretroviral therapy (cART, also known as highly active antiretroviral therapy – HAART) was introduced. The WHO (2008) notes that if followed regimentally, cART can result in near-complete suppression of HIV replication, a reduction in onward transmissions and the development of opportunistic infections, and improved health outcomes. McArthur et al. (2010) note that treatment can consist of 3 or more antiretrovirals, with certain drugs being more effective at crossing the blood brain barrier. Mitchell (2004) also notes that certain combinations are thought to be more effective in suppressing CSF HIV-RNA and therefore impacting impairments associated with HIV associated neurocognitive decline.

Although the advent of cART has changed the classification of HIV from a fatal condition to a chronic lifelong condition (Kumar & Clarke, 2012), a number of

issues need to be held in mind. Firstly the administration of drug therapy is often a complex issue, with infected individuals often struggling to tolerate the short-term (e.g. diarrhea, rashes, and vomiting) and long-term (e.g. lipodystrophy) effects of the drugs (Volberding, 2003). Secondly, adherence can be difficult for some people to maintain due to an often large number of drugs and complicated dosage regimes. Thirdly, Anthony and Bell (2008) note that cART does not cure an individual of HIV and the virus will continue to reside in sanctuary sites even in those who adhere strictly to their medication protocols. The CNS is one of the key sanctuary sites for the virus due to the restricted immune surveillance of this area. The failure of cART to completely rid the body of the virus has a number of consequences including the development of drug resistant viral strains.

Taking a broader perspective, Kumar and Clark (2012) note that global estimates indicate that only a quarter of those who need treatment are able to access it. The authors further note that for each person starting treatment, there are approximately two new infections, thus indicating the growing size of the problem. It is also worthy of note that cART is the global standard of care and access in areas with the highest levels of need (sub-Saharan Africa) is extremely limited; The UNAIDS (2013) estimated only 8 million people worldwide have access to anti-retroviral drugs.

1.3.1 Has the Advent of cART Influenced the Neuropathology of HIV?

Anthony and Bell (2008) note that since the advent of cART in the developed world, individuals no longer routinely progress from the asymptomatic phase directly through to AIDS. However the authors also note that recent evidence suggests that the drugs have not only influenced the incidence and clinical course of the disease, but also the neuropathology.

Opportunities for exploring the impact of HIV on neuropathology in the cART era have been limited, principally because the treatment has reduced the number of HIV-associated deaths in the early stages of disease. Those who have died are thought to have done so due to other causes such as associated risk factors (e.g. drug overdoses) or comorbid illnesses and infections (e.g. Hepatitis C). In support of this, neuropathological investigations into such cases have highlighted

increased inflammation in the absence of infection caused by HIV or other opportunistic viruses (e.g. Ellis et al., 2007).

However Anthony and Bell (2008) note that in spite of this, there are strong arguments to suggest that cART has had an impact on the neuropathological profile of HIV. They cite evidence to suggest that the areas of infection appear to have changed since the pre-cART era; this era saw inflammation in the basal ganglia, however the cART era has seen infection and inflammation in the basal ganglia, the hippocampus and the fronto-striatio-cortical loops. Consequently HIV is no longer associated solely with damage to the sub-cortical regions, but also with damage impacting cortical regions and circuits.

Anthony et al. (2006) further report their study showed that neurodegenerative proteins (hyperphosphorylated Tau) can be seen in the normal aging process, but not at the high levels found in people with Alzheimer's disease and in those treated with cART. Therefore the authors conclude that the levels may be linked to accelerated neurological decline in these two groups.

In support of this, Valcour, Skikuma, Watters, and Sacktor (2004) also reported high levels of proteins and suggest that older groups with HIV present with neurocognitive impairments not found in younger controls. The authors argue that this may be due to the toxicity of drugs used in cART, or due to the presence of co-factors such as hepatitis. They note that it is unlikely that ageing with HIV is a causal factor, as patients with HIV lived for approximately 15 years in the pre-cART era and showed no evidence of increased levels of proteins. Consequently the authors conclude that elevated levels of these proteins appear to be unique to the period of cART, and that the resulting levels of inflammation in certain brain regions are similar to those found in sufferers of AIDS.

As mentioned the virus is able to hide in areas where immune-surveillance is poorer (such as the brain). Anthony and Bell (2008) note that since cART has increased the lifespan of those infected with HIV, this has resulted in certain sites having longer exposure to the virus and, again, the evolution of drug resistant strains.

1.4 HIV-associated Neurocognitive Decline (HAND)

The neuropathology resulting from HIV infection can lead to a number of impairments characterised by varying degrees of behavioural, cognitive, and motor difficulties. This triad of impairments is known as HAND.
Prevalence estimates of HAND vary greatly from 30% (Lindl et al., 2010), to 50% (Gannon, Khan, & Kolson, 2011) to 60% (Fischer-Smith & Rappaport, 2005), though there is general agreement that prevalence of the severest form of impairment (HIV associated Dementia) has greatly reduced since the advent of cART (Sacktor, 2002).

1.4.1 Categorisation of HAND

Navia, Jordan and Price (1986) provided one of the earliest reports of HIV associated Dementia (HAD), and labelled the combined presentation of cognitive impairment, motor dysfunction, and behavioural changes as 'AIDS Dementia Complex'; however Catlan and Burgess (1996) criticised the term for assuming these impairments formed a distinct syndrome.

In 1991 The American Academy of Neurology AIDS task force formulated a two-tiered classification system consisting of 'HIV associated dementia' (which included behavioural, motor and psychological difficulties) and 'minor cognitive motor disorder' for those presenting with less severe impairments (Woods et al., 2009). In 1995 an additional category of 'sub-syndromic neuropsychological impairment' was included to capture those presenting with mild cognitive deficits but with no impairment in activities of daily living (Grant & Atkinson, 1999). However Griffin and Gerhardstein (2010) criticised these early attempts at classifying HAND due to their poorly defined categories, which resulted in a lack of specificity between degrees of cognitive deficit.

Other attempts have also been made to formulate a diagnostic system, with the most recent and widely accepted being formulated in Frascati, Italy by the National Institute of Health (Antinori et al., 2007). This classification framework ranges from 'no impairment' through to 'dementia'. It attempts to take account of advancements in neuropsychological assessment tools and treatment protocols,

in addition to considering the impact of co-morbid conditions (Griffin & Gerhardstein, 2010):

i. Asymptomatic Neurocognitive Impairment (ANI)

Approximately 30% of HIV suffers present with mild neurocognitive difficulties which are thought to have a minimal impact on every day functioning (McArthur et al., 2010).

ii. Mild Neurocognitive Disorder (MND)

Reportedly found in 20-30% of individuals (Sacktor, 2002) who present with mild to moderate difficulties in two or more cognitive domains, and some difficulties in everyday functioning. McArthur et al. (2010) highlight that those in this category often present with poor medication adherence and therefore increased morbidity and mortality risks.

iii. HIV Associated Dementia (HAD)

Reportedly found in approximately 1-2% of HIV sufferers (McArthur et al., 2003). This presentation is characterised by moderate to severe difficulties in two or more cognitive domains, severe difficulties with activities of everyday living, and decreased survival rates (McArthur et al., 2010).

1.4.2 Has cART Impacted the Incidence & Prevalence of HAND?

As discussed in section 1.3.1, a number of authors have commented on the impact of cART on the prognosis of those infected with HIV whilst others have argued that the brain is a sanctuary site for the virus. Letendre et al. (2008) argue cART may not be neuroprotective since some antiretrovirals are unable to cross the blood brain barrier, and are therefore unable to effectively curb viral replication in the brain. Consequently it is likely that some individuals may go on to develop drug resistant viral strains, thus leading to increased viral replication and decreased CD4 cell counts.

In support of this argument Heaton et al. (2010) found that 44% of those treated with drug therapy continue to show viral replication and CNS inflammation. This inflammation is thought to be implicated in the pathogenesis of HAND. In fact

this study found that prolonged immunosuppression is linked to a higher risk of HAND even after cART related immune-recovery, lending further support to research highlighting that HIV continues to exist in sanctuary sites. Further Robertson et al. (2007) note that resistance to antiretrovirals and the increase in survival rates of people with HIV may mean that the brain continues to be exposed to both the direct and indirect effects of the infection. This argument is inline with those posited earlier suggesting the prolonged survival of those with HIV lengthens the brain's exposure to the virus.

Further Tozzi et al. (2007) note that neurocognitive decline was not reversed in 62% of individuals who had been treated with cART for 5 years. They also found that CD4 counts, viral load, age, and stage of HIV were not correlated with neurocognitive deficits thus lending support to the findings of Anthony and Bell (2008) who note that HAD appears to correlate with neuro-inflammation rather than directly with viral load or HIV encephalitis.

In contrast however, Cysique et al. (2007) reported 41% of their sample showed improvements in cognition at 48 week follow-up. Further Robertson et al. (2010) tested individuals who had discontinued cART. Improvements in cognitive functioning were maintained at 24, 48, 72 and 96 week after discontinuation. The authors note however that practice effects may have accounted for a proportion of their findings. A recent systematic review conducted by Joska, Gouse, Stein, and Flisher (2010) noted that eleven of the 15 studies entered into the analyses reported improvements in cognition. The authors concluded that although it is likely cART improves cognition, elimination of all impairments may not be possible. However the findings of this study may not be robust enough to draw firm conclusions given that the average study timeframe was only six months, and also given the small number of studies entered into the final analysis.

A longitudinal research design was employed to examine the effects of cART on cognitive performance by Hayman-Abello (2007) who reported that 386 adults at different disease stages were tested at baseline and 180 tested again at follow-up. Those on cART were found to score higher on cognitive measures than those not engaged in therapy. Longitudinal analyses utilising reliable change indices

found that at follow-up 65% of the HIV group had stable cognitive profiles, 10% demonstrated improvements, and 26% demonstrated decline. The study also reported however that the long-term effects of cART on cognitive status were mediated by factors such as initial cognitive impairment level, and estimated IQ.

Finally, exploration of the existing evidence base also highlights some differences in Pre- and Post-cART era cognitive profiles. Heaton et al. (2011) note that Pre-cART impairments were characterised by deficits in processing speed and motor skills, however Post-cART profiles appear to show evidence of additional difficulties with executive functioning and new learning.

1.4.3 The Validity of the Frascati Classification Framework

Despite the popularity of the classification system developed by Antinori et al. (2007) a number of authors have recently questioned its utility. Robertson et al. (2007) have commented that the framework does not adequately account for cognitive fluctuations, and also that there is a no account of corresponding neurological biomarkers.

The category of ANI has attracted particular criticism. Glissen, Price and Nilsson (2011) highlight that studies have reported on the increasing numbers presenting with symptoms indicative of this level of impairment. However the authors question the utility of including this category in the classification framework since it does not require evidence of functional impairment. However Heaton et al. (2011) argue that the category usefully captures those who are yet unaware of emerging difficulties and may be at risk of further decline. In response Glissen et al. (2011) highlight the ethical implications of labeling those who do not present with significant degrees of cognitive difficulties, or any functional deficits, in clinical settings. This perspective casts doubts over the ecological validity and necessity of the construct, given that there is limited clinical relevance (Torti, Foca, Cesana, & Lescure, 2011). The authors also question the specificity of the category after reporting that 16% of the general population would be classified as impaired under the current criteria.

This leads the discussion to consider broader criticisms of the way diseases are

socially constructed, such as those posited by authors such as Sontag (1991), who highlight that particular constructions can distort the truth about a disease (by labeling a particular presentation as an 'impairment' when it does not 'impair' an individual in any way). She also highlights that thinking about an illness can cause more suffering than the illness itself. This is particularly relevant in this case given the stigma reported by sufferers of HIV, and the additional stigma that may result from this second label. This situation is further exacerbated by the lack of treatment/support protocols in place for those who are diagnosed with ANI.

Further, to the best of the author's knowledge, there is currently no research evidence indicating that those presenting with ANI are at increased risk of additional impairment, and thus there is a need for research on the construct's predictive validity.

1.5 HAND & Demographic Considerations

1.5.1 Gender

According to the WHO (2008) 50% of those living with HIV globally are women. However there are some regional variations e.g. in Sub-Saharan Africa Women constitute 60% of the HIV population, however in the UK between 2001 – 2013 only 17% of those diagnosed with HIV were women (UNAIDS, 2013).

Most research in this area is conducted with male participants since they are the most infected group in the Western world (Fox-Tierney Ickovics, Cerreta, & Ethier, 1999). Failde-Garrado, Alvarez, and Simon-Lopez (2008) note that female participants are often excluded from research in the medical field to ensure homogeneity of samples. However the authors question whether it is valid to generalise norms obtained from studies using principally male participants to the female population. The authors also note that there has been an increase in the incidence, and therefore prevalence, of HIV in women in recent years but this has not been coupled with an increased exploration of the neuropsychological characteristics of HAND in female groups. The authors further argue that females with HIV may be more vulnerable to cognitive impairment due to complex pre-

morbid histories.

Mason et al. (1998) found differences between HIV+ and HIV – women in motor speed, verbal memory, and attention. Durvasula, Miller, Myers, and Wyatt (2001) also reported differences in psychomotor speed. Further Maki et al. (2009) reported that women with HIV demonstrated greater deficits in verbal learning, delayed recall, and working memory than their male counterparts after being matched for important variables (e.g. stage of disease).

Failde-Garrado et al. (2008) conducted a study to compare patterns of neuropsychological impairment between male and female participants. Deficits between genders did not differ strongly enough to reach levels of significance however the authors noted that females showed a trend towards slightly higher rates of impairment (51.9% in males and 54.8% in females). Further the authors also found that although male participants presented with higher levels of impairment in visual memory, attention and abstract reasoning, females showed higher levels of impairment in psychomotor speed/attention and verbal memory for prose.

1.5.2 Age

The likelihood of developing any dementia increases with age in the normal population, with 1 in 20 over the age of 65, and 1 in 5 over the age of 85 predicted to develop, for example, Alzheimer's disease (Department of Health, 2009a).

Valcour et al. (2004) note that although the advent of cART has increased the life expectancy of those with HIV, the implications of long-term infection and the cumulative toxic effects of antiretroviral therapy, in addition to age related vulnerability to dementia, warrants cause for concern. Their study reported higher rates of HAD in older participants, with this group also presenting with higher rates of cardiovascular diseases, other comorbid conditions, side effects from medications to treat these conditions, and less resilient immune systems.

Others have noted that acquiring HIV later in life is linked to poorer outcomes

both in terms of greater risks in progression to AIDS (Belanger, Meyer, Carre`, Coutellier & Deveau, 1997) and in terms of poorer responses to cART (Kaufmann et al., 2013).

In conclusion Gonzelez and Cherner (2008) note that normal ageing and HIV may increase vulnerability to neurocognitive decline. In terms of the dual effect on particular cognitive domains, Grant (2008) and Gonzelez and Cherner (2008) note that although language skills do not sharply decline with age, areas that are more vulnerable include reaction time, psychomotor speed, and the ability to solve complex problems.

1.5.3 Education

Grant (2008) highlights the positive impact of years of education on test performance. Particularly, he notes that exposure to education renders better performance on verbal fluency tests and those that require strategic planning. Grant notes that factoring in the impact of education is important and recommends making reference to norms developed with healthy controls with comparable years of education to ensure any deficits can be fairly attributed to the impact of HIV, rather than the impact of lower levels of education. However Manly et al. (2011) note that years of education are an inadequate measure of educational opportunity and exposure, and that quality of education is more important. They argue that reading level is a reliable measure of this after reporting that their study found reading ability was discrepant from number of years of schooling, and had a stronger relationship to neuropsychological test performance.

1.5.4 Cognitive Reserve

Stern (2000) observes it has been repeatedly suggested that degree of brain pathology/damage is not directly proportional to cognitive and behavioural manifestation of that damage. Vance et al (2014) have suggested that such disparities can be understood in terms of the *cognitive reserve* hypothesis. Cognitive reserve refers to the amount of injury the brain can sustain without any impact on functioning. Stern notes that two models, which are not exclusive, have broadly conceptualized the construct. The first is the brain reserve capacity

model and the second the cognitive reserve model. The brain reserve capacity model suggests that those with larger reserve ability are able to tolerate a high degree of pathology before the onset of symptoms. The cognitive reserve model however highlights the role of cognitive processes in curbing the impact of pathology through the ability of cognitive networks. Morgan et al. (2012) note that cognitive reserve is operationalized as verbal IQ, academic achievement or occupational status. They further argue that in individuals with HIV, the cognitive reserve model would suggest the level of synaptodendric impairment at which an individual with high cognitive reserve develops HAND would be significantly greater in comparison to an individual with lower levels of cognitive reserve capacity. This hypothesis has indeed materialized in the findings of, for example, Pereda et al (2000) who reported higher levels of impairment in multiple cognitive domains in those with lower levels of cognitive reserve. This study utilized multiple markers of cognitive reserve including years in education, educational achievement and estimates of pre-morbid ability and therefore the conclusions drawn may be considered robust.

A further study, by Morgan et al (2012) attempted to explore the role of cognitive reserve in vulnerability to developing HAND, and also concluded that individuals with low cognitive reserve levels were more likely to develop and experience cognitive and functional deficits than those with high cognitive reserve markers. This study also used multiple markers of cognitive reserve (years of education, verbal IQ level, and occupational status) in addition to a measure of reading ability. As argued above, this is a useful measure of quality of educational exposure; the benefits of this measure over other measures of educational exposure were discussed above. Finally Patel et al (2013) reported that cognitive reserve is a robust predictor of performance in attention/working memory and verbal fluency.

1.5.5 Culture & Ethnicity

Most research into diseases takes place in Western countries. However the highest prevalence rates are in other regions; as mentioned earlier sub-Saharan Africa has the highest number of people living with HIV, the highest number of new infections, and the highest number of AIDS related deaths (UNAIDS, 2013).

This discrepancy may result in people from all over the world, with contrasting cultural experiences, being assessed with tests and norms developed with Western populations.

Manly et al. (2011) note that validation of assessment tools accounting for cultural factors has started to take place recently. However the authors also note that this normative data, whilst being a step in the right direction, may not always be useful since samples often exclude HIV negative candidates who may be at high risk of contracting the infection e.g. intravenous drug users or those with mental health difficulties.

Further the authors reported that in their study, demographic factors accounted for a large proportion of the variance in tests of psychomotor speed and executive function between HIV + and HIV – participants. Of particular importance were factors associated with ethnicity, and quality of education. The influence of culture and education are important considerations since it has been well documented that those from ethnic minority backgrounds, and those with poorer educational experiences often perform poorly on cognitive measures and are therefore more vulnerable to false-positive diagnoses. Manly et al. report that in their study they found that reading level was a strong indicator of quality of education in ethnic minorities, which in turn also had the strongest impact on variance in test scores - more than HIV status and years of education.

In line with Manly et al.'s study, Rohit et al. (2007) reported that specificity for detection of impairment increased by 20% in African American participants when cognitive test scores were adjusted for reading level. The authors also note that the same pattern was not found among American participant of European origin.

1.6 HAND & Risk Factors

A number of authors, including Patel et al (2013), have argued that there is a high prevalence of comorbid conditions amongst the HIV population, each of which increases vulnerability to, and severity of, cognitive impairment. Hepatitis C is discussed separately in section 1.7 and mental illness in section 1.8 due to their high prevalence in those with HIV. Age, also known to increase vulnerability to

cognitive impairment was discussed in section 1.5.2. However Patel et al (2013) highlight other significant risk factors which increase vulnerability to impairment including vascular diseases and substance use. Their study used a 'risk severity score' based on the aggregated effects of various risk factors including age, vascular disease, substance use, and cognitive reserve. This risk score was found to be predictive of cognitive test outcomes on measures of learning and memory, executive functioning, verbal fluency and motor functioning. Particularly, the risk severity score was predictive of memory and verbal fluency in older participants, and of working memory and executive function deficits in younger participants. This study thus highlights that risk cannot be ignored when exploring cognitive deficits in HIV.

Further Anand, Springer, Copenhaver, and Altice (2010) explored the reciprocal relationship of risk factors and HIV related cognitive impairment; they argue that as impairment increases, ability to self-care declines (e.g. take medication, avoid risk-taking, etc.), thus further negatively impacting cognition.

1.7 HAND & Hepatitis C

Rates of Hepatitis C are particularly prevalent in those with HIV due to the common modes of transmission (Sherman, Rouster, Chung & Rajicic, 2002). However Rotman and Liang (2009) note that prevalence data of HIV/HCV varies widely between studies, and that this is because the mode of exposure greatly impacts the likelihood of transmission. In intravenous drug users who are also HIV+, prevalence rates are reportedly as high as 93%, however transmission through sexual intercourse is somewhat inefficient, and consequently only 10% of transmissions occur in this way.

Studies have found poorer global performances on neuropsychological assessments in HIV+/HCV+ participants in comparison to those who are HCV+/ HIV- (e.g. Letendre et al., 2007).

Further, Thein et al. (2007) reported higher rates of subtle impairments in attentional skills in HIV/HCV co-infected participants in comparison to HIV+ only

participants. However the study was conducted with a relatively small sample (45 participants) and this may explain why the difference did not reach significance. Further, Ryan, Morgello, Isaacs, Naseer, and Gertis (2004) reported findings indicating that those co-infected with HIV and HCV were more likely to have executive function deficits.

1.8 HAND & Mental Health

1.8.1 General Mental Health

Anand, Springer, Copenhaver and Altice (2010) highlight the reciprocal relationship that HIV can have with mental health difficulties, both in terms of increasing vulnerability to contracting the virus, and in terms of developing difficulties after diagnosis. The authors further note that factors such as mental ill-health can reduce medication adherence. This can lead to increased morbidity and mortality.

Conversely, in their longitudinal study Prince, Walkup, Akincigil, Amin, and Crystal (2012) found that the odds of contracting HIV in participants with and without serious mental illnesses did not differ. In fact the authors go on to note that their study found that people with serious mental illnesses were 23% less likely than people without to receive a positive HIV diagnosis.

1.8.2 Psychosis & Severe Presentations

HIV prevalence rates for the general population are thought to be approximately 0.87% (Perälä et al., 2007). Cournos and McKinnon (1997) note that rates of HIV infection in those with schizophrenia are estimated to be between 4% and 23% and are therefore much higher.

Angelino and Treisman (2008) argue that schizophrenia can impact executive functioning, and consequently result in excessive risk-taking behaviors and difficulties in negotiating safe sex practices. This coupled with the often downward spiral in social and economic circumstances experienced by sufferers of schizophrenia can result in individuals finding themselves in situations where

they are vulnerable e.g. involved in coercive sexual situations.

1.8.3 Mood

Nakasujja et al. (2010) note that depression is more frequently observed in those with HIV than any other mental health difficulty, and Tucker, Buram, Sherbourne, Kung, and Gifford (2003) estimate that rates can be as much as 2-3 times higher than those observed in the general population. Others have reported that the incidence of depression increases as HIV progresses (Lyketsos et al., 1996).

However Carter, Rourke, Murji, Shore, and Rourke (2003) note that in their study of cognitive deficits in HIV, depression was not significantly related to test scores. Interestingly Castellon et al. (2006) argue that depression is a multi-dimensional construct; their study found that motivation, a commonly used indicator of depression, was found to be significantly linked to verbal memory, executive functioning, and motor performance. As these cognitive domains have also been highlighted as key areas of impairment in those with HIV, further research is needed to account for the variance attributable to each factor individually.

1.8.4 Anxiety

Ferrari, Lapp and Peretti (2011) note that cognitive difficulties are often reported in those suffering from severe anxiety and anxiety disorders. However Prejean (1998) compared the neurocognitive performance of those with HIV and those without, whilst matching the two groups for anxiety level; he found that the two groups did not differ in terms of their neurocognitive functioning, thus failing to find a relationship between cognitive dysfunction and anxiety.

However Micali, Zirilli, and Abbate (2011) conducted a longitudinal study of HIV+ men. They reported evidence to suggest that changes found between baseline, 6 month follow-up and 18-month follow up scores were indicative of a strong relationship between increased anxiety and reduced cognitive performance. The authors suggest that one hypothesis about this relationship is that accelerated disease may result in particular psychiatric disorders such as anxiety. However given the strong body of research indicating the impact of anxiety on cognition in the general population, an alternative hypothesis may be that anxiety accelerates

dysfunction in whose who are HIV+; further research is required to inform the debate.

1.9 Neuropsychological Assessment & HAND

Blanch, Munoz-Moreno, Reverte and Ayuso-Mateos (2012) and Nath et al. (2008) note that even though cART has led to a sharp decrease in HAD, other forms of HAND are rising in prevalence. Blanch et al. (2012) note that neurocognitive changes can be detected in the very early stages of HIV infection, and since HIV is associated with a number of adverse consequences including poor quality of life and progression to AIDS if not properly managed, there has been much interest in early detection of neurocognitive deficits in this group.

As Grant (2008) and Woods et al. (2009) note, neuropsychological assessment can offer:

1. Detection and assessment of the extent of cognitive difficulties;
2. Profiling cognitive strengths and weaknesses to develop supportive strategies to maintain current levels of functioning, and also to lessen the impact of deficits on day-to-day functioning;
3. Provide a means for monitoring changes in neuropsychological status that may be related to treatment and/or disease progression;
4. Support decisions about the appropriateness of care plans e.g. adherence to complex medication regimes.

Carey et al. (2004) have noted that measures used to screen for other types of dementia (e.g. Mini Mental State Examination; Folstein & Folstein, 1975) have not demonstrated sensitivity to the earliest stages of HAND. The authors argue that this may be because the MMSE was devised with cortical dementias in mind (e.g. Alzheimers) and thus assess cognitive skills such as naming and praxis rather than skills associated with prefrontal-striatal (sub-cortical) areas (e.g. information processing, executive functioning, and working memory).

In light of this Power, Selnes, Grim, and McArthur (1995) devised the HIV

Dementia Scale which has demonstrated superior sensitivity and specificity in comparison to other brief measures since it assesses deficits associated with subcortical dementias describe above. However Richardson et al. (2005) have argued that even this measure is not sensitive enough to the earliest signs of impairment in HAND. Other attempts at developing brief measures have also been made (e.g. International HIV Dementia Scale, Sackter et al., 2005) with mixed results, and it has long been argued that comprehensive batteries have better rates of sensitivity and specificity than screening measures when considering a diagnosis of any dementia.

1.9.1 The General Profile of HAND

As mentioned above subcortical functions, in addition to some cortical areas, are affected by HIV. However Schouten, Cinque, Gisslen, Reiss and Portegies (2011) note that the profile of HAND is still principally subcortical in nature since the most impaired domains are executive functioning, attention and new learning.

Grant (2008) and Nath et al. (2008) note that in the early stages difficulties in speed, motor functioning and attention are evident. As impairment further increases mental slowing, fine motor movements, gait disturbances and short-term memory difficulties become apparent.

Woods et al. (2009) note that the scattered nature of HIV associated pathology may present difficulties to neuropsychologists attempting to identify profiles of cognitive deficits. Cherner et al. (2007) provides some guidance on the issue and suggest that the following should be assessed in those presenting with HAND (i) attention and working memory (ii) executive functioning (iii) language (iv) memory (v) motor skills and (vi) processing speed.

The following sections will provide brief summaries of literature found on the impact of HIV on key cognitive domains. However Levine et al. (2008) provide a cautionary note that the performance of any particular skill will usually require multiple cognitive abilities to be intact for successful execution. Consequently the sections below are ‘artificially’ divided to enable an assessment of the current literature.

1.9.2 Attention & Information Processing Speed

Levine et al. (2008) note that attention is a multifaceted skill and summarising the current evidence base can be difficult since there is a lack of consistency in definitions and methods of assessment.

To provide some clarity Grant (2008) notes that attention is a complex ability that is constructed of many individual processes including orientating oneself to a stimulus, choosing it whilst ignoring others, and maintaining and shifting focus when necessary.

In HIV simple attention is reportedly preserved when assessed on tests such as Trails A (Grant 2008) except in the case of advanced disease. However tasks which involve more complex attention (e.g. divided and sustained attention), especially under time pressure, are reportedly very sensitive to HIV decline (Levine et al., 2008). These deficits are thought to have functional relevance e.g. in terms of the person's ability to adhere to medication routines and carry out other tasks of independent living (e.g. Marcotte et al., 2006; Sorenson, Martin, & Robertson, 1994).

Grant (2008) and Levine et al. (2008) note that assessments of attention are often timed, and are therefore closely connected to information processing speed. Further Woods et al. (2009) note that bradyphrenia (decline in processing speed) is evident on tests with (e.g. trail making tests) and without (e.g. the Stroop test) motor components.

However a small number of studies exploring only information processing were found. For example Baldewicz et al. (2004) conducted a longitudinal study which explored cognitive functioning in 59 HIV positive participants in comparison to 55 HIV negative participants; they found that HIV positive clients in different stages of the disease scored lower on tests of information processing than controls throughout the duration of the study. These findings suggest that tests of processing speed have good sensitivity to HAND.

Further, it has also been highlighted that processing speed and attention have a role in supporting higher order skills and that impairments in these skills can result in deficits in other cognitive domains (Hardy & Hinkin, 2002).

1.9.3 Motor Skills

A number of authors have commented that deficits in this cognitive domain are considered common in HAND and are reportedly a central feature of HIV-related cognitive deficits (Dawes et al., 2008; Rosca, Rosca, Chirileanu, & Simu, 2011).

Robertson et al. (2007) have reported difficulties with slowed gait velocity and Carey et al. (2004) reported difficulties with the grooved pegboard task in individuals with HIV, a test of performance speed and fine motor skills. McArthur et al. (2010) point to impairments in rapid eye movements and frontal release signs. All authors commented that declines in performance are directly correlated with progression in disease. In line with this, a further study by Ogunrin and Odiase (2006) noted that performance in this domain was worse in participants with lower CD4 counts.

Grant (2008) notes motor tests tend to be easy to administer in clinical settings, are thought to be culture free, and are therefore a useful tool in assessing impairment in this group.

1.9.4 Visuo-Spatial Functions

Heaton et al. (1995) and Woods et al. (2009) note that the occipital and parietal lobes, and therefore visuo-spatial perception, are not usually affected by HAND. However Sharma (2005) argues that connectivity of the basal ganglia (a key site of attack by the virus) to the dorsolateral prefrontal cortex, and posterior parietal lobes may result in parietal lobe dysfunction and consequently visuo-spatial dysfunction. Her study compared the performance of 20 HIV+ participants (at various disease stages) and 20 HIV- controls on tests of visuo-spatial perception. Performance on more complex tests indicated poorer map reading, spatial problem solving, and impaired constructional praxis in the HIV+ group. Sharma argues that these findings are indicative of impairment of the basal ganglia and parietal lobe connections, and consequently of spatial impairment in this group.

1.9.5 Language

Language difficulties are not typically a central feature of the early stages of HAND, and if present (e.g. anomia or comprehension difficulties) are often indicative of additional comorbidity (e.g. Alzheimer's disease; Backman, Jones, Agyuero-Torres, & Fratiglioni, 2003). However Grant (2008) notes that if an aspect of language is impaired, it tends to be performance on word generation tasks (i.e. complex skills such as fluency). In support of this Rippeth et al. (2004) reported that 40% of their sample with HAND displayed evidence of verbal fluency impairment – a skill associated with frontostriatal systems and executive functioning.

1.9.6 Learning & Memory

Grant (2008) defines working memory as the first stage of the remembering process, comprising temporary storage and manipulation of auditory, visual or other sensory information. It is highly dependent on attention and executive function skills. Martin et al. (2001) reported immediate 'online' memory manipulation impairments in those with HIV infection, and Farinpour et al. (2000) reported working memory deficits across visual and verbal modalities. Stout et al. (1995) reported finding difficulties even in asymptomatic seropositive participants. Further, Bassel, Rourke, Halman, and Smith (2002) reported that degree of working memory impairment is associated with subjective reports of memory complaints.

New information moves from temporary storage in working memory to the next stage, which supports learning and remembering. Heaton et al. (1995) showed that 50% of their sample in varying stages of HIV disease demonstrated difficulties in learning different types of information, including explicit and procedural information. The authors also noted that those with HIV tend to score worse on tests of learning both verbal and non-verbal information in comparison to controls. Woods et al. (2009) and Grant (2008) note that tests of episodic memory (e.g. tests involving learning a story) and of list-learning are among the most sensitive to early HAND.

Murji et al. (2003) suggest difficulties in new learning are the result of faulty executive coding rather than a deficit of memory formation, and are similar to difficulties seen in other subcortical dementias (e.g. Parkinson's Disease). Supporting evidence comes from Delis et al. (1995) who compared the performance of 18 HIV+ participants with controls on the California Verbal Learning Test, with results suggesting that the index group exhibited both encoding and retrieval deficits; the authors therefore concluded that a subcortical memory profile was present in this group. Further Peavy et al. (1994) note that free recall of verbal material is often lacking in strategic encoding techniques (e.g. semantic clustering), and Castelo, Sherman, Courtney, Melrose and Stern (2006) note that this is consistent with impairment to the frontostriatal loop of the brain.

Literature on prospective memory ('remembering to remember to do something') is particularly useful to explore in this group given the importance of this skill in, for example, remembering to take medication. This skill is often impaired as a result of problems with intention formation and difficulties in retrieval of future intentions (Carey, Woods, Rippeth, Heaton, & Grant, 2006). However Woods et al. (2009) note that prospective memory deficits are not often reported by this group, perhaps due to a lack of awareness of them. Rourke, Halman, and Bassel (1999) note that this lack of awareness may also be linked to executive function deficits, and that both are central to carrying out tasks of everyday living, engaging in social situations, engaging in occupation, etc. Consequently, prospective memory will be discussed below in the context of executive functioning (Section 1.8.7)

Information that is in long-term storage is usually robust and resistant to decay, even in those with dementias such as Alzheimer's disease unless the disease is well progressed. In line with this Manly et al. (2011) reported that the memory loss in their sample of individuals in the advanced stages of HAND was indicative of difficulties with retrieval.

It is also worthy of note that a number of studies have reported on the impact of risk factors on memory in those with HIV. For example Heinz, Fogler, Newcomb, Trafton and Bonn-Miller (2014) report that their study found problematic alcohol

use impacted retrieval based aspects of memory functioning. A drawback of this study is that it utilised a self-report assessment of memory functioning – the Everyday Memory Questionnaire. However other studies have also reported memory difficulties in comorbid individuals with HIV and alcoholism e.g. Fama et al (2009) reported episodic memory impairments in their sample using the MicroCog computerised assessment tool.

In addition to substance use, the literature base has also explored the impact of other risk factors that are thought to potentiate the impact of memory impairments in HIV. Seider et al (2014) conducted a longitudinal study which concluded that age and HIV interact to produce larger declines in verbal memory over time whilst Woods et al (2013) concluded poorer visuo-spatial temporal order memory deficits in older adults.

1.9.7 Executive Functioning

As note earlier, executive deficits are implicated in a range of neuropsychological presentations and there is strong consensus that impairment in this cognitive domain is a common and central feature of HAND (Dawes et al., 2008; Rosca et al., 2011).

1.9.7.1 Executive Functioning Skills

The term 'executive functioning' encapsulates a number of complex higher-order skills including mental flexibility, abstract reasoning, initiation, planning, decision-making, set-shifting (holding a number of tasks in mind), social behaviour, affect and motivation (Hodges, 2007). Burgess and Alderman (2012) note that the term refers to cognitive abilities that enable a person to determine goals and formulate new and useful ways of achieving them. They enable people to effectively resolve the challenges they encounter in everyday life, and cope with new situations (Burgess & Simons, 2005). Duncan and Owen (2000) highlight their centrality to everyday life by explaining that some executive functions are required in many situations (e.g. attention and arousal) whilst others are only required in particular circumstances (e.g. multitasking).

Hodges (2007) notes that executive functions support behaviour to be appropriate and modifiable and those with frontal lobe damage show impairments in these abilities e.g. they may demonstrate poor planning and failure to cope with changes.

There are a number of studies exploring different types of executive function. Grant et al. (1987) note that subtle disturbances in abstraction can be detected using the Halstead Category test in those who are medically asymptomatic, though deficits are more strongly present in latter stages of the disease. Difficulties have also been reported with set shifting/switching when assessed with the Wisconsin Card Sorting test (Carter et al., 2003), and with the Trails B test (Heaton et al., 1995). Response inhibition problems have been found using the Stroop color word test (Tozzi et al., 1999) and also in decision-making (as reported by Martin et al., 2004). Further, Tate et al (2011) highlight the importance of recent clinical history (CD4 counts obtained in the last twelve months) on performance in particular tests of executive functioning (e.g. a computerised tests of switching and verbal inhibition).

Moradi, Miraghaei, Parhon, Jabbari, and Jobson (2013) conducted a recent study in Tehran comparing thirty-four individuals with HIV to locally-matched healthy controls on measures of executive function and autobiographical memory, arguing that retrieval of specific memories is cognitively effortful and can be impaired in those with executive dysfunction. They reported lower performances on the Wisconsin Card Sorting test and the Tower of London test in the index group (in addition to poorer performances on tests of autobiographical retrieval). There are a number of strengths of this study including the use of culturally normed measures and, as mentioned, the use of a control group that was matched not only culturally but also geographically. However the study may lack generalizability since the sample was small, and the control group was self-selected. Further the authors used ‘duration of having HIV’ as a variable; it may be argued that it is difficult to know exactly when an individual acquired HIV. Consequently individuals often harbour the virus for indeterminate periods of time without knowing they are infected or presenting with any symptoms.

Consequently it is unsurprising that this variable did not prove to be correlated with other variables in this study (i.e. executive and autobiographical measures).

Exploration of prospective memory (remembering to remember), was briefly explored in section 1.9.2, but is particularly relevant to this discussion since Doyle et al (2013) note that the cognitive architecture of this skill is heavily dependent on frontostriatal systems and executive functioning. Time based prospective memory (the neurocognitive capacity to remember to undertake a task at a particular moment in the future) is particularly important for maintaining independence and, as argued earlier, plays a key role in medication adherence (Contardo, Black, Baeuvais, Dieckhaus & Rosen, 2009). Doyle et al.'s study explored this skill in fifty-five individuals with HAND and a comparison group using the Memory for Intentions Screening Test. Their study found that those with HIV demonstrated poorer clock-checking rates than the control group. However, a number of compounding factors may have impacted the findings of this study. Firstly, there appeared to be higher rates of anxiety and depression in the HAND group than in the control group as measured by the Profile of Mood States (McNair, Lorr, & Droppleman, 1981). Secondly, the study may have limited ecological validity since those with CNS opportunistic infections were excluded from participating in the study and Heaton et al (2011) have argued that only 7-10% of the HAND population do not present with these infections. This may limit the generalizability of Doyle et al.'s study. However, an interesting conclusion of the study is that time based prospective memory was found to be positively correlated with performance on a test of verbal fluency, thus indicating that both are dependent on cognitive flexibility and self-monitoring.

Sahakian et al. (1995) conducted a study with HIV+ male patients using a test of spatial working memory, the Tower of London test (which assesses higher-level planning ability), and an attentional set-shifting test (the Wisconsin Card Sorting Test). HIV+ participants were more likely to be impaired in all three tests of executive function in comparison to controls. However a number of criticisms may be made about the study. Firstly, since only male participants were assessed for this study, the generalizability of the findings may be limited particularly since section 1.5.1 highlighted evidence to suggest that profiles of impairment may

differ between males and females. Secondly, the authors, though passing comment, did not systematically document how performance on the three tests varied in relation to each other. Further, the authors failed to highlight that they only assessed particular types of executive function skills however their conclusions implied 'global' executive function deficits in this group. This is not a criticism unique to this study, and literature searches failed to find research exploring how a range of executive functions varied in relation to each other. Additionally, as demonstrated in the literature review above, studies often use a range of measures of executive functioning, and explore different types of executive skills, thus making it difficult to synthesize the evidence. Consequently there is a gap in the literature base exploring the profile of executive function deficits in HAND.

1.9.7.2 Theoretical Foundations of Executive Functioning

Executive functions are thought to be supported by the frontal lobes of the brain**.** Hodges (2007) notes that this area is the 'chief executive officer' of intellectual functioning and is connected to, and orchestrates, virtually all other cortical and subcortical structures. Consequently damage to this area can have widely dispersed effects on cognition. However as noted above, Ellis et al. (2007) indicate this is an area, alongside the basal ganglia, and the posterior parietal cortex, that is often targeted by the neurotoxic and neurodegenerative processes inflicted by HIV. Damage can result in devastating effects on an individual's ability to maintain independence (Cattie et al., 2012).

A number of theories have explored how the executive function system supports development of, and adaptation to, new ways of behaving. Burgess and Alderman (2012) note that although theories frequently change, some theories, or aspects of theories, have stood the test of time and one such theory is described by Norman and Shallice (1986). This perspective states that behaviour is determined by thought or action schemas (sets of actions or cognitions closely associated through practice). Schemas can be triggered by routine events in the environment since there are well-learned links between environmental stimuli and our responses to them (e.g. whilst driving and stopping at a pedestrian crossing). However Shallice (1988) noted that in novel situations, or where well-learned

responses are no longer useful and need to be inhibited, another system (the supervisory attentional system) is required to modify schema activity. Here, impairment of the supervisory system will result in the continual selection of the previously useful schema and result in behavioural inflexibility. The authors also noted that it may be the case that when the focal activity is not linked to environmental cues, a deficit in the supervisory system may lead striking environmental cues to provide excessive attention distractibility. Hence Burgess and Alderman (2012) conclude that dysfunction of the supervisory system may explain two resultant outcomes following frontal lobe damage – excessive rigidity and excessive distractibility.

1.9.7.3 Executive Function Assessment

Later revisions of Shalice's theory have noted that different areas of the prefrontal cortex are connected internally with each other, and externally with other brain structures; thus the interconnected nature of all brain structures make simple function-to-structure localisation improbable. Therefore Burgess and Alderman (2012) conclude that selecting tests on the basis of the impaired brain regions would not be clinically helpful.

However the authors note that some guidelines are available for selecting tests of executive function given what is already known about dysexecutive syndromes and what theoretical approaches tell us. Consequently Burgess, Alderman, Evans, Emslie, and Wilson (1998) highlight that tests of executive function should at the least include assessments of inhibition, measures of executive (short term/working) memory ability, and tests of multitasking.

Given our discussion above about the impact of damage in one area leading to impairment of functionality in other parts of the brain, any research exploring executive function would need to include a core composite battery. This would allow assessment of strengths and weaknesses in particular cognitive domains.

1.9.7.4 The Role of Executive Functioning in Maintaining Independence

HAND is often coupled with diverse psychological, cognitive, and medical consequences which can impact independence and the ability to fulfil activities of

daily living. Woods et al. (2009) report that as many as 50% of those with HAND will have some degree of functional impairment. Further, Vance, Fazeki and Gakumo (2013) note that complex tasks are likely to be impaired in earlier stages of disease (e.g. cooking) and simpler tasks (e.g. dressing) later.

Chaytor (2005) highlight the importance of considering the relationship between neuropsychological assessment and 'real world' functioning ability.
Heaton et al. (2004) reported difficulties in executive functioning have been found to be strongly linked with a decline in everyday functioning and Ellis et al. (2007) highlight that people with HAND are more likely to be unemployed and have poorer medication management skills. Marcotte et al. (2006) have written about the impact of HAND on the ability to drive.

Consequently the importance of executive functioning skills in the maintenance of independence becomes clear when we consider, for example, the impact of slower information processing speed and inattention (e.g. on the ability to use information in decision-making processes), and switching difficulties (e.g. on the ability to switch between competing demands).

1.10 Justification

As noted above the advent of cART has changed the classification of HIV from a fatal condition to a chronic lifelong condition. However HIV and cART can cause neuropathological and neurotoxic damage to the central nervous system, and thus result in HAND. Since cART is supporting people to live longer, the prevalence of HAND is predicted to increase.

Executive function deficits are a key feature of HAND, and are often linked to impairments in activities of independent living. However assessment screens used in clinical settings are often insensitive to early impairment and this may have implications on obtaining appropriate care and support. Further, since it is not always possible to assess multiple types of executive function in clinical settings it is important to explore whether particular executive function skills are

more susceptible to decline than others i.e. it would be useful to know whether HIV is paired with a particular profile of executive function deficits. A critique of the current literature base is that there are currently no studies exploring this. A further critique is that when individual executive function abilities are explored (e.g. abstraction), the findings are generalised to suggest 'global' impairment across all other executive functions, and this may not be the case.

1.11 Aims & Research Questions

The aim of this study is to explore whether specific subdomains of executive functioning are affected (whilst others relatively preserved), or whether they are globally impaired. Consequently the study will explore the neuropsychological profile of executive function deficits in HAND.

It may also be the case (as often reported in studies of executive deficits) that impairments are highly idiopathic, with some patients affected in some domains and not in others. Further, there is little guidance in the literature for the clinician on which executive function tests to choose. The current study will attempt to explore these issues in a typical sample of HAND patients. Taking account of the variability in the sample, the 'group' level of the analysis will be supported and informed by a case series approach to identify and respect differences between presenting profiles.

The research question is as follows:

"What is the executive function profile of HAND?"

2. METHOD

2.1 Epistemology

Although a full description of the debates and developments in epistemological thinking is beyond the scope of this section, a brief summary will usefully set the context for the philosophical position taken by the researcher.

Barker, Pistrang, and Elliott (2003) note it is important for researchers to be aware of, and acknowledge, the philosophical context and assumptions under which their data is obtained. This awareness will guide, to a degree, coherent and informed choices about methodological designs, and the conclusions that can be drawn from a particular study. Godfrey-Smith (2000) notes that the discipline of epistemology is concerned with such philosophical questions about knowledge; it explores where knowledge comes from, how it is acquired, and how we know or believe things to be true.

Seventeenth and eighteenth century philosophers (e.g. Locke, Hume) argued that our senses (e.g. sight) are the single true source of knowledge about the world, and that 'truth' could only be obtained empirically by scientific methods. This perspective became known as Positivism, and it underpins the belief that it is possible to observe and describe phenomena objectively in a 'theory-neutral' way, for the purposes of prediction and control.

A shift in thinking was influenced by theorists such as Hanson, Kuhn, and Feyerabend who argued that the perspective of the observer influences what is perceived. This difference in opinions has been articulated via the *theory-ladenness of observation* debate (Godfrey-Smith, 2000). Godfrey-Smith summarises the key issues as follows:

> *"…can observational evidence be considered an unbiased and neutral source of information … or do observations tend to be 'contaminated' by theoretical assumptions in a way that prevents them from having this role…"* (p. 155)

This questioning of neutrality became the foundation of various more critical, post-positivist views, and Willig (2008) notes is it now generally accepted by most perspectives that observation is selective.

One such perspective, critical realism, argues that although there is a reality that exists it cannot be completely known, as observation is a process influenced by human error and biases (Trochim, 2000).

In spite of the research questions lending themselves to more positivist epistemologies, the critical realist approach was adopted by the researcher of this study due to the critiques of writers such as Sontag (1991; briefly explored in the introduction). These critiques highlight the social construction of diseases such as HIV and their associated impairments. They lead us to be mindful that neuropsychological domains – and indeed executive functions – are also constructs subject to refinement and change. Hence although empiricist methods are being used to obtain the data, the author retains a critical awareness of the constructs under study, and of the possible impact of personal perspectives on what is found.

2.2 Participants

2.2.1 Recruitment

Participants for the study were recruited from a charitable multidisciplinary neurorehabilitation hospital based in London. The hospital provides specialist care for people with HAND. It has 16 inpatient beds and provides day services for a further 60 people.

2.2.2 Eligibility for Inclusion

Individuals are referred to the hospital with a wide variety of psychological and medical conditions. Consequently core inclusion and exclusion criteria were developed at the start of the study.

Core inclusion criteria required that participants had a diagnosis of HIV, some symptoms indicative of HAND, were English speakers, and that they were over the age of 18. Further criteria are explored in the sections below.
However the list only served as a guide, and the site consultant and clinical psychologist assessed suitability of patients for inclusion on a case-by-case basis. Their decisions were made on the perceived/hypothesised impact of untreated medical (e.g. infections) and psychological (e.g. active psychosis/depression/anxiety) comorbidities on cognitive functioning.

2.2.2.1 Medical Comorbidities

Following discussions with the consultant physician, and after screening referrals made to the inpatient unit, it was noted that syphilis, meningitis (crytococcal and tuberculous), and toxoplasmosis are frequently seen comorbid infections and can cause, amongst other things, confusion, cognitive decline, and memory loss. However it was agreed that people presenting with these infections would be invited to participate in the study after their conditions were treated. This was also the case for those presenting with urinary tract infections and other inter-current acute infections.

However those with progressive multifocal leuoencephalopathy (PML), which is thought to result in irreversible clumsiness, aphasia and memory loss were not recruited. Further, those with Hepatitis (B and C) were also excluded due the impact of the disease on global cognitive performance. CNS tumours and lesions are commonly seen in inpatients presenting at the unit and can have various effects on cognition depending on their location. Consequently participants with present tumours and lesions were not invited to participate in the study.

Participants with a history of substance use were invited to participate unless there was clear evidence of any misuse-associated brain damage (e.g. Wernicke-Korsakoffs disease).

2.2.2.2 Psychological Comorbidities

As noted in the introduction, there are reportedly high rates of anxiety and depression in HIV patients. Depression has been linked to low levels of

motivation, and anxiety to off task activity and distraction. Due the high levels of prevalence it was decided to include participants with mild and treated forms.

Less frequently, clients with active psychosis (or a history of psychosis) also attend the unit; it was decided that these service users would be invited to participate if their symptoms were not currently active. Those presenting with other psychological difficulties were assessed for inclusion on a case-by-case basis.

2.2.2.3 Learning Disabilities

During the recruitment phase of the study, no patients with learning disabilities were admitted to the unit. However it was decided that those presenting with learning disabilities would not be included in the study due to the likely impact of their disabilities on test performance.

2.2.2.4 English Facility

Although level of spoken English did not effect access to routine neuropsychological assessments, only those who were fluent English speakers were invited to partake in the study due to the inherent bias of neuropsychological measures against those who do not have good command of the English language.

2.2.2.5 Consent

Only patients who were independently able to consider taking part in the study and provide consent were recruited.

2.2.3 Recruitment Procedure

Participants were only recruited from the inpatient unit of the hospital as this allowed easier access to information about current health status and, therefore, informed choices about who would be suitable for the study.

Neuropsychological assessment is offered to all inpatients as part of the standard assessment and treatment protocol, and is carried out by either the researcher (in my capacity as a trainee clinical psychologist) or the site clinical psychologist. All

referrals to the unit are screened by the hospital consultant and the clinical psychologist, thus allowing them to identify potential participants for the study.

When a patient was deemed suitable for neuropsychological assessment, they were approached and provided with an explanation about (routine) neuropsychological assessment processes, information about how long the standard assessment was expected to take (1.5 hours approximately), and information about how the results may be used to inform clinical care.

The patient was then also informed about the study and the additional testing time (approximately 45 minutes), provided with an information sheet, a consent form, and answers to any questions they had. (Please see Appendices B-D for UEL Ethics Committee documentation, approved Participant Information sheet, and Consent Form). Participants were also assured that their choice to partake in the study had no bearing on the clinical care they would receive.

2.2.4 Participant Characteristics

16 participants were assessed for the study. Participant characteristics are shown in Appendix E. There were 6 females and 10 males. Their ages ranged between 23 and 72 years (mean 49.25). Six were born in the UK (1 British Asian, 2 Black British, 3 White British) and one participant was born in the USA (White). All of these participants had English as their first language. One participant was Portuguese (though born in the Congo). One participant was Congolese, one Ghanaian, one Kenyan, one Nigerian, one St Lucian and one Zimbabwean. Two participants were Ugandan.

Referring clinicians assessed level of English facility in those who were not primary English speakers to determine suitability of candidates for the study. The mean number of years of education in the sample was 10.94 and the range 4 – 17 years. Four Participants had tuberculosis in the past and three participants had toxoplasmosis. Four participants had histories of psychiatric difficulties and one of substance misuse.

Eight candidates who were deemed suitable for the study declined assessment for both clinical and study purposes. 6 candidates consented to neuropsychological assessment for clinical purposes but declined inclusion of their data in the study. Consequently these candidates were only administered the core (service) battery.

2.3 Design

As this was an exploratory study, a cross section correlational research design was employed to investigate possible relationships.

Sample size was guided by numbers utilised by other exploratory studies of subcortical dementias (e.g. Abrahams et al, 2000). Although a power calculation was considered, it was decided it might not be helpful in this case since the aim of the study was to measure size of effect, and this is relatively independent of sample size (Clark-Carter, 1999). However, since a study is considered more powerful if the number of participants is greater, attempts to obtain as large a sample as possible were made given time, resource, and referral rate constraints.

2.3.1 Testing Materials

A battery assessing premorbid functioning, current cognitive status, and executive functioning was utilised.

2.3.1.1 Assessment of Premorbid Functioning

The *Weschler Test of Adult Reading (*Weschler, 2001) was used since the ability to read irregular words is usually resistant to cognitive decline until latter stages of disease (Strauss, Sherman, & Spreen, 2006). Normative data was obtained from a representative sample of 1134 American participants and 331 British participants (as determined by census data) and is published in the test manual. The manual reports that an equal number of males and females were recruited in the American sample between the ages of 16-64, however the older age groups included more women. The UK sample also included more females and males.

Participants are presented with a list of 50 irregular words and asked to correctly pronounce them aloud. None of the words have phonemic pronunciations, thus minimising the participant's ability to say the word based on previously learned rules; the participant is therefore forced to rely solely on previously learned pronunciations/knowledge of the word. Consequently it is thought to have good clinical utility in assessing level of cognitive ability before onset of disease or injury. The numbers of words correctly pronounced are compared to normative data to provide scaled scores, percentile ranks, and indices of function.

The test also provided a measure of fluency in English (although no participant was excluded for achieving low scores on this measure, and their facility to speak and understand English was assessed by referring clinicians before being approached by the researcher).

2.3.1.2 Assessment of Current Functioning

The Repeatable Battery for the Assessment of Neuropsychological status (RBANS; Randolph, 1998) was used to assess current neurocognitive deficits/status. Normative data is based on a sample of 540 American participants between the ages of 18 to 89, and is published in the test manual. Information on the gender of participants is not provided, however data on ethnicity is included: 81% of the sample were White American, 13% African Americans, and 7% Hispanic Americans.

Although there are a plethora of batteries available, the RBANS was chosen for a number of reasons. Firstly, the battery is used by the service and employing it in the study meant that there would be no differences to the clinical care of patients who did not participate in the study. Secondly, it covers areas associated with HIV cognitive impairment, but also allows consideration of other profiles (e.g. it can also identify profiles indicative of other diseases and syndromes such as Alzheimer's disease).

Further, the battery was selected due to its reported reliability and utility when working with neurologic injury or disease (Hodges, 2007). It is brief to administer

(taking approximately 30-45 minutes), and is suitable for use at the patient's bedside (Lezak, Howieson, & Lorig, 2004).

An additional benefit to using the RBANS is that it is a comprehensive battery assessing different cognitive abilities. Individual tests in comprehensive batteries are co-normed, thus allowing easier comparisons between tests; this method is preferable to using subtests from different composite batteries.

The battery assesses function of five cognitive domains through performances on thirteen subtests (see Table 2.3-1).

Table 2.3-1 RBANS subtests

Cognitive Domain	Subtest	Test Description
Attention	Forward Digit Span	Participants are asked to repeat strings of numbers, which increase in length as the test progresses.
	Coding	Participants are presented with a sheet of paper which has a printed key pairing the numbers 1 to 9 with nonsense symbols. Underneath the key are rows of symbols and empty boxes and participants are asked to fill in the boxes with the number that is paired to the symbol in the key above. Participants are given 90 seconds to complete this task.
Immediate Memory	List Learning	Participants are verbally presented with a list of 10 unrelated words and asked to immediately repeat as many as they can remember, across four trials.
	Story Learning	Participants are verbally presented with a 12-item short story and asked to repeat as many details as they can remember, across two trials.
Visuospatial	Figure Copy	Participants are asked to directly copy a complex drawing comprising 10 components.
	Line Orientation	Participants are presented with a drawing consisting of 13 lines fanning 180 degrees from a single point. Underneath this figure, ten target items are presented consisting of two target lines, and participants are asked to identify which lines the target matches from the figure.
Delayed Memory	List Recall	After a 20-minute delay, participants are asked to recall words that were presented in the list learning subtest.
	List Recognition	Participants are presented with a list of twenty words – ten of which are from the List Learning subtest, and ten that are distractor items. Participants are asked the identify the words that were part of the List Learning subtest.
	Story Recall	After a 20-minute delay, participants are asked to recall as many details as possible about the story presented in the Story Learning subtest.
	Story Recognition	Participants are asked to answer 10 yes/no questions about the story they learned for the Story Learning Subtest.
	Figure Recall	Participants are required to redraw the figure they copied for the Figure Copy test after a 30 minute delay.
Language	Picture Naming	Participants are presented with line drawings of 10 objects that they must name.
	Semantic Fluency	Participants are given a semantic category and asked to name as many exemplars as possible in 60 seconds.

2.3.1.3 Assessment of Executive Function

A number of authors have detailed skills that should be assessed by executive function batteries (see Burgess & Alderman, 2012, and Burgess et al., 1998). These include verbal fluency, sequencing, inhibition, working memory, and rule deduction. The test set was designed with these recommendations in mind.

Table 2.3-2 Executive Function Assessment Battery

	Function	Tests
1	Word generation - verbal fluency	Verbal Fluency – DKEFS (Delis, Kaplan, & Kramer, 2001).
2	Word generation – category fluency	Semantic Fluency – DKEFS (Delis et al., 2001)
3	Switching	Verbal Switching – DKEFS (Delis et al., 2001)
4	Verbal working memory	Digit span forwards – WMS-III (Wechsler, 1997)
		Digit span backwards – WMS-III (Wechsler, 1997)
5	Verbal initiation	Hayling Test, Sentence Completion 1 (Burgess & Shallice, 1997)
6	Verbal inhibition	Hayling Test, Sentence Completion 2 (Burgess & Shallice, 1997)
7	Visual sequencing	Trails A (Reitan, 1992)
8	Visual switching	Trails B (Reitan, 1992)
9	Visual working memory	Spatial span, Kaplan Baycrest Neurocognitive Assessment (KBNA; Leach, Rewilak, Richards, & Proulx, 2000)
10	Rule deduction	Brixton Test (Burgess & Shallice, 1997)
11	Processing Speed & attention	Verbal production test, based on Simple recitation – WMS-III Mental Control, items 1-4, (Wechsler, 1997)

1. Word Generation/Letter Fluency

Verbal Fluency test – DKEFS (Delis et al., 2001). This test allows assessment of word generation skills. Participants are given a specific letter ('F', 'A', and 'S') and asked to give as many words as possible beginning with that letter in one minute. Normative data is provided in the DKEFS test manual, and is based on 1750 American participants aged between 8-89. The normative sample was based on equal number of males and females in the younger age groups, though more females in the older age groups. The ethnicity of the sample was considered representative of the American population.

2. Word Generation/Category Fluency

Semantic Fluency test – DKEFS (Delis et al., 2001). This test allows assessment of semantic retrieval strategies. Participants are given categories ('animals' and 'boys names') and asked to provide as many exemplars as possible in one minute. Normative data is provided in the DKEFS test manual, and is based on 1750 American participants aged between 8-89. The normative sample was based on equal number of males and females in the younger age groups, though more females in the older age groups. The ethnicity of the sample was considered representative of the American population.

3. Switching

Switching - DKEFS (Delis et al., 2001). Participants are given two categories ('fruit' and 'furniture') and asked to switch between them, providing self-generated exemplars from each in turn, as many times as possible within one minute. Normative data is provided in the DKEFS test manual, and is based on 1750 American participants aged between 8-89. The normative sample was based on equal number of males and females in the younger age groups, though more females in the older age groups. The ethnicity of the sample was considered representative of the American population.

4. Verbal Working Memory

a. Digit span forwards WMS-III (Wechsler, 1997) Participants are asked to repeat strings of numbers increasing in length.

b. Digit span backwards – WMS-III (Wechsler, 1997). Participants are asked to repeats strings of numbers increasing in length, in reverse order. This test allows assessment of participants' ability to temporarily hold and manipulate information.

Normative data was obtained from 1250 American participants aged between 16-89 and is published in the test manuals.

5. Verbal Initiation

Hayling Test 1 – Sentence Completion (Burgess & Shallice, 1997). This test allows for assessment of response initiation and processing speed. Here participants are presented with 15 sentences and asked to provide a word which completes the sentence, as quickly as possible. Normative data was obtained on 118 British participants aged between 18-80 and is published in the test manuals. 61 participants were females and 57 males. Race/ethnicity data was not reported.

6. Verbal Inhibition

Hayling Test 2 – Sentence Completion (Burgess & Shallice, 1997). This test allows for the assessment of response suppression and thinking speed. Participants are presented with 15 sentences with a word missing at the end and are asked to provide a nonsensical word to complete the sentence, one that is unconnected to the sentence in every way. Normative data was obtained on 118 British participants aged between 18-80. 61 participants were females and 57 males. Race/ethnicity data was not reported.

7. Visual Sequencing

Trails A (Reitan, 1992). This test allows assessment of visual sequencing without alternation and is timed, thus allowing for assessment of visual processing speed. Participants are presented with a sheet containing numbers from 1 to 25 scattered across a page, and are asked to connect them sequentially as quickly as possible. Normative data is provided by Davies (1968) based on 540 British participants, and is provided in the test manual.

8. Visual Switching

Trails B (Reitan, 1992). This test allows assessment of visual sequencing and alternation. Participants are presented with a sheet of paper with circles containing both numbers (1 to 13) and letters (A to L) scattered randomly. The participant must join the circles sequentially in ascending order, whilst alternating between numbers and letters (i.e. 1-A-2-B-3-C and so forth). This is a timed task. Normative data is provided by Davies (1968) based on 540 British participants, and is provided in the test manual.

9. Visual Working Memory

Spatial span, KBNA (Leach et al., 2000). This test allows assessment of visuo-spatial short-term memory. The participant is presented with a sheet of paper with randomly scattered dots. The researcher touches particular dots and the participant is asked to touch the same items, in the same order. Normative data was obtained from 700 American participants aged between 20 – 89 years and is provided in the test manual. 78% of the sample were White Americans, and 53% females.

10. Rule Deduction

Brixton Test (Burgess & Shallice, 1997). This test allows for the assessment of visuospatial concept formation/rule deduction. Participants are presented with 56 cards, each with ten circles. One of the circles is coloured and the participant is required to determine which of the circles will be coloured on the following card, based on the position of the coloured circle on preceding cards. Normative data was obtained on 118 British participants aged between 18-80. 61 participants were females and 57 males. Race/ethnicity data was not reported.

11. Processing Speed/Attention

Verbal Production test. This test is based on the Simple Recitation test (WMS III; Wechsler, 1997) and involves speeded verbal output of rote sequences (e.g. months of the year). Norms have recently been established by Blupert (2014) and are based on 60 British primary English language speakers (32 females and 28 males).

2.4 Analysis

Raw scores from each test were converted into age-scaled scores (with a common mean value of 10 and a standard deviation of 3), derived from published norms in test manuals and research literature as noted above (please see Appendix F for ranges and subjective labels based on Slick, 2006).

Correlational analyses were used to explore possible relationships between tests.

Additionally, patterns within individual profiles were explored with case controlled analyses.

2.5 Procedure

Participants were tested alone, usually in their rooms (ward staff were always made aware of the assessment). A brief outline of the assessment process was again given to the participant, including further discussion of the study information sheet and consent form if requested. It was made clear to participants which tests were part of the routine neuropsychological assessment protocol and which were part of the executive skill battery (i.e. the additional research component).

Participants were informed that they would receive a 30-minute break midway through the assessment to prevent motivation being negatively impacted by fatigue and boredom. They were also offered the opportunity to split the assessment across two test dates if they preferred and were reminded of this throughout, as recommended by the UEL Ethics Committee. However this was not taken up by any of the participants.

A brief initial assessment was conducted with each participant to ascertain number of years in education, occupational status, ability to speak English, and any other factors that may impact performance on the assessment (e.g. mood, ability to hear, etc.). With permission, information on latest CD4 counts and viral load was also collected from medical notes to allow examination of the relationship between disease severity and test scores.

Following this the battery was administered; the WTAR was administered first, followed by the RBANS, and then the executive function tests. A break would be offered after the RBANS to ensure that an appropriate amount of time had lapsed between the immediate recall and delayed recall tasks.

After assessment participants were offered verbal debriefing, and were informed that they would receive feedback and a brief written report approximately one week later. This would include a summary of their strengths and weaknesses, and also some compensatory strategies if applicable. They were also made aware that, with their consent, a full report would be sent to the team consultant, the HIV consultant, and the HIV clinical nurse specialist for the purposes of informing future care.

2.6 Ethics

Ethical approval was sought from the University of East London Ethics Committee. Before providing approval the committee asked for minor amendments. These included adding tick boxes alongside each statement in the consent form, ensuring participants received feedback following their assessments, and, as mentioned, offering assessment over two appointments. These amendments were accommodated into the research protocol.

2.6.1 Obtaining Fully Informed Consent

The study recruited participants who were assessed by the consultant and the clinical psychologist as being able to consider participation and provide consent.

Identified candidates were approached and informed about the study when discussing an appointment for routine clinical assessment. They were allowed up to a week to consider participation. If they agreed, their decision was discussed again in more detail at the start of the assessment in order to ensure adequate time to raise any questions or concerns. They were then asked to sign a consent form.

2.6.2 Right of Withdrawal

The right to withdraw from the study was highlighted to each participant with the assurance that this would not impact his or her clinical care. This was also explained in the participant information leaflet.

2.6.3 Anonymity & Confidentiality

Because of the nature of the study, data was not gathered anonymously. To protect confidentiality, participant data sheets were assigned numbers for identification purposes. Thereafter numbers (instead of names) were entered into record databases and statistical programmes used in the analysis. Further, any participants discussed in the final report were referred to by their participant numbers, thus ensuring confidentiality.

Completed test sheets were stored in locked NHS filing cabinets, in accordance with the Data Protection Act (UK Parliament, 1998) for 5 years.

2.6.4 Protection of Participants

Participants were continuously monitored for signs of fatigue and distress during testing, and breaks were offered as appropriate. Verbal debrief at the end of testing was provided to participants and, with their consent, a report sent for the unit consultant, their HIV consultant, and their clinical nurse specialist for the purposes of informing appropriate care.

2.6.5 Protection of the Researcher

No risks to the researcher were identified at the start of the project and this held true throughout collection of data. However it was agreed at the start of the study that should any issues arise, these would be discussed with the allocated Director of Studies, and if appropriate, senior clinicians at the Hospital.

3. RESULTS

3.1 Exploration of Participant Data

Field (2011) notes that the first stage of analysis involves obtaining measures of central tendency, in addition to measures of spread and shape. These processes allow exploration of the data for errors and outliers, and to determine whether it conforms to the assumptions necessary for parametric examination.

Table 3.1-1 shows that age, education, and WTAR scores were principally normally distributed (Skewness <1, Kurtosis <3, and Shapiro Wilk Significance >1; Field 2011). In terms of measures of variability, all had large standard deviations.

A larger proportion of CD4 counts in the sample were low thus (slightly) positively skewing the data. However the Kurtosis statistic suggests that this data was normally distributed (Kurtosis <3). Viral load scores in the sample were also positively skewed, and required thresholds were not reached in the Kurtosis and Shapiro-Wilk analyses thus suggesting non-normal distributions in this sample.

Table 3.1-1 Descriptive Statistics & Analyses of Distribution for Participant Characteristics

	Min	Max	Mean	SD	Skewness (SE:0.564)	Kurtosis (SE:1.091)	Shapiro-Wilk (Sig)
Age (yrs)	23	72	49.25	12.668	-.486	.753	.442
Education (yrs)	4	17	10.94	4.024	-.109	-.460	.397
WTAR	3	15	9.27	3.826	-.271	-.838	.517
CD4	2	991	233.25	278.450	1.696	2.685	.002
VL	0	100000000	6653022.13	24905931.812	3.993	15.958	.000

3.2 Exploration of Test Data

Test data (in the form of scaled scores) was also analyzed to establish descriptive statistics and distribution characteristics.

The Kurtosis analysis in Table 3.2-1 demonstrates that the data mainly had platykurtic frequency distributions (i.e. broader, flatter distributions that are considered non-normal; Clark-Carter, 1999). Further, positively skewed distributions were observed on coding, and negatively skewed distributions on figure copy and picture naming.

Other variables were not skewed. However Shapiro-Wilk values indicated that the data deviated from the normal distribution. Consequently analyses with parametric tests were not undertaken.

Mean scores suggest that in this sample, performances on many tests (digit span forwards, digit span backwards, figure copy, picture naming, delayed list recall, delayed figure recall, letter fluency, and spatial span) fell within the *average* ranges (Figure 3.2-1 and Table 3.2-1). However the standard deviations were large (Table 3.2-1), indicating wide variability within the scores for each subtest. Group level means also indicated that coding, list learning, list recognition, Brixton, Hayling 1, Hayling 2, and Trails A were within the *impaired* and *below normal* ranges. Again, these means were associated with wide variation in scores. However these results confirm that processing speed (as demonstrated in coding and Trails A) and executive functioning (as demonstrated by the Brixton and Hayling tests) are amongst the most affected in this sample.

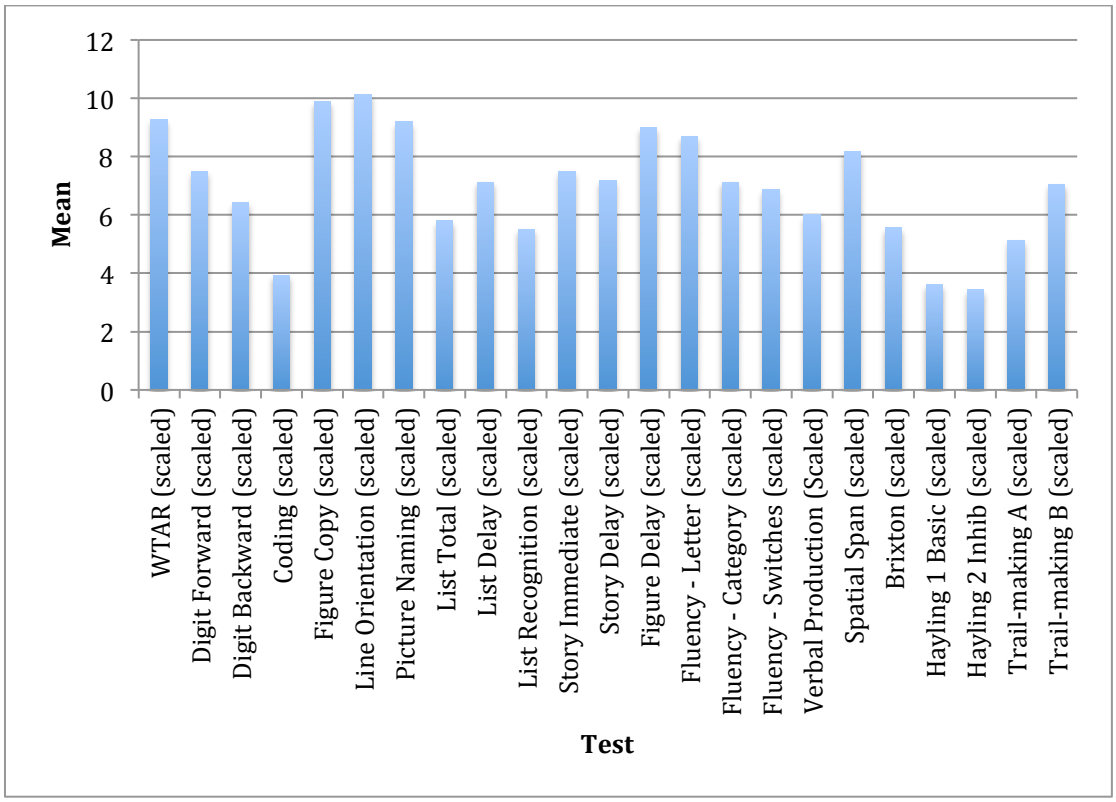

Figure 3.2-1 Histogram of Group Test Means

Table 3.2-1 Descriptive Statistics & Analyses of Distribution for Neuropsychological Test Data

	Min	Max	Mean	SD	Skewness	Kurtosis	Shapiro-Wilk (Sig)
Digit Forward (scaled)	2	15	7.50	4.243	.284	-1.113	.428
Digit Backward (scaled)	2	12	6.44	2.920	.385	-.713	.255
Coding (scaled)	1	14	3.94	3.838	1.518	1.926	.005
Figure Copy (scaled)	1	14	9.88	4.588	-1.229	-.072	.001
Line Orientation (scaled)	3	15	10.12	3.243	-.516	-.092	.734
Picture Naming (scaled)	1	12	9.19	3.816	-1.201	.064	.001
List Total (scaled)	1	14	5.81	4.053	.663	-.588	.247
List Delay (scaled)	1	14	7.13	4.129	.470	-.816	.255
List Recognition (scaled)	1	12	5.50	4.817	.397	-1.852	.003
Story Immediate (scaled)	1	17	7.50	4.967	.397	-.662	.390
Story Delay (scaled)	1	15	7.19	4.722	.205	-1.231	.349
Figure Delay (scaled)	2	16	9.00	4.163	.032	-.905	.824
Fluency - Letter (scaled)	1	19	8.69	5.351	.216	-.922	.573
Fluency - Category (scaled)	1	19	7.13	5.726	.659	-.600	.182
Fluency - Switches (scaled)	1	15	6.88	5.005	.347	-1.407	.051
Verbal Production (Scaled)	1	14	6.00	3.967	.249	-.619	.257
Spatial Span (scaled)	4	15	8.19	3.188	.652	-.181	.125
Brixton (scaled)	1	12	5.56	3.949	.261	-1.226	.063
Hayling 1 Basic (scaled)	1	6	3.62	2.062	-.047	-1.702	.007
Hayling 2 Inhib (scaled)	1	6	3.44	2.308	-.057	-2.043	.001
Trail Making A (scaled)	1	12	5.13	4.455	.360	-1.830	.004
Trail Making B (scaled)	1	13	7.06	4.008	-.180	-1.351	.434

3.3 Relationships between Tests

Spearman's rho analyses were conducted in order to explore relationships between variables. Scaled scores from all participants were entered into the analysis. However one of the participant's did not wish to undertake the WTAR test. Consequently the data was excluded pairwise (i.e. the data obtained for this participant was included for all calculations except those in which they had no score; Field, 2011). The following sections provide a summary of the key associations found, and report on medium to large effect sizes (i.e. 0.30 or greater, as guided by Cohen, 1992)

See Appendix G for the full correlation matrix).

3.3.1 Demographic Data

Data obtained from this sample suggests that in terms of demographic variables (age, years of education, WTAR, CD4 counts, and viral load) a strong correlation was found between CD4 counts and viral load (r = -.794). This finding is in keeping with what would be expected in the HIV population i.e. as viral loads increase, CD4 counts decrease. A medium effect was found between WTAR and education (r = .433) and again this was in keeping with what would be expected.

3.3.1.1 CD4 Counts, Viral Loads, and Test Performance

CD4 counts were found to be correlated with story learning (r = .441), verbal production (r = .578) and spatial span (r = .627). Viral load was found to be negatively correlated with the WTAR (r = -.428) digit span forwards (r = -.544), verbal production (r = -.675) spatial span (r = -.595), and letter fluency (r = -.482).

3.3.1.2 Age and Test Performance

Age was found to be significantly related to figure copy scores (r = .542) and spatial span (r = .518).

3.3.1.3 Education and Test Performance

Education was significantly correlated with core cognitive functions (e.g. coding r = .557; story immediate recall r = .570; story delayed recall r = .614; list learning r = .632; list delay r = .545; figure copy r = .817; figure delay r = .786).

It was also found to be correlated with executive function skills (digit backwards r = .704; letter fluency r = .638; category fluency r = .669; switching fluency r = .626; Hayling 1 initiation trial r = .562; Trails A r = .666; Trails B r = .514; spatial span r = 624).

The relationships found between education and test performance are in keeping with what would be expected, and previous literature would suggest that education has a positive relationship with test performance (e.g. Grant 2008).

3.3.1.4 Premorbid Ability and Test Performance

Premorbid ability, as established by WTAR scores, was found to be associated with core cognitive tests (e.g. list learning r = .614; story delayed recall r = .611) and executive function tests (e.g. digit span backwards r = .720; Brixton test r = .448; Hayling 1 r = .435; Trails A r = .454).

3.3.2 Attention & Information Processing

Digit span forward was found to be strongly associated with digit span backward (r = .663). Coding was found to be strongly associated with figure copy (r = .633), figure delay (r = .745) and spatial span (r = .646) perhaps highlighting some the common skills shared by these tests (motor control, attention, visuo-spatial perception). Coding was also strongly associated with letter fluency (r = .662), category fluency (r = .624), and switching fluency (r = .588) perhaps reflecting the shared speed of information processing involved.

3.3.3 Visuo-Spatial Skills

Visuo spatial skills were assessed using line orientation and figure copy subtests. Line orientation was found to be correlated with picture naming (r = .502), Trails A (r = .568) and Trails B (r = .704). Figure copy was correlated with spatial span (r = .660) and Trails A (r = .709). These correlations point to the shared functions necessary for completion of these tests e.g. attention and visuo-spatial perception.

3.3.4 Learning & Memory

Tests of new learning and delayed recall were all found to be strongly associated with each other and this finding is in keeping with what would be expected given that they address similar skills. Interestingly associations were also found across modalities; figure recall was associated with list recall (r = .792) again highlighting the core functions shared by these tasks (e.g. attention, memory formation, and recall skills).

They were also found to be associated with other domains. E.g. letter fluency was strongly associated with list learning (r = .827), category fluency associated with story recall (r = .843). Again these results are likely to reflect commonality in what these tests assess (e.g. language and memory retrieval strategies).

3.3.5 Executive Function

As noted above, executive functions were strongly associated with memory ability and visuo-spatial perception.

It was also found that executive function skills were associated with each other in this sample. For example correlations were found between executive verbal skills (e.g. Hayling 1 and letter fluency, r = .672; Hayling 2 and category fluency, r = .639) and between visuo-spatial executive skills (e.g. Trail Making A and spatial span, r = .507). Correlations were also found in tests of different modalities (Hayling 1 and Trails A, r = .855; Hayling 2 and Trails B, r = .694). These findings are perhaps suggestive of functions shared by these processes e.g. attention, concentration, rule

formation, and retrieval skills.

Figure 3.2-1 highlighted that in terms of group means Hayling 1 and 2 had the lowest scores (alongside Trails A and coding) whilst letter fluency, category fluency, switching and Trails B were stronger. However Hayling 1 was positively correlated with letter fluency (r = .672), category fluency (r = .795) switching (r = .667) and Trails B (r = .690). Similarly Hayling 2 was also positively correlated with all of these skills (letter fluency, r = .633; category fluency, r = .639; switching, r = .699; Trails B, r = .694). These correlations between the strongest and weakest executive function tests may indicate that Hayling 1 and 2, whilst assessing abilities common to the other tests (hence their positive correlations), may also tap into functions which are not assessed by other tests, and which degenerate earlier in this group (i.e. verbal initiation and inhibition).

3.4 Individual Profile Analyses

Barker et al. (2003) note that individual case analysis allows for a closer inspection of factors that may be missed in group level analyses, and also an exploration of whether group indices shed any new light on relationships between scores in individuals. Since this study took an exploratory approach, this part of the analysis is particularly important.

Further, it would be useful to consider the extent to which group differences are reflected in individual scores since the group level means were associated with large standard deviations. Consequently neuropsychological profiles and prominent background factors for each participant were explored.

3.4.1 Participant 1

3.4.1.1 Background Information

Participant 1 is a 23-year old female of Black British (Nigerian) origin. She moved to England with her family shortly after birth and attended full time education until the age of 21. She has a degree in History and at the time of her admission, was training to be a professional chef.

This participant was diagnosed with HIV at the age of 2. She started taking anti-retroviral medication at the age of 10, though used it intermittently until the age of fifteen due to intolerable side effects. She has a long-standing history of chest infections. At the age of 21 she was found to have a rectovaginal fistula and had to have an ileostomy. She has a history of depression but did not report low mood at the time of testing. Her CD4 count is 57 and her viral load 59000.

3.4.1.2 Primary Task Scores

Primary task scores for Participant 1 are shown in Figure 3.4-1.

Participant 1 had a WTAR score suggesting *high average* premorbid ability.

This participant had intact verbal attention skills (digit span forward subtest) and working memory (digit span backwards subtest).

Her performances on tests of information-processing speed, visuo-spatial perception, language, new learning, and recall were all intact. However her verbal production score was *impaired* and therefore not in keeping with what would be expected given her profile. It may be the case that this participant failed to grasp the basic rubric of the test, and thus adopted a defective strategy.

This participant's strongest performances were in tests of verbal and semantic fluency, indicating sound word generation ability. Performances on a test of rule deduction (Brixton), and visual sequencing and switching were also in tact. Her

weakest executive skills appeared to be in the area of verbal initiation and inhibition (Hayling 1 and 2), perhaps indicating poorer executive control of verbal rules.

3.4.1.3 Summary & Discussion of Participant 1

This participant acquired HIV at a young age, possible through vertical transmission, and there are a number of authors reporting the impact of this on cognition. For example Ravindran, Rani and Priya (2014) showed poorer performances on tests of attention, language, verbal memory and learning, and executive functioning in a sample of 8-15 year olds in comparison to controls. However the experimental group for this study was recruited from a care home for children with HIV in India, whilst the control group all resided with their parents; performance in part may therefore have been attributable to the social circumstances of the participants. Nagarajan et al (2012) however report similar findings in their study when comparing performances of sixteen children with HIV to those of fourteen controls, all of whom were living with their families in Los Angeles.

Paramesparan et al. (2010) explored the cognitive function of vertically infected children surviving into adulthood since these individuals will have undergone stages of neurodevelopment in the presence of HIV infection and cART. They reported 67% of their sample had impairments in psychomotor function, executive function, memory and attention, noting this to be much higher than those with horizontal transmission rates (19%).

Interestingly, Participant 1 did not appear to demonstrate impairments inline with the literature above. The cognitive reserve hypothesis may be helpful in explaining her performance, and it may be the case that her educational and occupational achievements curbed the impact of any pathology.

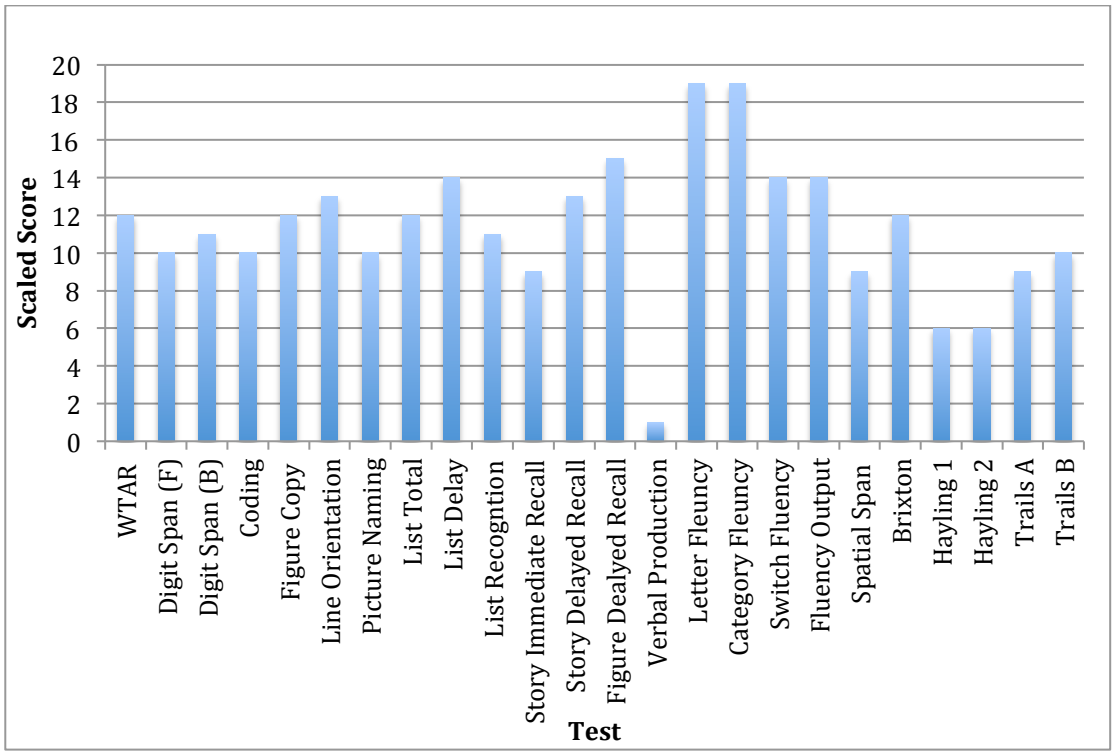

Figure 3.4-1 Histogram of Scaled Scores for Participant 1

3.4.2 Participant 2

3.4.2.1 Background Information

Participant 2 is a 46-year old male of British (Indian) origin. He was born in India and moved to the UK at the age of 4. He was expelled from school at the age of 15 and spent some time in prison before moving to Canada to start a business. He was diagnosed with HIV at the age of 26. He has a longstanding history of drug and alcohol use, and attended rehabilitation for this in the past. He is currently maintained on methadone. He was diagnosed with tuberculosis in 2010. His CD4 count is 32 and his viral load 1196.

3.4.2.2 Primary Task Scores

Primary task scores for Participant 2 are shown in Figure 3.4-2 **Histogram of Scaled Scores for Participant 2**.

Participant 2 had a WTAR score suggesting *average* premorbid ability. This participant demonstrated relative strengths in language, visuo-spatial perception, semantic fluency, and tests of sequencing and switching. However the profile showed severe impairment in coding; other areas of weakness included new learning and delayed recall of verbal information though registration appeared slightly stronger. Visuo-spatial memory was also slightly lower than expected.

Performances in tests of spatial attention were within the *below normal* range perhaps indicating weaker visual working memory; verbal initiation and inhibition were also *below normal* perhaps indicating weaknesses in executive components of semantic recall processes and new rule formation.

3.4.2.3 Summary & Discussion of Participant 2

This participant presented with impairments in processing speed, attention, verbal executive skills, new learning, and delayed recall of verbal information. HIV infection

may have played a part in this presentation, however a number of comorbid risk factors may also have contributed to the profile.

Patel et al (2013) note that substance misuse is common in the HIV population and there is a greater risk of poor cART adherence, thus leading to poorer clinical outcomes. Mintzer, Copersino and Stitzer (2005) found attention, information processing speed, and working memory deficits in those engaged in methadone maintenance therapy. However Applebaum, Otto, Richardson and Safren (2010) compared the performance of 80 opiate-dependent HIV+ participants to 80 opiate dependent HIV- participants recruited from methadone clinics, and were unable to replicate the findings of Minzter et al,; they reported that when exploring the respective roles of depression, HIV and substance misuse with multiple regression analyses, only HIV status was found to be predictive of neuropsychological impairment, particularly on tests of attention, speed and verbal memory. However, the authors noted that neuropsychological performance across both groups was poor and this may have impacted the ability of the study to find more divergent profiles.

In summary although the literature suggests a strong role for HIV in this neuropsychological profile, it is also likely that substance use, and possibly methadone, contributed to the findings.

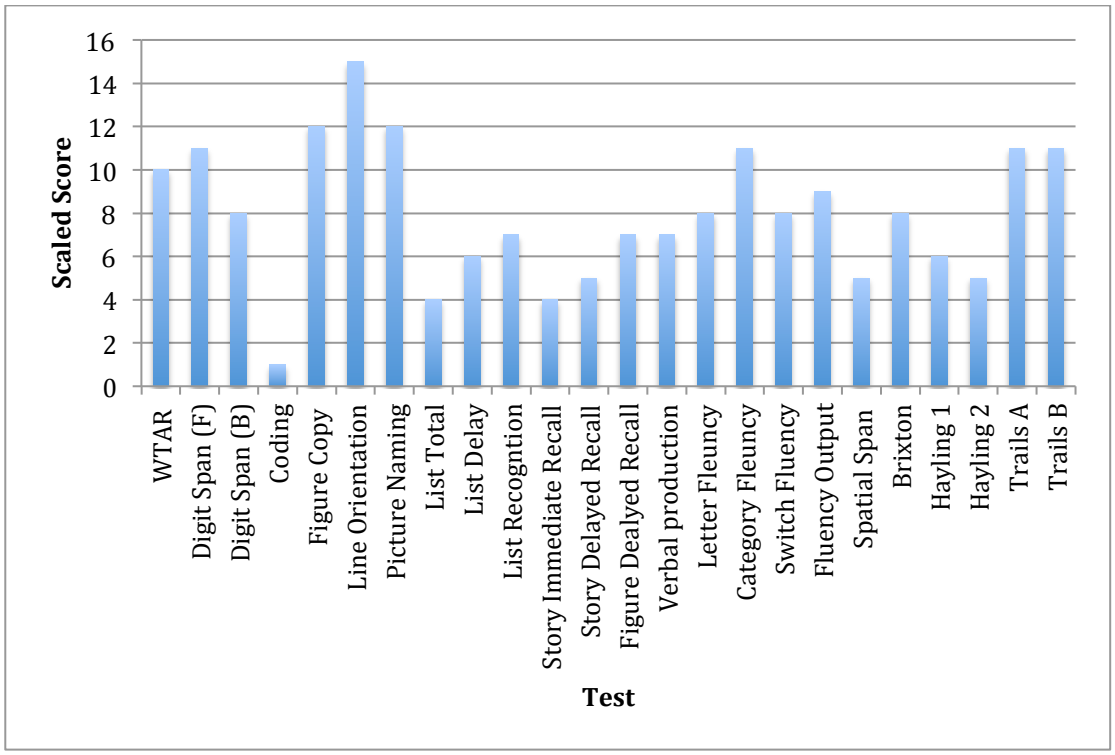

Figure 3.4-2 Histogram of Scaled Scores for Participant 2

3.4.3 Participant 3

3.4.3.1 Background Information

Participant 3 is a 40-year old female of Nigerian origin. She reported attended school in Nigeria until the age of 12 and then studied quantity surveying for four years. She arrived in the UK three months prior to her admission to the HIV unit, and was diagnosed with HIV one month prior to her neuropsychological assessment. A recent MRI reported evidence indicative of toxoplasmosis. Her CD4 count is 177 and her viral load 202.

No further collateral information was available for this participant

3.4.3.2 Primary Task Scores

Primary task scores for Participant 3 are shown in Figure 3.4-3.

Participant 3 had a WTAR score suggesting *low average* premorbid ability. Her profile highlighted relative strengths in visuo-spatial perception (line orientation), and verbal and visuo-spatial attention. However poorer performances were noted in tests involving motor functioning (figure copy, coding) perhaps indicating impairment in motor skills and psychomotor slowing. Impairments in immediate and delayed visual and verbal memory were also observed (list learning, delayed list recall, list recognition, story learning, delayed story recall, and figure recall subtests).

On the executive function tests, letter fluency was slightly stronger than category fluency though performances on both tests fell within the *impaired* range perhaps indicating weaknesses in word generation and strategy formation techniques. However these results may be the consequence of a more general language impairment, since her performances in all tests involving language functioning fell within the *impaired* range; an alternative explanation to account for the results is that the performances were impacted by English being her second language. Poor performance in the Brixton test may indicate poor rule deduction.

3.4.3.3 Summary & Discussion of Participant 3

This participant presented with impaired performances in many domains including motor functioning, memory, language, and executive functioning.

As noted above, English being her second language may have impacted some of this participant's performances. However since she also scored lower than expected on tests involving visual components (e.g. copying, rule deduction) it may be the case that other factors, for example HIV-associated impairment, also played a role in the profile. Further, Levine et al (2008) conducted an exploratory study suggesting that in comparison to HIV+ participants without evidence of central nervous system opportunistic infections (such as toxoplasmosis) those with these conditions had poorer neuropsychological functioning in general, but performed significantly poorer on measures of processing speed. However the authors argue that since processing speed is a key deficit reported in those with HAND, it may be the case that these opportunistic infections potentiate the effects of HIV on cognition.

The above study may provide an explanation for this participant's poor performances on tests with timed components e.g. coding, Hayling tests, fluency. Further this may also explain the finding that she performed significantly better on Trails B than Trails A; success in Trails A is significantly dependent on processing speed, whilst Trails B is also dependent on executive switching. This finding would therefore suggest that executive switching is less impaired for this participant.

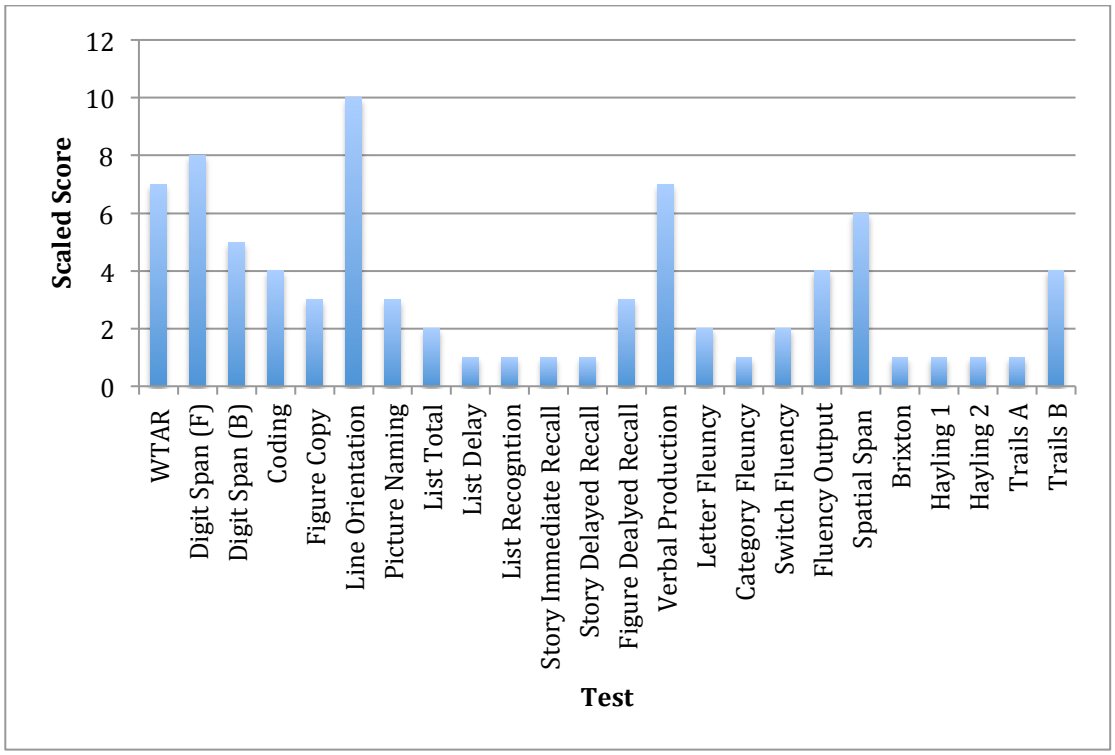

Figure 3.4-3 Histogram of Scaled Scores for Participant 3

3.4.4 Participant 4

3.4.4.1 Background Information

Participant 4 is a 43-year old male of Congolese origin, who received 9 years of formal education. He moved to England at the age of 26 and worked as a taxi driver and security guard. He was diagnosed with HIV in 1996 and had a brain tumour removed in 1998. He has a history of tuberculosis. He was admitted to the unit for rehabilitation following a fall. His CD4 count is 479 and his viral load was <40 (undetectable).

3.4.4.2 Primary Task Scores

Primary task scores for Participant 4 are shown in Figure 3.4-4.

Participant 4 had a WTAR score suggesting *average* premorbid ability. His scores on tests of attention were lower than expected. Motor difficulties were evident in the coding, figure copy, and Trials A subtests, although higher performances on the line orientation and picture naming tests suggest visuo-spatial perception is intact.

On verbal memory tests, performances suggested *impaired* registration and learning, and *below normal* memory for unconnected verbal information. In comparison, immediate and delayed recall on subtests involving semantically connected information (story-learning) was stronger.

On tests of executive functioning, phonetic and semantic fluency were within the *average* range suggesting intact word generation and strategy formation skills. Further, switching was one of the strongest skills in this profile (verbal switching and Trails B) indicating intact cognitive flexibility. However response initiation and inhibition (Hayling test 1 and 2) were within the *below normal* and *impaired* ranges respectively.

Visuo-spatial attention appeared intact (spatial span) and there was also evidence of sound rule deduction skills (Brixton).

3.4.4.3 Summary & Discussion of Participant 4

This participant performed lower than would be expected in motor skills, processing speed, attention, new learning, verbal initiation and inhibition. However he also demonstrated strengths in other areas including visuo-spatial perception, delayed recall, verbal fluency and switching. Interestingly, this participant performed more poorly on Trails A (a test of processing speed) in comparison to Trails B (a timed test of visual switching). It may be argued that, since performance on the coding task was also impaired, it is likely that this participant's performance suggests that processing speed is more impaired than executive skills in this case. However as noted above, performances in other executive skill tests fell in the *impaired* ranges.

In summary, it may be argued that although there was some evidence of HIV associated decline, this participant's performance led to a 'patchy' profile. This may be the result of a number of protective factors including a (relatively) high number of years of formal education and a low viral load.

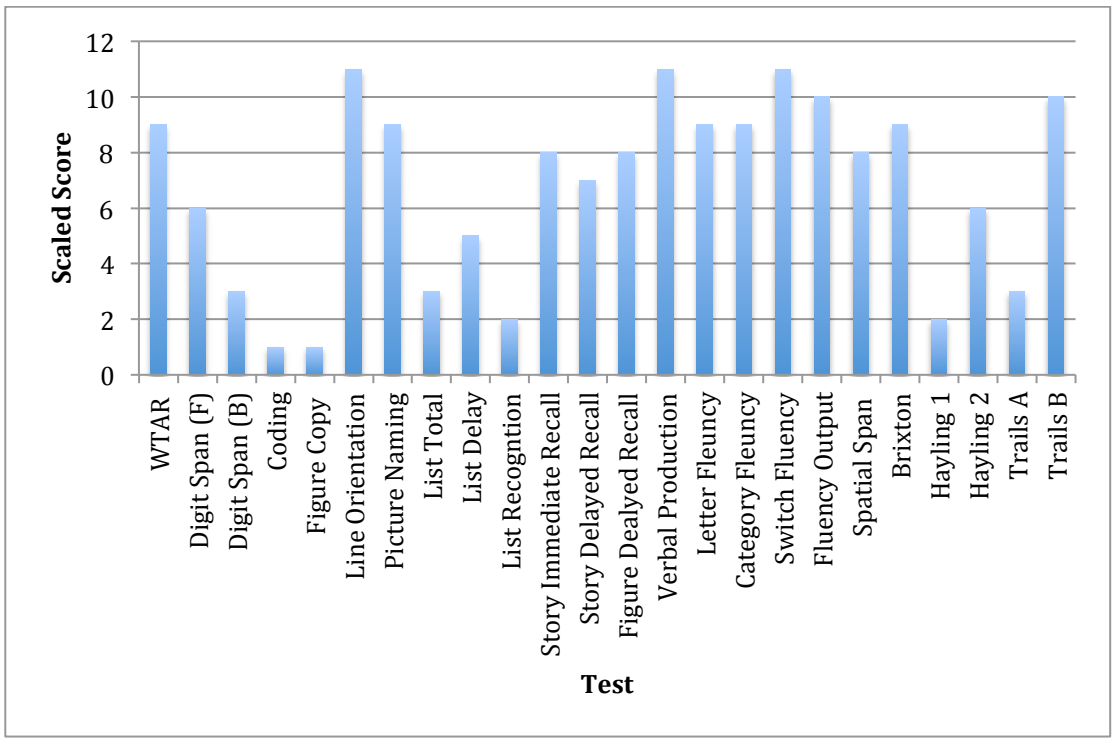

Figure 3.4-4 Histogram of Scaled scores for Participant 4

3.4.5 Participant 5

3.4.5.1 Background Information

Participant 5 is a 57-year old male of British origin. He reported leaving school at the age of 16 and having a number of occupations throughout his life including making silverware and being a cleaning supervisor at a shopping centre. He was diagnosed with HIV two months before his neuropsychological assessment. He has pancytopenia, pneumocystis pneumonia, and Kaposi's Sarcoma of the face, palette and tongue. He was receiving treatments for these conditions. His CD4 count is 38 and his viral load 3 million.

3.4.5.2 Primary Task Scores

Primary task scores for Participant 5 are shown in Figure 3.4-5.

Participant 5 had a WTAR score suggesting *below normal* premorbid ability.
In line with this attention and information processing speed were also found to be within the *below normal* range. However motor skills, visuo-spatial perception and naming to confrontation appeared to be intact (figure copy, line orientation, and picture naming subtests), in addition to recall of visuo-spatial information (figure delayed test). Registration, learning and memory for verbal information were within the *low average range* (list learning, list recall, list recognition, story learning, and story recall subtests).

Verbal fluency appeared to be intact, though semantic fluency and verbal switching were particularly strong indicating sound executive language ability and cognitive flexibility. Visual sequencing and switching (Trails A and B) also appeared intact. However verbal initiation and inhibition were *below normal*.

3.4.5.3 Summary & Discussion of Participant 5

This participant had a low WTAR score, and performances in attention, processing speed, verbal initiation and inhibition were in line with this. However, this participant performed higher than would be expected given his estimated premorbid ability level

in other domains; motor functioning, language, visuo-spatial perception, memory, fluency and switching all fell within *average* ranges.

It is difficult to explain this anomaly. One explanation may be that, since this participant attended formal education until he was 16, he was able to grasp the rubric of the assessment effectively thus supporting his performances. It may also be the case that this participant may have poorer reading skills given his occupational status, and therefore the WTAR may have provided a conservative estimate of his overall abilities.

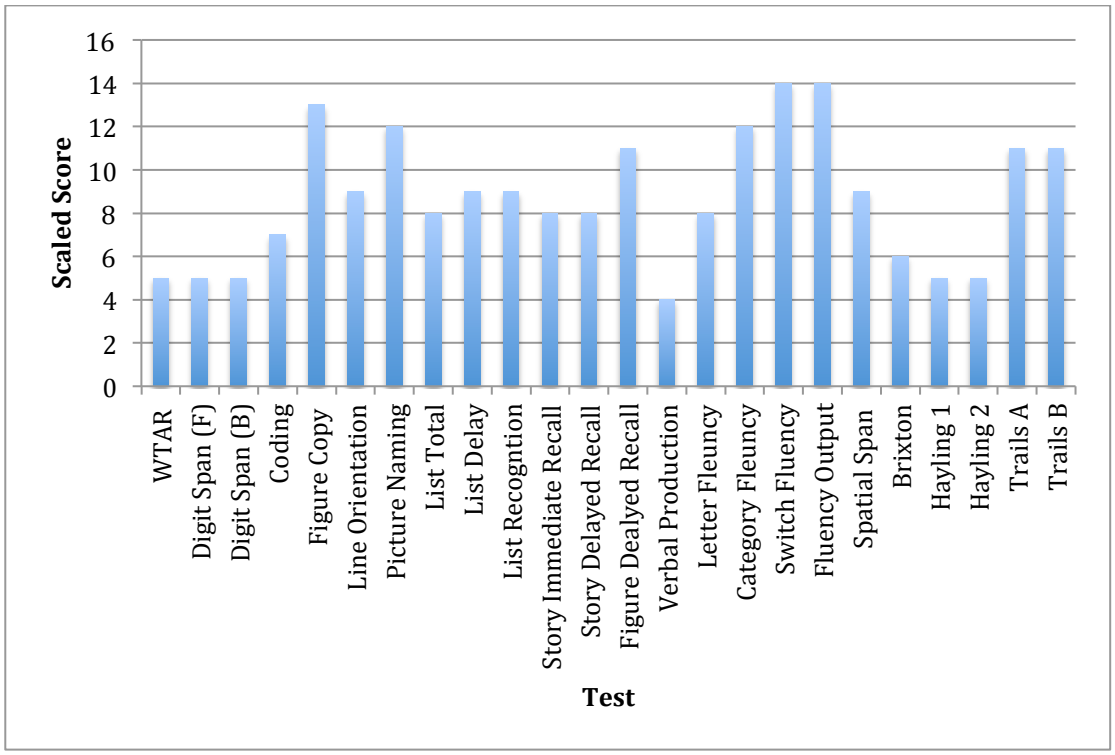

Figure 3.4-5 Histogram of Scaled scores for Participant 5

3.4.6 Participant 6

3.4.6.1 Background Information

Participant 6 is a 56-year old male of Ghanian origin. He reported attending formal schooling in Ghana between the ages of 7-16. He then trained to be a teacher, and taught primary school children for 15 years. He immigrated to England at the age of 44. He had a stroke in the same year, and was diagnosed with HIV in 2006. He also has a history of toxoplasmosis. His CD4 count is 680 and his viral load <40 (undetectable).

3.4.6.2 Primary Task Scores

Primary task scores for Participant 6 are shown in Figure 3.4-6.

Participant 6 had a WTAR score suggesting *average* premorbid ability. Verbal and visuo-spatial attention test performances were in line with this (digit span and spatial span subtests).

Performances on tests involving motor function, attention and psychomotor speed were impaired across the profile (coding, Trials A & B). However this participant's score on the figure copy subtest, which only has a motor component and is not performed under time pressures like the previous three subtests, was intact.

Visuo-spatial perception also appeared intact (line orientation), alongside visuo-spatial memory (figure delayed recall subtest).

In terms of verbal memory, list learning was *impaired* though recall was stronger suggesting that although the capacity for learning information may be impaired, what is learned is retained. However on the story learning subtest, learning trial scores fell within the *average* range, suggesting that it was easier for this participant to learn semantically connected information.

Performance was intact in the letter fluency subtest, however impaired in the category fluency subtest suggesting some difficulties with semantic retrieval, rather than a language impairment per se. Impaired performance on the verbal switching, initiation, and inhibition subtests provided evidence of difficulties in cognitive flexibility.

3.4.6.3 Summary & Discussion of Participant 6

This participant presented with impairments in motor functioning, attention, psychomotor speed, category fluency, verbal switching, verbal initiation and inhibition.

It may be that some of the impairments are attributable to HIV, however this participant presented with a number of comorbid factors which may also have negatively impacted his performances. This participant had toxoplasmosis, and as noted above in the case of participant 3, Levine et al (2008) argue that such opportunistic infections appear to exacerbate cognitive impairments in those with HIV.

Further, this participant had a stroke at the age of 44. Patel et al (2013) note that those with HIV demonstrate a higher prevalence of vascular risk factors than the general population, and Foley et al (2010) reported poorer cognitive profiles, with cardiovascular factors and HIV negatively impacting processing speed, learning/memory, and executive functioning. Consequently, it may be the case that this participant's vascular history contributed to his performance.

Also worthy of note, this participant was born and schooled in Ghana and a number of authors have agued that neuropsychological assessments designed in the West are unsuitable for people from different cultures (e.g. Shah, Oomen, & Wuntakal, 2005).

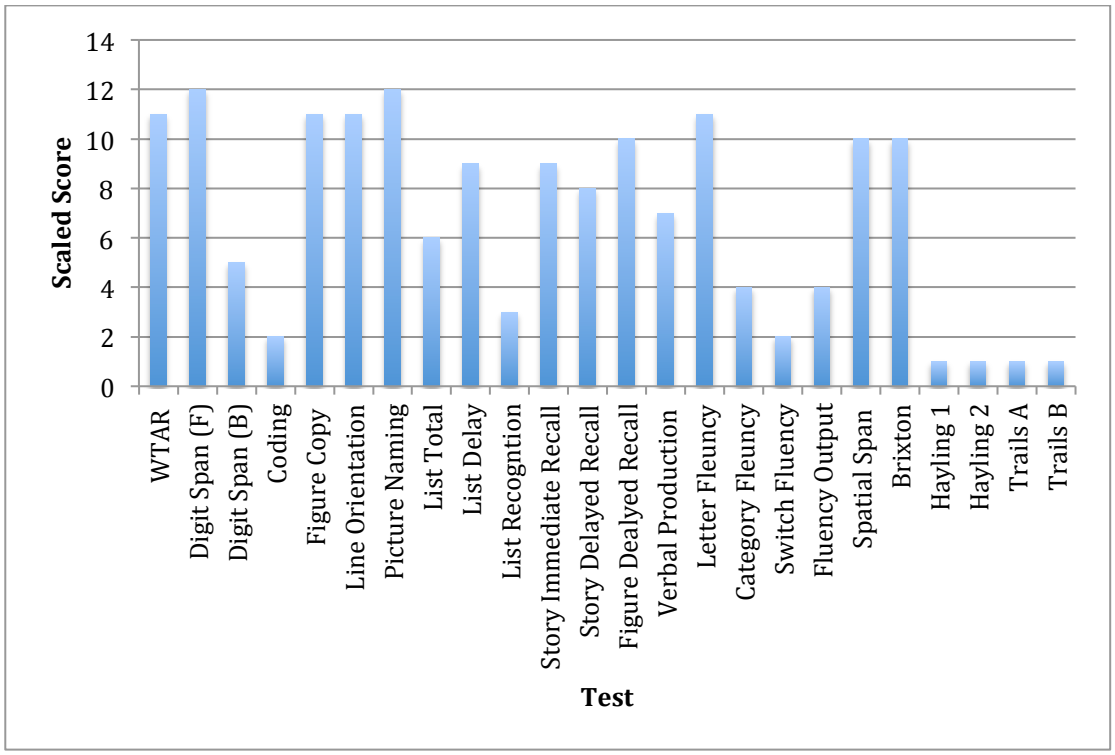

Figure 3.4-6 Histogram of Scaled scores for Participant 6

3.4.7 Participant 7

3.4.7.1 Background History

Participant 7 is a 49-year old male of Congolese origin, who was diagnosed with HIV in 1997. He had tuberculosis in 2008. His CD4 count is 75 and his viral load 916.

In the clinical interview this participant reported arriving in the UK one month before his admission to the HIV unit. He declined the opportunity to provide any further collateral information.

3.4.7.2 Primary Task Scores

Primary task scores for Participant 7 are shown in Figure 3.4-7.

Participant 7 had a WTAR score suggesting *impaired* premorbid ability. Performances in line with this were evident throughout the assessment, with impairments detected in attention and information processing, language, and verbal functions (learning, recall, initiation, inhibition, and cognitive flexibility).

However this participant had relatively strong performances in subtests involving visuo-spatial skills (including figure copy, line orientation, delayed figure recall and spatial span), indicating an area of preserved ability.

3.4.7.3 Summary & Discussion of Participant 7

This participant's profile indicated impairment in many domains, however visuo-spatial skills were in tact. It is likely that HIV and toxoplasmosis played a role in the results, alongside issues relating to the suitability of the assessment battery for a person from a different cultural background, however it is difficult to fully contextualise this participant's profile given the limited collateral information.

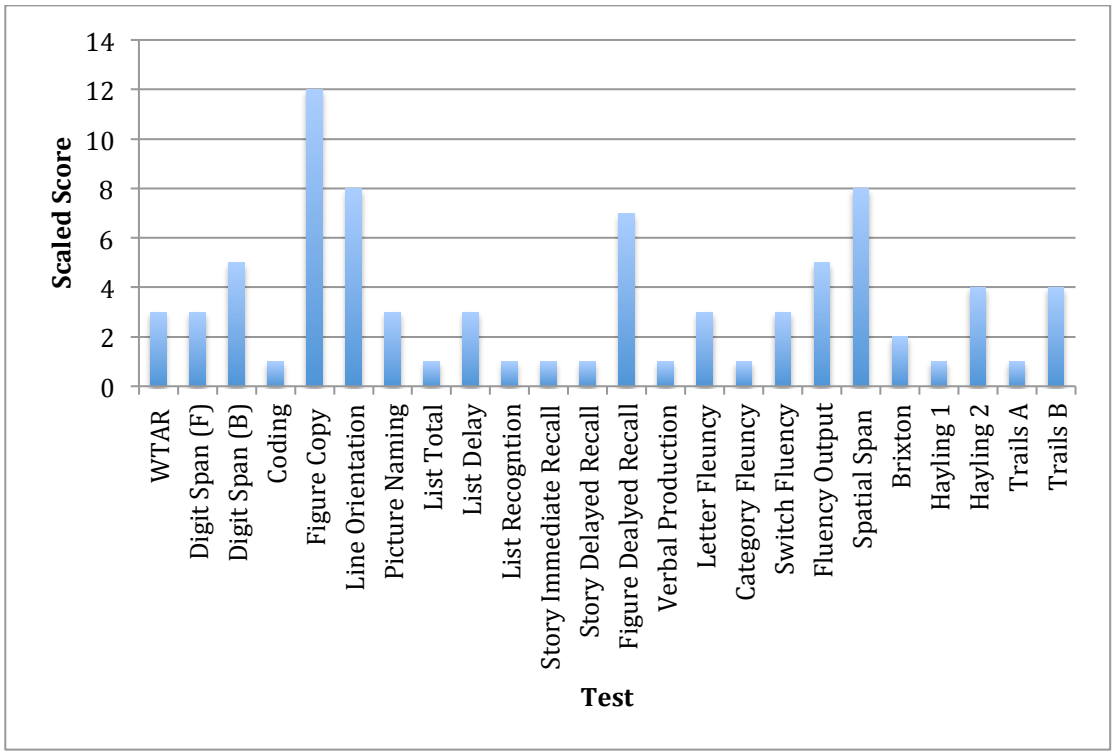

Figure 3.4-7 Histogram of Scaled scores for Participant 7

3.4.8 Participant 8

3.4.8.1 Background History

Participant 8 is a 48-year old male of Ugandan origin. He reported attending formal education until the age of 16 and then working in the family business. He arrived in the UK at the age of 46.

Participant 8 was diagnosed with HIV in 1992, aged 27. He has a history of depression and PTSD but was reportedly stable at the time of neuropsychological assessment. He also has a history of tonic-clonic seizures, and an MRI indicated 'non-specific deep white matter signal abnormality in the left parietal lobe'. His CD4 count is 241 and his viral load 1386132.

3.4.8.2 Primary Task Scores

Primary task scores for Participant 8 are shown in Figure 3.4-8.

Participant 8 had a WTAR score suggesting *average* premorbid ability. Performance in an assessment of verbal attention (digit span) was in line with this, as were performances in assessments of visuo-spatial skills (figure copy and line orientation).

However impairments in other domains were observed throughout the assessment. Language impairments were observed in tests of naming to confrontation, letter fluency, semantic fluency, verbal switching, verbal initiation and inhibition. Verbal memory functioning (registration, learning, delayed recall) was also impaired alongside visuo-spatial memory. Further, performances in tests of executive functioning highlighted impairments in rule deduction, sequencing and switching (Brixton, Trails A, Trails B, and category switching).

3.4.8.3 Summary & Discussion of Participant 8

This participant's profile indicated strengths in attention and visuo-spatial skills, though impairments in other domains were evident.

Although this participant reported receiving 12 years of formal education, and therefore would be expected to have reasonable cognitive reserve, he also presented with a number comorbid conditions, all of which may be impacting his profile. For example depression has been associated with poorer performances on effortful tasks such as those with timed components (e.g. Coding, Trails). However since the participant did not report any current difficulties with depression, and Gibbie et al (2006) argue that an improvement in neurocognitive test scores can occur in those with HIV who have been treated for their low mood, other factors may have been at play in this particular profile.

Moradi et al. (2013) reported that those in their study with comorbid PTSD and HIV performed worse on executive tests (the Wisconsin Card Sorting Test and the Tower of London Test) than controls. Further parietal lobe functioning has been implicated in language production (Lezak et al., 2004) and this participant's MRI indicated some evidence of abnormality in this area.

Further Lee and Clason (2008) highlight the impact of epilepsy on learning and memory.

In summary, this participant presented with a number of comorbid risk factors in addition to HAND which may have impacted his cognitive and executive profiles.

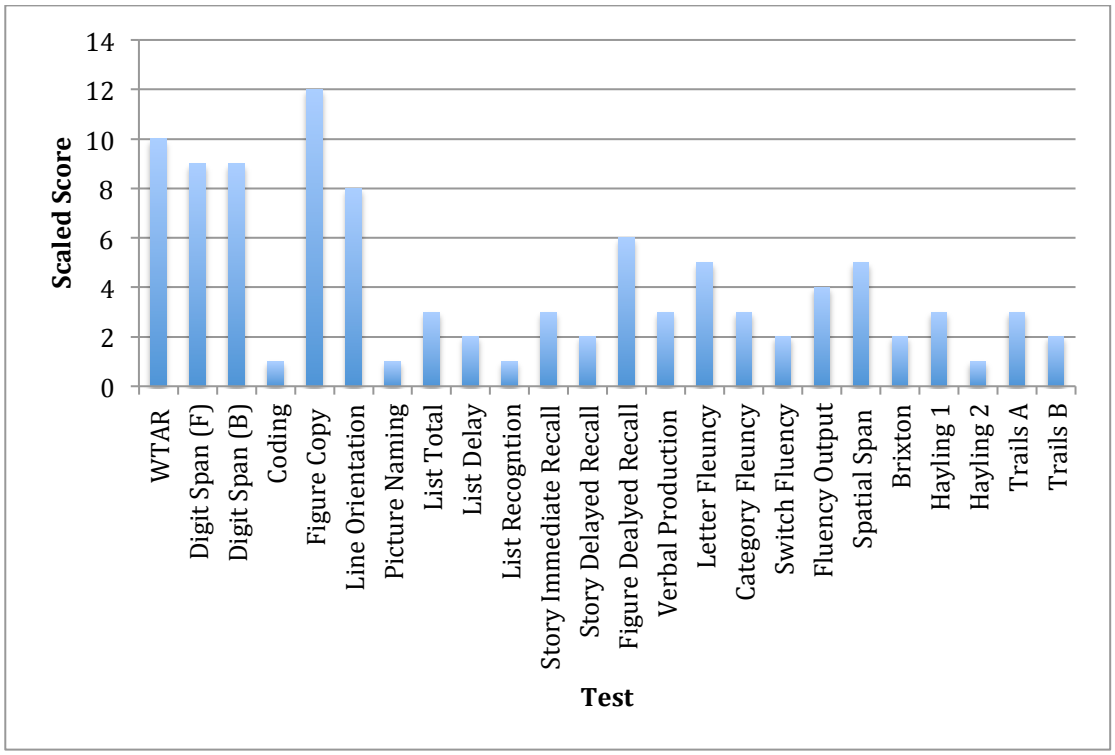

Figure 3.4-8 Histogram of Scaled scores for Participant 8

3.4.9 Participant 9

3.4.9.1 Background History

Participant 9 is a 54-year old female of Zimbabwean origin, who reported attending fulltime education from the age of 7 for four years. She worked as an insurance clerk until she moved to England at the age of 39. She then became a professional carer.

Participant 9 was diagnosed with HIV three months prior to admission. Her CD4 count is 2 and her viral load 100 million.

3.4.9.2 Primary Task Scores

Primary task scores for Participant 9 are shown in Figure 3.4-9.

Participant 9 had a WTAR score suggesting *below normal* premorbid ability. Performances in verbal and visuo-spatial assessments of attention (digit span and spatial span subtests) were in line with this. Performance on a test of attention involving motor skills and information processing speed was within the *impaired* range.

This participant gave her strongest performances in tests of visuo-spatial perception (figure copy, line orientation, and picture naming subtests). However on an assessment of visuo-spatial memory (figure delayed recall) she scored within the *below normal* range.

In terms of verbal abilities this participant appeared to demonstrate impairment in new learning (list learning and story learning subtests), recall (list delay and story delay subtests), and registration of verbal information (list recognition subtest).

On assessments of executive function, this participant scored within the *impaired* range on tests of rule deduction (Brixton), verbal initiation and inhibition (Hayling 1 and 2), word generation/fluency, and verbal switching. She scored within the *below*

normal range on a nonverbal assessment of switching and sequencing (Trails B). This is an anomaly given her weaker performance in Trails A and is likely to reflect further evidence of impaired processing ability, though with some degree of preserved cognitive flexibility.

3.4.9.3 Discussion & Summary of Participant 9

This participant's relative strengths were in visuo-spatial skills. However her performances were impaired in all other domains. Although some of these performances were in line with what would be expected given estimates of her premorbid functioning level, it may also be the case that this estimate is of limited clinical utility since she received only 4 years of formal education. It is therefore likely that disease severity (as indicated by her low CD4 count and high viral load) impacted her performances in this assessment (Heaton et al., 2011) alongside factors such as limited cognitive reserve.

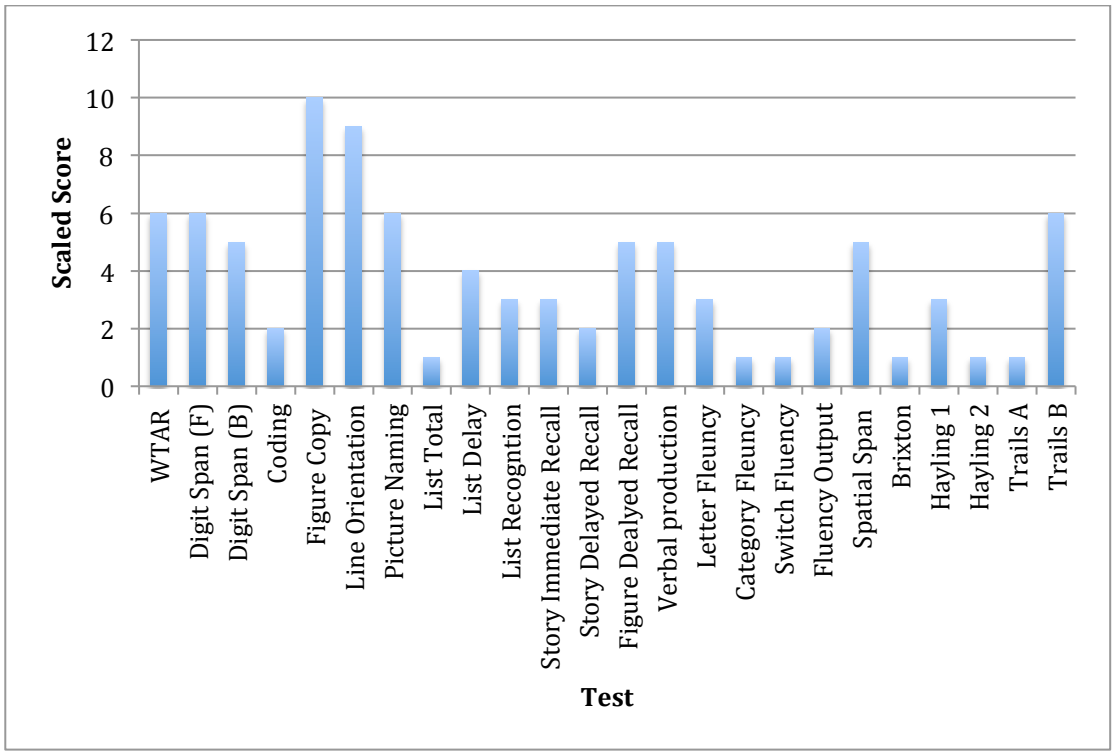

Figure 3.4-9 Histogram of Scaled scores for Participant 9

3.4.10 Participant 10

3.4.10.1 Background Information

Participant 10 is a 47-year old female of Ugandan origin who immigrated to the UK at the age of 26. She declined the opportunity to provide any further collateral information, noting only that she worked as a teacher.

Participant 10 was diagnosed with HIV two months prior to admission. Her CD4 count is 77 and her viral load 80,000. There was no evidence of opportunistic infections or other illnesses in the medical notes.

3.4.10.2 Primary Task Scores

Primary task scores for Participant 10 are shown in Figure 3.4-10.

Participant 10 had a WTAR score suggesting *average* cognitive ability. Her performances on tests of attention and information processing fell within the *impaired* range.

Performances on assessments of visuo-spatial perception (line orientation and picture naming subtests) were within the *high average* range. Her performance on the figure copy task fell within the *below normal* range, and this may have been the result of impaired motor functioning, as demonstrated by her poor performances on other tests with psychomotor components (coding, Trails A, Trails B).

Assessments of immediate memory and delayed recall fell within the *below normal* range, though memory for a story was stronger than memory for a list of words.

This participant scored within the *impaired* range on tests of verbal fluency/word generation (letter fluency and category fluency subtests), rule deduction (Brixton), verbal initiation and inhibition, and visual sequencing and switching. Her

performance on a test of spatial attention was her strongest in the executive function tests.

3.4.10.3 Summary & Discussion of Participant 10

This participant's profile demonstrated relative strengths in visuo-spatial perception and spatial attention. Although there was also some evidence of delayed memory ability, clear impairments were observed in all other cognitive domains and executive function skills. Interestingly, this participant performed relatively better on digit span backwards in comparison to digit span forwards. It may be the case that this is the result of impaired attentional skills, whilst also suggesting that working memory is relatively stronger in comparison to other skills.

In the absence of other collateral information, it is likely that this participants profile is reflective of disease severity, and therefore of HAND.

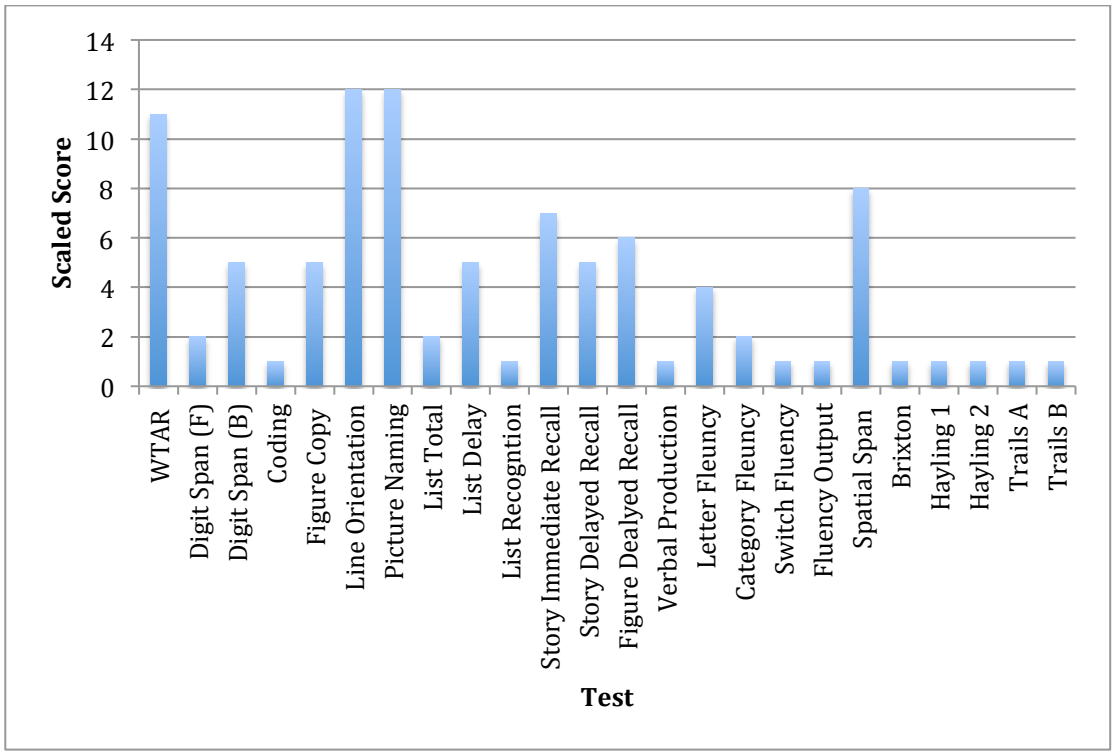

Figure 3.4-10 Histogram of Scaled scores for Participant 10

3.4.11 Participant 11

3.4.11.1 Background Information

Participant 11 is a 67-year old male of British origin. He was educated to degree level in Scotland before pursuing a career in the air force, and then later a career in the construction industry abroad.

Participant 11 returned to England one month before his admission to the HIV unit and received his diagnosis following a fall.

His CD4 count is 180 and his viral load 140. There was no evidence of opportunistic infections or other illnesses in the medical notes.

3.4.11.2 Primary Task Scores

Primary task scores for Participant 11 are shown in Figure 3.4-11.

Participant 11 had a WTAR score suggesting *superior* premorbid ability. His verbal attention skills appeared to be inline with this, however on an assessment of processing speed he scored within the *impaired* range. This finding may have been accounted for by the participant reporting a sprained wrist, however on other 'pen and paper' tests with time pressures (Trails A and B) his performances were within the *average* ranges.

Visuo-spatial perception and visuo-spatial memory appeared to be intact. New learning of verbal information and delayed verbal recall was also intact, with story learning and delayed story recall being particularly strong (*superior* range).

Performances on the executive function battery were more variable; verbal fluency (both letter and category), verbal and visual switching, and visual sequencing were intact. Performance on a test of spatial attention (spatial span) was particularly

strong. However performances on tests of rule deduction (Brixton), and verbal initiation and inhibition fell within the *impaired* ranges.

3.4.11.3 Summary & Discussion of Participant 11

Participant 11 presented with a number of strengths across his profile. It is difficult to know exactly when he acquired HIV, however it may be inferred from his profile that any resultant cognitive impairments are yet to emerge. It may also be the case that he has relatively strong cognitive reserve as indicated by his educational and occupational history, and this may have played a role in the strong performances he gave.

However this participant's score on coding and verbal production (assessments of processing speed) were not in keeping with the rest of his cognitive profile. Further, in terms of his executive skill profile, his performances on the Brixton and Hayling tests were lower than expected. Since Participant 11 tended to perform relatively lower on tasks involving speed or those with timed-components, this may have accounted for his performances in the Hayling tests, were processing speed is a key component.

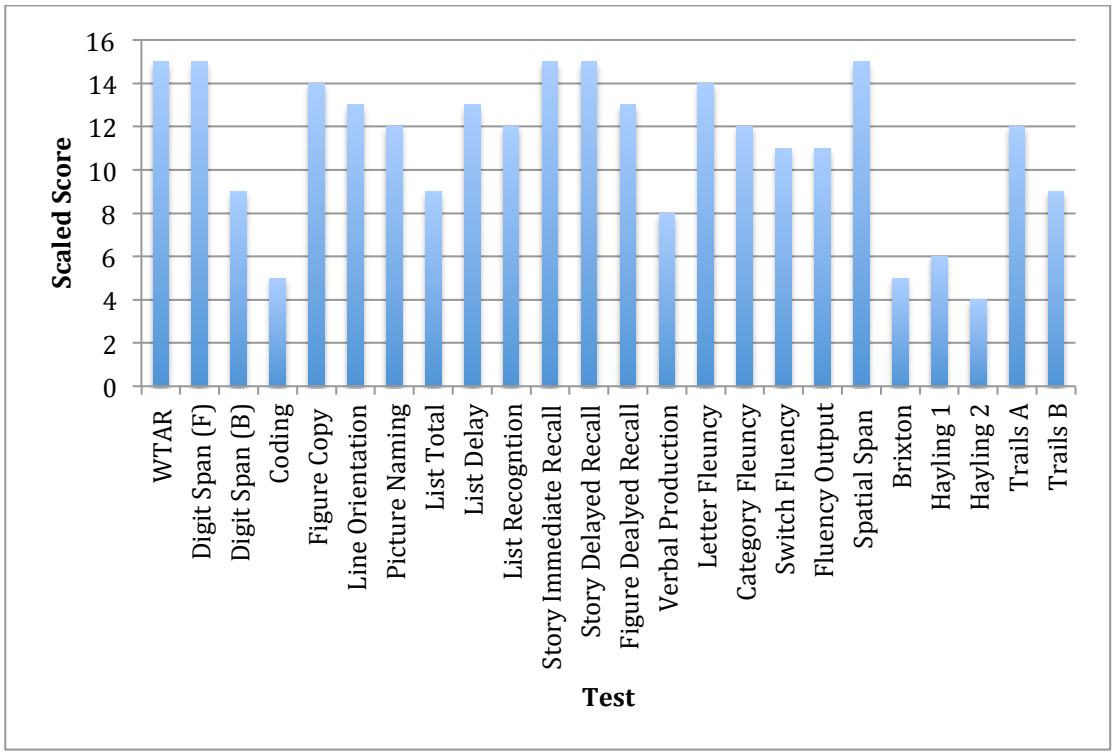

Figure 3.4-11 Histogram of Scaled Scores for participant 11

3.4.12 Participant 12

3.4.12.1 Background Information

Participant 12 is a 26-year old female of Kenyan origin. She moved to England at the age of 16 and recently enrolled in a nursing course.

Participant 12 was diagnosed with HIV and pneumocystis pneumonia in 2004. In 2010 she was diagnosed with toxoplasmosis and tuberculosis. She has a diagnosis of delirium with psychotic features although was stable at the time of neuropsychological assessment. Her CD4 count is 4 and her viral load 1.1 million

3.4.12.2 Primary Task Scores

Primary task scores for Participant 12 are shown in Figure 3.4-12.

Participant 12 had a WTAR score suggesting *very impaired* premorbid ability. Her scores on tests of attention, working memory, and information processing were in line with this.

Her performances on tests of visuo-spatial perception and visuo-spatial memory fell within the *average* ranges, thus indicating an area of preserved ability.

This participant was impaired in tests assessing list learning; however her scores on the registration task (list recognition) fell within the *high average* range suggesting that whilst registration of new information is intact, processes involved in learning and memorising were impaired. Her performances on story learning and recall fell within the *average* range, suggesting that this participant was able to utilise previously learned semantic rules to support learning and memory (a strategy she may not have been able to utilise when learning a list of unconnected words).

In terms of executive functioning, letter fluency was intact suggesting preserved verbal executive skills. However category fluency fell in the *below normal* range perhaps suggesting an impairment in semantic memory, or in contrast to her

stronger performance on story recall where information was coherently presented to her, an impairment in retrieval strategies. However her verbal switching ability was intact.

Finally, performances in spatial attention, rule deduction, verbal initiation, verbal inhibition, visual sequencing and visual switching all fell within the *below normal* and *impaired* ranges suggesting poor executive flexibility and functioning.

3.4.12.3 Summary & Discussion of Participant 12

Participant 12 presented with strengths in visuo-spatial skills, registration, and story learning. However impairments were observed in attention and list learning. In terms of the executive function profile, this participant presented with strengths in letter fluency and switching but poorer performances on other measures.

There are a number of factors that may have impacted this participant's performances. Low CD4 counts and high viral load may have impacted the result (Heaton et al., 2011), and her performances on tests of processing speed may have been attributable in part to the impact of toxoplasmosis (Levine et al., 2008). Further, executive functioning is thought to be impacted by psychotic presentations (e.g. Barnett & Fletcher, 2008)

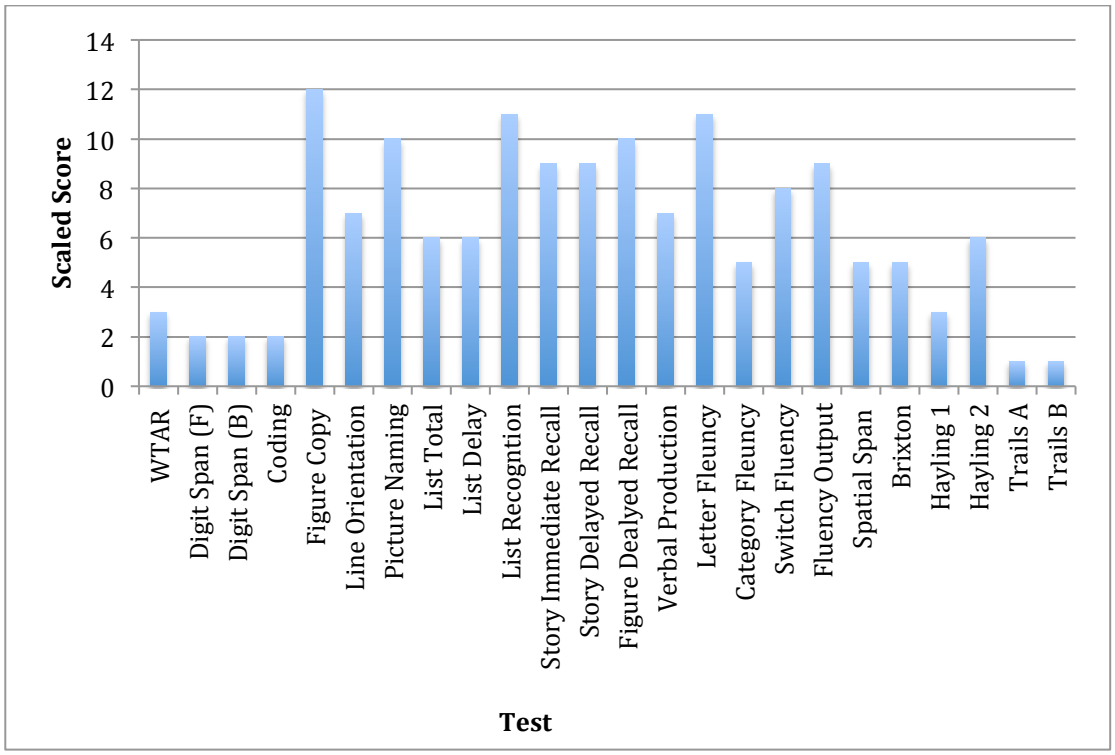

Figure 3.4-12 Histogram of Scaled scores for participant 12

3.4.13 Participant 13

3.4.13.1 Background Information

Participant 13 is a 53-year old female of St Lucian origin. She reported attending school infrequently until she moved to England at the age of 16, and thereafter worked as a machinist for four years.

She was diagnosed with HIV at the age of 32. She has a history of anxiety and depression secondary to bereavement, though was stable at the time of her neuropsychological assessment. Her CD4 count is 40 and her viral load 100,000

3.4.13.2 Primary Task Scores

Primary task scores for Participant 13 are shown in Figure 3.4-13.

This participant declined an assessment of premorbid functioning (WTAR).
She scored within the *impaired* range for attention, working memory, and information processing speed.

Visuo-spatial perception was also within the *impaired* range alongside visuo-spatial memory. Further, immediate memory and delayed recall of verbal information again fell within the *impaired* range, though delayed list recall was slightly stronger.

In terms of executive functioning, this participant's performance again fell within the *impaired* range; exceptions to this are her scores on switching accuracy (switching output) and Brixton (rule deduction), both of which fell within the *low average* range.

3.4.13.3 Summary & Discussion of Participant 13

Since participant 13 declined the opportunity to provide an estimate of her premorbid ability, comparisons to current functioning were not possible. Another issue that impacted formulation is that this participant reported attending school infrequently and therefore comparisons of her performance to normative data may not be

clinically useful. It may also be the case that her educational status limited her cognitive reserve. Further, she presented with high viral load and the impact of this on cognitive processes cannot be ignored.

In support of these arguments, impairments were observed in many domains across this assessment.

Interestingly, this participant had an area of preserved ability in the language test (picture naming). Further her performance on the Brixton test – a test of rule deduction which was found to be one of the most challenging for many participants in this study – was also one of her strongest. It is difficult to explain this anomaly since other performances of executive functioning fell in lower ranges.

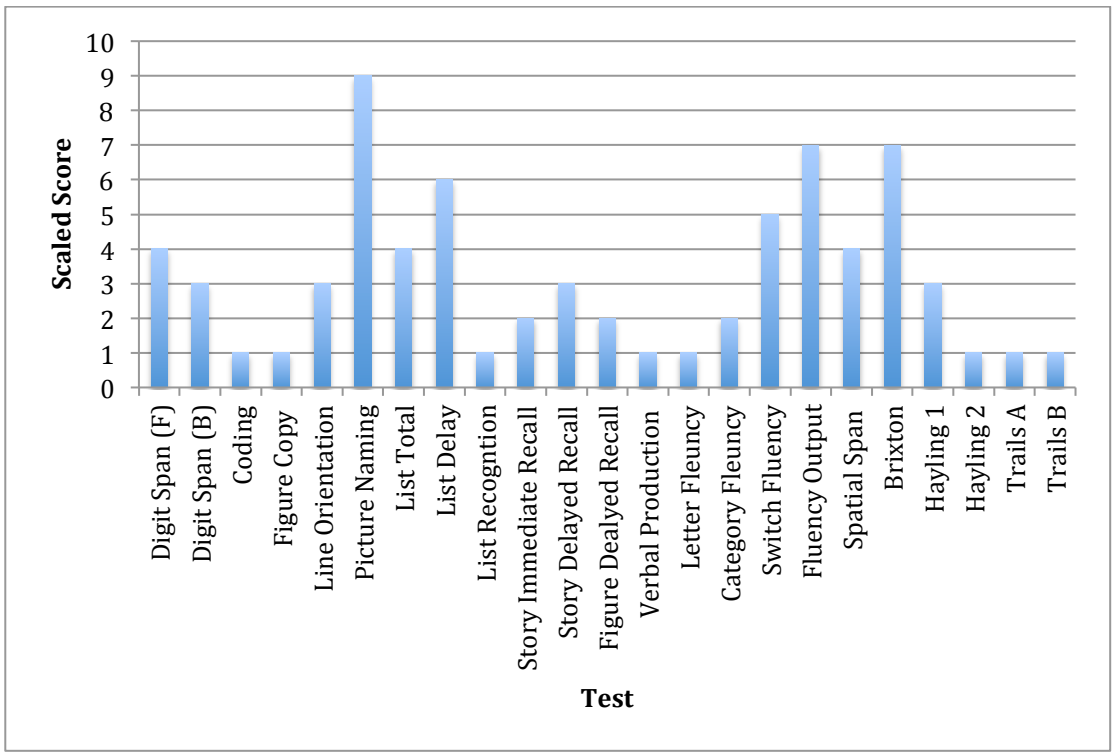

Figure 3.4-13 Histogram of Scaled scores for participant 13

3.4.14 Participant 14

3.4.14.1 Background Information

Participant 14 is a 50-year old Black British male. He reported attending school until the age of 14.

He was diagnosed with HIV at the age of 42 and has a history of frequent hyperglycaemic attacks. His CD4 count is 991 and his viral load <40 (undetectable).

3.4.14.2 Primary Task Scores

Primary task scores for Participant 14 are shown in Figure 3.4-14.

Participant 14 had a WTAR score suggesting *average* premorbid ability. This was inline with his performance on verbal and visuo-spatial tests of attention (digit and spatial span subtests). However on an assessment of information processing speed he scored within the *impaired* range indicating psychomotor slowing.

Performances in tests of visuo-spatial perception and visuo-spatial memory were within the *high average* and *superior* ranges indicating an area of cognitive strength.

List learning and delayed list recall scores fell within the *below normal* range however story learning and story recall scores fell in the *average* and *high average* ranges, perhaps highlighting stronger skills for learning semantic information.

In terms of performances on assessments of executive function, this participant scored within the *superior* range on letter fluency indicating strong language skills. However he scored within the *below normal* range in the semantic fluency subtest, perhaps indicating poor strategies for the retrieval of semantic information.

Performance on a test of rule deduction (Brixton) was within the *impaired* range. Verbal initiation and inhibition scores (Hayling A and B) were within the *below*

normal range, perhaps providing evidence of poor executive control strategies. Trails A fell within the *average* range however Trials B fell in the *high average* range indicating good sequencing and visuo-spatial switching skills.

3.4.14.3 Summary & Discussion of Participant 14

Participant 14 presented with impaired performances in coding and recognition memory, though list learning and list recall were also lower than expected. In terms of his executive function profile, Participant 14 presented with weaker performances in the Brixton and Hayling tests. McCrimmon, Ryan and Frier (2012) argue that cognitive profiles impacted by diabetes show evidence of impaired psychomotor slowing and executive functioning. However in this participant's case it may be that processing speed was more impaired than cognitive flexibility, since his score in Trails B was higher than scores obtained in the Trails A and coding tests.

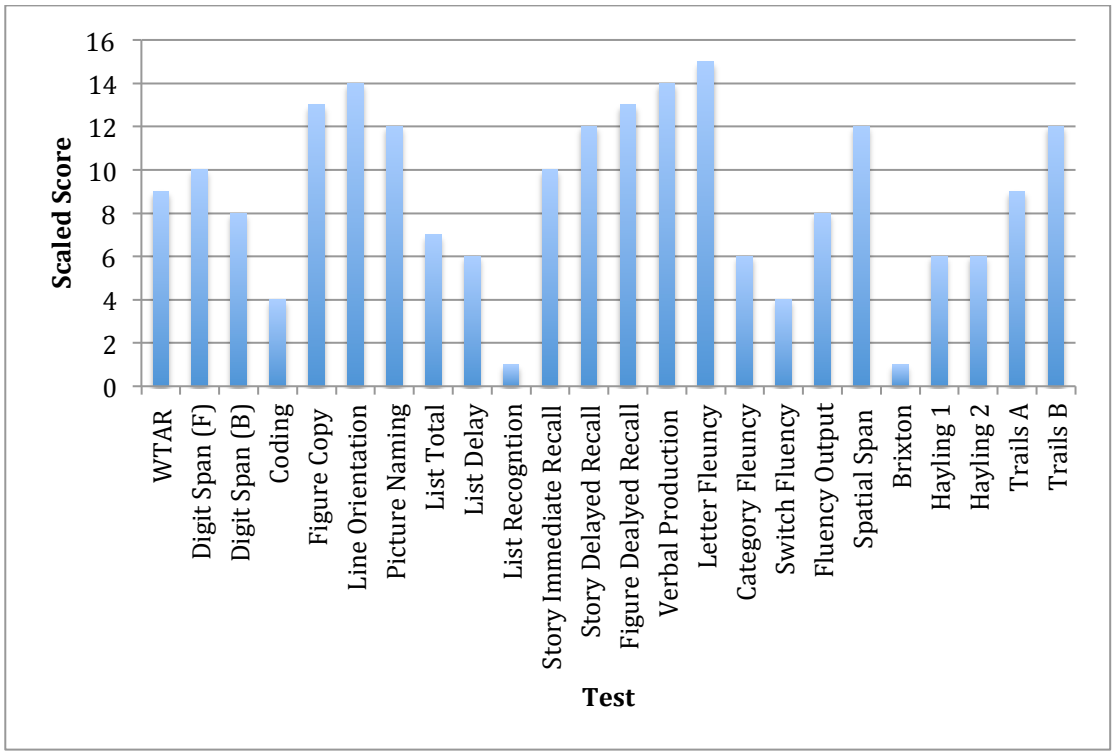

Figure 3.4-14 Histogram of Scaled scores for participant 14

3.4.15 Participant 15

3.4.15.1 Background Information

Participant 15 is a 72-year old British male, who reports attending full-time education until the age of 17.

Participant 15 diagnosed with HIV at the age of 54. He has a history of frequent UTIs and is also diabetic. His CD4 count is 359 and his viral load 728.

3.4.15.2 Primary Task Scores

Primary task scores for Participant 15 are shown in Figure 3.4-15.

Participant 15 had a WTAR score suggesting *superior* premorbid ability.

This participant's attention and information processing scores were lower than expected given his premorbid ability.

On a line orientation test this participant performed within the *below normal* range however he scored within the *superior* range on a figure copy test, perhaps highlighting a weakness in fine perception ability.

Immediate memory and recall were intact and an area of strength for this participant.

In terms of executive function skills, letter fluency, semantic fluency, and verbal switching were all intact, indicating strong word generation and strategy formation skills. In comparison to verbal attention (digit span subtest), spatial span was also intact. However performances on assessments of verbal initiation, verbal inhibition, and spatial rule deduction were lower than expected; this may indicate impairments in executive retrieval and perseverance.

3.4.15.3 Summary & Discussion of Participant 15

Participant 15 presented with lower then expected performances in attention, working memory, processing speed, and visuo-spatial perception. His performance on Digit Span A (a test of attention) was weaker than his performance on Digit Span B (a test of working memory). This performance may perhaps suggest that attentional processes are more severely impaired and may be the combined result of his comorbid conditions, as discussed below.

His executive function profile presented with impaired performances in the Hayling, Brixton and Trails tests.

This participant presented with a number of factors that may have impacted his cognitive and executive profile including mild/moderate disease severity (Heaton et al., 2011), and diabetes (McCrimmon et al., 2012). However, this participant was also the eldest participant assessed for this study, and Patel et al (2013) have argued that older participants with HIV are more vulnerable to cognitive impairment. However, this participant's profile only demonstrated selected impairments; it may be that his premorbid ability i.e. his cognitive reserve, is curbing the impact of disease processes.

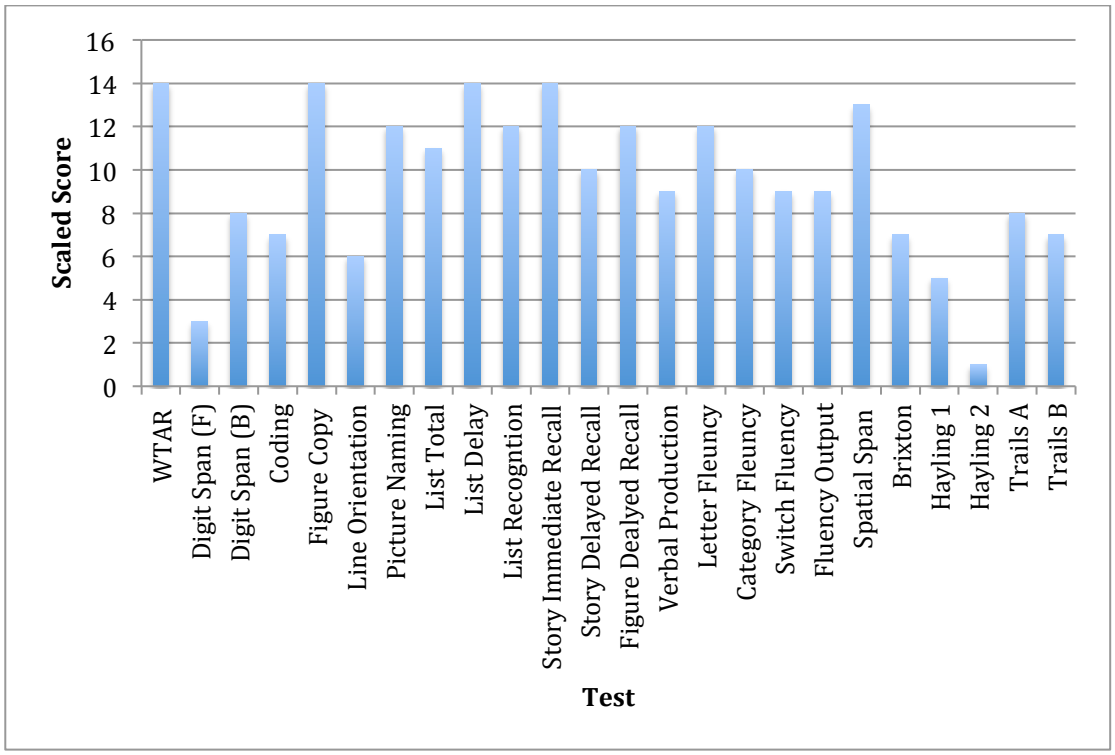

Figure 3.4-15 Histogram of Scaled scores for participant 15

3.4.16 Participant 16

3.4.16.1 Background Information

Participant 16 is a 57-year old American male, who reported attended fulltime education until the age of 22. He then developed a career in IT.

Participant 16 was diagnosed with HIV at the age of 33. He suffers from chronic inflammatory demyelinising poly-neuropathy. His CD4 count is 300 and his viral load <40 (undetectable). There was no evidence of opportunistic infections or other illnesses in the medical notes.

3.4.16.2 Primary Task Scores

Primary task scores for Participant 16 are shown in Figure 3.4-16.

Participant 16 had a WTAR score suggesting *superior* premorbid ability. His performances throughout the assessment were principally in line with this and he demonstrated strengths in visuo-spatial perception, visuo-spatial memory, language, immediate memory, delayed recall, and attention (although verbal attention was much stronger than spatial attention).

Performances on executive function tests were also similarly strong and included strengths in verbal fluency, rule deduction and visual switching. However he scored lower than expected in tests of verbal initiation and verbal inhibition (Hayling 1 and 2), perhaps indicating a weakness in verbal initiation and perseveration.

3.4.16.3 Summary & Discussion of Participant 16

Participant 16 presented with *superior* premorbid ability. His performances in the assessment, though not always in this range, still principally scored at acceptable levels, providing little evidence of impairment. However it could be argued that his performances fell slightly lower than would be expected given *his* premorbid ability (rather than in comparison to population norms). Further, his performances on the

Hayling tests were not in keeping with his profile, indicating some evidence of executive difficulty. His performance in Trails B was stronger than his performances in Trails A, and as mentioned in discussions of other profiles with similar patterns, this may be the result of emerging evidence of processing speed difficulties.

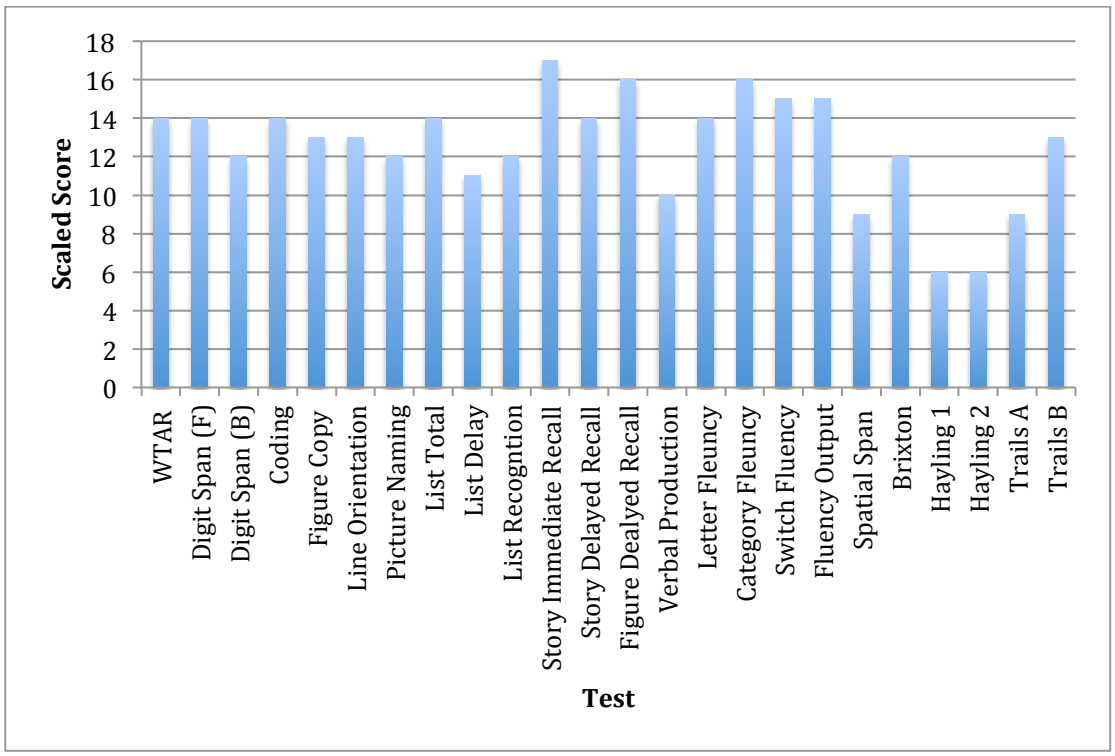

Figure 3.4-16 Histogram of Scaled scores for participant 16

3.4.17 Summary of Individual Case Analyses

Exploration of individual case profiles highlighted the heterogeneity of the sample in terms of age, gender, ethnicity, culture, education, and premorbid ability. All of these factors can contribute to the outcome of neuropsychological assessments.

In addition to demographics and HAND, the impact of risk factors on cognition were highlighted and discussed within the context of individual profiles. The discussion indicates that in the presence of comorbidities, it is difficult to locate impairment only attributable to HAND, since the evidence base strongly suggests that these risk factors impact domains also affected by HIV.

However group level analyses allow for exploration of commonalities, and these include the finding that the Hayling tests were the most difficult to complete for the majority of participants. Further, those with English as a second language, or who did not receive their education in the West appeared to perform consistently poorer than those who were schooled in American and England.

Some of the findings were not in keeping with what would have been expected. For example Participant 1 did not display cognitive impairments in line with what would be expected of a person who acquired HIV through vertical transmission, and who therefore underwent neurodevelopmental stages in the presence of HIV and ART. The possible role of cognitive reserve in curbing the effects of the virus was highlighted in this case, and in the case of others where disease state and risk factors appeared to impacting cognitive processes to a lesser degree than would be expected.

Other anomalies observed at the individual case level included stronger performances on digit span forwards in comparison to digit span backward, and stronger performances on Trails B in comparison to Trails A. These results are likely

to reflect impairments in attention and processing speed, and have been discussed within the context of individual case profiles where relevant.

It is also worthy of note that four participants declined the request to provide collateral information and the reasons for this occurrence within this context may be multifactorial; Reid and Walker (2003) highlight that secrecy, mistrust and shame are central features of the lived experience of HIV. Further, and in particular to the participants of this study, some reported believing that providing this information to health professionals may impact their receipt of social benefits and/or result in their being deported back to countries they no longer wished to live in.

4. DISCUSSION

4.1 Summary of Results

This study aimed to explore the cognitive functioning of people with HIV associated neurocognitive decline, with a particular focus on exploring whether a 'profile' of executive function deficits could be identified in this group.

4.1.1 Participant Characteristics

Reviews of individual profiles (neuropsychological test scores and background information) suggested that fourteen participants in the study had mild neurocognitive disorder (MND) and two had asymptomatic neurocognitive impairment (ANI), as assessed according to diagnostic criteria set by Antinori et al. (2007). These presentations were confirmed by multidisciplinary team consensus of the service providing assessment and treatment. This is a useful property of the sample since Blanch et al. (2012) report that with sensitive measures, HAND is detectable even at the earliest stages of disease, thus providing some evidence to suggest that the measures used in this study were sufficiently sensitive.

As noted in the results section, CD4 counts were positively correlated, and viral load negatively correlated, with verbal production and spatial span. Viral load was found to be negatively correlated with digit span forward. These results provide confirmatory evidence that psychomotor speed and attention are impacted by disease status.

Viral load was also found to be negatively correlated with the WTAR, digit span forwards, verbal production, spatial span, and letter fluency ($r = -.482$).
However no other correlations were found between these participant characteristics and test scores. It may be the case that other correlations were not found due to the size of the sample, however Tozzi et al. (2007) reported similar findings; their study concluded that test performance was most strongly predicted by severity of cognitive

impairment at the point of cART initiation. It was not possible to collect data on cART initiation in this sample, and it may be the case that this variable influenced the results of the study. Researchers may wish to consider this factor when formulating their investigations in the future.

The group level WTAR score indicated that the sample was of typical premorbid ability, as found in the general population. This is a useful finding since it allows for (cautious) inferences to be made about how HIV may impact different cognitive functions.

Both years of education and premorbid ability levels were found to be associated with stronger test performances. This finding is in keeping with the current literature base (e.g. Farinpour, et al., 2003; Hayman-Abello, 2007; Manly et al., 2011). However a strength of the current study is that both years of education and reading ability were taken into account in multivariate analyses. It may be the case that these two variables are linked to exposure to situations that support stronger test performances e.g. familiarity with words, puzzles, language, manipulation of information, etc. Other factors that may have played a part in the results (and are perhaps linked more to education than premorbid ability) include 'test-wiseness', and engagement with the testing processes.

More generally, it may also be the case that the cognitive reserve hypothesis can be drawn upon here. The findings of this study were broadly in keeping with this hypothesis, and the conclusions of Pereda et al (2000), in that those with higher WTAR scores and levels of education tended to show lower levels of decline. A further finding of the current study is that those who were schooled in different countries generally performed poorer than those who were schooled in the West. However they also tended to have fewer years in formal education and this may provide some explanation for their lower scores, although cultural factors may also have played a part.

4.1.2 General Cognitive Function

Heaton et al. (2011) and Schouten et al. (2011) outlined differences in subcortical and cortical impairments associated with HAND, with the former being linked to impairments in processing speed and motor skills, and the latter to impairments in executive functioning and new learning. The discussion below will highlight that both cortical and subcortical features were evident in this sample, and may be linked to the documented widening of the cognitive profile associated with HIV infection (e.g. Cysique, Maruff & Brew, 2004).

Please see appendix F for subjective range descriptions (based on Slick, 2006). As mentioned in section 2.4, standardized scaled scores were used for all statistical analyses, thus allowing for comparisons to be made across the different batteries/measures used in the study.

4.1.2.1 Attention and Processing Speed

This sample of participants demonstrated a significant impairment in the coding subtest – a measure of attention and processing speed. Previous studies have also indicated impairment in these domains (e.g. Rosca et al., 2011). However tests of simple attention (digit span forward and spatial span) fell within the *low average* range perhaps indicating that processing speed and motor function are more affected than simple attention in this sample. Again this is in keeping with previous research suggesting that simple attention deficits often present in the latter stages of disease (e.g. Grant, 2008; Heaton et al., 1995).

Trails A and verbal production scores fell within the *below normal* range. These findings again provided support for the impact of HAND on processing speed. Baldewicz et al. (2004) note that tests of processing speed have good sensitivity to HAND.

These results could have significant implications since Levine et al. (2008) report that processing speed impairments are linked to difficulties in completing activities of

daily living. Further, Harding and Hinkin (2002) highlight the importance of processing speed and attention in supporting higher order processes.

4.1.2.2 Learning & Memory

In terms of memory, list learning mean scores fell within the *below normal* range perhaps indicating poor strategic encoding techniques, and were therefore in line with previous studies in this area (Delis et al., 1995; Murji et al., 2003; Peavy et al., 1994). However slightly stronger performances on the list recall test suggested that what is learned is retained.

Performance in story memory tasks fell within the *low average* range. The slightly better performance on story tasks in comparison to list tasks may be attributable to the semantic processes supporting memory for stories, whilst list learning is more dependent on attentional processes.

Grant (2008) and Woods et al. (2009) note that both story learning and list learning are sensitive to HAND, however this study found that participants performed slightly better on story learning than list learning, suggesting divergent sensitivity between the two tests; list learning appeared to be more sensitive and may be more clinically useful for those in the early stages of disease, while story-learning may be a more appropriate for those in latter stages. However since the tests measure slightly different functions, they may be most helpfully employed in combination.

4.1.2.3 Visuo-Spatial Skills

Visuo-spatial skills (as assessed by the figure copy, figure delayed recall, and line orientation tests) were intact, and therefore in keeping with the current literature base which suggests that the occipital and parietal lobes are not usually affected in the earlier stages of disease (ANI and MND stages; e.g. Heaton et al., 1995).

4.1.2.4 Language

Additionally, language skills, as assessed by the picture-naming subtest were unimpaired indicating that simple expression deficits were not evident in this sample. Woods et al. (2009) report similar conclusions in their summary of the literature base.

In summary, group level scores for the general cognitive battery were in keeping with the wider consensus in the current literature base. This is a useful finding in that it suggests, in spite of its relatively small size, the sample obtained may be considered typical of the wider HAND population in question.

4.1.3 Executive Function Battery Analysis

Working memory as assessed by digit span backwards was within the *below normal* range and in keeping with the current evidence base. For example Stout et al. (1995) found working memory deficits even in those with ANI. Notably however the two participants with ANI in this sample did not demonstrate impairments in this function.

Letter fluency scores fell within the *average* range whilst category fluency scores fell within the *low average* range. These findings are not in keeping with the evidence base where impairments in frontostriatal regions (and therefore letter fluency) are documented early in disease, whilst impairments in temporal regions (associated with semantic memory storage) are thought to present only in latter stages of the disease (e.g. Grant, 2008; Rippeth et al., 2004). Closer inspection of individual case profiles suggests that participants either in the early stages of HAND, or who showed low levels of impairment (participants 1, 11, 15, 16) scored particularly highly on the letter fluency test and this may have affected the results. Further of the remaining twelve participants – all of whom showed clear evidence indicative of HAND – nine scored comparably or higher on letter fluency than category fluency, leaving only three profiles showing the reverse pattern. It is difficult to interpret this finding, however a meta-analysis conducted by Iudicello et al., (2007) found that

both category and letter fluency deficits were comparable once important variables have been controlled for (e.g. age and stage of disease). The authors conclude that this finding is likely the result of general damage to frontal systems.

Verbal initiation and inhibition tasks (Hayling 1 & 2) yielded the lowest scores in the battery, indicating marked difficulties with verbal executive functions. This finding was consistent both at group level analysis and also in the individual case profiles; a number of participants who generally performed in the higher ranges scored within the *below normal* and *impaired* ranges for these tests (e.g. participants 1, 5, 11, 15, 16). This finding is in keeping with research suggesting that language difficulties associated with HAND, especially in the earlier stages, are more likely to be linked to the effectiveness of executive control (Murji et al., 2003). However scores on Hayling 1 (verbal initiation) were also impaired so deficits in inhibition may only account for some of this picture; poor initiation scores are likely to have been impacted by slow verbal output speed.

Interestingly, studies using different tests have also reported difficulties in response inhibition in those with HAND e.g. the Stroop test (Tozzi et al., 1999). It may be the case that problems in this domain will prove to be a useful indicator of cognitive changes associated with HIV infection.

Scores on a test of working memory and visuo-spatial rule deduction (Brixton) fell within the *below normal* range indicating difficulties in these functions. Individual profile examination confirmed that the majority of participants scored poorly on this test, with only the two participants with ANI scoring within the *average* ranges. To the best of the author's knowledge, the current study is the first to find this pattern in a sample of participants with HAND. This finding may be explained by previous studies indicating that, in the earlier stages of disease, complex attention and working memory become impaired. The finding might further be explained by excessive rigidity as hypothesised by Shallice's faulty attentional system theory,

since participants appeared to find it difficult to develop alternative strategies in light of changing patterns.

Trails B scores fell within the *low average* range. Although Heaton et al. (1995) have previously reported impairments in this test in those with HAND, the findings of this study suggest that processing speed is impacted rather than the executive function ability show-cased in the test, since performances on both Trails A and coding fell in the *below normal* range.

In summary – at group level – working memory, verbal initiation and verbal inhibition, rule induction, and processing speed appeared to be impaired in this sample. Verbal fluency, attention span, and visuo-spatial switching appeared to be intact. Consequently this is the profile of executive functions obtained from this sample of participants with HAND. In light of these results, it would be useful for clinicians working in this field to consider using digit span backwards, Hayling initiation, Hayling inhibition, and Brixton tests when assessing this client group.

4.1.4 Correlations Between Tests

Correlational analyses were undertaken to explore the data for associations between variables. Although these analyses do not lead to indications of causality, they highlight possible relationships, which may warrant further study.

Tests of attention and information processing speed were correlated with performances on other tests (e.g. figure copy, figure delay, fluency); this is perhaps reflective of shared processes underpinning these tests e.g. attention, motor skills. Further, visuo-spatial skills were correlated with each other, as were tests of learning and memory. In all cases this is again likely to be the result of shared and interdependent skills.

Further, executive functions were found to be correlated both with performances in other cognitive domains (attention, information processing speed, language, visuo-

spatial skills, and memory) and with each other. Again this is not surprising given that many cognitive skills share core components and are interdependent (Hodges, 2007).

In summary correlational analyses highlighted the interdependent nature of cognitive functioning, and many variables were correlated with each other. The hypotheses of Dawes et al. (2008) may provide one useful explanation of these findings. They note that to greater or lesser degrees the following processes underpin test performance: attention/working memory, executive function, motor function, processing speed, and visual and verbal memory.
However, the correlational analyses also resulted in some unexpected findings. For example, age was found to be associated with figure copy and spatial span. Interestingly levels of premorbid ability were found to be correlated with many tests however were not found to be correlated with verbal inhibition (Hayling 2). It is difficult to interpret these findings since complex executive skills would be expected to be linked to cognitive ability. Further, figure copy was found to be associated with list recall. As noted above, this is likely to be the result of shared cognitive processes required to complete each task.

4.1.5 Individual Case Analyses

Individual case analyses were undertaken for each participant to explore the possible impact of co-factors. This was deemed appropriate since descriptive analysis of group level data indicated large standard deviations, and the sample appeared to vary widely in terms of medical and background features.

4.1.5.1 Demographic Factors

As mentioned above, when examined individually, fourteen profiles showed clear evidence of mild neurocognitive disorder. There did not appear to be any patterns in terms of age, gender, or background within this group.

The remaining two participants showed evidence indicative of ANI since they had lower than expected scores on some of the executive function measures. This is further evidence that executive function difficulties are amongst the very earliest signs of HAND. One participant was born, raised, and schooled to graduate level in England and the other in America. Both had high premorbid ability scores. However, no other similarities between their profiles were found.

4.1.5.2 Culture and Language

Six participants in total were schooled in England and as mentioned one was schooled in America (participants 1, 2, 5, 11, 14, 15, and 16). Their levels of education varied; however all left formal education either at their sixteenth birthday or later except participant 5 who reported leaving school shortly after his tenth birthday. Broadly, the majority of these participants scored in the *average* ranges on most tests involving language throughout the assessment.

Upon inspection it appeared that participants 3, 7 8, 9, 10, and 13 were the most impaired in the sample. Interestingly, as mentioned above all of these participants had English as their second language. Two of these participants scored within the *average* range in the picture-naming test (a test of simple expression and language ability). The remaining four scored within the *below normal* range. However all of these participants scored within the impaired ranges in the verbal production and fluency subtests. Consequently their performances may have resulted from the impact of English being their second language. This argument is in line with literature in this area (e.g. Shah, Oommen & Wuntakal, 2005). Further support for this viewpoint comes from the finding that (broadly speaking) these participants appeared to perform slightly better in tests with visuo-spatial components than those with language components (e.g. line orientation, figure copy, spatial span). Interestingly Siedlecki et al., (2010) have argued that Western educational systems highly value verbal abilities but other cultural systems value and nurture different cognitive skills; the results described above may be explained to some degree by this perspective.

4.1.5.3 Core Test Battery and Executive Function Battery

In terms of the RBANS scores, except for the pattern described above, there did not appear to be any other consistent findings at individual profile level. Attention, visuo-spatial perception, new learning and memory ability all appeared to vary widely between individuals. This finding is in keeping with those of Dawes et al. (2008) who also reported that their study did not find a 'typical' profile of impairment in those with HAND.

Executive function deficits are also often reported to be highly variable both within individuals and between groups (Burgess & Alderman, 2012) and this was true of the sample obtained for this study. Closer examination of individual profiles did not identify any patterns in executive functioning; for example executive verbal test scores did not consistently fair better than executive visuo-spatial scores or vice versa, and there did not appear to be any links with medical or psychological factors and performance on the executive battery. It may be the case that a bigger sample is needed to discover such patterns. However an interesting finding is that in the case of three individual profiles, performance on the digit span backwards test was stronger than the performance given by these participants in the digit span forwards test. Since the digit span forward test assesses attention, a skill often cited as being impaired by the pathological effects of HAND, it is likely that in these cases working memory ability was stronger whilst attention was more impaired.

Further as noted throughout, the Hayling test, and the inhibition trial in particular, appeared to be the most difficult for participants in the majority of cases.

4.1.6 Summary & Interpretation of Findings

16 participants in varying stages of disease were assessed, and their scaled scores indicated that – at group level – they were typical of the wider HAND population. An executive function battery highlighted that verbal fluency, simple attention and visuo-

spatial switching were intact whilst working memory, verbal initiation, verbal inhibition, complex attention, and processing speed were impaired in this sample.

This finding is interesting in the context of the existing evidence base. Considering Shallice's supervisory attentional systems theory, the finding that verbal fluency and visuo-spatial switching were less impaired indicates that the attentional system is able to maintain a degree of control over retrieval and working memory systems. Further it would appear that, in the case of letter fluency, the cognitive flexibility required to develop new rules is still intact.

As mentioned above, Heaton et al. (1995) highlighted that performance on Trails B was impaired in their sample. However, the findings of this study show componential factors account for impairments found in this test. Further, previous research (e.g. Woods et al., 2009) has argued that working memory impairments present at the very earliest stages of disease, however the results of this study indicate that performance on digit span backwards was less impaired than digit span forwards – indicating that attention may be more impaired than working memory.

As highlighted in section 3.4, participants in this study presented with a number of comorbid health conditions (e.g. toxoplasmosis and diabetes) and risk factors (e.g. substance use), which may have played a role in the profiles obtained in this study. These points were discussed within the context of individual case profiles, alongside relevant research. Consequently any conclusions drawn about the role of HIV-associated cognitive decline need to be made with caution. The findings of the study appeared to suggest that many of the conditions explored resulted in impairments in domains similar to those affected by HAND e.g. processing speed, attention, and executive functions. However not all executive function skills were impaired equally in the current study, and this is a useful finding both at group level and at individual case level.

4.2 Clinical Implications

Executive functioning is a broad term encapsulating higher order cognitive abilities; these include mental flexibility, initiation, planning, decision-making, and set shifting (Burgess & Alderman, 2012). These functions are central to formulating and achieving goals, to ensuring behaviour is appropriate and modifiable, and to maintaining independence (Burgess & Alderman, 2012; Duncan & Owen, 2000; Hodges, 2007). Executive functions are a key marker of HIV associated cognitive impairment (Dawes et al., 2008; Rosca et al., 2011) due to the predilection of the disease for frontrostriatal regions of the brain (e.g. Rippeth et al., 2004). These impairments can present at the earliest stages of disease (Vance, Fazeki & Gakumo, 2013). Of particular importance to the population in question is the effect that impaired executive functioning can have not only on the quality of life (e.g. the ability to maintain independence; Cattie et al., 2012) but also in situations dependent on maintaining optimal health and preventing disease progression e.g. medication adherence (Heaton et al., 2004).

A criticism of the current literature base, and in turn clinical practice, that led to this study is that although executive function deficits are recognised as central to HIV, it is not often acknowledged that the term encompasses a ‘collection’ of functions; a test of a particular executive function is often considered to be representative of all executive abilities. In clinical settings clinicians may select tests on the basis of familiarity or convenience rather than on the basis of their clinical usefulness. Consequently it would be clinically informative to know whether particular functions are more impaired than others.

The findings of this research provide some evidence to suggest that particular executive functions are more intact (e.g. verbal fluency, visuo-spatial switching) whilst others may be more impaired (verbal switching, initiation, and inhibition, verbal working memory, complex attention and rule deduction). Although this study did not

control for stage of disease, individual profile analyses highlighted that this picture was broadly similar at group and individual case level.

The implication of this is that if only a single preserved or impaired skill is assessed, it may result in a clinician misinterpreting a presentation. In turn his could lead to a delay in receiving the appropriate care and treatment. Further, clinicians are often stretched for time and resources, and it would be unethical to assess participants with a number of tests without some hypothesis about what is being looked for. Use of an executive function battery, which has been developed based on current evidence in the field, could support clinicians in ensuring that the areas most likely to be impacted by HIV are assessed.

Further, deficits in complex executive functions, for example working memory as assessed by digit span backwards and visuo-spatial switching as assessed by Trails B, may be attributed to higher levels of impairment without acknowledgment of the impact of componential processes. This study highlighted that comparing the performances of these tests to the performances given in digit span forwards and Trails A indicates that it may not be working memory and visuo-spatial switching that are impaired, but processing speed and attentional processes.

A key implication of this is the need for clinicians to consider the impact of these componential factors when formulating their findings, since these may influence subsequent treatment planning e.g. when designing cognitive strategy programmes. This finding may also have implications for those working with other diseases which impact executive function e.g. Alzheimer's disease.

It may be beneficial for clinicians to retain an awareness of these issues when assessing this multi-faceted construct; profiles of executive functions can then be used to tailor appropriate strategies to support preservation of current levels of functioning. This is particularly important since gradual decline in one area can be coupled with decline in other areas given the highly interconnected nature of

cognitive processes and brain structures (Hodges, 2007). Further Murji et al. (2003) have highlighted how other cognitive functions e.g. memory, are heavily dependent on executive function skills. Consequently the importance of maintaining executive functioning cannot be underestimated both in terms of limiting impact on other cognitive domains, but also in terms of maintaining quality of life.

Since HIV infection affects people from all over the world it is important for clinicians to find culturally sensitive measures in order to avoid making false positive diagnoses. This is perhaps a concern impacting the wider field of neuropsychology, since numerous studies have highlighted the effects of language and culture on test performance. As Manly et al. (2011) have noted, some attempts to account for cultural factors have been made, however developing complete batteries of appropriate tests for the wide variety of ethnic groups that use our services may be unrealistic; therefore use of culture fair tests may be a more achievable goal. On the basis of the findings of this study, it might be useful to assess for attention, processing speed, working memory, and visual-spatial switching if culturally appropriate tests are not available (e.g. coding, Trails tests, spatial span). However it is worthy of note that some researchers have argued that the very notion of a 'culture-fair test' is a fallacy (e.g. Siedlecki et al., 2010). Although these arguments should not be ignored, it is also important to consider the useful ways in which clinicians are currently practicing whilst suitable solutions are being found. Consequently, formulation skills are central in ensuring that a patient's context, in addition to test scores, are taken into account to obtain the clearest picture about what impairments the individual is experiencing.

4.3 Critical Review

4.3.1 Epistemological Perspective & The Wider Context

As highlighted in the method section, a critical realist perspective was chosen by the researcher whilst conducting this study, though realist methods were utilised when collecting and analysing data. The perspective allows researchers to retain

awareness that perspectives (and therefore theories) are context-bound and therefore fallible; the approach was deemed appropriate after exploring ideas about the societal construction of diseases and the importance of keeping peoples 'lived experiences' in mind.

In the view of the researcher it would be useful to retain awareness of these issues in clinical practice too. Constructs and theories change as our understanding of an area develops, however our diagnoses impact people's lives, in terms of the labels that we give (and the stigma attached) and also in terms of the constrains and implications of these labels. For example we are gatekeepers of services and our labels can award support and treatment, but can also provide weight to decisions to constrict activities, such as driving.

This is in line with the critiques of Sontag (1991) who highlights that societal models of coping with illness have inadvertent consequences including socially constructed realities (for example, diagnostic labels), which can isolate sufferers of a disease. Carlson (2005) presents a similar argument by noting that 'lived realities' are the combined result of actual cognitive deficits and the socio-political context in which a person lives.

4.3.2 Sample & Test Material Limitations

A number of factors will have affected methodological rigour of the study, and consequently the reliability and validity of the findings.

Recruitment for this study took place within a limited timeframe from a single service. Consequently the sample obtained was small in size and, as mentioned throughout the report, varying in terms of age, ethnicity and background factors. The clinical presentations of the participants also varied greatly. Although this is reflective of the participants who would ordinarily use the service, given the small sample size, conclusions could only be drawn tentatively. However it may be argued that this is the nature of exploratory studies, in spite of the common belief that samples should

be tightly controlled for key variables. Another important consideration comes from Heaton et al. (2011) who have estimated that only as few as 7-10% of those with HAND will not present with comorbidities. Consequently to have tried to control the recruitment more rigorously may have negatively impacted not only the numbers obtained, but also the ecological validity of the findings.

In spite of these limitations it is important to keep in mind that the aim of the study was to explore whether a particular phenomena could be observed in a particular population. It would have been unethical to run a large study without some evidence that such a phenomena exists in the first instance. Additionally, although the evidence base is clear about the impact of certain comorbidities on cognitive presentations, it is less clear of the impact of others. Further research into these areas is needed and ruling out participants to ensure clinical homogeneity would not have been ethical until more conclusive evidence is available. With these arguments in mind tentative conclusions can be considered to lay the foundations of future enquiry.

Further, whilst the inclusion and exclusion criteria of the study attempted to control for the degree of impairment caused by more well-known comorbidities on cognitive functioning, it became clear that in order to obtain enough participants to conduct the study, the criteria had to be applied thoughtfully. This involved working closely with the consultant in the service, who was supportive and helpful in thinking through the suitability of patients for the study. Although this ultimately meant that someone other than the researcher decided which participants were suitable for the study, this arrangement felt manageable due to the consultant's extensive knowledge about the field, and also given that he held a full overview of the patient's conditions.

It was sometimes difficult to obtain full histories from patients. Further, it was frequently reported by members of the multi-disciplinary team that patients often do not want their families or other members of their social networks to know that they are patients in a HIV rehabilitation unit. Some had only recently received their

diagnoses and others only recently arrived from other countries. This impacted the study in a number of ways e.g. it was not possible to obtain collateral information from others about the everyday functioning of patients to supplement medical and neuropsychological profiles. This additional information may have added a very useful dimension to the study.

In fact, in the initial stages of the project, one of the questions this study proposed to answer was how well executive function impairments mapped onto impairments in everyday functioning. However this question had to be reviewed due a number of time and resource constraints. One of the issues included limited availability of collateral information from carers as discussed above. A further issue that became apparent is that the occupational therapists within the service no longer administered a single measure of functioning as part of the standard service assessment, and in order to answer a question about everyday functioning an additional measure (e.g. the Naturalistic Action Test; Shwartz, Segal, Veramonti, Ferraro, & Buxbaum, 2002) would have needed to be included in the study. This would have had time and resource implications since an additional test could take up to an hour to administer, and would require the use of additional facilities (a kitchen). However this may be a useful avenue for future studies to explore.

Whilst participant factors can impact conclusions, factors associated with test materials can also influence the results. The Centre for Reviews & Dissemination (2008) notes that it is important for tests used for diagnostic purposes to be both sensitive (to the earliest stages of disease) and specific (i.e. able to discriminate between different diseases). An issue that is often overlooked in the field of neuropsychology is that many tests are unable to assess any given skill in a completely ‘pure’ manner; a fundamental premise of this study is the notion that tests, whilst assessing one skill often assess others, or can be dependent on other skills being intact (for example in the Brixton test both visuo-spatial perception and short term memory skills are required). There is therefore a possibility that the

results were reliant on the methods used to assess the skills and as more sensitive/pure tests become available (if ever) the results may change.

It would also be useful to discuss the methods used to assess performances of participants. If time and resources had allowed, it would have been useful for this study to compare the performances of participants with those of matched healthy controls. However, since this was not feasible, it was noted in the method section that published normative data was used by this study. However the normative data for each study was obtained using different samples, from different continents (E.g. the normative samples for the Hayling tests were obtained in the UK using only 118 participants, whilst the DKEFS norms were obtained with 1750 American participants). This could have implications on the findings of this study. Firstly the ethnic diversity of this country differs significantly to that of America where, for example, Hispanic groups make up a significant proportion of the population. Further a significant number of the participants in this study had never been schooled in England and many of the tests used in this study have been reported to have significant positive correlations with education (E.g. the RBANS; Duff et al., 2003). Further education systems around the world differ in terms of their availability, quality and delivery styles, and this may also have impacted the results.

Consequently, since a complete co-normed with battery with consistent normative data could not be used in this study, caution is needed when interpreting the data. Further, it is also useful to remember that a number of participants had *low average* or *impaired* premorbid ability estimates. It may be the case that this was a true reflection of their achievement levels, or indeed that reading ability was impaired. Consequently comparing them to *population means* (I.e. normative data) throughout the assessment battery may not have been instructive since their profiles would have fallen into the impaired ranges whether there was genuine impairment or not. If time and resources had allowed, it would have been useful to reassess participants again in the future to obtain truer profiles of impairment.

However the methods used by this study (a single assessment point using a number of different tests) are similar to those often used both in research and in clinical practice, where researchers and clinicians are only able to assess patients once, and are required to utilise different batteries to assess the skills of interest to them.

In spite of the above, this study had a number of strengths. Firstly it utilised an executive function battery guided by previous research (Burgess et al., 1998; Cherner et al., 2007). Further it aimed to account for the impact of differing educational experiences by taking on board the recommendations of Manly et al. (2001) and using reading ability to measure premorbid functioning, in addition to level of education in the analyses. Finally Barker et al. (2003) note that small N studies are useful in combining research and practice, and this study has been able to make a number of recommendations that may enhance clinical practice.

4.3.3 Professional Issues & Personal Reflections

Whilst undertaking this research I held a dual role within the service – that of researcher and that of a trainee clinical psychologist. I found the service well accustomed to research, and the team supportive in ensuring the goals of the project were met.

When negotiating the research with the team, it was agreed that a neuropsychological report would be written for each participant. Although this is fair and ethical given the time that participants were donating to the study, managing the demands of the research, the time necessary to write reports and to give feedback, and my clinical duties besides, was challenging at times. Conversely I learned first hand about managing the multiple roles that qualified psychologists often take on within services (Onyett, 2007). Additionally, since I was a clinician within the team, my position allowed me to take on a broader perspective of the difficulties that patients' were presenting with, and the therapeutic utility of neuropsychological tests (and therefore the clinical utility of research into this area). Further, although the data obtained for the study was also used to inform patient care, I couldn't help but be

drawn to the critiques of Ruff (2003) who notes that neuropsychology's primary focus on assessment now needs to by matched by further developments in treatment approaches.

Finally Speer (2002) highlights the importance of reflecting on the power in the relationship between the researcher and the researched and I wondered whether my dual role lead to some confusion or uncertainty for prospective participants about whether they had a choice in taking part in the research. However I feel confident that my fellow clinicians and I held this dilemma in mind when the research was being described to the patients, and maximised opportunities to ensure their informed consent e.g. discussing the research with participants on multiple occasions, showing each participant which assessments were part of the core service assessment and which tests were for study purposes before any assessment processes began.

4.4 Future Research

Although areas for future research have been indicated throughout the report, it would be useful to briefly revisit the issue here.

Since this research established a profile of executive skill deficits based on a small sample, it would be useful to carry out the research with a larger sample in the future. This would allow more robust conclusions to be drawn, and would also allow for more control over demographic factors and co-morbidities (for example, age, stage of disease, point of cART initiation, English language levels). Further, in order to increase the robustness of the findings it would be useful to employ additional analytic measures which could support reliability and validity of the conclusions e.g. using inter-rater reliability measures with the WTAR.

As mentioned above, it would be useful to explore objective measures of daily functioning and their relationship to executive function tests. This would add to the literature in terms of increasing the ecological and predictive validity of executive function batteries.

This study was only able to explore particular executive functions. Future studies may benefit from looking at the impact of processing speed and attentional processes in other higher order abilities e.g. reasoning, abstraction, problem-solving. Additionally, particular tests were used by this study; these are not the only measures available to assess executive functions and it may be useful for future studies to explore which tests are more sensitive in detecting particular executive deficits. For example the Mental Alternation Test (Salib & McCarthy, 2002) is a verbal equivalent of the Trails B test, and comparing sensitivity between the two tests may be a useful endeavor.

Finally, as discussed above, HIV affects people from all over the world. To ensure that service delivery is equitable, it is important for future studies to explore culturally sensitive ways of assessing impairments across different groups.

4.5 Conclusion

To the best of the author's knowledge this is the first study to explore a profile of executive function deficits in those with HIV associated neurocognitive decline. The findings suggest that verbal initiation, verbal inhibition, working memory and processing speed were impaired whilst simple attention, verbal fluency, and visuo-spatial switching were intact in a mixed sample. The findings were then interpreted and discussed within the context of the existing evidence base.

The clinical utility of the findings was explored and it was recommended that clinicians should consider the use of executive function batteries, rather than be

reliant on the results of a single measure, since the findings of this study indicate that certain skills are more impaired than others.

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Appendix A

Stages of HIV Infection
(Adapted from WHO HIV/TB manual, 2007, pp. 31-32)

i. *Acute Infection Phase*

Approximately 2-4 weeks, or even as long as three months after exposure to the virus 40-90% of people will experience extreme flu-like symptoms including lymphadenopathy, fever, joint pain, and rashes. Neurological diseases may also occur including meningitis.

At this time, the virus inhabits CD4 cells to replicate and destroy them in the process, thus resulting in large amounts of virus being produced in the body.

Many infected individuals may seek help however correct identification of the symptoms is seldom made, with clinicians often confusing the signs for other causes e.g. malaria. Further, standard serological tests only become positive 1-3 months post infection and hence at the stage an individual presents, the results are likely to be negative.

ii. *Asymptomatic HIV Infection/Clinical Latency*

Latency follows the initial infection phase where infected individuals can remain asymptomatic for longer than ten years. During this phase HIV reproduces at relatively low levels, with individuals able to maintain low viral loads and healthy CD4 counts without the use of medications in the early years of this phase. It is also possible that there is an absence of other symptoms and opportunistic infections.

iii. *HIV Disease & AIDS*

Most, if not all, those infected by HIV will develop HIV-related diseases and AIDS if untreated. This phase is characterised by critically low levels of CD4 cells (below 200 cells per cubic millimetre of blood). Consequently cell-mediated immunity is severely impaired and there is a high risk of opportunistic infection and tumours.

Early signs include weight loss, oral candidiasis and tuberculosis. Pneumonia and meningitis may present later however the rate of progression is dependant on virus and host characteristics. However all of these diseases can be fatal, with people diagnosed with AIDS typically surviving three years. However someone with a dangerous opportunistic infection has a likely life expectancy of one year.

Appendix B

UEL Ethics Committee Documentation

ETHICAL PRACTICE CHECKLIST (Professional Doctorates)

SUPERVISOR: Matthew Jones Chesters **ASSESSOR:** Rachel Smith

STUDENT: Amardeep Johal **DATE (sent to assessor):** 04/03/2013

Proposed research topic: Executive Function Deficits in HIV-associated Neurocognitive Decline

Course: Prof Doc Clinical Psychology

1. Will free and informed consent of participants be obtained?	YES* see below 1
2. If there is any deception is it justified?	N/A
3. Will information obtained remain confidential?	YES
4. Will participants be made aware of their right to withdraw at any time?	YES* see below 2
5. Will participants be adequately debriefed?	YES* see below 3
6. If this study involves observation does it respect participants' privacy?	NA
7. If the proposal involves participants whose free and informed consent may be in question (e.g. for reasons of age, mental or emotional incapacity), are they treated ethically?	NA
8. Is procedure that might cause distress to participants ethical?	YES * see below 4
9. If there are inducements to take part in the project is this ethical?	NA
10. If there are any other ethical issues involved, are they a problem?	NO

APPROVED

	YES, PENDING MINOR CONDITIONS	

MINOR CONDITIONS:

1: It would be better on the consent form if the participant could tick a box to agree to each of the conditions rather than sign the whole form.

2: When will data be destroyed? This should be in keeping with the data Protection Act and might include what you will do with the data of participants who withdraw.

3: You say that a report will go to the team consultant – will it go to the participant too? What will be fed back to them straight after the session as the tests will take time to score?

4: You might consider conducting the assessment over two shorter sessions for the benefit of the participants, or at least offering this.

Assessor initials: RS Date: 7.3.13

RESEARCHER RISK ASSESSMENT CHECKLIST (BSc/MSc/MA)

SUPERVISOR: Matthew Jones Chesters **ASSESSOR:** Rachel Smith

STUDENT: Amardeep Johal **DATE (sent to assessor):** 04/03/2013

Proposed research topic: Executive Function Deficits in HIV-associated Neurocognitive Decline

Course: Prof Doc Clinical Psychology

Would the proposed project expose the researcher to any of the following kinds of hazard?

1	Emotional	NO
2.	Physical	Yes
3.	Other (e.g. health & safety issues)	NO

If you've answered YES to any of the above please estimate the chance of the researcher being harmed as: LOW

APPROVED

	YES, PENDING MINOR CONDITIONS	

MINOR CONDITIONS:
Think of the safety of you as a researcher and how you will ensure this. What type of room will you use? Who will know you are there? These are people you have never met before and might have very little information about.

REASONS FOR NON APPROVAL:

Assessor initials: RS Date: 6//3/13

For the attention of the assessor: Please return the completed checklists by e-mail to ethics.applications@uel.ac.uk within 1 week.

SCHOOL OF PSYCHOLOGY
Dean: Professor Mark N. O. Davies, PhD, CPsychol, CBiol.

UEL
University of East London
www.uel.ac.uk

School of Psychology

Professional Doctorate Programmes

To Whom It May Concern:

This is to confirm that the Professional Doctorate candidate named in the attached ethics approval is conducting research as part of the requirements of the Professional Doctorate programme on which he/she is enrolled.

The Research Ethics Committee of the School of Psychology, University of East London, has approved this candidate's research ethics application and he/she is therefore covered by the University's indemnity insurance policy while conducting the research. This policy should normally cover for any untoward event. The University does not offer 'no fault' cover, so in the event of an untoward occurrence leading to a claim against the institution, the claimant would be obliged to bring an action against the University and seek compensation through the courts.

As the candidate is a student of the University of East London, the University will act as the sponsor of his/her research. UEL will also fund expenses arising from the research, such as photocopying and postage.

Yours faithfully,

Dr. Mark Finn

Chair of the School of Psychology Ethics Sub-Committee

Stratford Campus, Water Lane, Stratford, London E15 4LZ
tel: +44 (0)20 8223 4966 fax: +44 (0)20 8223 4937
e-mail: mno.davies@uel.ac.uk web: www.uel.ac.uk/psychology

Appendix C

UEL Ethics Committee Approved Participant Information Sheet

Who am I?

My name is Amber Johal. I am a trainee clinical psychologist studying at the University of East London. My email address is u1138186@eastlondon.ac.uk. My phone number is XXXX XXXXX.

What is the research about?

My study aims to examine the impact of HIV infection on an individual's ability to make plans and judgments, and on their ability to cope with tasks of everyday living. This information will help us to understand how HIV impacts the brain's ability to cope with a variety of situations and tasks.

This information will help us to develop new approaches to psychological assessment and intervention.

What is required of me if I decide to take part?

If you agree to take part, you will be asked to complete a set of psychological tests. It will take approximately 2.5 hours in total although this can be split into two sessions if you prefer. However you are allowed to withdraw from the study at any time if you later change your mind (and the information you have provided will be destroyed and not used).

The assessments aim to explore a wide range of abilities e.g. problem-solving, remembering, comprehension and will involve a mixture of verbal responses and pen-and-paper exercises.

What happens afterwards?

You will receive feedback from the assessment approximately one week later

and you will also receive a written summary of the assessment. However I will be available to discuss any concerns or questions you have throughout the process.

With your permission the results of the assessment will be fed back to the multidisciplinary team and will inform your care planning.

What will happen to the information I provide?
All the information you provide for the purposes of the study will be anonimised, and kept strictly confidential and separately from personal information the service holds about you.

What will happen to the results of the research study?
The results obtained from this research will be incorporated into a doctoral thesis that will be submitted to the University of East London. The thesis may be published in an academic journal in the future, however identifiable data on individual participants will not be included in any report or publication.

Who can I contact if I have any questions?
If you have any further questions, you can contact:

- Amber Johal (XXXX Hospital and at the University of East London. Tel: XXXXX XXXXXXXX)
- Dr Alison Jones (XXX Hospital. Tel: XXXX XXXXX)
- Dr Matthew Jones Chesters (Clinical Psychologist at the University of East London. Tel: XXXXX XXXXXXXX)

Thank you
Amber Johal

Appendix D

UEL Ethics Committee Approved Consent Form

UNIVERSITY OF EAST LONDON

Consent to participate in a research study

Executive Function Deficits In HIV-Associated Neurocognitive Decline

Please read the following statements and tick if you agree.

1. I have the read the information sheet relating to the above research study and have been given a copy to keep. The nature and purposes of the research have been explained to me, and I have had the opportunity to discuss the details and ask questions about this information. I understand what is being proposed and the procedures in which I will be involved have been explained to me. (*Tick box if you agree* □)

2. I understand that my involvement in this study, and particular data from this research, will remain strictly confidential. Only the researcher(s) involved in the study will have access to identifying data. It has been explained to me what will happen once the research study has been completed. (*Tick box if you agree* □)

3. I freely and fully consent to participate in the study which has been fully explained to me. Having given this consent I understand that I have the right to withdraw from the study at any time without disadvantage to myself and without being obliged to give any reason. (*Tick box if you agree* □)

Participant's Name (BLOCK CAPITALS)
…….

Participant's Signature
……..

Researcher's Name (BLOCK CAPITALS)
……..

Researcher's Signature

……

Date: ……..……

Appendix E

Table of Participant Characteristics

No.	Age	Sex	Ethnicity & Country of Birth	Education (years)	CD4	Viral Load	Notes
1	23	F	Black British – England	16	57	59000	Longstanding history of chest infections and depression. Rectovaginal fistula
2	46	M	British Asian – England	10	32	1196	History of substance misuse. TB
3	40	F	Black African – Nigeria	7	177	202	Toxoplasmosis
4	43	M	Portuguese – Congo	9	479	<40	TB
5	57	M	White British – England	13	38	3000000	Pancytopenia, pneumocystis pneumonia, and Kaposi's Sarcoma of the face, palette and tongue
6	56	M	Ghanaian – Ghana	9	680	<40	Stroke in 2001. Toxoplasmosis.
7	49	M	Congolese – Congo	15	75	916	TB
8	48	M	Ugandan – Uganda	11	241	1386132	History of depression and PTSD. Tonic-clonic seizures
9	54	F	Zimbabwe – Zimbabwean	4	2	100000000	
10	47	F	Ugandan – Uganda	10	77	800000	
11	67	M	White British – England	17	180	140	
12	26	F	Black British – Kenya	10	4	1100000	Pneumocystis pneumonia, Toxoplasmosis, TB, delirium with psychotic features
13	53	F	St Lucian – St Lucia	4	40	100000	Anxiety and depression
14	50	M	Black British – England	11	991	<40	Hyperglycaemia
15	72	M	White British – England	12	359	728	Frequent UTIs
16	57	M	White German – America	17	300	<40	Chronic inflammatory demyelinising poly-neuropathy

Appendix F

Table of Scaled Scores and Subjective Labels (Based on Slick, 2006)

Scaled Score	Subjective Range
19	Very Superior
18	
17	
16	
15	Superior
14	
13	High Average
12	
11	Average
10	
9	
8	Low Average
7	
6	Below Normal
5	
4	Impaired
3	
2	
1	

Appendix G

Correlational Matrix

Table G-1 Correlational Matrix

		Age (years)	Education	CD4	VL	WTAR
Age (years)	rho					
	Sig.					
Education	rho	0.288				
	Sig.	0.28				
CD4	rho	0.271	0.192			
	Sig.	0.31	0.476			
VL	rho	-0.185	-0.211	-.794**		
	Sig.	0.494	0.433	0		
WTAR	rho	0.38	0.431	0.454	-0.428	
	Sig.	0.163	0.109	0.089	0.111	
Digit Forward	rho	0.21	0.297	0.364	-.544*	.565*
	Sig.	0.436	0.263	0.165	0.029	0.028
Digit Backward	rho	0.263	.704**	0.294	-0.26	.720**
	Sig.	0.324	0.002	0.269	0.33	0.002
Coding	rho	0.362	.557*	0.152	-0.25	0.402
	Sig.	0.168	0.025	0.575	0.351	0.137
Figure Copy	rho	.542*	.817**	0.18	-0.17	0.373
	Sig.	0.03	0	0.505	0.529	0.17
Line Orientation	rho	-0.121	0.308	0.242	-0.473	0.43
	Sig.	0.656	0.246	0.366	0.064	0.11
Picture Naming	rho	0.463	0.364	0.239	-0.357	.517*
	Sig.	0.071	0.165	0.372	0.175	0.049
List Total	rho	0.357	.632**	0.273	-0.351	.614*
	Sig.	0.174	0.009	0.306	0.183	0.015
List Delay	rho	0.438	.545*	0.151	-0.278	.637*
	Sig.	0.09	0.029	0.576	0.296	0.011
List Recognition	rho	0.369	.529*	-0.082	-0.113	0.49
	Sig.	0.16	0.035	0.763	0.678	0.063
Story Immediate	rho	0.412	.570*	0.441	-0.479	.636*
	Sig.	0.113	0.021	0.088	0.061	0.011
Story Delay	rho	0.315	.614*	0.322	-0.42	.611*
	Sig.	0.234	0.011	0.225	0.105	0.015
Figure Delay	rho	0.285	.786**	0.375	-0.466	0.503
	Sig.	0.285	0	0.153	0.069	0.056

*= Correlation is significant at 0.05; **= Correlation is significant at 0.01 (2-tailed)

Table G-2 Correlational Matrix (continued)

		Age (years)	Education	CD4	VL	WTAR
Verbal Production	rho	0.267	0.098	.578*	-.675**	0.25
	Sig.	0.317	0.719	0.019	0.004	0.369
Fluency - Letter	rho	0.142	.638**	0.434	-0.482	.575*
	Sig.	0.601	0.008	0.093	0.059	0.025
Fluency - Category	rho	0.184	.669**	0.152	-0.259	.548*
	Sig.	0.495	0.005	0.574	0.332	0.035
Fluency - Switches	rho	0.162	.626**	0.056	-0.246	0.305
	Sig.	0.549	0.01	0.836	0.358	0.268
Fluency - Output	rho	0.146	.646**	0.041	-0.254	0.278
	Sig.	0.59	0.007	0.879	0.343	0.315
Spatial Span	rho	.518*	.624**	.627**	-.595*	.584*
	Sig.	0.04	0.01	0.009	0.015	0.022
Brixton	rho	0.077	0.272	0.149	-0.334	0.448
	Sig.	0.778	0.308	0.583	0.206	0.094
Hayling 1 Basic	rho	0.244	.562*	-0.029	-0.116	0.435
	Sig.	0.363	0.024	0.916	0.67	0.105
Hayling 2 Inhib	rho	-0.292	0.455	0.031	-0.274	-0.095
	Sig.	0.273	0.076	0.909	0.304	0.737
Trails A	rho	0.296	.666**	0.136	-0.201	0.454
	Sig.	0.266	0.005	0.616	0.455	0.089
Trails B	rho	0.089	.514*	0.108	-0.256	0.247
	Sig.	0.742	0.042	0.691	0.338	0.375

*= Correlation is significant at 0.05; **= Correlation is significant at 0.01 (2-tailed)

Table G-3 Correlational Matrix (continued)

		Digit Forward	Digit Backward	Coding	Figure Copy	Line Orientation	Picture Naming	List Total
Digit Forward	rho							
	Sig.							
Digit Backward	rho	.663**						
	Sig.	0.005						
Coding	rho	0.358	.525*					
	Sig.	0.173	0.037					
Figure Copy	rho	0.293	.640**	.633**				
	Sig.	0.27	0.008	0.008				
Line Orientation	rho	.696**	.532*	0.226	0.203			
	Sig.	0.003	0.034	0.401	0.451			
Picture Naming	rho	0.277	0.288	0.428	.536*	.502*		
	Sig.	0.299	0.28	0.098	0.032	0.048		
List Total	rho	0.426	.545*	.782**	.689**	0.277	.646**	
	Sig.	0.1	0.029	0	0.003	0.3	0.007	
List Delay	rho	0.322	0.425	.687**	.614*	0.234	.728**	.915**
	Sig.	0.224	0.101	0.003	0.011	0.384	0.001	0
List Recognition	rho	0.295	0.387	.690**	.632**	0.159	.530*	.755**
	Sig.	0.267	0.138	0.003	0.009	0.557	0.035	0.001
Story Immediate	rho	0.401	0.464	.670**	.679**	0.389	.739**	.854**
	Sig.	0.124	0.071	0.004	0.004	0.137	0.001	0
Story Delay	rho	0.424	0.472	.697**	.657**	0.435	.720**	.908**
	Sig.	0.102	0.065	0.003	0.006	0.092	0.002	0
Figure Delay	rho	0.436	.576*	.745**	.762**	0.459	.620*	.863**
	Sig.	0.091	0.02	0.001	0.001	0.074	0.01	0
Verbal Production	rho	0.409	0.161	0.343	0.357	0.354	0.398	0.384
	Sig.	0.116	0.552	0.194	0.175	0.178	0.127	0.142
Fluency - Letter	rho	0.482	.567*	.644**	.662**	.519*	.593*	.827**
	Sig.	0.059	0.022	0.007	0.005	0.039	0.015	0
Fluency - Category	rho	0.481	.564*	.624**	.618*	0.486	.622*	.882**
	Sig.	0.059	0.023	0.01	0.011	0.056	0.01	0
Fluency - Switches	rho	0.281	0.33	.588*	.505*	0.216	0.386	.789**
	Sig.	0.291	0.211	0.017	0.046	0.421	0.14	0
Fluency - Output	rho	0.333	0.358	.606*	.543*	0.279	0.398	.792**
	Sig.	0.207	0.173	0.013	0.03	0.295	0.127	0
Spatial Span	rho	0.371	0.472	.646**	.660**	0.381	.634**	.625**
	Sig.	0.157	0.065	0.007	0.005	0.146	0.008	0.01
Brixton	rho	0.378	0.231	0.287	0.113	0.168	0.318	.623**
	Sig.	0.149	0.39	0.28	0.677	0.534	0.23	0.01
Hayling 1 Basic	rho	.515*	.665**	.561*	.688**	0.475	0.484	.745**
	Sig.	0.041	0.005	0.024	0.003	0.063	0.057	0.001
Hayling 2 Inhib	rho	0.217	0.151	0.317	0.307	0.465	0.244	0.471
	Sig.	0.419	0.577	0.232	0.248	0.07	0.362	0.066
Trails A	rho	.567*	.661**	0.493	.709**	.568*	.544*	.676**
	Sig.	0.022	0.005	0.052	0.002	0.022	0.029	0.004
Trails B	rho	0.338	0.468	0.467	0.476	.704**	.559*	0.482
	Sig.	0.2	0.067	0.068	0.062	0.002	0.024	0.059

*= Correlation is significant at 0.05; **= Correlation is significant at 0.01 (2-tailed)

Table G-4 Correlational Matrix (continued)

		List Delay	List Recognition	Story Immediate	Story Delay	Figure Delay	Verbal Production	Fluency - Letter
List Delay	rho							
	Sig.							
List Recognition	Sig.	.806**						
	rho	0						
Story Immediate	Sig.	.813**	.749**					
	rho	0	0.001					
Story Delay	Sig.	.873**	.749**	.963**				
	rho	0	0.001	0				
Figure Delay	Sig.	.792**	.709**	.894**	.912**			
	rho	0	0.002	0	0			
Verbal Production	Sig.	0.249	0.364	.621*	.501*	0.48		
	rho	0.353	0.166	0.01	0.048	0.06		
Fluency - Letter	Sig.	.757**	.650**	.910**	.922**	.945**	.536*	
	rho	0.001	0.006	0	0	0	0.032	
Fluency - Category	Sig.	.820**	.760**	.764**	.843**	.840**	0.363	.804**
	rho	0	0.001	0.001	0	0	0.167	0
Fluency - Switches	Sig.	.708**	.708**	.599*	.700**	.731**	0.329	.611*
	rho	0.002	0.002	0.014	0.003	0.001	0.214	0.012
Fluency - Output	Sig.	.698**	.717**	.618*	.722**	.763**	0.361	.648**
	rho	0.003	0.002	0.011	0.002	0.001	0.169	0.007
Spatial Span	Sig.	.650**	0.459	.745**	.708**	.783**	0.466	.726**
	rho	0.006	0.074	0.001	0.002	0	0.069	0.001
Brixton	Sig.	.659**	.569*	0.439	0.488	0.493	0.146	0.463
	rho	0.006	0.021	0.089	0.055	0.052	0.589	0.071
Hayling 1 Basic	Sig.	.653**	.606*	.615*	.708**	.669**	0.353	.672**
	rho	0.006	0.013	0.011	0.002	0.005	0.18	0.004
Hayling 2 Inhib	Sig.	0.33	0.364	0.476	.567*	.664**	0.393	.633**
	rho	0.212	0.166	0.062	0.022	0.005	0.132	0.008
Trails A	Sig.	.588*	.553*	.567*	.643**	.675**	0.384	.628**
	rho	0.017	0.026	0.022	0.007	0.004	0.142	0.009
Trails B	Sig.	0.391	0.4	.523*	.561*	.638**	0.464	.566*
	rho	0.134	0.124	0.038	0.024	0.008	0.07	0.022

*= Correlation is significant at 0.05; **= Correlation is significant at 0.01 (2-tailed)

Table G-5 Correlational Matrix (continued)

		Category Fluency	Fluency - Switches	Fluency - Output	Spatial Span	Brixton	Hayling 1 Basic	Hayling 2 Inhib
Fluency - Category	rho							
	Sig.							
Fluency - Switches	Sig.	.883**						
	rho	0						
Fluency - Output	Sig.	.896**	.993**					
	rho	0	0					
Spatial Span	Sig.	.533*	0.395	0.405				
	rho	0.034	0.13	0.12				
Brixton	Sig.	.686**	.700**	.666**	0.206			
	rho	0.003	0.003	0.005	0.445			
Hayling 1 Basic	Sig.	.795**	.667**	.709**	0.331	0.343		
	rho	0	0.005	0.002	0.21	0.193		
Hayling 2 Inhib	Sig.	.639**	.699**	.748**	0.207	0.389	.537*	
	rho	0.008	0.003	0.001	0.442	0.137	0.032	.
Trails A	Sig.	.855**	.715**	.749**	.507*	0.351	.855**	0.497
	rho	0	0.002	0.001	0.045	0.182	0	0.05
Trails B	Sig.	.698**	.607*	.646**	0.419	0.211	.690**	.694**
	rho	0.003	0.013	0.007	0.106	0.434	0.003	0.003

*= Correlation is significant at 0.05; **= Correlation is significant at 0.01 (2-tailed)

Table G-6 Correlational Matrix (continued)

		Trail A	Trail B
Trails A	Sig.		
	rho		
Trails B	Sig.	.759**	
	rho	0.001	

*= Correlation is significant at 0.05; **= Correlation is significant at 0.01 (2-tailed)