Social Cognition and HIV: Exploring the Profile of Cognitive Impairments in HIV-associated Neurocognitive Disorders (HAND)

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A Thesis submitted in partial fulfilment of the requirements for the Professional Doctorate in Clinical Psychology at the University of East London

August 2016

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List of Acronyms

AIDS	Acquired Immunodeficiency Syndrome
ANI	Asymptomatic Neurological Impairment
ASC	Autism Spectrum Conditions
cART	Combined Antiretroviral Medication
CD4+	Cluster of Differentiation 4
CNS	Central Nervous System
CPE	CNS Penetration Effectiveness
DKEFS	Delis-Kaplan Executive Function System
FtD	Fronto-temporal Dementia
HAD	HIV-associated Dementia
HADS	Hospital Anxiety and Depression Scale
HAND	HIV-associated Neurocognitive Disorders
HIV	Human Immunodeficiency Virus
MND	Mild Neurological Disorder
I-NOS	Impairment Not Otherwise Specified
PFC	Pre-frontal Cortex
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RMET	Reading the Mind in the Eyes Test
SC	Social Cognition
ToM	Theory of Mind
WTAR	Wechsler Test of Adult Reading
QCAE	Questionnaire of Cognitive and Affective Empathy
QCAE-AES	QCAE Affective Empathy Scale
QCAE-CES	QCAE Cognitive Empathy Scale

Acknowledgements

I would like to express my gratitude to the participants and staff at both recruitment sites who gave their time to participate in this study. Without you this research would not have been possible.

To Dr Matthew Jones Chesters at the University of East London, I am sincerely grateful for all the time you have given in supporting me through this process, and the invaluable knowledge and humour you shared with me along the way.

Finally, thank you to my friends and colleagues who offered their advice and support along the way, and a special thank you to Suzy Young, whose support, words of encouragement and positive feedback at the closing stages of this research made more of an impact than she knows.

Abstract

The success of combined antiretroviral therapy has transformed Human immunodeficiency virus (HIV) infection from an acute and life-limiting condition to an enduring but treatable illness, marked by fluctuations in HIV-related health consequences and co-morbidities. HIV-associated neurocognitive disorders (HAND) are one such possible consequence and are of particular concern in light of their sustained high prevalence in people with otherwise well-managed HIV infection. Given the neuropsychological profile of HAND (affecting frontostriatal brain regions and associated executive functions), it has been suggested that HAND may have implications for social cognition; that is to say, the cognitive capacities that facilitate social interaction. Thus, the current study aimed to explore social cognitive performance in the neuropsychological profile of HAND.

A diverse HIV-positive cohort (N=16), recruited across two outpatient services, were administered the *Social Stories Questionnaire* (Lawson, Baron-Cohen, & Wheelwright, 2004), *Reading the Mind in the Eyes Test* (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001), and the *Questionnaire of Cognitive & Affective Empathy* (Reniers et al., 2011), alongside a standard neuropsychological battery. Using IMB SPSS v22, an exploratory group-level bivariate correlational analysis compared group scores against published normative data, and further Individual Profile Analyses explored cognitive differences within rather than across individuals to investigate trends not apparent at group-level.

The sample demonstrated reliable performance weaknesses on both tests of social cognition (RMET and SSQ), independent of executive function and in the absence of global of specific impairments. Individual Profile Analyses revealed that these impairments were unrelated to stage of infection and occurred alongside (not before) cognitive decline in other core domains. Recommendations for further research are offered, drawing upon a critical review of the methodology employed. Clinical implications include; suggestions for increasing professional curiosity and empathy; psychoeducation; and the role of clinical neuropsychology in contributing to the development of the wider understanding of the potential emotional and behavioural sequelae of HAND.

1. INTRODUCTION

A literature review was conducted to provide a comprehensive background of the literature in the field of HIV infection and treatment and identify and summarise the relevant research regarding social cognition in HIV-associated neurocognitive disorders (HAND). A 'narrative approach' to this endeavour was taken as it presented a suitable method with which to efficiently review the vast and rapidly evolving literature characteristic of this particular field. Key terms relevant to the research area (e.g. 'HIV', 'HAND', 'cognitive impairment', 'social cognition', and 'social functioning') were entered into literature databases (PsychInfo, Pubmed and Science Direct); available abstracts were screened for appropriate themes and where appropriate full articles obtained. Due to the minimal research into social cognition impairments in HAND, the search was broadened to include research into social cognition in further neurological conditions in which the prefrontal cortex is implicated, including frontotemporal dementia (FtD) and Autism Spectrum Conditions (ASC).

Before moving onto the literature concerning social cognition and HAND, a brief history of HIV will be provided, with signposting to further information where necessary, to provide the necessary contextual framework for the current study.

1.1. The Human Immunodeficiency Virus (HIV) Epidemiology

1.1.1. HIV Virology and Transmission

The Human Immunodeficiency Virus (HIV) is a retrovirus that affects the cells of the immune system, leading to progressive deterioration in immunity and increased susceptibility to opportunistic infections, diseases and cancers. The strength of an individual's immune system can be detected by laboratory tests and reported as the 'CD4 count'. This test is a measurement of CD4+T lymphocyte cells in specific blood sample; determining the extent to which HIV has depleted the glycoprotein molecules on the surface of immune cells (Bartlett, 2000; Hazenberg, Hamann, Schuitemaker, & Miedema, 2000).

The virus is transmitted between humans through the transfer of infected bodily fluids. In the UK, this process occurs most commonly through unprotected sexual

intercourse, transmission of contaminated blood (blood transfusions), sharing of contaminated needles, and between mother and infant during pregnancy, childbirth and breast feeding (Kumar & Clark, 2012). If left untreated, HIV can take on average ten years to develop into acquired immunodeficiency syndrome (AIDS); a condition characterised by a CD4 count below 200cells/mm3 and increased vulnerability to potentially life-limiting infections and cancers.

The concept of 'episodic disability' was developed by O'Brien et al. (2008) in conjunction with service-users in an effort to develop a comprehensive framework for understanding the health related consequences of living with HIV. This phrase reflects how HIV is characterized by unpredictable periods of wellness and illness: the concept of 'disability' reflects the real-life impact and health-related setbacks that can occur due to HIV and its associated treatments, and the term 'episodic' reflects the fluctuations of said experiences.

The cluster of cognitive impairments conceptualised as 'HAND' are one of the many possible consequences of HIV infection. However, contrary to the majority of HIV associated and AIDS-defining illnesses, the cause and temporal progression of neurocognitive impairment remains complex and unclear; equivocally linked with individual CD4 levels and HIV virology. Whilst some studies report a modest association between CD4 counts and neurocognitive impairments (Bornstein et al., 1991; Childs et al., 1999; Stern et al., 1991), others have failed to find a relationship (Miller et al., 1990; Yaakov Stern, 2001). A comprehensive understanding of why HAND occurs, and the difficulties in treating HIV virology are required and presented throughout the introduction.

1.1.2. Worldwide and National Prevalence

The United Nations programme on HIV/AIDS (UNAIDS) estimated that, worldwide, there are approximately 36.9 million people living with HIV worldwide. Within the last year, around 2 million people were newly diagnosed, and 1.2 million people who died from AIDs-defining illnesses (UNAIDS, 2015).

Relative to this global prevalence, the UK has a relatively small HIV epidemic, with 103,700 people believed to be living with HIV, of whom 69,200 were men and 34,000 women (Public Health England, 2015a)(Public Health England, 2015a). This equates

to a national prevalence of 1.9 per 1000 people (aged 15 and over), a statistic which has gradually increased since 1990, reflecting the advancements in medical treatment and subsequent improved life expectancy; ongoing viral transmission; steady numbers of new diagnoses; and a gradual rise in sexually transmitted diseases in the wider sexual health context.

An estimated 17% (18,100) of people living with HIV in the UK are believed to be unaware of their infection status; at risk of unmedicated viral replication and naive transmission. However, this number has gradually declined from 25% in 2010, following targeted public health initiatives (Public Health England, 2015a, 2015b).

1.1.3. Natural History of HIV

There are two main strains of HIV; HIV-1 and HIV-2. Each have different origins and evolutions, and are believed to be the result of multiple cross-species transmissions and the subsequent mutations of the simian immunodeficiency viruses (SIVs); present in African primates well before the emergence of HIV in the Human species (Sharp & Hahn, 2011; Worobey et al., 2010).

HIV-1 has been found to be closely related to the SIV-cpz strain found in chimpanzees, who may have developed the virus after consuming smaller species of animals, themselves infected with two different SIV strains which may have mutated into a third strain able to pass between chimpanzees and humans (Bailes et al., 2003; Sharp & Hahn, 2011). Less infectious and far rarer than HIV-1; HIV-2 is instead closely related to a strain of SIV found in sooty mangabeys monkeys (Chen et al., 1997). However, it is HIV-1 that is widely accepted as the principal cause of the AIDS pandemic, responsible for the vast majority of global HIV infection cases today.

It is believed that both HIV-1 and -2 may have been transferred to human by means of the handling and consumption of infected meat; known as the “hunter” hypothesis. Sharp and Hahn (2011) suggest that in most cases the “hunters” own immune response would have been successful in fighting off the SIV infection, but on a few occasions the virus must have managed to adapt itself within the new human host, mutating into HIV-1, in most incidences.

The first transmissions of SIV-cpz to HIV-1/2 in humans may have occurred as early as 1920, in Kinshasa in the Democratic Republic of Congo (Faria et al., 2014). At which time, specific social factors are believed to have contributed to the conditions in which rapid transmission of the virus between people in the area was made possible, including, for example, the thriving railway transport system which saw over one million people travel through Kinshasa each year: facilitating the spread of the virus and the consequential development of the global pandemic (Faria et al., 2014).

However, HIV did not receive global attention until the 1980's in the USA, when a pattern of rare diseases including Pneumocystis Pneumonia and Kaposi's Sarcoma were reported among a group of men (Hymes et al., 1981). The term 'AIDS' first took form to describe this pattern of unexpected opportunistic infections and diseases in 1982 and, a year later, these become seen as 'secondary infections' following the progression of a primary infection of HIV. First named HTLV-III/LAV (human T-cell lymphotropic virus-type III/lymphadenopathy-associated virus) the virus later became known as HIV.

1.1.3.1. Alternative Perspectives

For the last three decades, prominent disagreements have existed with regards to the HIV and AIDs phenomenon. Although subsequent advancements in research and medicine have led to some of these alternative theories being discredited, dissention remains, with a wide range of critiques and alternative theories to the dominant hypothesis offered. Goodson (2014) reviews and summarises the key disputes into four categories, including; retroviral molecular markers; transmission electron microscopy; images of retroviral particles; efficacy of anti-retroviral drugs; and epidemiological data. It is beyond the scope of this study to further discuss these factors but, as noted by Goodson (2010), the acceptance of uncertainty and awareness of divergent ideas and perspectives is an important part of scientific enquiry, and a duty for health professionals in ensuring that clinical practice is grounded in rigorous scholarly and ethical standards.

1.2. HIV Treatment

1.2.1. Antiretroviral Therapy

The primary treatment for HIV infection is currently combined antiretroviral therapy (cART), a pharmacological medication which slows down, and thus controls, the harmful effects of the virus on the immune system. In order for cART to have a powerful and long-lasting effect against HIV it is sometimes necessary to take a combination of three or more types of cART. Effective cART can suppress viral replication in the blood to the extent that HIV becomes undetectable. This event improves individual health outcomes and diminishes risk of transmission. In 2014 in the UK, 91% of people diagnosed HIV infection were on antiretroviral treatment plans, with 95% of them achieving undetectable viral loads. Therefore, the advent of cART in 1996 and the subsequent medical advancements have radically changed the prognosis and health outcomes of living with HIV infection in the UK: whereas a diagnosis of HIV once meant death, the estimated life expectancy for people with HIV infection (where cART is widely available) is now the same as the unaffected population (May et al., 2014).

Currently, combined cART does not eliminate HIV from the body. This means, despite the otherwise successful treatment, people with HIV can have long standing latent HIV reservoirs where HIV RNA (viral load) can persist. This limits control over viral replication and disease prognosis, and necessitates the indefinite use of cART as part of a life-long treatment program (Gates & Cysique, 2016). Furthermore, adherence to cART is particularly important as reduced levels of the drugs in the person's blood can re-enable viral replication and the development of resistance to the current drug and others like it (Hinkin et al., 2002; Levine et al., 2005).

1.2.2. Commencing cART

The recommended timing for commencing cART has been a widely contested topic. However, the British HIV Association (BHIVA, 2015) guidelines for the treatment of HIV positive adults now recommend that cART should commence as soon as possible after diagnosis. This guidance reflects the results of the large multicentre international RCT study called the 'Strategic Timing of Antiretroviral Treatment' (START) study. Described by Gate and Cysique (2016, p. 5) as "*the* RCT needed to

settle the debate over benefits versus adverse effects of early cART", the START study reported that people with a CD4 count of more than 500 cells pcm showed greater benefits from starting early cART than those whose CD4 count had fallen to 350 cells pcm (The INSIGHT START Study Group, 2015).

Gate and Cysique (2016) note early cART is not without its long term concerns in terms of cumulative toxicity and potential neuro/cardiotoxicity, as well as variable adherence level in different HIV populations. The authors also speculate that with more people starting treatment earlier, the clinical prevalence of HAND is likely to shift even further towards milder forms, highlighting the need for early detection standardised screening tools validated for longitudinal assessment.

1.2.3. cART Toxicity and Adverse Side-effects

Although cART regimens are essential for the effective treatment of HIV infection, the chemical compounds also have intrinsic toxicity causing adverse side effects as part of routine use including Hepatotoxicity; Hyperglycaemia; Hyperlipidaemia; Lactic acidosis; Lipodystrophy, Diarrhoea and Skin rashes (Macarthur, 2013; Mind Exchange Working Group, 2013).

Such side effects have serious implications for treatment adherence. For example, non-infectious cART-related diarrhoea is a common side effect, occurring in 15% to 20% of HIV patients. Diarrhoea can disrupt patients' lives, negatively impacting quality of life, daily functioning and mood; significant factors contributing to whether individuals are willing and able to stick to strict medication regimes (MacArthur & DuPont, 2012). Supplementary treatments are emerging to treat certain cART-related side effects, and recommendations have been offered to addressing the impact of such experiences on adherence in clinical practice (Chordia & MacArthur, 2013; Macarthur, 2013).

Some cART types have also been associated with impairments in neuropsychological performance (Ciccarelli et al., 2011) and mental health difficulties (Foster, 2003). Robertson et al. (2010) reported improved cognition for up to 96 weeks in a group of immunologically and virologically stable people who elected to pause their cART regimens. The literature regarding the neurotoxic effect of cART is revisited later.

1.3. HIV-associated Neurocognitive Disorders (HAND)

1.3.1. Nosology of HAND

The terminology used to conceptualize HIV-associated changes to cognitive functioning has undergone substantial evolution since its initial characterization. Prior to 1991, a single disorder known as ‘HIV-associated dementia’ (HAD) captured the pathology of the observed cognitive impairment caused by severe immune suppression. The ‘minor cognitive motor disorder’ (MCMD) category was then introduced for patients with cognitive complaints who failed to meet the diagnostic threshold for HAD. Subsequently, with the introduction of the "Frascati Criteria," Antinori et al. (2007) proposed that existing classifications be revised into three tiered categories of impaired neuropsychological test performance and functional impairment under the umbrella term of ‘HIV-associated neurocognitive disorders’ (HAND). From most to least severe, the levels of impairment are; HIV associated dementia (HAD), Mild Neurological Disorder (MLD) and Asymptomatic Neurocognitive Impairment (ANI). A diagnosis of HAND requires acquired impairment in at least two cognitive abilities. HAD requires marked impairment, MND requires mild impairment, and ANI is clinically observable but does not interfere with daily function (Letendre, 2011). See Appendix A for further diagnostic criteria.

Although this nosology is used widely in clinical and research settings, it has not been universally adopted. Critics argue that the relevant biological substrates, prognostic significance and therapeutic implications of the categories are not clearly established (Gisslén, Price, & Nilsson, 2011). A diagnosis of ANI can be awarded without evident functional impairment in daily living, based only upon an observed performance on formal neuropsychological testing. Gisslén, Price and Nilsson (2011) argue that this leads to over-estimated prevalence rates of neurological pathology in the normal HIV clinical population. However, Gates and Cysique (2016) argue that without the sensitive Frascati Criteria, the majority of HAND cases in cART-treated cohorts would be excluded from RCTs leading to a significant and far reaching impact on research into the neurocognitive consequences of HIV infection. Assuming that the global prevalence rates for mild HAND may represent ‘‘the tip of the iceberg’’ of HIV associated neuropsychological change, Gates and Cysique (2014) advocate for the inclusion of ANI and MND subtypes into RCTs and longitudinal studies for

monitoring and evaluation of treatment effects. Furthermore, a diagnosis of ANI is associated with a 2-fold increased risk of symptomatic HAND, as compared to a diagnosis of normal cognition (Sacktor et al., 2015). Neuropathological changes often precede the onset of neurodegenerative disorders by decades and build up slowly over time (Jansen et al., 2015), and this provides evidence for the clinical value of ANI in assessment and early intervention in HAND, enabling targeted and timely care provision.

1.3.2. Prevalence

In the pre-cART era, severe cognitive impairment was common in individuals with HIV infection and affected up to 50% of patients before death (Grant et al., 1987; Nightingale et al., 2014). At that time, HAD was a progressive disorder leading to death within months. However, since the advent of cART, prevalence estimates for HAD have fallen from 16% (McArthur et al., 1993) to less than 5% (Heaton et al., 2010).

Milder subtypes of HAND have, in contrast, persisted and increased in incidence alongside the reduced mortality of HIV (Heaton et al., 2011). These expressions of HAND appear in the earlier stages of infection, which, in line with cART slowing down the progression of the illness, is a period of time that is maintained for much longer then before (Heaton, Clifford, & Franklin, 2011). The persistence and progression of cognitive impairment in the cART era is well supported by brain imaging studies which show the continued deleterious impact of HIV infection on the brain in the post-cART era (Harezlak et al., 2011; Hua et al., 2013)

In a large (N=1555) diverse sample of people with HIV infection, Heaton et al. (2010) reported that 52% of the sample had some form of HAND. This estimate broke down into 33% with ANI, 12% with MND, and 2% with HAD. In comparison to this, in the more recent Multicentre AIDS Cohort Study (MACS), Sacktor et al. (2015) reported overall prevalence rates of 25%–33% of HAND. This is somewhat lower than that observed in the aforementioned study, but may reflect demographic and clinical differences among these cohorts.

As such, although the exact prevalence estimates of mild forms of HAND vary depending on the population and neurocognitive tools and definitions used

(Nightingale et al., 2014), it is widely acknowledged that mild forms of HAND remain a significant problem for patients whose HIV is otherwise well controlled. Consequently, disruption to everyday neurocognitive functioning is one of the most common complications experienced by people with HIV (Sanmarti et al., 2014).

1.3.3. Neuropathogenesis of HAND

There is no single causal biological mechanism behind the neurocognitive consequences of HIV infection. The primary hypothesis concerns the impact of HIV on the central nervous system (CNS), one of the target systems where HIV can be detected. Soon after primary infection, HIV RNA may cross the blood brain barrier (BBB). HIV RNA concentrations can then accumulate, leading to HIV-related neuropathology. In untreated HIV replication, the BBB becomes increasingly permeable, allowing the crossing-over of many cell types. This may, in part, explain the greater prevalence of HAD in the pre cART era and why - since cART has successfully controlled HIV RNA replication - HAD has decreased in frequency and severity (Heaton et al., 2011). Gates and Cysique (2016) note that further research is needed to determine how relevant this model is for accounting for the neuropathology of HIV in the context of long-term virally suppressed HIV infection and cART exposure.

A further theory of HIV neuropathogenesis looks at the differential levels of HIV RNA located in the cerebrospinal fluid (CFS) and the blood, following evidence that the virus can be detected in the CFS in the absence of comparable levels in the blood (Canestri et al., 2010; Edén et al., 2010). Termed CFS 'viral escape' (Ferretti, Gisslen, Cinque, & Price, 2015); the cause of this phenomenon has been attributed to insufficient 'CNS penetration effectiveness' (CPE) of cART to areas in the CFS where HIV replication has occurred. This hypothesis has been used to explain the sustained prevalence of milder subtypes of HAND, and had led to a surge of research into higher CPE cART regimes based on the assumption that these will proffer better cART treatment results with reduced prevalence of mild HAND. However, few studies have since supported this assumption (Smurzynski et al., 2011; Sterne et al., 2009) and the actual levels of HIV needed in the CNS in order for HAND to develop is currently unknown. Studies have shown that HAND can develop and progress despite viral suppression in both the blood *and* CSF in 10–30 % of

cases (Antinori et al., 2007; Canestri et al., 2010). Cross et al. (2013) investigated the differential cognitive outcomes of people using ARTs with different CPE levels, for one year. Participants treated with cART were more likely to maintain or improve cognitive function compared to those without cART, but there was no difference in cognitive outcomes based on CPE levels. Furthermore, in some cases, high CPE cART have been associated with *increased* cognitive impairment (Ciccarelli et al., 2011; Marra et al., 2009; Reust, 2011); higher rates of HIV dementia (Caniglia et al., 2014); and other adverse side effects including: sleep disturbances, abnormal dreams, depression, fatigue, vomiting, fever, and headaches (Reust, 2011).

Decloedt, Rosenkranz, Maartens and Joska (2015) reviewed the multiple mechanisms which may affect the CPE of cART, concluding that the relationship between CPE and virological control is non-linear, multifaceted and dependant on numerous factors. Accordingly, there remains a consensus in the literature that the clinical relevance of CSF viral escape hypothesis is not yet well understood, and it is unclear what persistent levels of HIV RNA in the CSF mean for the development of HAND (Gates & Cysique, 2016).

As well as viral replication, there are many other factors that may contribute to HAND pathogenesis, including the role of intrathecal inflammation (Cysique et al., 2013; Gongvatana et al., 2013; Harezlak et al., 2011) and the interaction between chronic immune activation and aging on the CNS (Cysique, Bain, Brew, & Murray, 2011). Furthermore, where cART is widely available, drug resistance, poor adherence, and phenomenon of cART neurotoxicity (Berger & Clifford, 2014) are all factors which may contribute to or intensify the pathogenicity of HIV and the development of neuro-cognitive impairment (Patel et al., 2013).

The relationship between the potential neurotoxic effects of cART and the development of milder forms of HAND is still relatively unclear. Although cART has seen an irrefutable reduction in the more severe forms of HAND, its function as either a protective or causal contributing factor in the development of the milder forms of HAND is an ongoing debate. While some studies report modest improvements in neurocognitive function in people with HAND after starting antiretroviral treatment (Al-Khindi, Zakzanis, & van Gorp, 2011; Cohen et al., 2001; Cysique et al., 2010; Tozzi et al., 2007) other studies contend that the cART has a

negative impact on cognitive function (Ciccarelli et al., 2011; Robertson, Liner, & Meeker, 2012) or no impact at all on mild neurocognitive impairment (Kore et al., 2015). Such inconsistencies are partly due to the fact that variables in the medical field have, up until now, been in a state of constant change and therefore hard to measure. Furthermore, it is difficult to differentiate potential universal negative side effects from health issues caused by the HIV infection itself interacting with the social determinants of health.

1.3.4. Onset and Temporal Progression of HAND

HIV infection may start affecting neurocognitive function immediately after infection (Reger, Welsh, Razani, Martin, & Boone, 2002; Sacktor & Robertson, 2014; Weintraub, Wicklund, & Salmon, 2012), however, unlike many other neurodegenerative conditions such as Alzheimer's and Huntingdon's diseases, HAND is not invariably progressive. Indeed, Heaton et al. (2015) reported that there are variable clinical trajectories in HAND, stating that neurocognitive change is common and people may demonstrate considerable recovery of cognitive functions, decline, or static impairment.

1.3.5. Treatment of HAND

Gates and Cysique (2016) report that no individual agent or specific treatment plan has unequivocally yielded benefits for treating or preventing HAND. However, given that advanced immunosuppression remains the strongest correlate of neurocognitive impairment (Heaton et al., 2010; Heaton et al., 2011), the primary treatment of HAND follows the aforementioned BHIVA guidelines (i.e., promptly commencing cART) to control viral replication and boost immune health.

Weber et al. (Weber, Blackstone, & Woods, 2013) note that, over the last two decades, the treatment of HAND has fallen in the shadow the of the virological management of HIV infection. The authors elucidate the relative sparsity of research investigating the efficacy of cognitive rehabilitation for HIV-associated neurocognitive impairment and advocate for the development, validation, and clinical deployment of cognitive neurorehabilitation interventions tailored to the needs of persons living with HIV. Although such efforts can be seen in recent studies by Livelli et al. (2015), and Casaletto et al. (2016), which report positive findings with regards to the potential for

neuropsychological techniques to manage and improve cognitive impairments in HAND, this remains a new and emerging field of treatment.

1.4. HAND co-morbidities

Over 90% of individuals with HIV infection are believed to have some form of co-morbidity, including a range of medical, psychological, and co-morbid conditions (Heaton et al., 2009, 2011). The Antinori et al. (2007) online supplement provides detailed guidelines for classifying the most commonly encountered co-morbid conditions experienced by people with HAND, and whether they should be considered incidental, contributing, or confounding with regards to their impact on HAND.

Gates and Cysique (2016) highlight the complex and idiosyncratic interaction between HAND and co-morbidities, emphasising that although certain co-morbidities may suggest a non-HIV cause for cognitive impairment, they may also compound or interact HIV's effect on the CNS in a more complex nuanced manner. This marks a shift in focus away from the more traditional clinical practice of 'identify and separate' 'pure HAND' from co-morbidities, to an acknowledgement of the fluctuating and interactional nature of HIV chronicity, co-morbidities and HAND. This view is in keeping with the aforementioned concept of 'episodic disability' (O'Brien et al., 2008).

1.4.1. HAND; Social Co-morbidities

HIV infection is most prevalent in under resourced and economically marginalized and oppressed global areas. Although cART is considered the universal gold standard of HIV treatment, access to said treatment in areas with the greatest prevalence remains the most limited. It is beyond the scope of this study to pay credence to the geopolitical context in which this longstanding inequality occurs, but an awareness of the global disparity is fundamental to an understanding of why, in considering the HIV-related health consequences, social co-morbidities are a substantial factor. Indeed, Tedaldi et al. (2015) advocate that HAND literature should focus on the intersectional nature of physical and social co-morbidities in a global assessment schema.

1.4.1.1. Educational Experience and Culture

Due to inherent cultural biases within the test materials, individuals from certain racial and ethnic groups can disproportionately obtain lower scores on a broad range of cognitive assessment task in comparison to their counterparts (Bernard, 1989; Gurland, Wilder, Cross, Teresi, & Barrett, 1992; Manly et al., 1998). This puts said groups at risk of incorrect test interpretation and false-positive diagnoses following test administration (Manly et al., 2011). In view of this, 'education attainment' has been used as a way of accounting for these differences, as it is an additive life experience which relates to many of the biases in test materials, and varies between different demographic groups. Furthermore, it has been shown to have a significant impact on neuropsychological test performance.

Educational attainment can be quantified using 'total years of education' or 'quality of education' (as assessed using reading ability). However, the latter has been shown to be a stronger predictor of cognitive performance in groups most commonly affected by this phenomenon (Dotson, Kitner-Triolo, Evans, & Zonderman, 2008, 2009), and has been reported to account for a large proportion of the variance in tests of psychomotor speed and executive function between participants with and without HIV infection (Manly et al., 2011).

More structural efforts to address said cultural and educational biases were made by Manly et al. (2011) who sought to collect and develop more appropriate normative data for selected neurocognitive tests using a large group of ethnically and educationally diverse HIV-uninfected, high risk women, as well as their HIV-infected counterparts.

1.4.1.2. Poverty and Trauma

Tedaldi et al. (2015) note that poverty and exposure to adverse life experiences may deplete the 'cognitive reserve' of people prior to contracting HIV. The cognitive reserve hypothesis is the notion that humans have extensive neuronal connections that can protect neurons when they are subjected to injury through oxidative stress or inflammation. The available protection can be influenced by positive or negative neuroplasticity (Patel et al., 2013; Vance, Fazeli, Grant, Slater, & Raper, 2013). This hypothesis may be particularly relevant for the global population of people living with

HIV, of whom so many are from impoverished living conditions, with exposure to limited social resources, violence, and cumulative traumatic experiences (Spies, Fennema-Notestine, Archibald, Cherner, & Seedat, 2012). If life experiences can erode neurocognitive reserves, then impairment occurring in the context of HIV infection may occur as a result of pre-existing idiosyncratic cognitive decline. This is supported by a study by Troeman et al. (2011) where childhood trauma was demonstrated to have an impact on functionality and quality of life for people living with HIV infection.

1.4.1.3. Stigma

In one of the first studies to consider the contextual factors that contribute to the experience of living with HIV, O'Brien et al. (2009) exposed the continued impact of stigma in exacerbating people's experience of HIV-related disability. People with HIV-infection reported experiencing stigma from family, work colleagues, employers and health care providers due to their HIV status, sexual orientation, ethno-cultural background, employment status and/or gender. These experiences were reported to be associated with problems such as low self-esteem, elevated stress, anxiety and depression, and shame and embarrassment, and present barriers to social inclusion, for example; inability to work, and difficulty initiating or maintaining personal relationships (O'Brien et al., 2009). Experiences of stigma have been shown to exacerbate depression for those living with HIV (Relf & Rollins, 2015) as well as intersect with other forms of discrimination (Galvan, Davis, Banks, & Bing, 2008), and contribute to negative plasticity in the cognitive reserve hypothesis.

1.4.2. HAND; Physical Co-morbidities

1.4.2.1. Age

Although individuals with HIV infection are now able to live longer healthier lives than in the pre-cART era, as yet, little is known about the impact of ageing on HAND. One prediction is that the prevalence of HAND will continue increase alongside people with HIV living longer (Gates & Cysique, 2016; Heaton et al., 2015; Kupprat et al., 2015).

Valcour et al. (2004) highlighted the unique health concerns of older people, specifically noting the cumulative neurotoxic effect of cART, and its interaction with aging, immune activation, and HIV associated co-morbidities. In this study, older participants were found to have higher rates of HIV associated dementia (HAD), less resilient immune systems, and higher rates of other co-morbidities related to HIV and medication side effects, than other HIV age cohorts.

Gate and Cysique (2016) state that the ageing process may have the potential to actually alter the profile of neurocognitive deficits in HAND, either by accelerating HIV-related neurocognitive decline, or by involving new cognitive deficits not typical of HIV-related brain injury.

1.4.3. HAND; Psychological Co-morbidities

Rates of anxiety and depression in people living with HIV are common, with prevalence as much as two to three times higher than those observed in the general population (Tucker, Burnam, Sherbourne, Kung, & Gifford, 2003), and higher than any other mental health difficulty in people living with HIV (Nakasujja et al., 2010). Such difficulties can interact with the demands of coping with, and managing, a long-term health condition in a multitude of ways. For example, the difficulty in structuring daily life and following strict treatment plans can lead to increased rates of medication non-adherence, which in itself can lead to worse health outcomes, neurocognitive impairment and increased mortality (Ammassari et al., 2004; Anand, Springer, Copenhaver, & Altice, 2010).

The prevalence of HIV infection in people with a diagnosis of ‘schizophrenia’ is higher than the general population, estimated to be between 4% and 23% (Cournos & McKinnon, 1997; Perälä et al., 2007). Furthermore, both ‘schizophrenia’ and ‘bipolar’ disorder are higher in people with HIV-infection who also have substance misuse problems, and those who are from lower socio-economic backgrounds (Tedaldi et al., 2015) . The psychological experiences associated with such diagnoses have been shown to have a profound and complex interaction with cognitive functioning, either directly or indirectly as a result of neuroleptic medication (Kasper & Resinger, 2003).

1.5. Neuropsychology of HAND

1.5.1. Neuropsychology Assessment

Neuropsychological assessment is a performance-based method of assessing cognitive function. It is used to examine the observable cognitive consequences of brain damage and disease, and has several specific uses including collection of differential diagnostic information, assessment of treatment response, prediction of functional potential, and identification of rehabilitation and recovery treatment plans (Harvey, 2012).

Despite the unprecedented developments in brain imaging technology which have enabled researchers to look inside the active living brain to observe changes in brain structure and function, it remains the case that the presence of severe brain changes can be associated with nearly normal cognitive functioning, while individuals with no such lesions can have substantial cognitive and functional impairments. As such, clinical neuropsychological assessment continues to be of significant clinical value, both as a research method and a clinical assessment tool. Woods et al. (2009) advocate that the neuropsychological approach has particular value in HIV care, elucidating the component processes and cognitive mechanisms of HAND and informing clinical understanding and contributing towards the development of targeted therapeutic interventions.

1.5.2. Assessment Tools for HAND

The HIV Dementia Scale is shown to reliably identify people with HIV infection who are suffering with HAD, but has limited ability to detect ANI and MND (Sacktor et al., 2005). The Montreal Cognitive Assessment (MoCA) has also been trailed for use with people with HIV, and although a valid brief measure, it too lacks the sensitivity to differentiate the milder HAND categories (Chan, Kandiah, & Chua, 2012; Kim et al., 2016; Overton et al., 2013). At present, The Mind Exchange Group (2013) guidelines (the product of an evidence-based process to develop and consolidate practical guidance for the screening, diagnosis, treatment and prevention of HAND) recommend the use of the MoCA to identify individuals who may subsequently require formal neuropsychological testing.

Alternative methods of assessing the impact of cognitive impairment include efforts to ascertain “real world” functioning, such as self- or informant reports. However, information gathered in this way is vulnerable to several factors, including, mood; impaired self-awareness; and, variability in subjective perspectives. For example, those with low mood may over-report deficits that are not objectively apparent (Millikin, Rourke, Halman, & Power, 2003) due to negatively biased thoughts and rumination (Baert, De Raedt, & Koster, 2010). Alternatively, problems may be under-reported, by patients or informants due to a conscious or unconscious desire to minimize the problem. Accordingly then, neurocognitive testing offers the opportunity to gain from the richness of self-report information as part of a ‘clinical interview’, and then corroborate such information against performance on standardised tests.

The Mind Exchange Working Group (2013) guidelines advise that all patients with HIV should be screened for HAND as early as possible in their disease; however, such assessments are often unavailable in outpatient settings, and specialist HIV services vary in the extent to which they offer in-house assessments or refer externally for service provision.

The lack of routine and standardised assessments for HAND has implications for people with HIV infection and health services. Services without routine screening assessments are unable to track the development of HAND in individuals with HIV infection, leaving them unable to monitor the impact of cART, as well as the complex interaction between the multiple risk factors for cognitive impairment.

1.5.3. Neuropsychological Profile of HAND

Although each person’s brain is affected by HIV in a different way, the region’s most commonly affected appear to be the basal ganglia and the hippocampus, the frontal neocortex and the white matter tracts connecting these regions, and the cerebellar grey matter of the mid-frontal cortex (Wiley et al., 2006).

Younger and middle-aged adults typically display a ‘‘subcortical’’ cognitive profile of bradykinesia, bradyphrenia, executive dysfunction, and deficient memory encoding and retrieval (Heaton et al., 1995). Some researchers have queried whether the development and expression of HAND in older adults might display a more ‘cortical’ profile (e.g., temporal and parietal lobe) than that seen in younger people with HIV

infection, following evidence of pathology in HIV-infected individuals that may be similar to that observed in traditional “cortical” dementias (Ances et al., 2010; Gelman & Schuenke, 2004). However, this remains a controversial hypothesis and the research is yet unclear, with both Iudicello et al. (2012) and Scott et al. (2011) finding that the combined effects of HIV and aging did not result in a ‘‘cortical’’ pattern of cognitive deficit.

There is substantial variability in clinical expressions of HAND and the spectrum of impairments characteristic of HAND have evolved alongside the sustained aviremia and immune recovery following effective cART. In this changing context, further research is required in order to ascertain a distinctive pathophysiological mechanism or diagnostic pattern of HAND (Dawes et al., 2008). That said, the literature reports general trends of particular impairments, as outlined below.

Twenty-five years ago HAND presented as a severe motor and cognitive disorder in patients at advanced stages of infection, whereas now it typically manifests as milder and more common disturbances of psychomotor speed, processing speed, executive function, or memory (Heaton et al., 2010; Spudich, 2013). These trends are supported by the findings of a study by Heaton et al. (2011) which compared the characteristics of HAND in pre- and post-cART eras. The authors reported that pre-cART HAND saw impairments mostly in motor skills, processing speed, and verbal fluency, whereas post-cART era has seen an increase in learning and memory and executive function impairments.

The literature regarding the impact of HIV-infection on these specific areas and core domains is discussed below. Whilst the following sections have been artificially separated to enable a clear overview of the current literature, optimal performance of any particular cognitive ability typically requires multiple cognitive abilities to be intact for successful execution. Furthermore, the researcher acknowledges the socially constructed nature of these terms, and seeks to employ them as part of a pragmatic endeavour rather than as part of an essentialist discourse.

1.5.3.1. Attention and Working Memory

Attention is a multifaceted ability that involves the capacity to orientate oneself and maintain and shift focus in the context of multiple stimuli (Iudicello et al., 2008) and

attention deficits in HAND are thought to be among the earliest to develop (Butters et al., 1990; Heaton et al., 1995; Levine et al., 2008).

Heaton et al. (1995) used six neuropsychological measures to assess attention. Using a principal components analysis, the authors determined that the key underlying factors common among the multiple measures were “Attention/Speed of Processing” (as assessed by Digit Symbol, Digit Vigilance time, Trails Making Test Parts A & B) and “Attention/Working Memory” (as assessed by Digit Span). Thus suggesting that attentional factors were multifactorial and closely related to processing speed and working memory.

1.5.3.2. Motor Skills and Information Processing Speed

Woods et al. (2009) note that bradykinesia (i.e., slowed movement) and bradyphrenia (i.e., slowed information processing) are cardinal symptoms of HAND and may even underlie deficits observed in other neurocognitive domains.

Both conditions are characteristic of HAD, and used to be commonly observed in the pre-cART era, alongside impaired rapid eye movements, reduced gait velocity, hyper-reflexia and release signs (Heaton et al., 2011; McArthur et al., 1993). Whilst bradykinesia-associated impairments have drastically declined in the post-cART era (Baldewicz et al., 2004), bradyphrenia- associated impairments appear to have sustained a high prevalence in HAND. Within this context, it is important to note that the assessment and measurement of information processing ability is complicated by the ill-defined nature of ‘information processing speed’ and difficultly separating out impairments in this, from other areas, such as attention or working memory.

In a longitudinal study, Baldewicz et al. (2004) reported the participants with HIV scored lower than controls on tests of information processing throughout the course of the study. Further, Fellows, Byrd and Morgello (2014) assessed information processing speed in a sample of racially and ethnically diverse men and women living with HIV/AIDS and concluded that reduced information processing speed may be seen as a primary deficit in HAND, which may also account for other HAND impairments.

As identified above, information processing speed is closely related to attention (Levine et al., 2008). Both processing speed and attention are believed to have a fundamental role in supporting higher order skills, and impairment in these areas can result in deficits in other cognitive domains (Levine et al., 2008).

1.5.3.3. Learning and Memory

HAND is commonly associated with impairments in episodic memory and explicit memory (Iudicello et al., 2008; Woods et al., 2009). Mild to moderate deficits in episodic memory are common in the early stages of HAND in both verbal and visual memory tasks (Woods et al., 2009). Intermediate memory and semantic memory, in contrast, remain relatively intact, with deficits not appearing until the more severe stages of HAND (Heaton et al., 1995, 2004). As such, it appears to be difficulties involved in the process of learning new information which is characteristic of the profile of HAND, whereas learned information is often retained (Woods et al., 2009).

1.5.3.4. Executive Function

Executive function refers to a wide range of complex cognitive skills including abstract reasoning, evaluation, decision-making, planning, organising, set shifting and inhibiting automatic responses. These are associated with frontal lobe function; including (but not limited to) the frontal cortex, the basal ganglia and the posterior parietal cortex (Poletti, Enrici, & Adenzato, 2012; Stuss & Levine, 2002). Impairments in executive functioning are common and central to HAND in the cART era (Reger et al., 2002). HAND studies have consistently shown deficits in abstraction and problem solving (Heaton et al., 1995), inhibition (Hinkin, Castellon, Hardy, Granholm, & Siegle, 1999), set switching skills (Carter, Rourke, Murji, Shore, & Rourke, 2003; Reger et al., 2002) and social planning (Benedict, Mezhir, Walsh, & Hewitt, 2000).

Verbal fluency, another constituent of executive function, is also a substantial and common area of impairment in HAND, and has been so since the pre-cART area (Heaton et al., 2011). Rippeth et al. (2004) estimate that 50% of people living with HIV are impaired on verbal fluency tasks. A meta-analytic review of verbal fluency impairments in HIV infection reported that impairments ranged from mild-to-moderate in both letter and category fluency, and worsened with disease

progression (Iudicello et al., 2008). Furthermore, deficits in verbal fluency *switching* are uniquely predictive of self-reported declines in instrumental activities of daily living among older HIV-infected adults including medication and financial management (Heaton et al., 2004; Iudicello, Woods, et al., 2012; Woods, Morgan, Dawson, Cobb Scott, & Grant, 2006), a clear indication of the real-world implications of executive dysfunction.

1.5.3.5. Visuo-spatial Function

Research suggests that visuo-spatial cognitive abilities are relatively unaffected in HAND. Heaton et al. (1995) propose that this is because the associated regions of the brain – the occipital and parietal lobes - are some of the least affected by HIV virology.

1.5.4. Impact of HAND on Daily Living

Heaton et al. (2004) evaluated the 'real-world' impact of HAND in a group of 267 people with HIV infection. Participants with HAND performed worse on all measures of everyday functioning than those without, and cognitive impairments on tests of executive function, learning and memory, attention, and verbal abilities most strongly predicted functional impairments. Impairments in memory and executive functioning may be particularly disabling due to their functional implications for occupational employment, domestic or household responsibilities, social functioning and health care management. Impairments in executive functioning may also lead to increased impulsivity, poor planning and abstract thinking, and aggression (Gilbert & Burgess, 2008).

More specifically, an overview of the literature suggests that cognitive impairments are associated with difficulties with medication adherence (Hinkin et al., 2002; Levine et al., 2005); driving (Marcotte et al., 2004); employment, mood, fatigue, and interpersonal relationships (Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009). In addition to this, HAND has also associated with increased mortality (Ellis et al., 1997; Sevigny et al., 2007; Vivithanaporn et al., 2010).

1.6. Social Cognition

Social cognition refers to the range of cognitive mechanisms and processes that enable individuals to interact as social beings (Fiske & Taylor, 1991). Basic social interaction is essential for human survival, and as such, the effect of undetected impairment may potentially be very disabling and distressing for individuals and those in their social network (Saxe, Carey, & Kanwisher, 2004).

1.6.1. Background to Social Cognition

Social cognition is a relative new area of neuroscience, emerging from the literature of Evolutionary Psychology regarding the evolution of humans as a species equipped to function in social groups and Clinical Psychology research into disorders where impairments in social functioning are viewed as characteristic of the clinical presentation (e.g., ASC). That said, over the last two decades there has been growing research exploring social cognition in individuals with a diagnosis of schizophrenia (Green, Horan, & Lee, 2015), brain injury (Bibby & McDonald, 2005), the behavioural variant of FtD (Ruiz-Tagle, Musa, Lillo, & Slachevsky, 2015) and Huntingdon's Disease (Bora, Velakoulis, & Walterfang, 2016).

Historically, the neuroscience of social cognition has been dominated by conceptual framework of restrictive phrenology that links demarcated brain regions to underspecified social processes. Frith and Frith (2012) advocate for a break away from this reductive perspective, towards developing a mechanistic account of social processes. In view of this perspective, the authors explain that it is largely general mechanisms that enable our social processes.

Using a leading theory among many cognitive psychologists and neuroscientists, Frith and Frith (2012) make the distinction between implicit processes and explicit processes in social cognition; those that are automatic and those that are controlled. Adolph (2009) elucidates; at an implicit level, one has swift automatic social processes, fraught with biases and stereotypes of which we are often unaware. At an explicit level, there is the ability to consciously and strategically set up our behaviour to contribute to towards complex social means. A review by Lieberman (2007) outlines the various properties attributed to implicit and explicit processing in this

context, and Heyes (2011) provides an exploration of the problems raised by this distinction.

Frith and Frith (2012) outline a range of social processes which make up social cognition, including the perception and comprehension of biological status; the perception and comprehension of faces; the perception and comprehension of emotions; observational learning and copying; the attribution and tracking of others mental states; and, the ability to engage in reflective 'meta cognitive' discussion and thought processes. It is outside the scope of this study to comprehensively explore all of the social processes and underlying mechanisms which make up social cognition, and therefore, in keeping with the previous research (Ireland, 2011), the following discussion will focus on mentalising - the ability to attribute and keep track of the mental states of others.

Mentalising enables humans to understand one another with a high degree of precision, and is made up of both implicit and explicit social processes, both supported, in part, by general cognitive mechanisms. The implicit processes are involved in perspective taking and tracking the intentional states of others, and are likely shared with other social non-human species. The explicit processes, in contrast, refer to the conscious differentiation of mental states between self and other: that is, the articulated awareness that others' and one's own mental states can differ. This ability, the authors suggest, is more likely to be unique to humans along with our ability for 'meta-cognitive' self-reflective conversation (Adolphs, 2009; Frith & Frith, 2012).

Frith and Frith (2012) note that mentalising and 'Theory of Mind' (ToM) are often conflated in the literature, with mentalising often referred to as 'having a ToM'. The concept of ToM refers to an individual's ability to infer others' mental states; it is commonly considered to be a multidimensional construct and a key theory in the field of social cognition (Kalbe et al., 2010). However, the authors distinguish between mentalising and ToM on the basis that the linguistic connotations of the phrase '*theory of mind'* misleadingly implies *conscious* (i.e., explicit) processes only, thus obscuring the role of implicit processes.

1.6.2. Assessments of Social Cognition

Historically, in both general and clinical populations, social cognition has most commonly been assessed using tests devised from the ToM paradigm (Baron-Cohen, Leslie, & Frith, 1985).

ToM tests can also be described as tests of explicit mentalising (Frith & Frith 2012). These assessments involve the attribution of a character's beliefs; that is, they require participants to predict (and sometimes explain) behaviour based on a character's mental state. There are a variety of ToM tests now available, with more advanced ToM tasks presenting more complex situations.

As stated, difficulties with social communication are a key feature of ASC. A widely held theory which has been used to account for this is the idea that people with ASC have a deficit in ToM. This is based on the observation that sample groups of this nature have reliably been shown to perform more poorly on ToM tests than non-ASC controls (who are assumed to have no difficulty with social cognition). From this it is deduced that people with ASC struggle to see that other people's behaviour is motivated by underlying mental states (the basis of the ToM hypothesis), and that ToM tests tap into the impaired cognitive mechanisms inherent in people with ASC that bring about their real-life wide-spread difficulties with social abilities.

Begeer et al. (2010) compared the performance of people with ASC to a control group, on a novel test of ToM. The method of ToM assessment, in this study, involved using a ToM communication task which required real verbal interaction and thus 'online' processing of a social situation – markedly different to more traditional script- based tests of ToM. The authors hypothesised that the participants with ASC would show impaired performance relative to the controls, based on the aforementioned literature. However, the results found no such pattern, and the authors concluded that an absence of ToM deficits in verbal communicative interaction likely indicated an absence of systematically deficient ToM. A consideration of implicit and explicit processes of mentalising might also bare significance to these findings. Traditional ToM assessments typically assess explicit mentalising (Frith & Frith, 2012) and it is on these that the strength of the association between 'ToM deficits' and ASC is built (Frith & Frith, 2012; Yirmiya & Erel, 1998). However, the novel communication task used by Begeer et al. (2010) may have

involved different implicit and explicit processes, as well as underlying cognitive mechanisms, which may have influenced performance. Of note, although the ASC participants did not demonstrate deficit ToM, they did show a reduced tendency to use ‘mentalistic’ non-literal terms (e.g., affect-related words) to describe social narratives, than their non-ASC counterparts. So although there was a difference in communication styles which could be associated with social cognitive difficulties, it was not, in this instance, picked up by the ‘ToM’ test.

This relates to a critique of the ToM paradigm, which argues that a problematic interpretive leap has been made between the observable behaviour (performance on tests) and the existence of a hidden inner world of the 'mind' and of assumed mental processes (Shanker, 2004). Indeed, critics of the ToM paradigm have argued that the very idea that people with ASC have ToM deficits is an article of faith, contesting the validity and reliability of ToM. One such point concerns the discussion around what is a ‘normal’ score on the Reading the Mind in the Eyes Test (RMET), following variations in the literature (Baron-Cohen et al., 2001; Fine, 2011). Additionally, Fine (2011) highlights the impact that implicit cognitive biases can have on performance on ToM tasks: detrimentally affecting performance leading to misattribution of ‘impairment’ in certain groups (i.e., stereotype bias and gender).

Although substantial advancements have been made in determining the neural underpinnings of social cognition in recent years (Saxe, 2006), there remains a dearth in the development of assessment tools for social cognitive processes. These criticisms of ToM support a rationale for including multiple forms of assessment to allow for the cross-referencing of test outcomes.

1.6.2.1. Affective and Cognitive Theory of Mind

ToM has been conceptualised as comprising of two separate subcomponents; ‘cognitive’ and ‘affective’ (Stone et al., 1998). Cognitive ToM concerns the ability to use abstract reasoning to understand another person’s mental state, and affective ToM concerns the social-perceptual understanding of non-verbal emotional processing. In support of this differentiation, various studies have reported that individuals are differentially impaired on tests of cognitive and affective components of ToM. Torralva et al. (2015) found that patients with FtD were more impaired on

tests of affective ToM, than cognitive ToM, in the early stages of the disease. Similarly, both Ireland (2011) and Homer et al. (2013) reported that people with HIV infection demonstrated greater trends of impairment on a test of affective ToM (as assessed using the RMET) than on a test of cognitive ToM; and that performance on both tests was independent of each other.

1.6.2.2. Theory of Mind and Executive Function

The 'domain-general' hypothesis of ToM is the widely held view that ToM skills rely on executive functioning abilities in order to operate. This theory argues that impairments in ToM (and social cognition more generally) occur due to underlying impairments in executive functioning, for example, response inhibition (Henry, Phillips, Crawford, Ietswaart, & Summers, 2006). In support of this hypothesis, a study by Hughes and Russell (1993) - which looked at social dysfunction in children with ASC - reported that subjects social cognition impairments were secondary to a more general deficit in executive function, rather than a specific deficit in social cognition.

However, an alternative theory is that ToM is domain specific (Stone & Gerrans, 2006). This view posits that aspects of social cognition and executive functioning, whilst both associated with frontostriatal brain regions, may have distinct neural pathways which can be impaired without causing injury to the other. This is supported by several studies from the field of FtD - a spectrum of degenerative conditions associated with focal atrophy of the frontal lobes - which has a behavioural variant characterized by progressive deterioration in social function (Rascovsky et al., 2011). See Harciarek and Jodzio (2005) for a review in this area. In regards to HAND, both Ireland (2011) and Homer et al. (2013) reported that subjects demonstrated impaired performance on ToM tests, independent to impairments in executive function. Finally, Roca et al. (2010) argue that there is something specific to ToM skills for which executive functions do not account, and they advocate for the separation of ToM and executive function; emphasising the importance of assessing ToM independently to other cognitive domains.

1.6.3. Emotional Perspective Taking: Empathy

Also conceptualised as emotional perspective taking (Adolphs, 2009; Frith & Frith, 2012), Empathy has been identified as one of the most important mechanisms which contribute towards overall social cognition (Blakemore & Frith, 2004).

Until recently, there has not been a general consensus as to its definition. Existing descriptions have tended towards a view of empathy as involving either the recognition of emotion, the experience of it, or both (Batson, 2009; Blair, 2005; Decety & Lamm, 2006; Elliott, Bohart, Watson, & Greenberg, 2011; Gini, Albiero, Benelli, & Altoè, 2007; Lawrence, Shaw, Baker, Baron-Cohen, & David, 2004; Spinella, 2005)

However, Reniers et al. (2011) propose that instead of being at odds with one another, these elements of empathy are neurocognitive processes which, although partly separate, are encompassed within the wider concept of empathy. The authors pull together and synthesise much of the dominant literature on empathy, and propose a model which defines empathy as a multifaceted construct that can be delineated into two core parts, cognitive empathy and affective empathy. Cognitive empathy concerns one's ability to construct a working model of the emotional states of others, whilst affective empathy is the ability to be sensitive to and vicariously experience the feelings of others. Distinguishing cognitive empathy from TOM, Reniers et al. (2011) explains that optimal "cognitive empathic skills are likely to draw on many of the same underlying process that enable ToM, but, cognitive empathy is concerned with the attribution of *emotions* as opposed to *cognitions*, and as such the two constructs are potentially dissociable" (Reniers et al., 2011, p. 85).

Frith and Frith (2012) note that empathy, even though likely underwritten by a general mechanism of association learning, has some claim to be a specifically social process, having social content and being solely in the service of social functionality.

1.6.4. Prefrontal Cortex and Social Cognition

In a review on the neurobiology of social cognition, Adolphs (2009) notes that our neural mechanisms have evolved to allow for social interaction, and specialization may be evident at the level of neural processing. The prefrontal cortical regions of

the brain appear to be the areas that have expanded the most in human evolution (Holloway, 2002; Semendeferi, Armstrong, Schleicher, Zilles, & Van Hoesen, 2001) and are involved in uniquely human capacities, including numerous complex abilities required to negotiate the social word in which we live (Stuss & Levine, 2002). In line with technological advances, neuroimaging studies are beginning to identify structures that play a key role in guiding social behaviours and communication, including (but not limited to) regions of the prefrontal context (PFC). Adolphs (1999, 2009) cautions that many questions remain about the modularity or domain-specificity social cognition, its intersection with emotion and with communication, and about the methods best suited for its investigation.

Regions in the PFC have been implicated in social cognition dating back to the case of Phineas Gage (Damasio, 1994) which associated damage to the PFC with an impaired ability to plan and execute future activities; a reduced capacity to respond to punishment; increased inappropriate social manners, and an outward lack of concern for others, all alongside otherwise intact and normal intellectual functioning. Since then, existing studies in neuroscience offer various examples of where impairment to PFC is associated with impaired social ability. The medial prefrontal cortex has been linked to ToM abilities in a number of imaging studies (see Adolph, 1999 for a review of 17 studies) and, in lesion studies, damage to orbitofrontal cortex has been linked with impaired ability to recognize a violation of social norms in a social narrative (Bibby & McDonald, 2005; Stone et al., 1998). Furthermore, ASC too have been shown to correlate highly with structural abnormalities in the PFC (Happe & Frith, 1996).

Huntingdons and ftD are both degenerative neurological conditions which cause focal atrophy in the PFC. Studies from both conditions report progressive deterioration in social abilities and difficulty maintaining interpersonal relationships in line with neural damage and alteration (Kipps & Hodges, 2006; Rascovsky et al., 2011; Snowden et al., 2003).

1.6.5. Neural Correlates of Explicit Mentalising

Frith and Frith (2012) state that the cognitive mechanism for mentalising is carried by a network of frontal and temporo-parietal regions of the brain. Current research on the neural correlates of ToM (i.e., explicit mentalising), suggest that the act of

making inferences about mental states engages various regions in the PFC (Apperly, Samson, Chiavarino, Bickerton, & Humphreys, 2007; Koster-Hale & Saxe, 2013; Lieberman, 2014). The region of the PFC most commonly associated with ToM abilities appears to be the dorsomedial PFC (Schurz, Radua, Aichhorn, Richlan, & Perner, 2014), which is linked with perspective taking abilities and direct and reflected self-knowledge (Ochsner & Gross, 2005).

Despite a large body of literature implicating the dorsomedial PFC in ToM tasks, little is known about the neural underpinnings of the implicit mentalising (Frith & Frith, 2012).

With regards to the aforementioned distinction between cognitive and affective ToM, Shamay-Tsoory and Aharon-Peretz (2007) found that the dorsolateral PFC is linked to the 'cognitive' component of ToM whilst the ventromedial PFC has been associated with the 'affective' aspects of ToM. Kalbe et al. (2010) also investigated the possible neural correlates of affective and cognitive ToM in a study with healthy male subjects. The authors reported evidence for the functional independence of cognitive from affective ToM, and identified the possible role of the right dorsolateral PFC in cognitive ToM.

1.6.6. Social Cognition and Context

Social Cognition is sensitive to context, and the brain regions involved in social cognition are modulated in their activation by social context and volitional regulation (Adolphs, 2009). An example of how contextual information affects social information processing is shown in a study by Kim et al. (2004), which reported that information about faces was processed differently depending on context. A surprised face was interpreted as looking either afraid or happy, depending on the preceding priming sentence. Interpretation of context and degree of individual control varies between individuals and substantial differences exist in many of the processes and structures discussed above (Adolphs, 2009).

1.7. Social Cognition in HAND

Mild decline in social functioning is included in the classification criteria for ANI but impairment to social cognition is not explicitly defined as a component in the

neuropsychological profile of HAND (Andrea Antinori, Arendt, Grant, Letendre, & Muñoz-Moreno, 2013).

A small study by Ireland (2011) reported that participants (N=16) with HIV infection showed social cognition deficits which existed separately to that of other patterns of cognitive impairment including executive function performance. Assessment of social cognition was achieved using two tests of ToM, representing both cognitive ToM and affective ToM. Participants appeared more impaired on a test of 'cognitive ToM' (Strange Stories Task; SST) than the 'affective ToM' (RMET).

These findings were supported by the results of a study by Homer et al. (2013) who explored the impact of methamphetamine-use and HIV infection on performance on two measures of ToM, (the RMET and a Faux Pax Test) and a test of executive function (Stroop Colour and Word Test). The authors found that HIV infection was associated with impaired performance on the RMET, and methamphetamine-use was associated with impaired performance on the Faux Pas Task. The different performance across the two ToM tests was said to reflect the different underlying cognitive mechanisms required; in contrast to the RMET's basic "bottom-up" perceptual process, the Faux Pax Test may be rely on "top-down" script-based processing, where successful performance requires access to 'offline' overlearning knowledge about social norms and conventions rather than 'online' in-the-moment social processing (Homer et al., 2013). Thus, the authors concluded, certain everyday social communications may be dependent on pre-existing rote knowledge of social behaviour, and require little active social cognition. In view of this, individuals with HIV might rely on overlearning knowledge to compensate for impairment in 'online' mentalising. This view is supported by the results of a study by Porter, Coltheart and Langdon (M. A. Porter, Coltheart, & Langdon, 2008), who explored social cognition in individuals with Williams Syndrome, and reported that the subject demonstrated impaired performance on ToM tasks that did not involve social scripts, but no such deficits in similar tasks that did involve social scripts.

1.8. Rationale

As people with HIV in the UK continue to live longer and healthier lives, so the longevity and complexity of HAND continues to increase. In the context of the

emerging chronicity of HAND in the post-cART era, it remains the case that the cause and temporal progression of HAND remain unclear, and no cART or other therapy has shown unequivocal benefits for treating or preventing HAND. What remains, therefore, are the disabling effects of cognitive impairment for people with HIV in everyday life, including pervasive impact on quality of life, and potential compromise of treatment adherence impacting long-term virological control and HAND phenomenology. In this context, Clinical Psychology has a clear role in developing the wider understanding of the neurocognitive consequences of living with HAND, which in the current study, focuses on exploring the emotional and behavioural sequelae of HAND using the theory of social cognition.

The frontal lobe areas of the brain are implicated in HIV CNS infection, and, as reviewed above, there is a vast literature from non-HIV clinical populations detailing the relationship between PFC injury and social dysfunction; particularly so with explicit mentalising and emotion recognition (Amodio & Frith 2006). These skills may be critical to social communication (Saxe, 2006) and a key aspect of everyday social cognition and associated impairments may be disabling for those concerned.

Despite this, there is a relative dearth of research into the profile of social cognition impairments in HAND. In the last six years, studies by Homer et al. (2013) and Ireland (2011) both reported trends in impaired explicit mentalising and emotion recognition skills in people with HAND, independent to executive dysfunction or global cognitive decline. These findings suggest that social cognitive impairments may be characteristic of HAND, and although these results remain tentative and based on small numbers, they highlight the need for further research in order to explore, replicate and extend findings, and move closer towards conclusions generalizable to the clinical population. In view of this, the current study aimed to build upon existing research to explore the profile of social cognition impairments in the neuropsychological profile of HAND.

1.9. Research Questions

The following research questions were devised based on the findings and recommendations of Irelands (2011) study in which specific recommendations were made with regards to; the continued exploration of social cognition impairments

within a diverse HIV-positive adult cohort; the continued focus on specific ‘areas’ of social cognition with the view to remain within the same constructs within social cognition; and, the selection and application of different test materials for the assessment of social cognition in order to minimise confounding variables and improve ecological validity. Irelands (2011) recommendations for test materials are detailed alongside the rationale for each individual test selection in the ‘Method’ section.

The research questions are as follows:

1) What is the cognitive profile (areas of strength versus weakness) of social cognition in HAND? Does HAND affect, or differentially affect, for example
    a. cognitive-linguistic function e.g., comprehension of non-literal language
    b. emotion recognition e.g., of facial expression
    c. empathy e.g., capacity to engage with other persons.
2) Is there a correlation between stage of HIV illness and social cognitive functioning?

This study will employ a number of neuropsychological tests and questionnaires in order to explore the research objectives. Utility of such tests rests on the underlying assumption that visible and measurable performance echoes something about the invisible and unmeasurable internal biological functioning of the individual in their context. It is important to note that there are many variables which may affect performance on tests, separate to biological status. Where confounding variables cannot be controlled, they will be closely monitored and limitations of this approach will be held in mind and discussed in the results.

2. METHOD

2.1. Epistemology

Philosophical assumptions regarding ontology and epistemology are central to all scientific enquiry. Ontology represents the philosophy of *reality*; our conceptualisation of the world around us (Bunge, 1974); whereas epistemology denotes the philosophy of *knowledge;* our beliefs and assumptions about how we come to know about the world around us; including the scope, methods and limitations of such knowledge. Barker, Pistrang, and Elliott (2003) note the importance for researchers to acknowledge the philosophical context in which their data is obtained, as these assumptions underpin and guide the methodological design and possible data analyses. In view of this, a brief summary of the philosophical position taken by the researcher is provided below, although it remains outside the scope of this discussion to provide a historical review of - or current tensions within - the field.

The chief researcher identified as holding a critical realist perspective. Fleetwood (2005) explains that critical realism is a meta-theory for social sciences; concerned with the philosophy of science, ontology, epistemology, and aetiology, together with ideas about what constitutes an explanation, a prediction, and what the objectives of social science ought to be. This paradigm is one which posits that the world is real, and therefore open to scientific study, whilst remaining critical of our ability to know any such reality with any certainty due to fallibility and errors in observation and the inherent innumerable biases of the scientist.

Whilst these research questions might, typically, be associated with a more traditionally positivist epistemological paradigm, the choice to explicitly adopt a critical realist stance was informed by the researcher's desire to remain aware of the socially constructed nature of the concepts discussed so as to avoid reinforcing essentialist discourse. This awareness includes, but is not limited to, the artificial and evolving nature of the current conceptualisations of 'core neuropsychological domains and 'social cognition'. Further, Sontag (2002) discusses how the social construction of meaning attributed to diseases such as HIV-infection enables a consideration of how these theories have evolved over time in an otherwise invisible socio-political context, allowing, then, for an acknowledgment of how the uptake of

these constructions and metaphors into essentialist discourses can, in themselves, cause suffering for people with HIV, altogether separate to the impact of the biological illness.

Critical realism advocates for the use of multiple measures of assessment and analysis in order to learn as much about our reality as possible. In view of this, the current study included a clinical interview and a self-report measure as part of the information gathered alongside the neurocognitive assessments, and employed a bi-modal method of data analysis (group-level statistical analysis and individual-level case analysis) to, as best possible within the study resources, learn as much about the research questions as possible.

The present-day conceptualisations of cognitive impairment and social cognition will continue to evolve and change alongside developments in our understanding of neurocognitive domains and HIV-infection. However, whilst it is essential to remain critical of the subject matter and aware of the fragility of 'knowledge', in the immediate context, these constructs and theories offer a limited, yet meaningful and pragmatic apparatus with which to advance exploratory research. This kind of methodology in social sciences is one which is increasingly being recognised as befitting of a critical realist perspective (McEvoy, 2006; Olsen & Morgan, 2005).

2.2. Regulatory Ethical Approval

Study registration and ethical approval were first secured from the host University (see Appendix B - C) and from the NHS ethics committee (see Appendix D - E). Permission to conduct the study and to recruit from each NHS site was sought and obtained from each Trusts' internal Research and Development Team (Appendix F-G). Additionally, the Directorate covering one recruitment site required an Internal Scientific Peer Review authorisation, for which approval was sought and gained (Appendix H - J). All processes were completed prior to recruitment commencing.

2.3. Inclusion and Exclusion Criteria

2.3.1. Approach to Developing Inclusion Criteria

A small core set of essential inclusion criteria were developed for the study, followed by a list of broader considerations required to assess participant suitability; in this

way, a flexible approach was taken. Although strict exclusion criteria are often imposed in neurocognitive research (e.g., excluding co-morbidities), that approach in this instance was deemed impractical based on a number of factors, including the guidance from senior clinicians at each recruitment site, who were able to draw upon their expert understanding of the clinical population as well as their experience of supervising similar such studies. Additionally, previous studies which have attempted to recruit only 'pure' HAND (by excluding co-morbidities) have been required to relax exclusion criteria in order to recruit adequate samples (Ireland, 2011; Johal, 2014). Thus, given the chronic and episodic nature of HIV and its highly prevalent associated co-morbidities (Heaton et al., 1995), a flexible approach was advised. This strategy is in keeping with advice in the literature, which cautions against excluding common HIV-related co-morbidities in HAND research to avoid research samples becoming unrepresentative of the population (Robertson, Liner, & Heaton, 2009)

Assessment of a patient's suitability for inclusion was done on a case-by-case basis by the researcher in collaboration with the research supervisor, referring clinician, and if necessary, senior clinician and medical consultant.

2.3.2. Core Inclusion Criteria

The primary inclusion criteria were; a diagnosis of HIV infection; fluent English language comprehension and expressive abilities; older than 18 years old. These and further factors influencing eligibility are outlined below.

2.3.3. Language Facility

Participants were required to understand written and spoken English fluently, but not required to have English as a first-language. Although first-language English status would have been preferable given the language components of some of the test materials, the cultural-linguistic diversity of the target population made this unfeasible.

Where potential participants were referred directly to the researcher, their degree of English language facility was assessed by the referrer who was well placed to identify language ability. Where potential participants were identified from a waiting list, language facility was identified through liaising with the site consultant. Suitability

was checked again at first contact and assessed during testing; participant's performance on a test of reading individual words (the Wechsler Test of Adult Reading; WTAR) which gave an indication of language facility during the test battery.

2.3.4. HIV and HAND Diagnosis

A diagnosis of HIV was required; however, a diagnosis of HAND was not necessary given that ANI - the most common form of HAND – is 'asymptomatic' and therefore likely to be under-diagnosed in services were neuropsychology testing is not routinely offered. People with ANI present with mild neurocognitive difficulties which, although clinically determinable, are thought to have a minimal impact on their everyday functioning. Given that neither of the two recruitment sites operated routine neuropsychological assessments, limiting the recruitment criteria to only include those with a pre-existing diagnosis of HAND would serve to restrict the pool of potential participants to those with more pronounced impairments. Furthermore, it could be confidently assumed that all potential participants would have explicit neurocognitive symptom or complaint, as participants were identified from a waiting list for neurocognitive assessment or referred directly by clinicians based upon an existing clinical need.

HAND status was noted from participants' medical files but not used for exclusion purposes as the variability would inform the profiling process. HAND status was classified as belonging to one of four levels; Impairment not otherwise specified (I-NOS), ANI, MCD, and HAD.

2.3.5. Medical Co-morbidities

Within the NHS context, all potential participants attended routine health examinations which screened for HIV-related illnesses which might also cause CNS complaints. Following discussions with the site consultant physician, it was noted that Hepatitis B and C are frequently seen co-morbid infections. Although these can impact global cognitive performance, it was agreed that relevant people would be invited to participate as long as they were under treatment and maintaining usual levels of daily functioning. Medical conditions such as Stroke, Dementia and Encephalopathy are also associated with HIV infection, and participants were

considered suitable for participation following an assessment of type, severity and capacity to consent.

CNS tumours, metabolic diseases, and delirium are frequently seen in individuals where untreated or resistant HIV infection is present. However, no individuals were encountered who presented with these conditions. This was consistent with the outpatient demographic, where a high proportion of patients are cART-adherent with undetectable viral loads and well managed immune strength.

2.3.6. Substance Use

The literature states that substance use is highly prevalent among people living with HIV and AIDS (Colfax & Guzman, 2006; Gonzalez, Barinas, & Cleirigh, 2011; Williams et al., 2010). This finding was consistent with reports from senior clinicians at both recruitment sites who reported common use of 'club drugs' (e.g., MDMA, gamma-hydroxybutyrate (GHB), Rohypnol, and ketamine) amongst a large sub-section of registered patients. However, no such history presented in the recruitment phase.

It was agreed that potential participants would not be excluded from participant based on a history of substance use unless there was evidence of associated brain damage (e.g., Korsakoffs dementia). However, individuals with long-term current and multiple substance use (e.g., crack-cocaine and heroin) were not invited to participate do to the impact that this would have had on baseline cognitive functioning (Casaletto et al., 2016; M. Lezak, Howieson, Bigler, & Tranel, 2012).

2.3.7. Psychological Co-morbidities

There is a higher than average prevalence of anxiety and depression for individuals with HIV. Both conditions, and their associated pharmacological treatments, are shown to influence cognition and performance on neuropsychological testing in non-clinical populations (Ferreri, Lapp, & Petetti, 2011; Goldstein & Mcneil, 2003; R. J. Porter, Gallagher, Thompson, & Young, 2003) with anxiety linked to distraction and off-task rumination, depression linked with low motivation and effort, and pharmacological treatment having an impact of cognitive performance (M. Lezak et al., 2012).

However, the literature regarding the impact of anxiety and depression on neurocognitive test performance of people with HIV reports conflicting findings. Some studies have reported that depression and/or anxiety significantly confound performance on cognitive tests; for example, Rourke et al. (1999) reported that depressive symptoms account for variation in test performance. Additionally, in a study by Castellon et al. (2006), low motivation (a key factor in depression) was associated with impaired verbal memory, executive functioning, and motor performance; cognitive domains which also feature as key areas of impairment in those with HIV.

In contrast, others studies report no such relationship (Carter et al., 2003), or report that depression affects *subjective complaints* of cognitive impairment but not objectively assessed cognitive impairment itself (Carter et al., 2003; Millikin et al., 2003). This inconsistency is, in part, likely influenced by variability in test materials, assessment criteria and sample groups, and further complicated by the nature of both anxiety and depression as being multi-dimensional constructions (Castellon et al., 2006). Nonetheless, neuropsychological testing for HAND routinely includes assessment of mood and anxiety to allow for some standardised consideration of the extent to which mood state may be a confounding influence on test performance.

In recognition of the elevated prevalence of psychological co-morbidity in the target population, and acknowledging the guidelines of Gibbie et al. (2006) who advise that an improvement in neurocognitive test scores can occur in those with HIV who have been treated for their low mood, it was agreed that potential participants would not be excluded from the study if they presented with mild-moderate anxiety. Status would be assessed at several points, including; the clinical judgement of referring clinicians; the researcher; and, the Hospital Anxiety and Depression Scale (HADS) at time of testing, to assess severity and ‘caseness’ of anxiety and depression. Similarly, any potential participants with a ‘bi-polar’ or ‘psychosis’-related diagnosis whose experiences were well managed would also be considered appropriate, and only excluded in the event of acute or untreated symptomology due the inseparable and acute confounding influences of such experiences on test performance (M. Lezak et al., 2012).

2.3.8. Learning Disabilities

Gillberg (2003) reports that learning disabilities affect 1-2.5% of the general population in the Western world, and a person with a learning disability may have difficulty learning and managing daily living skills due to impaired cognitive processing before the age of 18 years, resulting in an IQ score below 70. The neurocognitive tests and associated normative data used in the current study are inappropriate for use with individuals who have a severe baseline cognitive and functional impairment (Randolph, Tierney, Mohr, & Chase, 1998). For this reason, it was agreed that patients who met this criteria would not be invited to participate.

2.3.9. Capacity to Consent

As this study sought to recruit individuals with some degree of cognitive impairment, each potential participant's capacity to consent to considered. Only patients with capacity to make the decision to take part in the study and provide consent were contacted and invited to participate in the study. See the 'Ethical Issues' section for further considerations regarding capacity, consent, and HIV-infection.

2.4. Recruitment Procedure

Participants were recruited from two multi-disciplinary HIV outpatient services in London. An NHS clinical sample was sought as the organisational context proffered specialist healthcare services in which people who met the inclusion criteria could be located, alongside available and up-to-date medical health information necessary in order to determine participant suitability and ensure ethical participation. Recruiting from NHS services also ensured that the sample would be as representative of the target population as possible. This research is in keeping with the NHS ethos and constitutional commitment to continuous improvement (NHS constitution for England, 2012); any pertinent results from this study might serve to inform the direction of future research, contributing knowledge with which to inform the development of evidence-based services.

The chief investigator informed the staff teams at each site about the study, by presenting the study rationale and recruitment procedure at their multi-disciplinary clinical team meetings. After this point, due to variability in service provision, a different recruitment strategy was required for each.

As Site A did not have an internal neuropsychology service, senior on-site clinicians invited suitable participants to the study and those who consented were referred directly to the researcher and on-site supervisor.

Site B had an internal neuropsychology assessment service as part of their Clinical Psychology service provision. Therefore, suitable participants were identified from a patient waiting list for neurocognitive assessments.

At both sites, the researcher checked the referred participant's medical files to identify their contact preferences (in line with strict Trust confidentiality protocols). Phone and email contact was then established with referred participants to assess suitability, provide verbal information about the study, obtain consent, and arrange an assessment slot. Where suitability was unclear, supervision was sought and the appropriate actions were decided, before the patient was invited to participate.

2.5. Assessment Procedure

All participants were invited to attend a two hour assessment appointment at their registered NHS service, where they were seen in a private clinic room. Information about the study was provided to the participant in writing, using the Participant Information Sheet (see Appendix K). Once verbal and written consent was gained (see Appendix L), a brief clinical interview established educational history, occupational status, English ability, mood and cognitive complaints. Following this, the test battery was administered.

The WTAR was administered first, followed by the UK version of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and finally the social cognition tests. A 30-minute break midway was offered in order to minimise the effects of fatigue. If declined, participants were monitored for signs of fatigue and reminded to stop if necessary.

Once testing had finished, participants were given the opportunity to reflect on the testing process and offered verbal debriefing. They were informed that they would

receive a full report within the month, which, with their consent, would be shared with the team consultant for the purposes of informing future care.

The Mind Exchange Working Group Guidelines (2013) advise that assessments should be conducted at times when the patient is not experiencing unnecessary fatigue, or severely low mood, and when medical status is generally stable. The procedure was devised with these factors in mind.

All participants were offered a direct or phone-based follow-up appointment to receive feedback and have the opportunity for their neuropsychological rehabilitation recommendations (if required) explained.

2.6. Design

A cross-sectional correlation design and an 'Individual Profile Analysis' were both employed to address the research questions, as together they enabled a detailed and descriptive exploration of a given number of variables, within a given time frame, within a representative group. This research design was deemed the best fit for the exploratory aims of the study; to observe the differences between the variables of interest within a sample of individuals with HIV and allow for a comparison to published normative data. The variables of interest were social cognition and executive function and their relationship to general cognitive functioning in a group of individuals with HIV with varying levels of cognitive impairment.

Since no data was to be manipulated, nor any trials or interventions offered, no control group was considered necessary. Although the inclusion of a comparator group may have enhanced the breadth of the study and the options of statistical data analyses, the resources required to operationalise and implement this recommendation were outside of the scope of this study due to the availability of time and resources.

2.6.1. Analysis

Participants' raw scores for each neurocognitive subtest were converted into scaled scores (mean value of 10, standard deviation of 3) using published norms in test manuals. Consequent analysis was conducted using IBM SPSS Statistics 22.

As stated above, an Individual Profile Analysis was also included. Described as the "mainstay of cognitive neuropsychology" (Towgood, Meuwese, Gilbert, Turner, & Burgess, 2009, p. 11); this approach focuses on differences within rather than across individuals, with each individual effectively serving as their own control. In keeping with the exploratory nature of present study, this type of analysis is particularly suited to the study of populations with heterogeneous deficits, and allows for an examination of factors that may be missed at group-level analysis.

2.6.2. Sample Size

The sought after sample size was guided by methodology employed in similar exploratory studies of neurological impairments; neuropsychological research frequently involves a small sample size, and this observation is consistent with the numbers (i.e., sixteen participants) recruited for similar research projects which have been conducted with individuals with HIV (Ireland, 2011; Johal, 2014).

As the research analysis was to focus on size of effect - which is considered relatively independent of sample size (Clark-Carter, 1999) a power calculation was not considered appropriate. However, efforts to obtain as large a sample as possible were made in acknowledgement that the power and validity of research increases with sample size.

2.7. Test Materials

A neuropsychological test battery was developed to measure social cognition and core cognitive domains (i.e., executive function, learning and memory, attention, visuo-perception, and language). In line with the research questions; this enabled a comparison of cognitive function across key (executive function and social cognition) and core (see above) domains, to ensure that any deficits in social cognition were not secondary to global or specific decline or language facility. The selected tests are discussed below, and for clarity presented in a table in Appendix M.

The RBANS UK version (Randolph et al., 1998) was used to assess attention, information processing speed, learning and memory, verbal function, and visuo-spatial function. There are several standardised neuropsychological test materials that can be used to assess for deficits in these areas and it is possible, for example,

to use various combinations of the Wechsler Adult Intelligence Scale (WAIS; Pearson, 2008) and Wechsler Memory Scale (WMS; Wechsler, 1997) to these means (M. Lezak et al., 2012). However, The RBANS was chosen for its best-fit with the study design. The RBANs has reported reliability and utility when working with neurological injury or disease (Hodges, 2007); assessing neurological impairment in individuals aged 20 to 89 years old, including deficits in HIV associated cognitive impairment, as well as profiles symptomatic of other co-morbid diseases and syndromes (Hebben & Milberg, 2009). The relative brevity of the RBANS, in comparison to other test batteries, enabled the assessment to be conducted in a one-off appointment, facilitating the overall reduction of the burden on the participant.

The RBANS test gives information about cognitive functioning in the following five areas; Immediate Memory, Delayed Memory, Visuo-spatial Function, Language and Attention, based on the administration of co-normed 12 subtests. 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.

As recommended by Lezak et al. (2004), the RBANS was supplemented with additional procedures. To provide a more thorough assessment of executive function, the Verbal Fluency from the Delis-Kaplan Executive Function System (DKEFS) set was included, as well as The Halstead Reitan version of the Trial Making Test; Part B (Reitan, 1955). To improve assessment of working memory, the Digit Span Backwards' test was included (to complement existing Digit Span Forward). To improve assessment of information processing speed, the Trail Making Test (Part A) was also included.

The development of this battery was consistent with the Mind Exchange Working Group Guidelines (2013) which advise that comprehensive neuropsychological testing for neuropsychological impairment in people with HIV should include a test battery of at least five neurocognitive domains, including attention/working memory, speed of information processing, executive function, verbal/language, learning/recall, and motor skills. Testing should be done using standard and

validated instruments for detection of HAND, and administered and interpreted by an appropriately trained professional.

2.7.1. Assessment of Premorbid Functioning

The WTAR (Wechsler, 2001) was used as one estimate of pre-morbid cognitive function. The ability to read words is believed to be resistant to cognitive decline until later stages of disease progression, and therefore performance is taken as representative of an individual's optimal level of functioning and well as English language facility (Strauss, Sherman, & Spreen, 2006). The test requires participants to read aloud a list of fifty words with atypical grapheme-phoneme relationships which require irregular pronunciations. This unfamiliar quality reduces the likelihood of the participant speaking the word correctly based on a generalisation of common sound-letter language rules, and instead requires them to rely on previous learning of the words. Participants are scored on a pass or fail criteria according to the number of words read correctly. These scores are then compared to normative data to provide an index of function.

However, since the WTAR assumes a 'normal' development of English reading skills prior to cognitive decline, it offers a less valid estimate of optimal functioning for speakers of English as a second language. In such instances, alternative methods of assessing pre-morbid ability are recommended. One such method is the 'best performance' approach which looks at the distribution and frequency of the best scores within the subjects own cognitive profile in order to determine optimal level of cognitive functioning (M. Lezak et al., 2012). In view of this, in addition to the WTAR, pre-morbid ability was also estimated using 'best performance' and educational attainment (as measured by total years of education).

Thus, a dual approach was taken to the assessment of pre-morbid ability; participants were compared to both the normative population (i.e., WTAR norms) as well as compared to themselves (i.e., best performance score and educational achievement).

2.7.2. Assessment of Attention and Information Processing Speed

The RBANS Digit Span and Coding subtests were used to assess attention. The Digit Span test requires participants to to repeat strings of numbers, which increase

in length as the test progresses. The Coding test involves scanning a sequence of symbols and completing numbers according to a corresponding shape given in an initial coding key, under timed conditions.

The Trail Making Part A (Reitan, 1955) was used to assess Information Processing Speed. This test pairs with the Trail making Part B test for an assessment of the task-set switching part of executive functioning.

2.7.3. Assessment of Learning and Memory

2.7.3.1. Verbal Learning and Memory

The RBANS List Learning and Story Learning provided an assessment of verbal learning. In the List Learning subtest, participants were verbally presented with a list of 10 unrelated words and asked to immediately repeat back as many as they could remember; this was repeated across four trials. In the Story Learning subtest, participants were verbally presented with a short story, comprising of 12 pre-defined units of information, and asked to repeat as many details as they could remember, using the same language; this task was repeated for two trials.

The RBANS List Recall and Story Recall provided an assessment of delayed memory. After a 20-minute delay following administration of the List Learning and Story Learning subtests, participants were asked to recall words/story narrative from each task to the best of their ability. The additional RBANS Story and List Recognition tasks assessed recognition memory.

2.7.3.2. Visuo-spatial Learning and Memory

The RBANs Figure Copy and Figure Recall subtests assessed visuo-spatial learning and memory. Participants were required to redraw the figure they had previously seen and copied for the Figure Copy test, after a 20 minute delay.

2.7.4. Assessment of Verbal Function

The RBANS Picture Naming and DKEFS Verbal Fluency subtests were used to assess Language function. For the Picture Naming test, Participants are presented with line drawings of 10 objects and asked to name them each, with available prompts. The DKEFS tests also serve as an assessment of executive function.

2.7.5. Assessment of Visuo-spatial Function

The RBANS Figure Copy and Line Orientation subtests were used to assess visuo-spatial/construction ability. For the Figure copy subtest, participants are provided with a complex drawing, comprising 10 components, presented in black ink on white paper, and asked to make a direct copy, with no memorial component involved. The Line Orientation subtest was a 10-item test in which participants were presented with a drawing consisting of 13 lines fanning 180 degrees from a central point. Underneath this figure, two unlabelled lines were presented. Participants were asked to match the lines with the original figure.

2.7.6. Assessment of Executive Function

Burgess and Gilbert (2008) advise that the following skills should be assessed as part of an assessment executive function; verbal fluency, sequencing, inhibition, working memory, and rule deduction. Most tests assess more than one of the above elements of executive functioning, and the following tests were chosen accordingly.

2.7.6.1. The DKEFS Verbal Fluency

The DKEFS 'FAS verbal fluency' subtest includes three separate tests which assess the following abilities associated with executive function; Letter Fluency, Category Fluency, Switching and Inhibition. These tests are considered sensitive measurements of verbal executive function, and place demand upon mental flexibility and self-regulation. Optimal performance is dependent upon inhibition of inappropriate responses and mental switching between different search strategies (Henry et al., 2006).

In Letter Fluency, participants were told a letter ('F', 'A', and then 'S') and asked to say as many words as possible beginning with that letter in 60 seconds. Participant were instructed against using proper nouns, nor the same word with different endings. In Category Fluency, participants were told a category ('animals' and 'boys' names') and asked to provide as many exemplars as possible in 60 seconds. In Switching, participants were given two categories ('fruit' and 'furniture') and asked to state as many alternating exemplars as possible. Success on these tasks required word generation and the ability to follow to specific rules. Each task lasted 60 seconds.

Normative data is provided in the DKEFS test manual, and is based on 1750 participants aged between 18-89 from United States of America (US). The ethnicity of the sample was considered representative of the US population.

2.7.6.2. The Brixton Spatial Anticipation Test

The Brixton Spatial Anticipation Test (Burgess & Shallice, 1997) was chosen to assess visuo-spatial concept formation/rule deduction. Participants are presented with a booklet 56 rectangle cards, each with ten identically spaced circles. The participant is required to predict 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.

2.7.6.3. Trail Making Part A and Part B

The Trail Making part A and B tests (Reitan & Wolfson, 2001; Reitan, 1955) were included to assess visual sequencing and switching skills. In addition to this, Trail Making A is also considered a test of information processing speed. For Trail Making A, participants are presented with a single A4 sheet containing circled numbers from 1 to 25 scattered across a page. They are talked through a sample, and then asked to connect the circles in numerical order as quickly as possible. For Trail Making B, participants were presented a similar task, but this time the circles containing both numbers (1 to 13) and letters (A to L) scattered randomly. The participant must join the circles sequentially, alternating between numbers and letters (i.e. 1-A-2-B-3 and so forth) as quickly as possible. Normative data for these tests is provided by Davies (1968) based on 540 British participants, and is provided in the test manual.

2.7.7. Assessment of Social Cognition

The current study chose the adult revised version of the RMET (Baron-Cohen et al., 2001) and the Social Stories Questionnaire (SSQ; Lawson, Baron-Cohen, & Wheelwright, 2004) as two tests of social cognition. In addition to this, the Questionnaire of Cognitive and Affective Empathy (QCAE; Reniers et al., 2011) was chosen as a self-report measure.

Pardini and Nichelli recommend (2009) the use of two different tests of ToM to enable a direct comparison within a given population. There are a range of potential ToM tests available. However, the current study aimed to address the research questions in a manner which would allow the results to be meaningfully compared to the results of previous studies exploring social cognition in HAND (Homer et al., 2013; Ireland, 2011). The limitations and future recommendations identified in said research were incorporated into the current methodology: these are addressed throughout the method section.

2.7.7.1. The Reading the Eyes in the Mind Test

The RMET (Baron-Cohen et al., 2001) is considered a test of emotion recognition and emerged from research into social cognition and mentalising ability deficits in ASC, a condition characterised by difficulties in social ability and associated with impairments in executive functioning skills and ToM: cognitive abilities most associated with the pre-frontal cortex.

Although other tests of emotion recognition are available, for example the Wechsler Advanced Clinical Scale 'Faces' test, this test was selected with the intention to explore whether the trends reported in previous research would be replicated with a different sample. Furthermore, it is a validated for use with a wide range of clinical populations and has been reported to be reliable and stable over a 1-year period, in a non-clinical sample of adults (Fernández-Abascal, Cabello, Fernández-Berrocal, & Baron-Cohen, 2013).

The RMET is considered to be a visual test (with only a minor element of reading required, complimented by a glossary of terms), whereas the SSQ is considered largely verbal in its cognitive demand. This difference in the tests is beneficial because the substantial reading involved in the SSQ makes it sensitive to language bias, whereas the RMET, being mostly a visual-orientated task, is relatively free from this concern.

The development of a valid control condition for the RMET was considered, as recommended by Ireland (2011), to explore the potentially influence of language bias on test performance. However, the means required to develop such a measure proved outside the available resources of the study. An alternative option to

developing a control condition was to use instead the child version/original version of the RMET (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997) which already includes a control condition. However, this measure was not appropriate for use with an adult population due to its relative simplicity. As such, the present study elected to use the revised adult version of the RMET (Baron-Cohen et al., 2001) without a control condition, with the view that the tests of speech and language in the wider assessment of cognitive would serve as an adequate assessment of the confounding effects of language on test performance in the RMET.

Regarding the administration of the RMET; participants were presented with a black and white picture of a face (showing only the eye region) and asked to choose one out of a multiple choice of four words which they felt best described the emotional state of the person in the picture. Thirty-six items in total, with equal numbers of men and women. Each eye image was approximately five by two inches, with two words printed above it and two words printed below. Participants were also provided with a glossary of terms to check at their leisure, as they were not under timed conditions.

2.7.7.2. The Social Stories Questionnaire

The SSQ (Lawson, Baron-Cohen, & Wheelwright, 2004) aims to assess the subjects understanding of non-literal cognitive-linguistic social processes required in the comprehension of social norms. This test was chosen to explore and build upon Ireland's (2011) findings of impaired performance in HIV-positive adults on the SST , (Happé & Happ, 1994), a test which, although similar in nature, was designed for use with children. As a more age-appropriate measure, the SSQ (Lawson, Baron-Cohen, & Wheelwright, 2004) was chosen for use in the present study; it contains discreet faux pas and was suitable for administering to adult populations.

The SSQ was originally developed as an adult version of a similar children's "Faux Pax" test (Baron-Cohen, O'Riordan, Stone, Jones, & Plaisted, 1999) and has been trialled with adults both with ASC and those considered 'neuro-typical' (Lawson, Baron-Cohen, & Wheelwright, 2004). As such, this test offered a more subtle assessment of subjects' cognitive social cognition, with a test similar to Ireland (2010) but in a manner more appropriate to the target population.

Regarding the administration of the SSQ; participants were required to read ten short stories which contained within them specific utterances made by one character which could upset another in the same story. Each story is divided into three sections, with at least four utterances in each section. Prompted by short questions at the end of each story, participants were required to identify whether one character in the vignette had said something which could be upsetting to another and, if so, identify the specific remark which caused offence (from multiple choice options). Ten of the sections contained a blatant target utterance, ten contained a subtle target utterance and ten contained no target utterance. Participants were scored according to the number of targets correctly identified. Each of the ten stories also included a control question and only those participants who answered all of these correctly were included in the analysis.

Using the RMET and SSQ together, the assessment benefited from having two tools that are described in the literature as assessing different parts of explicit mentalising skills; cognitive ToM, and affective ToM. The RMET is considered a test of 'affective ToM' as it requires the subject to accurately perceive the emotional affect of another; this relies on social-perceptual understanding of non-verbal emotional processing. In contrast, the SSQ is considered a test of cognitive ToM as it requires the participant to understand the cognitive perspective of other people in a social context.

2.7.7.3. The Questionnaire of Cognitive and Affective Empathy

The QCAE (Reniers et al., 2011) was chosen as a self-report measure to assess empathic experience and behaviour. Furthermore, the inclusion of a self-report measure in the present study was done to serve as a point of comparison to the performance-based neuropsychological assessment. The selection of three contrasting measures is in line with the epistemological position of the study; an approach to scientific inquiry which advocates for multiple and varied methods of assessment.

There are a range of available questionnaires which assess social cognition or mechanisms within social cognition, including – in no particular order - the Hogan Empathy Scale (Hogan, 1969); Interpersonal Reactivity Index (Davis, 1980); Empathy Quotient (Baron-Cohen & Wheelwright, 2004); Social functioning scale

(Birchwood, Smith, Cochrane, Wetton, & Copestake, 1990); the Socio-Emotional Questionnaire (Bramham, Mor, Ho, Bullock, & Polkey, 2009); and, the Empathy subscale of the Impulsiveness-Venturesomeness-Empathy Inventory (Eysenck & Eysenck, 1978). For the present study, the most recently devised QCAE was regarded as the most suitable; its internal items derived from several pre-existing measures (including the aforementioned Interpersonal Reactivity Index, Empathy Quotient, Hogan Empathy Scale, and Impulsiveness-Venturesomeness-Empathy Inventory) and thus benefiting from the strength of these validated questionnaires.

The QCAE was devised with the view to address the numerous, often conflicting, definitions of empathy in the literature, with the aim of drawing these together under one working definition of empathy to reflect the multidimensional nature of the construct. The measure also delineates cognitive empathy and affective empathy, by way of two separable subscales, to reflect the definitional debate regarding whether empathy involves recognizing psychological states (i.e., cognitive empathy) or experiencing it (i.e., affective empathy). A total of thirty-one items come together to provide an overall score that can be separated out into the cognitive empathy subscale (QCAE-CES) and the affective empathy subscale (QCAE-AES). Normative data is provided by Reniers et al. (2011), based on 925 adults within the United Kingdom.

2.7.8. Assessment of Mood

The HADS (Zigmond & Snaith, 1983) was chosen as it offered a brief, standardised and validated measure with which to assess anxiety and depression. In the accompanying literature, the authors state that the measure comprises of two separable subscales - anxiety scale and depression scale – which reliably divide into four ranges: normal, mild, moderate and severe. For both scales alike, raw scores of 0 to 7 could be regarded as being in the normal range; scores of between 8 and 10 acknowledged mild cases; 11–15 moderate cases; and 16 or above, severe cases. Furthermore, a score of 11 or higher indicated probable presence ('caseness') of a mood disorder and a score of 8 to 10 being just suggestive of the presence of the respective milder state (Snaith, 2003).

The deleterious effects of anxiety and mood on cognitive test performance are well documented (Chepenik, Cornew, & Farah, 2007; M. D. Lezak, 2004). As discussed,

such difficulties are common alongside HAND and needed to be accounted for during the assessment in order for their potential influence on self-reported neurocognitive performance as well as performance on neurocognitive tests to be taken into consideration.

2.8. Ethical Issues

2.8.1. Capacity to Consent

'Capacity to consent' refers to an individual's ability to make a specific decision for themselves: it involves their ability to understand, retain, and weigh up the information provided to them, and communicate their decision to others. The Mental Capacity Act (2005) states that "…a person lacks capacity in relation to a matter if at the material time he is unable to make a decision for himself in relation to the matter because of an impairment of, or a disturbance in the functioning of, the mind or brain".

This study sought to recruit people with some degree of HAND, which, as discussed, encompasses a cluster of heterogeneous and fluctuating cognitive impairments. By means of numerous cognitive mechanisms, cognitive impairment of this kind can directly impair an individual's ability to provide informed consent, and with this in mind, potential participants who were considered to be without capacity to consent were not invited to participate. In addition to this, given the fluctuating nature of HIV-related illnesses and cognitive impairment, it was predicted that participants' capacity to consent might fluctuate throughout the course of their involvement in the study, from the point of contact through to their assessment. In light of this, capacity was monitored throughout for change by both the researcher and the clinical team. If capacity was queried, the researcher sought the guidance of the medical consultant and clinical team. It was agreed with the staff teams that anyone deemed as not having capacity to consent at any stage throughout the testing process were to be withdrawn and any collected data excluded, although this eventuality did not occur during the study.

2.8.2. Informed Consent and Right with Withdraw

Written consent was obtained from each individual participant prior to testing. A Patient Information Sheet (Appendix K) outlined the research aims and procedures;

confidentiality; anonymity; the right to withdraw; and provided details the researcher's contact details in case they had any questions post participation.

Regarding the right to withdraw, participants were informed that they could do so at any time with no reason required, and no impact on the care received from the service. They were also informed that if they chose to withdraw from the study after the data had been anonymised, then the researcher would reserve the right to use anonymised data in the current study and further analysis that may be conducted.

The above information was provided to the participant twice, first verbally by telephone and then again at the appointment. This allowed a period of time during which to digest and understand the information provided. All participants were encouraged to ask questions prior to consenting. If participants agreed to participate, they were asked to sign a consent form (Appendix L).

2.8.3. Confidentiality and Anonymity

Participant data was handled in line with Trust Confidentiality and participant data was anonymised after each assessment was conducted. Participants were assigned anonymised identification numbers which were used for all research purposes (e.g., record databases and statistical programmes used to analyse the data).

Participants' completed test sheets were kept on-site and stored in a locked filing cabinets in accordance with the Data Protection Act, 1998. Participants were informed about the limits to confidentiality (e.g., in response to a risk to self or others) and, that post assessment, the researcher reserved the right to keep the anonymised data in order to conduct further analysis (see Appendix K).

2.8.4. Risk Assessment and Management

2.8.4.1. Protection of the Participant

The research design involved no deception. Potential risks to the participant included only minor effects such as fatigue and frustration as a result of test performance. All possible risks were discussed in the Participant Information Sheet (PIS) to ensure full and ethical transparency on behalf of the researcher.

To manage these risks, participants were monitored for signs of fatigue and distress, and breaks were offered. The researcher agreed in advance with the site teams that if participants became distressed during testing, the assessment would be paused, rescheduled or terminated. If anything of significant concern was evident throughout the performance (e.g., suicidality or disorientation); the clinical team would have been informed immediately.

At the end of cognitive testing participants were given time to ask questions about the administration and discuss their general experience of the assessment. In recognition of the numerous potential unknown affects that any assessment may have with regards to psychological triggers, particularly in potential vulnerably and highly stigmatised clinical population, participants were also provided with information signposting them to local community services for continued support in the aftermath of the assessment.

2.8.4.2. Protection of the Researcher

The researcher was aware of the health and safety policy, fire safety procedures, and first aid protocol for each recruitment site. No methodology-specific risks to the researcher were identified. However, it was agreed that should any issues arise, the researcher would discuss them in supervision with the allocated Director of Studies, and if appropriate, with senior clinicians at the recruitment sites.

2.8.4.3. Protection of the Staff Team

In both recruitment sites it was agreed that the neuropsychological assessments would serve as part of the multidisciplinary service offered by the team. Given that neuropsychological test administration and interpretation requires specialist knowledge, consideration was given to how the team would manage queries or concerns which arose out of the assessment once the research period had finished.

In Site B, inquiries could be managed by experienced clinical psychologists familiar with administering and interpreting neuropsychological tests. However, in Site A, where neuropsychological assessments were not part of the service, consideration was given to how to protect the staff team from situations such as feeling under-confident to answer patient questions regarding their neurocognitive assessment. To

minimise the risk of this happening, the researcher ensured the neuropsychological report included extensive recommendations for rehabilitation and support with cognitive functioning, tailored to the participant's cognitive profile of strengths and weaknesses. Participants were also informed about the one-off nature of the assessment, and that if they continued to have cognitive concerns then they should discuss with their clinician an external referral to the most locally commissioned neuropsychology service.

2.9. Participant Characteristics

Nineteen participants were recruited, of whom, two opted out before participating and one was omitted from analysis due to incompletion of tests in the assessment. See Appendix P for full Participant Characteristics information.

Of the 16 participants included in the analysis, nine were male and seven female. A chi-square goodness-of-fit test was conducted to determine whether an equal number of participants from each gender were included in the sample (see Table 1). The minimum expected frequency was 8. The chi-square test indicated that the two gender categories were equally represented (x^2 (1) = .250, p = .804).

The participant characteristics data was examined to explore whether the distribution of variables met the assumptions for non-parametric examination (Field, 2013). Age, summative education, CD4 count and HADS-anxiety raw scores were normally distributed (Skewness <1, Kurtosis <3, and Shapiro Wilk Significance > .05). In terms of measures of variability, all had large standard deviations. The mean age was 43.9 years old (range: 24 to 69); representing a working age adult sample. Nine participants were born in the UK (5 white British, 4 black British), all of whom had English as their first language. For the remaining seven, their countries of origin included Uganda, Burundi, Spain, Portugal, Singapore, and Somalia.

Premorbid ability was assessed using WTAR, total years of education, and highest preserved score. The mean summative education was 12.8 years (range of 6 to 19 years). All participants were able to speak and read English fluently. The mean WTAR Scaled Score was very slightly lower than the population mean, with a large standard deviation indicating a wide range in scores. This suggests that this sample's WTAR average score may not be representative of population mean.

All participants had a diagnosis of HIV with subjective cognitive complaints. With regards to physical co-morbidity; two participants had received treatment for Kaposi's sarcoma; one participant had Hepatitis C; and, one participant had undergone a Hysterectomy. Psychological co-morbidity was assessed using the HADS (Zigmond & Snaith, 1983); the mean raw score on the anxiety scale was 8.75; the mean raw score on the depression subscale was 7.25. The test's authors recommended that, for the anxiety and depression scales alike, raw scores of between 8 and 10 identify mild cases, 11–15 moderate cases, and 16 or above, severe cases. Thus the sample demonstrated mild elevated levels of anxiety compared to the typical population; a profile consistent with the literature (Rabkin, 2008; Shacham, Morgan, Önen, Taniguchi, & Overton, 2012)

Participants most recent CD4 count, viral load and diagnosis date were also noted for profiling purposes only. However, as diagnosis date did not represent the length of HIV illness, but contact with tertiary services, it was not included in the analysis.

This cohort were a working age adult sample, equally matched for gender, reporting with mild levels of anxiety. Ethically and culturally diverse, they all spoke fluent English, and were mostly virologically controlled and cART-adherent; and, accordingly, this is the population for which the consequent results will m

Table 1: Descriptive Statistics for Participant Characteristics

	Mean	SD	Min	Max	Skewness	Kurtosis	Shapiro-Wilk (sig.)
Age	43.9	10.5	24	69	.487	1.336	.674
Education	12.81	3.22	6	19	-.242	.442	.553
WTAR	9	4.24	13	1	-1.08	-.120	.005
HADS – Anxiety	8.75	4.69	2	17	.352	-.894	.489
HADS – Depression	7.25	4.49	2	18	1.283	1.104	.018
CD4	583.38	218.570	1	954	-.549	0.848	.846
VL	49758.25	159780.82	1	642167	3.856	15.130	.000

3. RESULTS

Information converting scaled scores into subjective labels is located in Appendix N.

3.1. Initial Exploration and Initial Analysis of Cognitive Tests

The sample's neurocognitive test data (scaled scores) were analysed first with a view to examine the general cognitive profile of the group before considering more specific deficits. The data was not normally distributed since many of the values were skewed and kurtosed (Skewness >1 and Kurtosis < 3); therefore, further analysis proceeded with non-parametric approaches (see Table 2).

A comparison of the subtest mean scores showed that performance on all of the neurocognitive tests fell within the 'average' range. Of these, there were six tests for which group performance fell lowest, including; Digit Forward, Fluency (Category), List Total, List Delay, Story Immediate, Story Delay. Standard Deviations were for all of these tests - except for Story Immediate and Story Delay - were large, indicating wide variability within subtest scores. Overall, these scores show that, at a group-level of analysis, this cohort demonstrated no impairment in any particular domain, suggesting that any forthcoming difficultly observed on social cognition tests will not be attributable to a core deficit.

As shown in Table 3, non-parametric Kolmogorov-Smirnov one-sample tests were used to compare sample means to hypothesised distribution (Mean: 10, SD: 3). Tests indicate that the mean scaled scores for Figure Copy, Line Orientation, Fluency (Letter) and Trails B in this sample were significantly different to the performance of the typical population.

3.2. Initial Exploration and Initial Analysis of Social Cognition Tests

A comparison of the social cognition test means (see Table 4) showed that performance on the RMET and SSQ fell in the 'low-average' range. Again, the standard deviations for these tests were large, indicating wide variability between individual subtests scores. Overall, these results demonstrate that performance scores on the RMET and SSQ were the most diminished in this cohort, out of all administered tests in the current study.

Non-parametric Kolmogorov-Smirnov one-sample test was used to compare sample means to hypothesised distribution (Table 5). Results indicate that the mean scaled scores for the RMET and SSQ in this sample were significantly different to the performance of the non HIV-positive population.

3.3. Associations between Variables

Spearman's Rho analyses were conducted to explore the relationships between demographic variables (age, education, reading ability, total HAD raw score) and neurocognitive test raw scores (social cognitive tests, List Total, Story Immediate, Category Fluency) based on areas of declined performance as identified in prior analysis of subtest means. Although no weaknesses in visuo-spatial function were observed, Figure Copy was also included in the analysis to explore an association with the RMET due to the substantial visual component in the cognitive burden of the RMET. Key associations and medium to large effect sizes are reported below (i.e. > 0.333). The full correlation matrix is given in Appendix O.

3.3.1. Age

Age did not correlate with either social cognition test, but had a moderate negative association with List Total (r = -.448)

3.3.2. Education

As would be expected, total years of education correlated with reading ability (WTAR; r = .741); List Total (r = .403); Story Immediate (.618); and Verbal Fluency Categories (r = .476). Of note, education also had a mild-moderate correlation with SSQ (r = .444) and QCAE-CES (.401).

3.3.3. Affect

The total HAD score has a weak correlation with the RMET (r =.383), and a moderate negative correlation with and SSQ (r = -.482), and QCAE-CES (r = -.462).

3.3.4. Verbal Function

The WTAR (i.e., 'reading ability' and 'language facility') had a strong correlation with education (r = .741); a moderate correlation with Story Immediate (r = .598) and Category Fluency (r = .527); and, a weak correlation with List Total (r -.331). Of

note, the WTAR also had a moderate correlation with the QCAE-CES (r = .525), and a weak correlation with the SSQ (r = .387).

The List Total subtest had a strong correlation with the Story Immediate subtest (r = .652), and a moderate correlation with the SSQ (r = .541) and QCAE-CES (r = .522). The Story Immediate subtest had a weak correlation with the QCAE-CES (r =.378).

3.3.5. Verbal Executive Function

The Verbal Fluency Category Test had a strong correlation with the List Total subtest (r = .730) and the Story Immediate subtest (r = .725).

The Verbal Fluency Category Test also had a weak correlation with the SSQ (r = .381) and QCAE-CE (r = .393).

3.3.6. Visual Function

The Figure Copy subtest had a weak correlation with the WTAR (r = .371) and the List Total (r = .390); and a moderate correlation with the Story Immediate (r = .585). No correlation was found with the RMET or any of the other social cognition group scores.

3.3.7. Associations between Social Cognition Tests

The SSQ and the RMET did not correlate with one another (r = .013). Similarly, the two QCAE subscales did not demonstrate a remarkable correlation with one another (r = .259).

The only notable correlation between the social cognition tests was found between the SSQ and QCAE-CES (r = .684). This association was not also reflected between the SSQ and the QCAE-AES (r = .098).

Table 2: Descriptive Statistics and Distribution Analysis for Neurocognitive Test Means (Scaled Scores)

	Mean	SD	Min	Max	Skewness	Kurtosis	Shapiro-Wilk (sig.)
WTAR	9	4.24	1	13	-1.08	- 0.120	.005
Digit Forward	8.13	3.737	2	14	- 0.330	- 0.870	.430
Coding	10.06	3.356	4	17	0.567	0.287	.364
Trails A	9.38	3.403	1	13	- 1.678	2.439	.001
Picture Naming	9.88	3.117	1	12	- 0.860	3.487	.000
Figure Copy	11.00	2.394	5	13	- 1.665	2.371	.001
Line Orientation	11.94	3.130	7	15	- 0.799	- 1.176	.002
Fluency (Letter)	9.25	5.580	3	18	0.382	- 1.628	.021
Fluency (Cat)	8.56	4.066	1	17	0.172	0.121	.977
Fluency (Output)	10.38	4.209	1	16	- 0.784	- 0.065	.269
Fluency (Switch)	10.06	3.941	3	16	- 0.262	- 1.015	.600
Brixton	10.25	3.454	2	14	- 1.195	1.054	.034
Trails B	10.81	3.449	1	14	- 1.903	3.851	.001
Trails Ratio	11.94	1.843	9	16	0.469	0.019	.671
List Total	8.31	3.301	3	15	0.320	- 0.547	.553
List Delay	8.94	3.924	1	16	- 0.249	- 0.043	.927
List Recognition	9.81	3.391	1	12	- 1.845	2.637	.000
Story Immediate	8.06	2.863	4	12	- 0.247	- 1.491	.063
Story Delay	8.81	2.482	4	13	- 0.293	- 0.295	.677
Figure Delay	9.69	3.945	4	16	0.177	- 1.344	.253

Table 3: Kolmogorov-Smirnov Test for Neurocognitive Tests Means (Scaled Scores)

Neurocognitive Test.	N	Test statistic	sig.
WTAR	16	.772	.590
Digit Forward	16	1.022	.247
Coding	16	.750	.627
Trails A	16	.978	.295
Picture Naming	16	1.010	.259
Figure Copy	16	1.522	.019*
Line Orientation	16	2.115	.000*
Fluency – Letter	16	1.635	.010*
Fluency – Category	16	1.240	.092
Fluency – Output	16	1.240	.092
Fluency – Switches	16	.772	.590
Brixton	16	.990	.281
Trails B	16	1.500	.020
List Total	16	1.385	.043
List Delay	16	.990	.281
List Recognition	16	1.272	.079
Story Immediate	16	1.228	.098
Story Delay	16	1.272	.079
Figure Delay	16	.990	.281

Table 4: Descriptive Statistics and Distribution Analysis Social Cognition Test Means (Scaled Scores)

Social Cognition Test.	Mean	SD	Min	Max	Skewness	Kurtosis	Shapiro-Wilk (sig.)
RMET	7.63	3.442	2	13	-.140	-.881	.578
SSQ	7.69	4.078	3	16	.885	.441	.035
QCAE-CES	8	4.367	1	14	-.653	-.904	.024
QCAE-AES	9	4.195	1	14	-.718	-.150	.089

Table 5: Kolmogorov-Smirnov Test for Social Cognition Test Means (Scaled Scores)

Social Cognition Test.	Df.	Test statistic	sig.
RMET	16	1.522	.019*
SSQ	16	1.990	.001*
QCAE-CES	16	1.059	.212
QCAE-AES	16	0.750	.627

Table 6: Non-Parametric Bivariate Correlation Analysis with Social Cognition Tests (Raw Scores)

Social Cognition Test.	RMET	SSQ	QCAE-CES	QCAE-AES
RMET	1.000	.013	-.304	-.042
SSQ	.013	1.000	.684	.098
QCAE-CES	-.304	.684	1.000	.259
QCAE-AES	.167	.098	.259	1.000

Table 7: Multiple Linear Regression to Explore Contribution to QCAE-CES score (Raw Scores)

Neurocognitive test.	Beta.	t.	Sig.
WTAR	.390	1.377	.151
Education (total years)	-.050	-.174	.865
List Total	.180	.733	.479
SSQ	.386	1.576	.143

3.4. Individual Profile Analysis

Each participant's cognitive profile was examined in the context of their relevant background information obtained from their clinical interview and medical files.

For each participant, a graph displays their distribution of converted scaled scores for performance on the HAD scales, social cognition tests, QCAE subscales, and neurocognitive battery.

For each participant, pre-morbid ability was estimated using reading ability as an overlearned ability (as measured using the WTAR), educational attainment (as measured by total years of education) and highest score among tests as an indication of level of ability. In this manner, pre-morbid ability was assessed by comparing participants to both the normative population (WTAR) as well as comparing them to themselves (highest score) and educational achievements.

Participant 1

Participant 1 was a fifty-seven year old white British male, born and educated in the UK. With English as his first language, he attended school from five to twenty-one, obtaining an undergraduate university degree. Occupation; employed full-time in professional management.

cART adherent, he was on his second cART regime since diagnosis (CD4 count = 575, = VL = 1, diagnosed = 2012). He had a history of depression and anxiety but was currently below-caseness on the HAD. His father had been diagnosed with Dementia of the Alzheimer's type in later life.

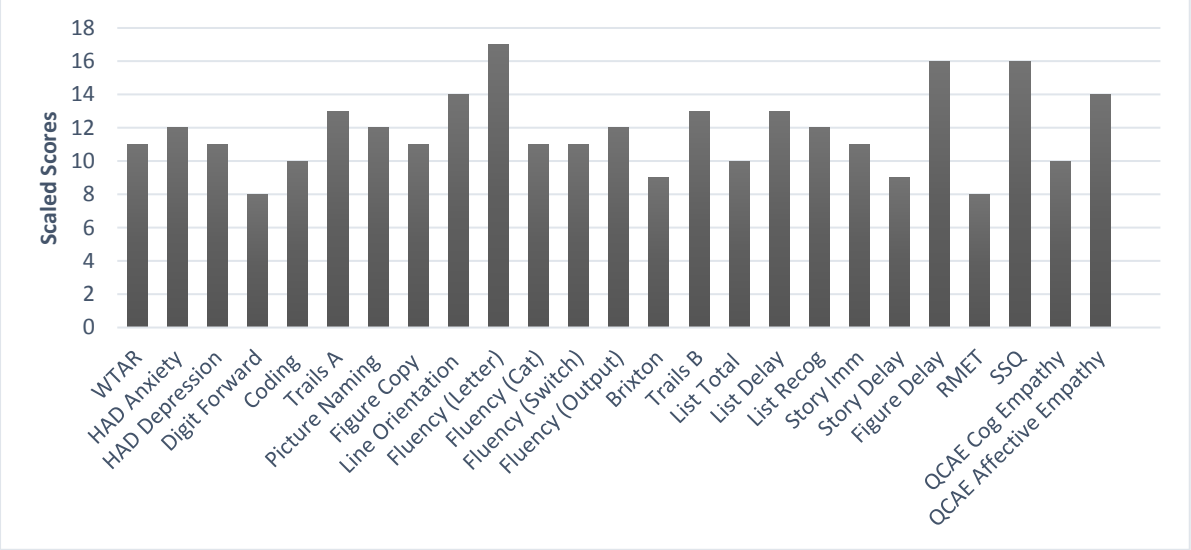

Figure 1: Scaled Scores for Participant 1

Figure 1 shows an intact unimpaired cognitive profile, with minor weaknesses in digit forward performance, in keeping with normal variation. Furthermore, the SSQ and QCAE subscale scores fall in the 'very superior', 'average' and 'high average' ranges, respectively.

In contrast, the RMET score falls in the 'average' range, suggesting impaired emotion recognition abilities.

Participant 2

Participant 2 was a forty-one year old black British male. Born and educated in the UK, he attended school from five to twenty-one years of age; obtaining undergraduate university degree. Occupation; full-time senior accountant. No current or historic cART use (CD4 count = 512, VL = 22174, diagnosed = 2014). HAD scores; below-caseness.

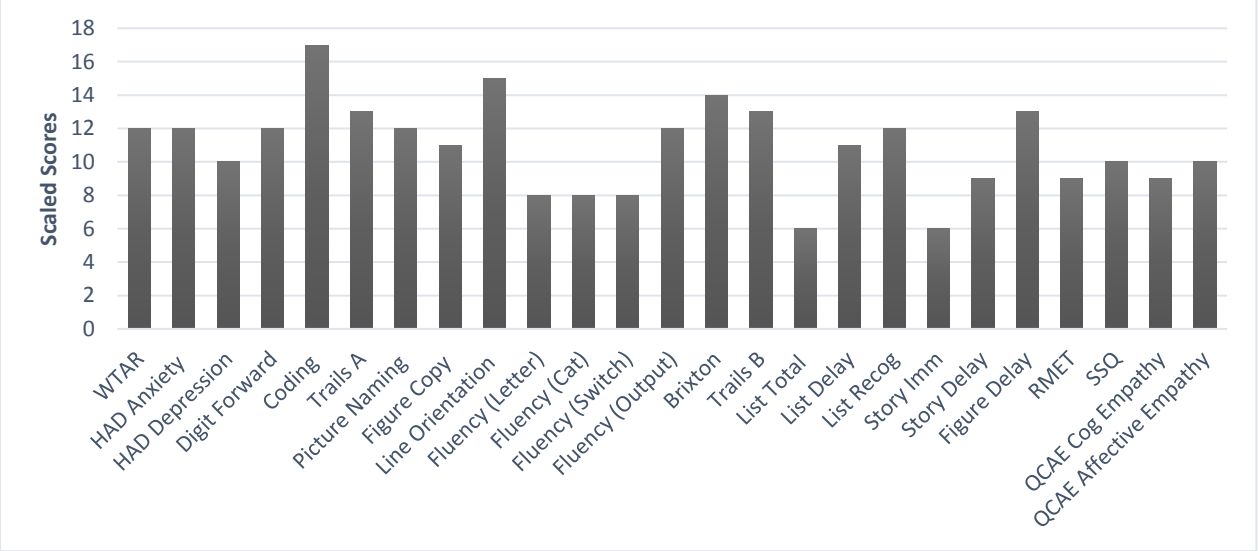

Figure 2: Scaled Scores for Participant 2

Figure 2 shows a cognitive profile with relative weaknesses in verbal fluency and verbal recall. This may reflect normal variation, or emerging difficulties with concentration and attention consistent with ANI.

All four social cognition scores are within the 'average' range for the normal population but towards the lower end of overall ability the context of the participants own specific cognitive profile.

Participant 3

Participant 3 was a thirty-three year old black British male. Born and educated in the UK: he attended school from five to twenty-one, obtaining an undergraduate university degree. With English as his first language, he also spoke two other languages fluently. Occupation: full time administrative work, and a civil rights advocate. He did not currently or historically take any cART (CD4 count = 587, VL = 42909, diagnosed = 2009). HAD scores: below-caseness.

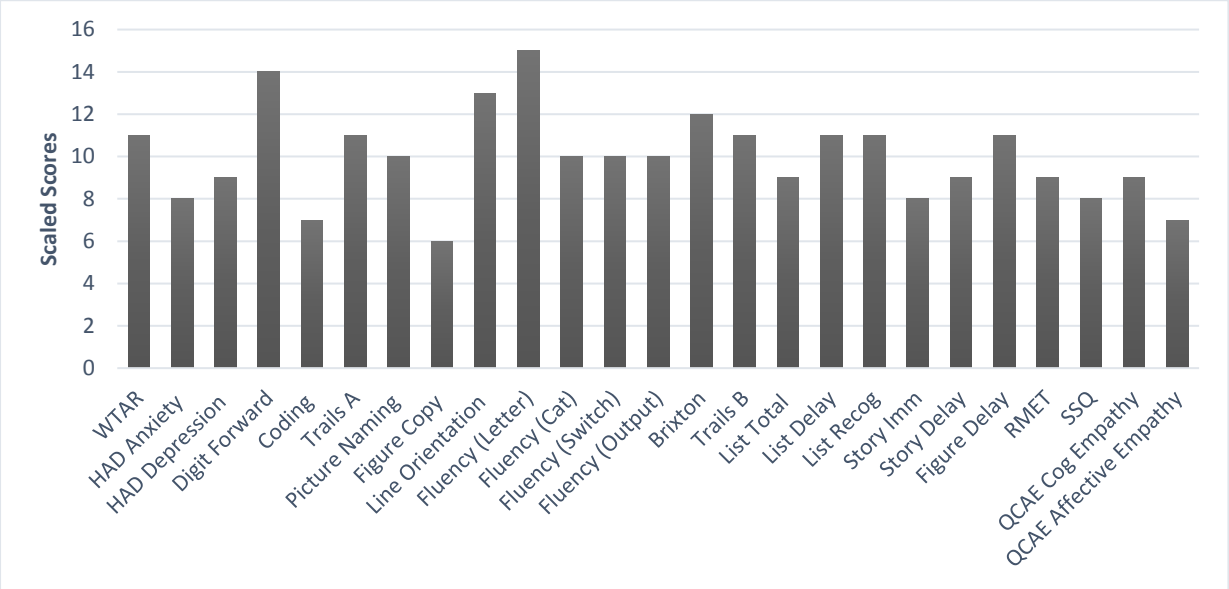

Figure 3: Scaled Scores for Participant 3

Figure 3 shows a cognitive profile with relative weaknesses on following subtests: Coding, Figure Copy, List and Story Immediate Recall. This may represent an emerging decline in attention and memory, consistent with ANI.

RMET, QCAE-CES and SSQ scores all fell in the ‘average’ range. In contrast, the QCAE-AES score fell in the ‘low-average’ range; with any impairment unlikely to be influenced by core deficits given comparative scores.

Participant 4

Participant 4 was a forty year old black Ugandan female. Born and educated in Uganda: she attended school from five to sixteen, including a short time at boarding school. A primary speaker of Luganda, she also spoke fluent English. Occupation; unemployed. She has a complex history of adverse and traumatic life experiences, and in 2013 she met with a Psychologist for support with severe anxiety, depression, and trauma. At the time of testing, she did not have symptoms associated with 'Post-Traumatic Stress Disorder', anxiety or depression: HAD scores: below-caseness. (CD4 count = 529, VL = 1, diagnosed = 2011).

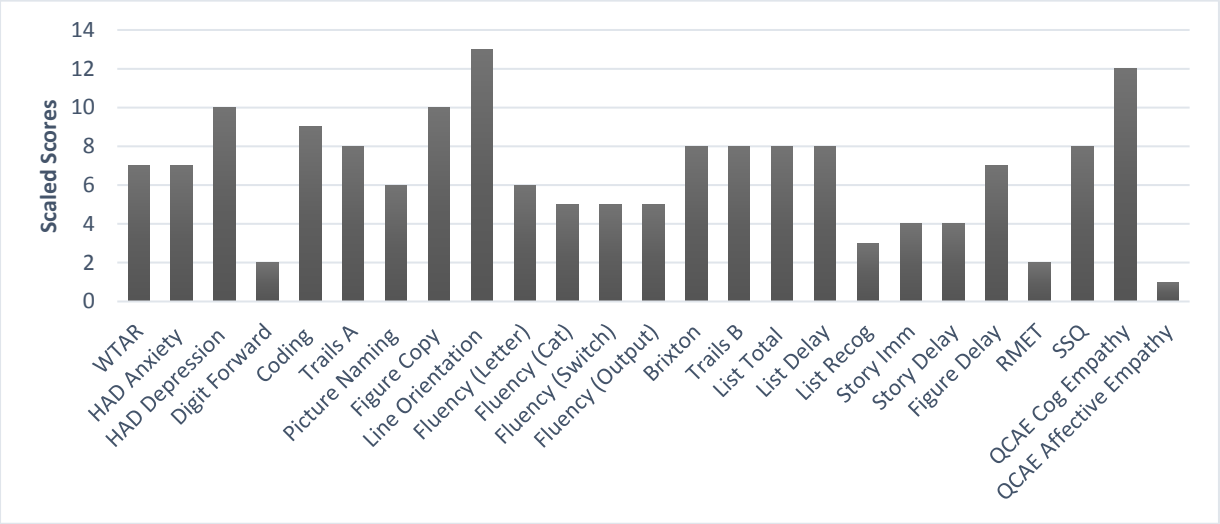

Figure 4: Scaled Scores for Participant 4

Figure 4 shows a cognitive profile with relative weaknesses in verbal attention, semantic verbal memory, and verbal executive function tests. 'Average' performance on the list-based learning and memory tests support the likelihood of an intact ability to encode and store information. Although these impairments may be overestimated due to second-language status, they are nonetheless consistent with the participant's subjective cognitive complaints and therefore might represent an emerging attentional or executive function weakness, consistent with MND. The SSQ score fell in the 'high-average' range and the QCAE-CES score fell in the 'average' range. In contrast, the RMET and QCAE-AES scores fell in the 'impaired' range and below.

Participant 5

Participant 5 was a forty-eight year old black Somali woman. Born and educated in Somalia with her 12 siblings, she attended school between the seven and fourteen years of age. She spoke Swahili and Somali as first languages, and also spoke fluent English. Occupation: unemployed. cART regimen changed seven times since 2003 due to side-effects and viral resistance, and twice admitted to HIV inpatient ward (CD4 count = 76, VL = 642167, diagnosed = 2003). Prescribed Mirtazapine for depression; she subjectively reported mild low mood, but reported severe depression on the HADS.

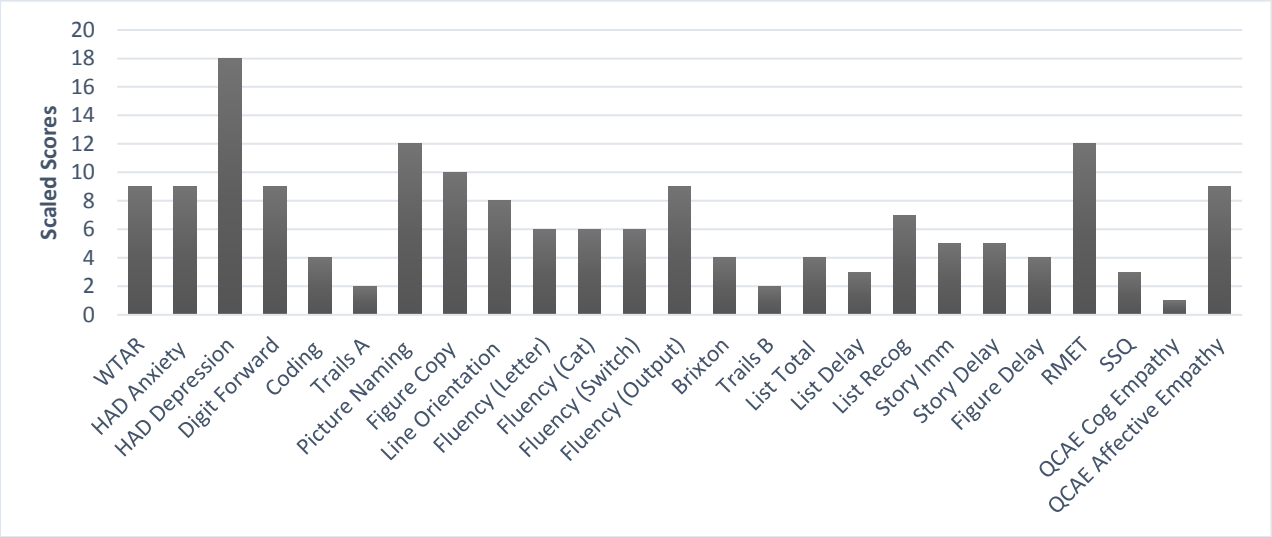

Figure 5: Scaled Scores for Participant 5

Figure 5 shows substantial impairment in processing speed, verbal and visual immediate memory, attention (e.g., encoding of to-be-learned material) and executive functions. The SSQ and QCAE-CES scores fell in the ‘impaired’ and ‘very-impaired’ ranges, respectively: suggesting a weakness in these areas separate to both the other two measures of social cognition. In the clinical interview, participant 5 self-reported marked functional decline in activities of daily living (ADLS) that were not attributable to co-morbidities or delirium. She demonstrated functional impairment in her unemployment due to cognitive impairment and self-report of dependence. Alongside the apparent moderate to severe cognitive impairment shown above, this profile is consistent with HAD although attribution of impairment to HAND is confounded by severe depression scores.

Participant 6

Participant 6 was a thirty-six years old white Spanish woman. Born and educated in Spain, she attended school from five to eighteen years of age, after which she moved to the UK where she obtained an undergraduate university degree in English Literature at the age of twenty-three. With Spanish as her first language, she was also fluent in English. Occupation: full time Research Nurse. cART commenced 4 weeks prior to testing (CD4 count = 441, VL = 88608, diagnosed = 2001). History of 'Post-natal Depression' and mild crone's disease, with no present symptoms of either. HAD scores; mild depression.

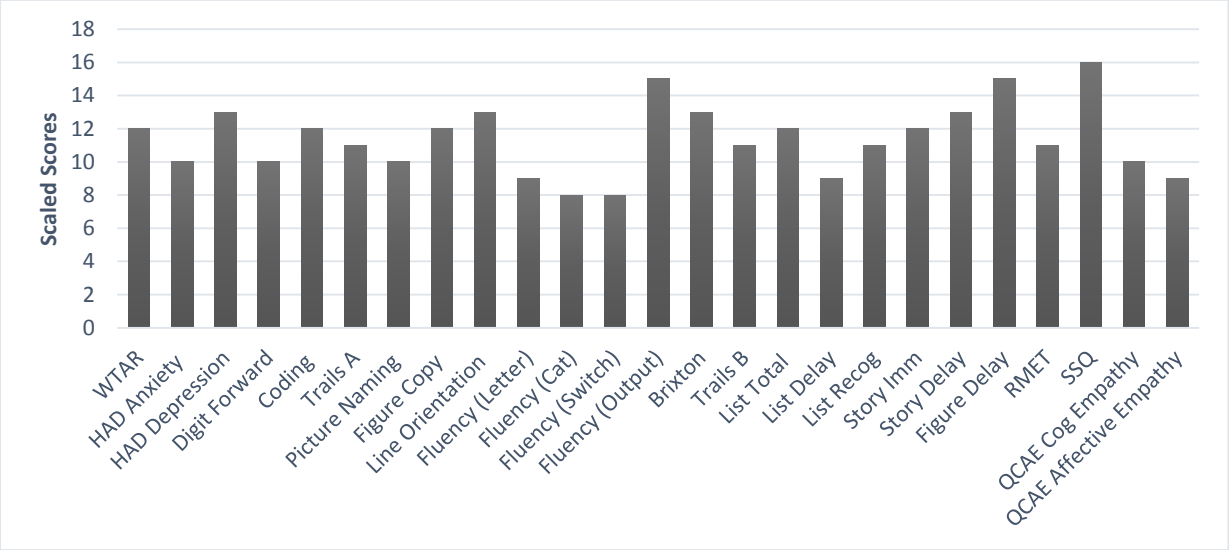

Figure 6: Scaled Scores for Participant 6

Figure 6 shows a strong cognitive profile consistent with estimated pre-morbid ability and normal variance, showing no evidence of impairments characteristic of HAND.

Scores on the QCAE subscales are slightly lower than others in the profile, however, any real-world difficulties here may be compensated for by the relative strengths in areas of executive function, particularly on tasks which required mental flexibility and multiple demands.

Participant 7

Participant 7 was a sixty-seven year old white British man. Born and educated in the UK, he attended Private School from five to eighteen years of age. Occupation; Horse-trainer, now retired. cART adherent; he described some tiredness and 'slowing-down' which he attributed to side effects (CD4 = 418, VL = Und, diagnosed = 1993). Currently treated for Shingles in left eye which caused some blurred vision. History of anxiety and depression though not currently: HAD scores; below-caseness.

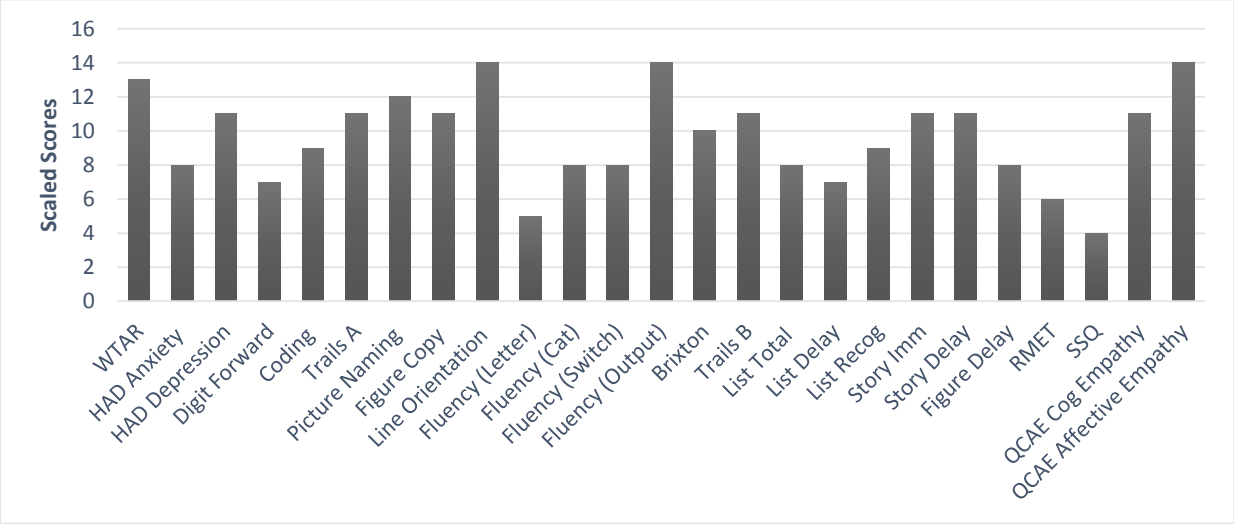

Figure 7: Scaled Scores for Participant 7

Figure 7 shows a cognitive profile with impaired performance on verbal executive function and some tests of learning and memory (List Total, List Delay, Figure Delay). That said, performance on Story Immediate, Story Delay and List Recognition subtests fall in the 'average' range, implying either normal variation or an emerging difficulty with episodic memory function and/or attention. This profile is consistent with ANI.

Both QCAE subscale scores fell in the 'average' range or above. In contrast, the RMET and SSQ scores fell in the 'low-average' and 'below- normal' range, respectively; suggesting an impairment in mentalising ability not secondary to core deficits or mood.

Participant 8

Participant 8 was a forty-nine year old black British woman. Born in the UK, she moved to Jamaica when five years old where she attended school from five to seventeen. Occupation; full time cleaner and an active member of her church community. cART adherent (CD4 count = 954, VL = Und, diagnosed = 2005). HAD: mild depression.

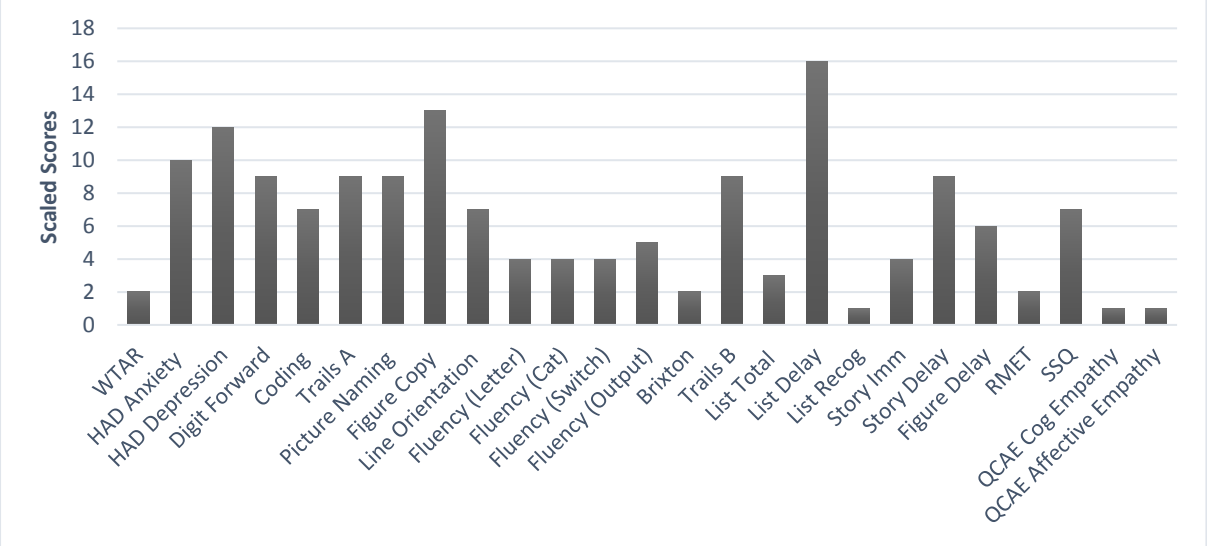

Figure 8: Scaled Scores for Participant 8

Figure 8 shows relative weaknesses in verbal and visual memory and executive function abilities; representing an emerging memory or executive function cognitive difficulty, consistent with HAND. In the clinical interview, participant 8 self-reported mild decline in everyday functioning including significant reduction in occupational responsibilities secondary to reduced cognitive abilities and decline in vocational functioning. This profile, alongside information collected in the clinical interview identified it as being consistent with emerging MND.

The SSQ score fell in the ‘low average’ range. In contrast, the RMET and both QCAE subscale scores fell in the ‘impaired’ range; suggesting greater impairment in emotion recognition and empathy.

Participant 9

Participant 9 was a forty-one year old black Ugandan woman. Born in Uganda, she was educated in Kenya from five to thirteen years of age, which she enjoyed but stopped attending due to the school's corporal punishment. In the UK, she attended and passed a college ESOL course in English language skills and is fluent in English. Occupation: full time shop assistant and single mother of two. cART adherent (CD4 count 594, VL = Und, diagnosed 2005). Medical history including Hypercholesterolaemia; Hypertension; Endometriosis; and a sub-total hysterectomy in 2014. HAD: severe anxiety.

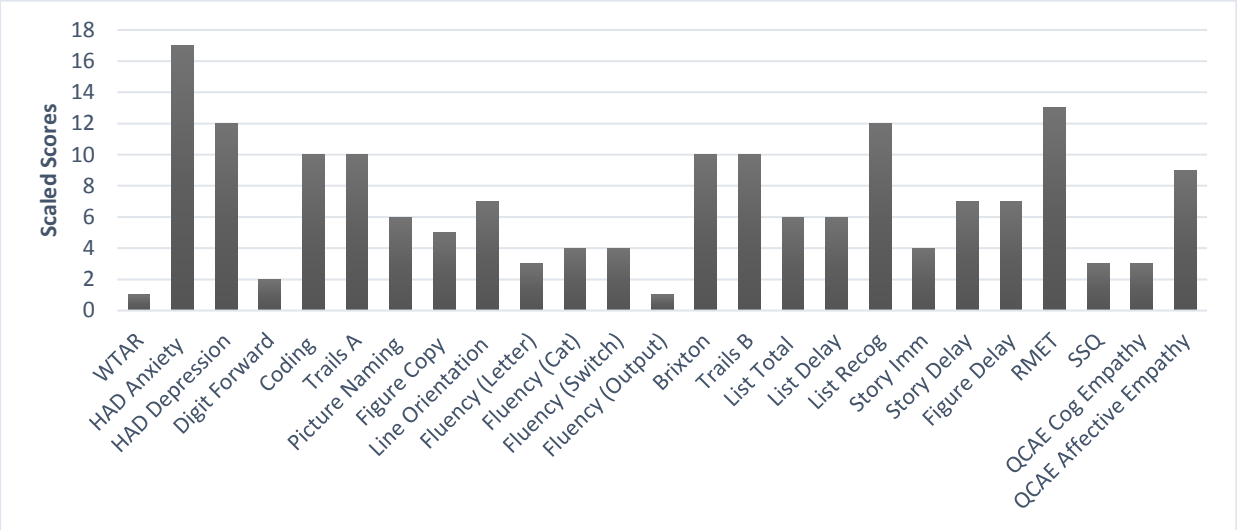

Figure 9: Scaled Scores for Participant 9

Figure 9 shows relative weaknesses in verbal attention, verbal memory, and verbal executive function tests as well as severe anxiety.

RMET scores and QCAE-AES scores fell in the 'high-average' and 'average' range, respectively. In contrast, SSQ and QCAE-CES scores fell in the 'impaired' range.

Although second-language status and presence of severe anxiety restrict interpretation, these impairments are consistent with the participant's subjective cognitive complaints and therefore might represent emerging attentional, memory or executive function weakness, consistent with MND.

Participant 10

Participant 10 was a forty-two years old white Portuguese woman. Born and educated in Portugal, she attended school from five to seventeen years of age. With Portuguese as her first language, she also speaks fluent English. Occupation; mother of three, part-time administrator, and an active member of a PTA group. cART adherent (CD4 count = 687, VL = Und, diagnosis = 2000); she also has a diagnosis of Hepatitis C, and was previously treated for mouth cancer. HAD scores; moderate anxiety and depression.

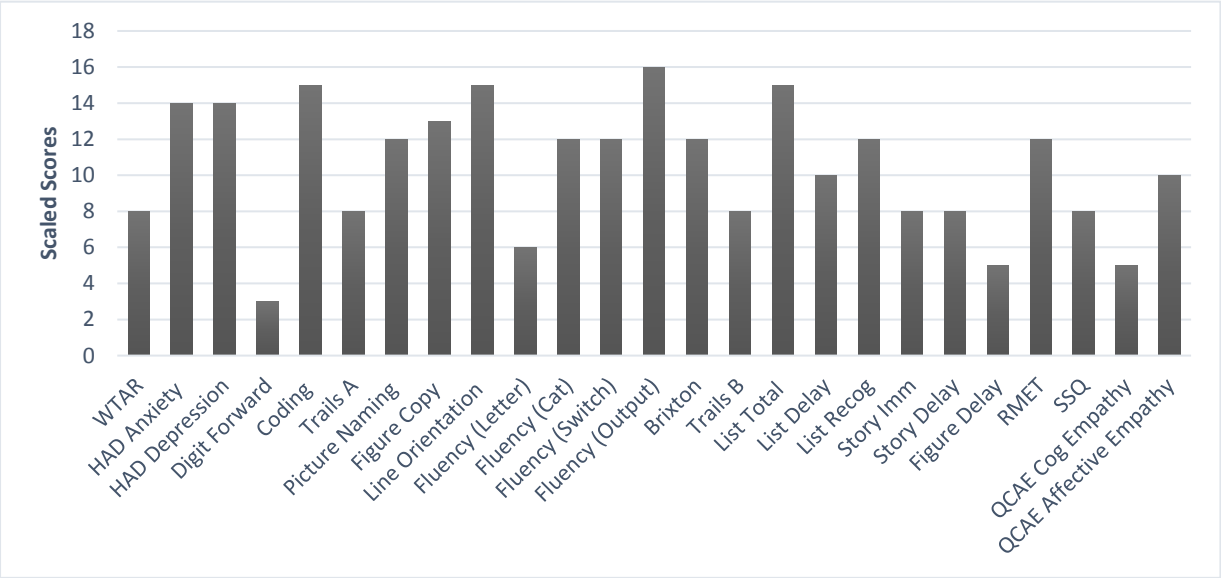

Figure 10: Scaled Scores for Participant 10

Figure 10 shows relative weaknesses in tests of attention (Letter Fluency, Digit Span Forwards and Backwards). These are consistent with subjective complaints of poor memory, verbal repetition and ‘zoning out’ during familiar tasks and may reflect an emerging attentional deficit, consistent with ANI.

The RMET, QCAE-AES and SSQ scores all fell in the ‘average’ range, whereas the QCAE-CES scores fell in the ‘below-normal’ range.

Participant 11

Participant 11 was a forty-nine year old black British man. Born in Ghana and educated in the UK from five to twenty-three years of age, obtaining a post-graduate qualification. Occupation; senior professional role. He was cART adherent (CD4 count = 869, VL= Und, diagnosis = 2002) and had a history of recurrent depressive episodes, but was not at the time of testing. HAD scores; mild depression.

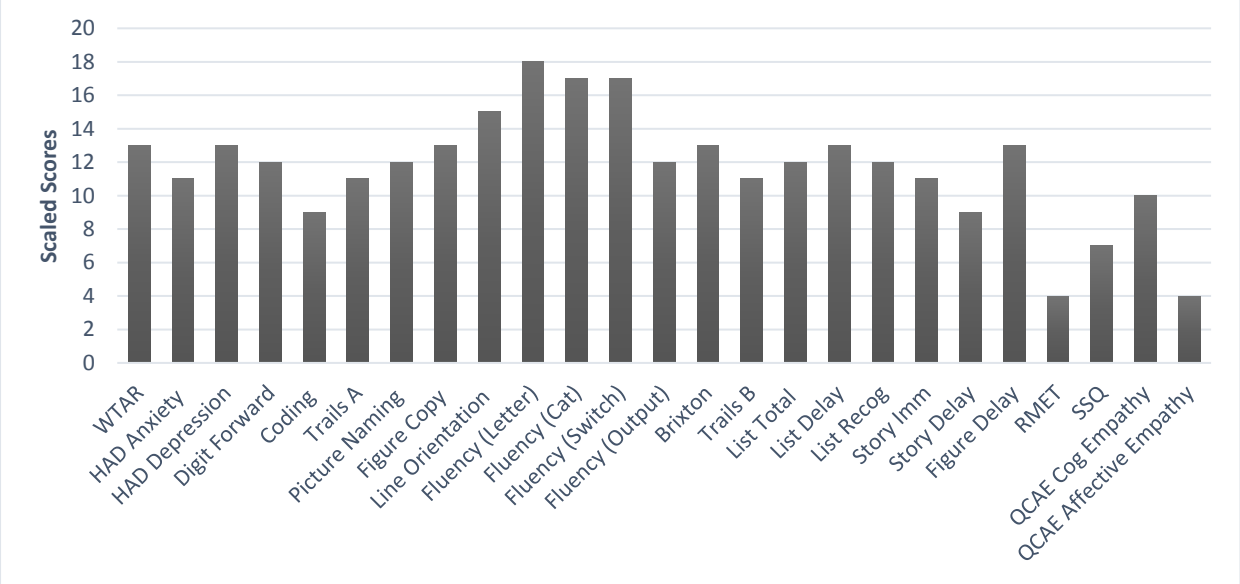

Figure 11: Scaled Scores for Participant 11

Figure 11 shows a cognitive profile mostly in keeping with the estimated high average pre-morbid ability. However, subjective complaints concerned reduced processing speed and attention over last 18 months, and the cognitive profile may be suggestive of early emerging difficulties with processing speed and attention, in keeping with emerging ANI.

RMET and QCAE-AES scores both fell in the ‘below-normal’ range, whereas SSQ and QCAE-CES fell in the ‘low average’ and ‘average’ range, respectively.

Participant 12

Participant 12 was a forty-three year old black British woman. Born and educated Burundi, she attended school from five to sixteen and, in the UK, later completed GCSEs in Maths, English and ICT, and started HND qualifications in English and Maths. She found latter studies difficult to engage with due to cognitive complaints. She came to the UK after first seeking asylum in Kenya due to the Burundi civil war. Her first languages are French and Swahili, and she also spoke fluent English. Occupation; unemployed, previously a supermarket cashier. She was cART adherent (CD4 count = 580; VL = Und; diagnosed = 2006) and reported current low mood and interpersonal difficulties. HAD scores; moderate mixed anxiety and depression.

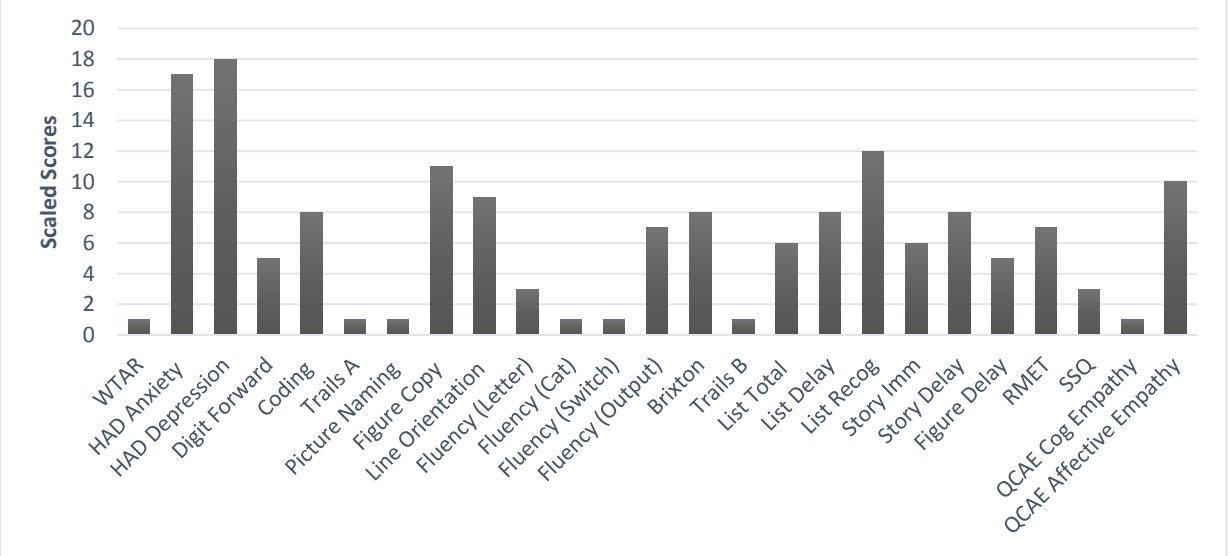

Figure 12: Scaled Scores for Participant 12

Figure 12 shows that performance on Trails A, Picture Naming, Fluency (Category and Switching) and Trails-B subtests all fell in the ‘profoundly’ impaired range; a pattern of impairment consistent with MND. Areas of impairment may be overestimated due to secondary language status and the confounding impact of co-morbid severe depression.

RMET and QCAE-AES scores fell in the ‘low average’ and ‘average’ range, respectively. In contrast, the SSQ and QCAE-CES scores fell in the ‘impaired’ and ‘very-impaired’ range, respectively.

Participant 13

Participant 13 was a forty-eight year old white British male. Born and educated in England, he completed a combination of private and state education between five to twenty-one years of age, obtaining a BTech Diploma. Occupation; unemployed and receiving ESA; previously employed in the Bar and Restaurant Industry. He is cART adherent (CD4 count = 704, VL = Und; diagnosis = 1997). Treated for Kaposi's sarcoma last year, currently experiencing poor sleep and fatigue. HAD scores; severe anxiety.

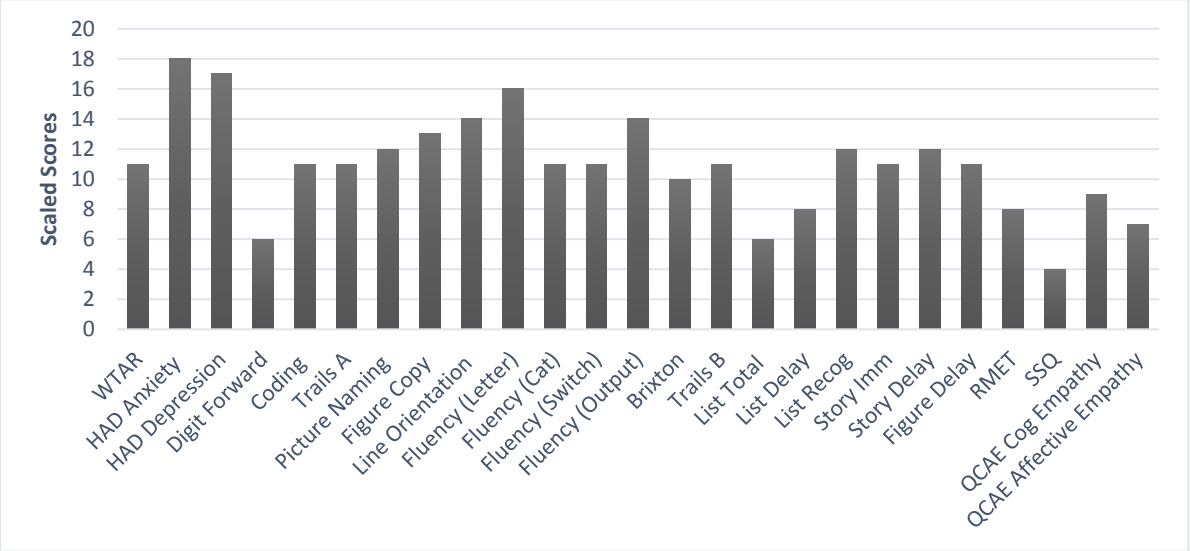

Figure 13: Scaled Scores for Participant 13

Figure 13 shows a mostly strong cognitive profile, but with 'low average' performance on the Digit Forward and List Learning subtest. However, there was strong performance on Story Learning, another test of immediate memory, signifying intact encoding and retrieval. Profile consistent with ANI, although impairments may be interrelated with severe anxiety score.

Social cognition test scores were amongst the weakest in the profile. Although RMET and QCAE-CES scores fell in the 'average' range; the QCAE-AES score fell in the 'low average' range, and SSQ in the 'below-normal' range.

Participant 14

Participant 14 was a twenty-three year old Malaysian male. Born and educated in Singapore, he attended school from four to eighteen, before completing two years of mandatory Army conscription in Singapore and moving to the UK to attend university. cART adherent, reported no side-effects and good current and historical health. (CD4 count =282, VL = 263, diagnosed = 2015). He reported experiencing cognitive changes after HIV infection, and again when starting the antiretroviral treatment, including a decline in processing speed and attention span. However, he feels like these difficulties have abated since. HAD scores; mild anxiety.

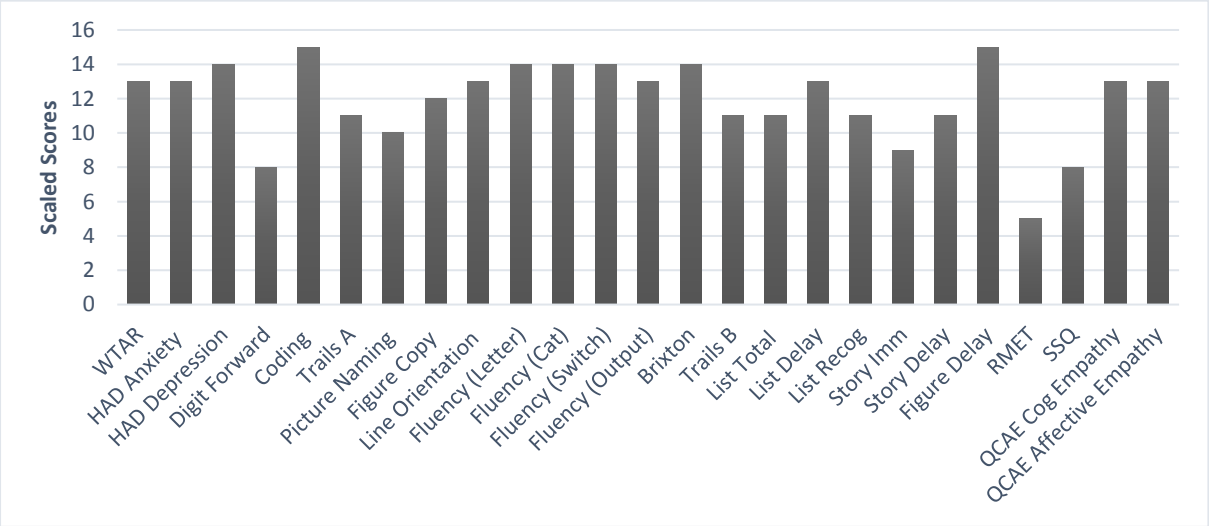

Figure 14: Scaled Scores for Participant 14

Figure 14 shows a well persevered cognitive profile. Slight weakness on List and Story Learning performance can be accounted for by performance anxiety experienced at time of testing.

The SSQ and QCAE subscale scores fell within the ‘high average’ range. In contrast, RMET was in the ‘below-normal’ range suggesting impaired emotional recognition abilities, not attributable to visual and language deficits.

Participant 15

Participant 15 was a thirty-three year old white British man. Born and educated in the UK, he attended school between five to sixteen years of age and remembers receiving additional learning support in secondary school. Occupation; full-time chef. He was cART adherent, on his second cART regime after experiencing adverse side effects from the first, including nightmares, nausea and dizziness (CD4 count = 720, VL= Und, diagnosed = 2012). He described a period of depression following his diagnosis, but no symptoms at the time of testing. HAD scores; moderate anxiety.

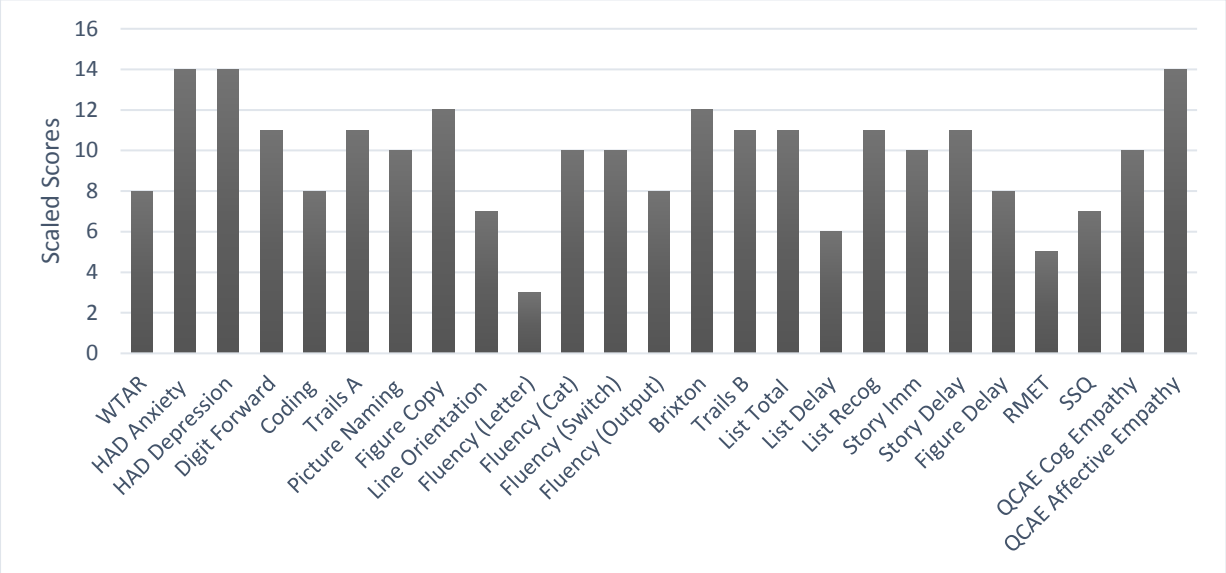

Figure 15: Scaled Scores for Participant 15

Figure 15 shows significant weaknesses on a test of Letter Fluency and List Delay (but average performance on Story Delay); suggesting a possible impairment in episodic learning or verbal function. This is consistent with subjective complaints of impaired short-term memory and is in keeping with emerging ANI.

Substantial impairment on the RMET and milder impairment on the SSQ are also observed, suggesting a disadvantage in emotional recognition and cognitive-linguistic skills not attributable to other core deficits.

Participant 16

Participant 16 was a fifty year old white British man. Born and educated in England, he attended school from five to eighteen years of age. He spent the first two years of his life in state provided child-care, after which he was moved to live with his mother. He described a difficult home-life growing up, which impacted his educational attainment. He was rarely absent from school, but struggled with Maths and English. Occupation; self-employed carpenter and set up his own business. He is cART adherent (CD4 count = 806, VL = Und, diagnosed = 1996). He partook in the SMART Research Trial, where he discontinued his cART for a controlled period of time in order to investigate his immune response: during this time he developed shingles and some minor infections before re-starting cART. HAD scores; mild anxiety.

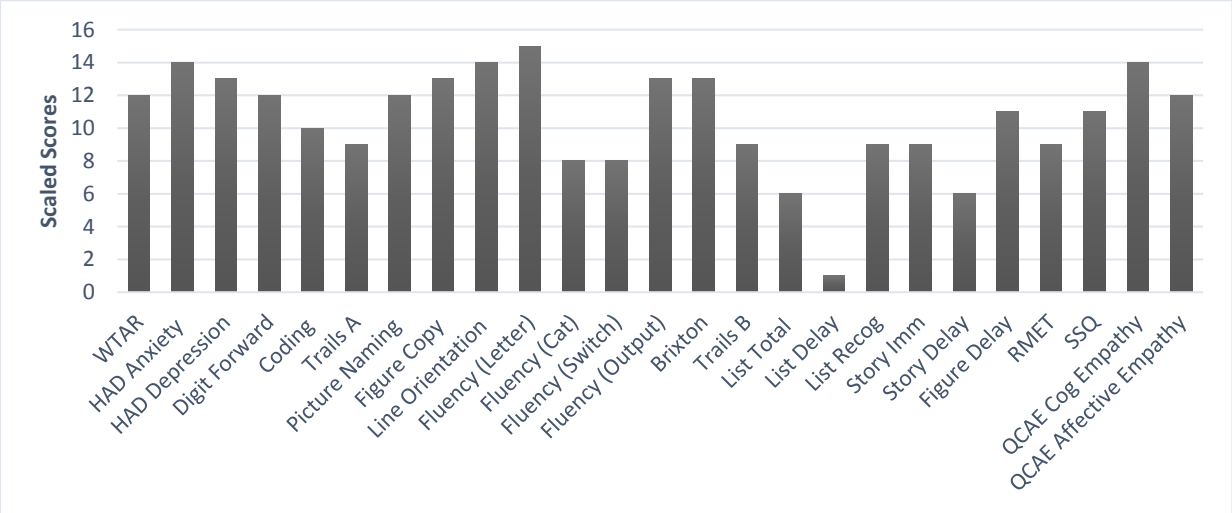

Figure 16: Scaled Scores for Participant 16

Figure 16 shows a profile of scores which fall in ‘average’ range and above on most tests; likely revealing an intact cognitive profile. Profound weakness on two tests of delayed memory (List and Story Recall) may be associated with performance anxiety at the time or testing, as corroborated by patient subjective feedback. Alternatively, these weaknesses may also be consistent with an emerging attentional deficit, in keeping with the patient’s subjective cognitive complaints. As such, this profile is consistent with HAND of the ANI nature.

4. DISCUSSION

This study aimed to explore the cognitive profile of social cognition in HAND. The research questions specially sought to address whether HAND differentially affected, cognitive-linguistic function (e.g., comprehension of non-literal language), emotion recognition (e.g., of facial expression), or empathy (e.g., capacity to emotionally engage with other persons).

4.1. Summary of Results

This study revealed that a cohort of 16 adults with HIV-1 infection demonstrated weaker performance on two measures of social cognition (i.e., RMET and SSQ) than people without HIV (i.e., test norms). Group-level analysis showed that these trends occurred in the context of a cohort with relatively well preserved level of cognitive functioning, with only mild weaknesses in attention, verbal learning and semantic verbal executive function. Individual-level analysis revealed that the social cognition impairments typically occurred alongside other areas of decline and not before, and were not related to stage of HIV infection. These findings support the previous research into the profile of social cognition impairments in HAND (Homer et al., 2013; Ireland, 2011). Taken together, these results indicate that impairments in the cognitive processes required for some aspects of social cognition (e.g., non-literal cognitive-linguistic processing and emotion recognition) may be characteristic of the neurocognitive profile of HAND, even in relatively mild stages of cognitive impairment.

The sections below offer a thorough breakdown of the above findings, including an analysis of the pertinent and confounding variables. An itemisation of the group-level analyses are offered first, and then considered within the context of the trends revealed by the Individual Profile Analyses.

4.2. Discussion of Group-Level Analysis

The findings from the subtest means and correlational analyses are discussed below. Whilst correlations do not demonstrate causality, they are useful at suggesting relationships between variables and identifying areas for further

exploration. However, the following results should be taken as representing trends in the data only.

4.2.1. General Cognitive Function

As an initial overview of the sample's general cognitive functioning prior to more in-depth interpretation; only mild weaknesses were apparent on Digit Forward (mean 8.13); Category Fluency (mean 8.56); List Total (mean 8.31) and Story Immediate (mean 8.06); suggesting minimal decline in areas of attention, verbal learning and executive function. Intact domains included; information processing (Coding and Trails A), visuo-spatial function (Line Orientation and Picture Copy) and visual executive function (Brixton Test and Trail Making B). However, as noted, all of these subtest means had large standard deviations. These trends appeared consistent with the literature regarding the characteristics of emerging HAND in the post-cART era (Iudicello, Woods, et al., 2012; Iudicello et al., 2008; Woods et al., 2009).

The specific areas of cognitive decline and interpretations of these finding are provided further below.

4.2.1.1. Attention and Information Processing

As stated, the group demonstrated performance in the low-average range on the Digit Span task, which serves as an assessment of verbal short-term memory stores and attention. Although previously thought to be a faculty relatively spared until later stage of disease progression, more recent literature purports that attentional deficits may be among the earliest to develop in HAND (Butters et al., 1990; Heaton et al., 1995; Levine et al., 2008). It is possible that this area of weakness also contributed to the lower group mean on the List Total task (see below).

4.2.1.2. Learning and Memory

Mild decline was observed on both the List Total and Story Immediate; tests of verbal learning and memory, whereas performance on the List Recognition task was within the average range. These results are in keeping with current research, on two counts; that which identifies that both tests are sensitive to HAND (Igor Grant et al., 2008; Woods et al., 2009), and that HAND typically sees impairment in learning new

information, whilst recognition and cued memory remain unaffected until the later stages of infection (Heaton et al., 1995; Iudicello, Kellogg, et al., 2012).

4.2.1.3. Executive Function

Performance on all tests of executive function fell in the 'average' range, with the exception of Category Fluency, on which the group demonstrated 'low-average' performance. This latter result is consistent with the literature which reports that verbal fluency impairment is the most frequently identified language deficit in HIV and is estimated to occur in approximately 40% of the population (Rippeth et al., 2004).

Additional impairments in executive function are reported as prevalent in post-cART HAND presentations (Gates & Cysique, 2016; Heaton et al., 2015; Woods et al., 2009) and the absence of such impairments in the current cohort may reflect the wide variability in the test scores obscuring impairments at a group-level. This theory is explored further in the coming Individual Profile Analysis.

Accordingly, therefore, impaired performance on the social cognition tests could not be explained by executive dysfunction. This provides support for the 'domain specific' notion, discussed in the introduction; that, rather than being solely reliant on executive function mechanisms, there is instead some degree of specificity to social cognition (Kipps & Hodges, 2006; Stone & Gerrans, 2006). These results draw similarly upon Frith and Frith's (2012) model of social cognition, supporting the view that the processes which make up social cognition – despite drawing largely on general cognitive mechanisms – may also require specialist processes which are yet to be fully understood.

4.2.2. Social Cognition

As an initial overview of the cohort's social cognition functioning prior to more in-depth interpretation; this cohort performed in the 'low-average' on both neurocognitive tests of social cognition; RMET (mean 7.63) and SSQ (mean 7.69). These were the largest disadvantages demonstrated on all the tests administered in the current study. QCAE scores for each subscale fell in the 'average' range.

4.2.2.1. RMET

The cohort demonstrated impaired performance on the RMET (equal to one standard deviation below the norm) suggesting disadvantaged emotion recognition skills. In addition to emotional recognition, successful performance on this task also required intact visual function and reading ability in order to visually scan the eye region of the image, and read the complex emotion-based lexicon. A review of the subtest means revealed that no equivalent group-level impairments were apparent in visuo-spatial function: a finding in keeping with the wider literature which reports that visual function remains intact until later stages of HIV infection (Heaton et al., 1995). With regards to reading ability, the cohort demonstrated slightly poorer performance on the WTAR than the population norm. Although this score was still within the 'normal' range, it might indicate a very mild weakness in this area which may have contributed to their performance on the RMET. However, this association was not reflected in the results of the correlational analyses (see Appendix O). As such, these findings suggest that the declined performance on the RMET was separate to both reading ability and visuo-spatial function, in this cohort.

4.2.2.2. The SSQ

The sample also demonstrated impaired performance on the SSQ. This test relies on several complex cognitive demands, including; a memorial component; several verbal and linguistic demands; the ability to identify violations in social norms; and, explicit mentalising skills. Therefore, success on this test requires the operation of several cognitive processes, and impaired performance can be secondary to various areas of weakness. To consider the role of verbal function here, relevant subtest means were compared. The SSQ requires intact reading skills, and, as discussed, the group performance on the WTAR was slightly lower than the population norm. Furthermore, Picture Naming, List Total, Story Immediate and Category Fluency all have primary linguistic and verbal components. Although performance on the former of these subtests appeared intact, there were mild weaknesses apparent on the latter three. Further correlational analyses pointed at an association between the SSQ and List Total ($r = .541$); Category Fluency ($r = .381$) and QCAE-CES ($r = .684$), suggesting that verbal function was associated with impaired performance on the SSQ, and that performance on these tasks was interdependent.

A shared component across the SSQ, Category Fluency and QCAE-CES was the social narrative embedded within the cognitive linguistic processing demands of each test. Successful performance on these tests requires the capacity to hold in mind the semantic arc of the statements, in order to generate an answer to the questions. The above results may point to a specific difficulty with non-literal linguistic processing in this cohort. Perspectives from the field of cognitive linguistics may be pertinent here, with regards to the role of non-literal language in social communication processes. Landau et al. (2010) explain that people make sense of the world partly through conceptual metaphors, which enable them to understand complex abstract social concepts through their understanding of more concrete concepts. Thus, far aside from being simply adornments of language, the authors argue that conceptual metaphors are cognitive mechanisms which play a key role in social cognition.

4.2.2.3. QCAE Subscales

Group performance fell in the 'average' range for both QCAE subscales. Furthermore, the two subscales did not correlate with each other (r = .259); suggesting relative independence, in this sample. This supports Reniers et al's (2011) view of empathy as multifactorial, and the construction of each subscale to tap into differentiated components of the construct.

Of note, the QCAE-CES also correlated with reading (r = .525), List Total (r = .522) Story Immediate (r = .378), and Category Fluency (r = .393); identifying (perhaps in a similar manner to the SSQ) a relationship between specific non-literal linguistic components of these tests.

4.2.3. Additional Correlations between Variables

4.2.3.1. RMET and SSQ

The correlational analysis failed to find an association between group-level performance on the RMET and SSQ (r = .013). This finding was in keeping with other findings in the literature regarding ToM, which have also failed to find relationship between the RMET and other social-script based assessments of cognitive ToM similar to the SSQ (Brent, Rios, Happe, & Charman, 2004; Homer et

al., 2013; Ireland, 2011; Kaland, Callesen, Miller-Nielsen, Mortensen, & Smith, 2008). As asserted by Ireland (2011) and Brent et al. (2004), it is possible that this finding reflects the different cognitive mechanisms required by each test, potentially reflecting their focus on 'cognitive' or 'affective' components of ToM, as discussed below.

As a test of affective ToM; the RMET concerns the social-perceptual understanding of non-verbal emotional processing. Successful performance requires the subject to have intact visuo-spatial function in order to scan, perceive and understand the information in their visual field. As a test of cognitive ToM; the SSQ concerns explicit mentalising skills. Successful performance requires intact language and memory based mechanisms, with participants required to comprehend and hold in mind non-literal social narratives. As argued earlier in the discussion, this test relies on a host of different cognitive mechanisms, particularly non-literal linguistic function and reading ability; areas of ability which were found to be mildly declined and interdependent in the current cohort.

As such, these findings support the idea that the two tests are assessing different mechanisms involved in ToM abilities. Unlike Ireland (2011) and Homer et al. (2013), this study found that the cohort of people with HIV infection were impaired across both tests – rather than just the affective ToM. Given the small sample size it is not possible to interpret this observation and further research with larger sample numbers are required before this trend can be generalised.

4.2.3.2. Mood

Moderate negative correlations between the HADS and the SSQ (-.482) and QCAE-CES (r = -.462) revealed that participants who reported lower rates of mood disturbance were more like to perform highly on these measures. Conversely, the relationship between the HADS and RMET went the other way; that is; the more anxious or depressed they were, the more likely they were to accurately perceive the emotional state of others. The findings of Chepenik et al. (2007) may offer some insight into the above findings; the authors reported that low mood was shown to influence memory for emotional words and facial emotion recognition, but not other cognitive processes; identifying a specific influence of mood on emotion-related

cognitive processes. Although this might explain why the HADS score was found to correlate with the SSQ and QCAE but not other cognitive tests, it does not explain the absence of a correlation with QCAE-AES, or the positive correlation with the RMET.

4.2.3.3. Education

As would be expected, education correlated highly with the WTAR (r = .741) as well as List Total (.403), Story Immediate (r = .618), SSQ (r = .444) and QCAE-CES (r = .401). This is in keeping with the shared language component of these tests. Contrary to the findings of Ireland (2011), education was not found to be related to performance on the RMET.

4.3. Discussion of the Individual Profile Analyses

As well as exploring the heterogeneity of the sample, the Individual Profile Analysis allowed for an exploration of the extent to which group differences were reflected in individual scores; allowing for participant's cognitive profiles to be located in their social contexts. This was particularly appropriate given large standard deviations associated with the subtest means.

4.3.1. HAND

Participants were categorised into one of four types (ANI, MCD, HAD, INOS) for the initial purpose of case analysis profiling only. Three participants reported subjective cognitive complaints but demonstrated no clear impairment on testing (INOS). Eight participants showed cognitive decline consistent with ANI, of which one had co-morbid severe anxiety. Four participants showed cognitive and functional impairments consistent with MND, of which reported co-morbid severe anxiety. Finally, one participant showed cognitive and functional impairments consistent with HAD, and they also had severe co-morbid depression. This is broadly consistent with the aforementioned trends in the literature which identify that milder forms of HAND are more prevalent in the post cART-era, even amongst a diverse sample.

4.3.2. Social Cognition

The Individual Profile Analysis revealed that a total of 13 participants demonstrated impaired performance on both the RMET and SSQ. This was consistent with the

group-level analysis; demonstrating impaired performance across both social cognition tests.

Most notably, the Individual Profile Analysis also revealed that, in contrast to what might have been inferred from the group-level analysis, impairment on social cognition tests tended to occur alongside cognitive decline in other areas, rather than as an isolated deficit. Furthermore, impairment on social cognitive did not show any relation to stage of HIV infection.

4.3.3. Executive Function

The earlier group-level analyses showed mild decline on the Category Fluency subtest only, in the domain of executive function. Further analysis of individual profiles revealed that three participants demonstrated impaired performance across both verbal and visual tests of executive function[1]. Five participants demonstrated impaired performance on verbal tests of executive function[2]. And finally, eight participants demonstrated intact executive function[3]. This shows a prevalence of impairment at the individual level which was not reflected in the group analysis statistics. One possible reason for this discrepancy is that, where no impairment was observed, participants typically performed in the 'high average' to 'superior' range, which may have elevated the group subtest mean scores.

4.3.4. Diversity

The Individual Profile Analysis revealed a heterogeneous sample; participants represented a diverse range of countries-of-birth, ethnicities, cultures, estimated pre-morbid ability and educational opportunity. It is important to acknowledge that all of these demographic and social factors can contribute to the outcome of neuropsychological assessments.

[1] Participant numbers; 5, 8, 12.
[2] Participant numbers; 4, 7, 9, 10, 15.
[3] Participant numbers; 1 2, 3, 6, 11, 13, 14, 16.

4.3.5. Education and Language

Eight participants[4] were educated within the UK and spoke English as a first language. The other eight participants[5] were educated outside of the UK, and all but one[6] of these had English as a second language. Of note, half of these participants[7] were educated in English-only speaking schools, with their first language being their language of communication at home. As a general observation, the four participants[8] who were schooled outside of the UK and educated in their first language, demonstrated some of the most disadvantaged cognitive profiles in the cohort. The exception to this trend is Participant 8, whose first language was English but educated in Jamaica; she showed profound impairments across domains. Whilst it is difficult to draw any conclusions from this pattern given the small sample size, it is possible that this observation reflects validity issues inherent in the neurocognitive tests used in the current study. This concern is revisited in the critical review.

4.3.6. Physical Co-morbidities

There was a relatively low presence of physical co-morbid conditions in the sample (see Appendix P); with fewer co-morbidities than in similar sized studies with HIV-positive populations (Ireland, 2011; Johal, 2014) and elsewhere in the literature (Cysique et al., 2010). This is likely due to several contextual factors. Firstly, participants were recruited from outpatient settings so their health statuses were, by virtue of their availability, relatively well-managed. Secondarily, in the post-cART context, those treated and cART-adherent, may experience greater periods of sustained viral suppression and healthy CD4 count levels, experiencing fewer secondary infections and diseases. This observation allows associations between performance on neurocognitive tests and cognitive function to be made with more confidence.

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[4] Participant numbers; 1, 2, 3, 7, 11, 13, 15, 16.
[5] Participant numbers; 4, 5, 6, 8, 9, 10, 12, 14.
[6] Participant 8 was educated in Jamaica, a Commonwealth Realm and former British Colony which has English as its national language.
[7] Participant numbers; 6, 8, 10, 14.
[8] Participant numbers; 4, 5, 9, 12.

4.3.7. Psychological Co-morbidities

A total of three participants reported severe anxiety and/or depression; four reported moderate anxiety and/or depression; three reported mild anxiety, and six participants'[9] scores fell within the normal range. Overall, seven[10] participants met the threshold for 'caseness' (the 'mild' category is not included in this division) indicating a probable presence of co-morbid anxiety and depression for this proportion of the cohort (Snaith, 2003). This is in keeping with the literature which reports high - and fluctuating - rates of psychological distress in the clinical population (Nakasujja et al., 2010; Rabkin, 2008; Shacham et al., 2012).

In view of this, it might be deduced that the cohort's poor performance on the RMET, SSQ and low self-report on the QCAE may have been influenced by the co-morbid levels of anxiety and depression. However, the extent to which these factors can reliably be said to have influenced participants test performance in the current study is unclear as the impact of mood on cognitive function and performance on neurocognitive tests varies equivocally in the research literature. The group-level correlational analysis, as stated, showed the HADS to correlate with performance on the RMET, SSQ and QCAE-CES, but *not* other core tests. However, the individual-level analysis, in contrast, revealed that impaired performance on social cognitive tests did not always occur in the context of high HAD scores, suggesting that – although there may well be an association between mood and social ability – these variables were not necessarily interdependent in the current study.

4.4. Critical Review

4.4.1. Sample Size

As acknowledged earlier, the current study included a small sample size which, although in keeping with exploratory research of this kind, limits the interpretations that can be drawn from the current data. In recognition of this fact, the statistical power of analyses was not relied upon, in favour of effect size, and results were reported as tentative trends within the sample cohort, rather than conclusions

[9] Participant number; 3, 4, 6, 7, 8, 11.
[10] Participant numbers; 5, 9, 10, 12, 13, 15, 16.

appropriate for generalisation to the population. A larger sample would allow for more powerful and sophisticated analyses, enabling more direct and specific hypothesis testing.

4.4.2. Normative data

Manly et al. (2011) argue that, when assessing for HAND, norms should be based on a population of HIV-uninfected individuals as closely matched to the HIV-infected group as possible. The norms used in the current study, and in much of the literature in the field, are those provided by the test publishers, and although adjusted by age, and sometimes gender, they are otherwise based on norm groups which do not reflect the ethnic, racial, educational and cultural diversity of the clinical population of people living with HIV in this country (Heaton et al., 2015) . Therefore, the extent to which tests scores can be meaningfully compared to them is a concern, and presents a major limitation in the group-level analysis of the current study and literature as a whole. However, the Individual Profile Analysis was less affected by these limitations, as participants were principally compared to themselves and not a normative groups. Nonetheless, the lack of representative demographic variables in the normative data increases the risk of cognitive impairment being over-diagnosed for certain individuals and groups.

More recently, efforts have been made to develop appropriate norms which more adequately reflect the demographic spread of the HIV clinical population (Manly et al., 2011), however, this endeavour in itself has been problematic due to difficulties involved in controlling for the influence of various co-morbidities on test performance in normative groups.

4.4.3. Factors affecting Performance; Cross-cultural Limitations

Consideration should be given to some of the inherent limitations in neurocognitive assessment and interpretation. The majority of neurocognitive tests carry the culture of white middle-class English-as-first language British and North American people, and, thereby, give people from these groups an advantage over test-takers whose socialization and life experiences have been different (Brown, Reynolds, & Whitaker, 1999; He & Vijver, 2012). This has implications for test score interpretation – as some people may perform poorly on the tests for reasons separate to cognitive

dysfunction – and can lead to false positives in diagnostic assessments, and over-reporting of deficits in people from certain backgrounds and groups. This is particularly pertinent issue for research in the field of HAND given the cultural-linguistic diversity across people living with HIV in the UK (Aiken & Lever, 2010; Anderson, 2008).

Cultural bias in neurocognitive testing is located in both the test content, and the test processes. For example, successful completion of the Picture Naming subtest in the RBANS relies on the participant having had exposure to, and familiarity with, certain objects and entities (e.g., a cannon, or a trumpet); demonstrating cultural bias in the test content. Furthermore, neurocognitive assessments as a whole require particular 'thinking styles' or behavioural patterns which may be more common in some cultures than others; for example, the process of sitting in a room with a unknown professional administering paper tests may be more common to people who have grown up in a paternalistic healthcare system.

With regards to educational bias, the Individual Profile Analysis revealed that the three subjects with the most impaired cognitive profiles were also from non-western backgrounds, born and educated outside of the UK, in languages other than English. A relevant concern here is that whilst educational attainment is an important factor in the interpretation of cognitive test scores, total years of education may not be equal to educational quality among different racial/ethnic populations, and the use of it as such may lead to inflated impairment rates among said groups (Ryan et al., 2005). Pereda et al (2000) reported that people who were schooled in countries others than the UK and USA generally performed poorer than those who were schooled in the West. The reasons for this are likely to be many and varied, including years of education, educational quality and approaches, and cultural and language factors. It is also possible cognitive reserve hypothesis can be drawn upon here. Education is one of many factors which can contribute towards the accumulation of positive cognitive reserve; as well as positive attachment histories, perinatal development and developmental history, nutrition and health and stress, to name but a few (Yaakov Stern, 2009).

Future research can partly account for these limitations by employing culturally adjusted neuropsychological measures which offer reading material which has been

translated into the participant's first-language; uses appropriate stimulus materials; and, uses normative data for demographically matched populations (Fletcher-Janzen, Strickland, & Reynolds, 2013) .

4.4.4. Assessment of Mood

Consideration here should also be given to the terms 'depression' and 'anxiety' which hitherto have been employed in an uncritical, arguably essentialist, manner. It is beyond the scope of this work to provide a suitable review of the socio-historical context of these terms, but it is, nonetheless, important to consider what is being spoken about when such words are employed. As well as being umbrella terms for a host of putative disorders in psychiatric discourse, the terms anxiety and depression are used in everyday parlance for a variety of states of distress. And it is in line with the former, that this study has used these terms.

The HADS was chosen here, as part of a pragmatic endeavour: the standardised and validated nature of the tool was of practical use to the research design, and allowed mood to be included in the analysis and reported in such a way so as to be considered valid and reliable. Although its relative brevity was an advantage for the current study, it also served as a limitation in the extent to which it may not offer a sufficiently comprehensive assessment of mood. Furthermore, the measure is limited in its specific focus on the loss of pleasure response [anhedonia] which is one of the two obligatory conditions for the formal classification of 'major depressive disorder' (Snaith, 2003) at the sacrifice of other states/sources of mood related distress. Future research might select an additional or alternative standardised measure with which to, more thoroughly, assess the milieu of subjective difficulties which may influence cognition and performance of neurocognitive tests.

4.4.5. Test Materials

Manchester et al. (2004) argue that one of the major limitations of neurocognitive assessments are their lack of ecologic validity when assessing executive functioning. Although this critique can, invariably, be applied to the assessment of any cognitive domain, it is a particularly relevant to the assessment of social cognition. Dealing with competing social demands in the real world requires both specific social processes and general cognitive mechanisms that may not be tested in the clinical

assessment environment. Furthermore, assessments are generally conducted within calm and quiet testing rooms where the participant is clearly presented with the target task, instructions, and parameters (e.g., time restrictions, rules, start and end times). Under these conditions, a participant may achieve a score that indicates no cognitive dysfunction, despite experiencing difficulties in daily life (Sbordone, 1996).

The SSQ requires that participants make accurate inferences about fictional-other's thoughts and feelings in hypothetical social stories; one's ability to succeed at this exercise is taken to reflect something of their explicit mentalising skills. Upon inspection of the SSQ, limitations are revealed with regards to the (arguably, dated) use of social norms and social lexicon. As with many tests, successful performance relies on the participant having been sufficiently socialised in specific social norms in order for them to identify the requisite violations of social norms. Participants from a younger generation, or those from different cultural backgrounds, may be less familiar with some of the encounters described, or finer social nuances in the language, and thus their performance may not be representative of their social ability – but rather their familiarity with a now non-dominant expression of English culture.

These limitations are not specific to the SSQ, but shared across many of the social cognition assessment measures available today. This highlights the need for the development of contemporary tests in the field of social cognition, including tests of ToM, which can be validated for use in research. With this is mind, it is recommended that future research into social cognition in HAND should consider using four different measures to those used here; two different tests of (affective and cognitive) ToM to further explore trends as well as construct validity; and, two non-ToM tests of social ability to explore the breadth of the trends in social cognition impairment. One such test of ToM, to replace the RMET, could be Begeer et al's (2010) Instructor Task as discussed in the Introduction.

The extent to which future research is designed with ecological validity in mind will depend on the research rationale. That is, whether the cognitive assessment is designed with the intent to assess for dysfunction or to predict everyday functioning. Although these are not necessarily mutually exclusive, their relative separation is often cited as the reason for the absence of the verisimilitude approach in traditional neurocognitive test materials (Spooner & Pachana, 2006).

Finally, the addition of a qualitative research component into research of this kind would offer a contrasting form of assessment with which to triangulate the study findings, and enable an exploration of constructions: in keeping with a critical realist perspective.

4.5. Clinical Implications and Summary of Recommendations

Although the underlying cognitive mechanisms and specific processes of social cognition are yet to be fully understood, we can be nevertheless be confident that as human beings in this society, our ability to comprehend and understand the abstract nuances of our social world is fundamentally important for our capacity to navigate daily life as adeptly as is possible. The current study demonstrated disadvantaged performance on two social cognition tests in a culturally diverse cohort of people with HIV infection, most of whom are cART-adherent with an undetectable viral load, with no comparable areas of neurocognitive decline across core areas of cognition, including executive function. Assuming that impairments on these measures demonstrates a reliable underlying difficultly, these trends may translate as real life difficulty with emotion recognition and coping with the social complexities of communicative exchanges in everyday life and, if undetected, may have pervasive and disabling influences on peoples social communication and interpersonal relationships.

Although the findings in the current study are too tentative to make concrete recommendations to national clinical guidelines or practice, they may still extend a pragmatic contribution to clinical knowledge. By this, the researcher refers to the potential of these findings to promote the extension of empathy towards patients who show complex emotional and behavioural presentations in outpatient settings by contributing to the way in which such presentations can be made sense of by clinicians. This is particularly significant because, at present, social cognition impairments may not be identified as indicative of HIV-related health consequences. Instead, patients conduct may become understood through the lens of reductive labels such as ‘difficult patient’ or ‘treatment resistant’ and, in this way, the understandable and meaningful expressions of cognitive impairment – that is, properties of the illness – risk being constructed as a problem in the patient’s pre-morbid ‘personality’. Through increased awareness of the potential emotional and

behavioural sequalae of HAND, dissemination of these ideas and findings can seek to increase awareness, understanding of, and empathy towards our patients, which, even in light of the tentative nature of these findings, can only be a worthwhile pursuit.

As well as contributing towards professional awareness, the current findings might contribute to the provision of 'psycho-education' within clinical discussions, as part of, or separate to, wider neurorehabilitation programmes for HAND. In their investigation into the relative benefits of 'meta-knowledge' (that is, patients' awareness of illness and their conscious knowledge of their own cognitive processes) Casaletto et al. (2016) argue that improved metacognition (i.e., awareness of neurocognitive impairments) is significantly associated with greater engagement with and motivation for treatment and reduced risk of early attrition. With this in mind, these findings might encourage a dialogue around the potential implications of pre-frontal lobe impairments and patients experience of cognitive changes, specific to social communication and emotion recognition, or otherwise (given the heterogeneous nature of HAND). The potential therapeutic benefits of psycho-education in listening to patients concerns, normalising anxieties and difficulties, and providing support, were witnessed throughout the process of the research methodology, where the researcher provided each participant with tailored feedback for test results and (where necessary) cognitive rehabilitation techniques. It is, however, important to practice caution when using the language of 'impairments' and 'deficits' in dialogue with patients, acknowledging the potential of such words to cause distress and influence negative cognitive schemas or self-narratives.

Together with previous research (Homer et al., 2013; Ireland, 2011) these findings advance the case for further exploratory research into the area of social cognition impairments in HAND. To summarise the recommendations identified in the critical review; future research should seek to replicate the exploratory approach using different and improved measures of social cognition with a view to explore construct validity, as well as to further explore the tentative trends reported in the current study.

Should said trends continue to emerge, then the rationale for more well-resourced research with a larger sample can be made, to explore areas of impairment with

more clarity and statistical power. Such research will contribute to the evidence base regarding the neurocognitive consequences of HAND, with implications for clinical practice including; the extension of neuropsychological assessments of HAND to include an assessment of social cognition; and, informing the development of neuro-rehabilitative therapy programmes for HAND.

4.6. Concluding Statement

In seeking to explore the existence of social cognition impairments in HAND, the researcher hoped to contribute towards a relatively new and emerging area of research located within the wider understanding of the neuropsychological consequences of HIV. Specific neuropsychological measures were chosen to allow the findings to be compared in a meaningful way to the tentative trends identified in previous small-scale research of this kind; matching up theoretical constructs and assessment techniques. The present sample demonstrated clear disadvantages in their performance on the two social cognition measures and these findings were interpreted both in comparison to normative scores, and in context, alongside the sample's educational and cultural circumstances, and individual life-experiences, and the wider literature regarding relevant PFC-implicated neurological conditions. Although the small sample size in the current study limits any concrete conclusions from being drawn from the results, these findings make a clear case for further well-resourced research into the emotional and behavioural consequences of HAND, and point to several potential clinical recommendations for consideration by clinical teams. What it means to live with HIV in the UK has drastically changed in the last three decades: with the health-consequences of HIV infection shifting from life-limiting, to chronic and manageable, it has never been more important to investigate the potential neuropsychological impact of HIV infection in order to adequately and sensitively respond to the varied needs of service-users.

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6. APPENDICIES

Appendix A **Revised HAND Criteria**

Adapted from (A. Antinori et al., 2007).

HIV-associated asymptomatic neurocognitive impairment (ANI)

- Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 SD below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual.
- The cognitive impairment does not interfere with everyday functioning.
- The cognitive impairment does not meet criteria for delirium or dementia.
- There is no evidence of another pre-existing cause for the ANI.

HIV-1-associated mild neurocognitive disorder (MND)

- Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 SD below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills.
- The cognitive impairment produces at least mild interference in daily functioning (at least one of the following): a
- Self-report of reduced mental acuity, inefficiency in work, homemaking, or social functioning.
- The cognitive impairment does not meet criteria for delirium or dementia.
- There is no evidence of another pre-existing cause for the MND.

HIV-1-associated dementia (HAD)

- Marked acquired impairment in cognitive functioning, involving at least two ability domains; typically the impairment is in multiple domains, especially in learning of new information, slowed information processing, and defective attention/concentration. The cognitive impairment must be ascertained by neuropsychological testing with at least two domains 2 SD or greater than demographically corrected means. (Note that where neuropsychological testing is not available, standard neurological evaluation and simple bedside testing may be used, but this should be done as indicated in algorithm; see below).
- The pattern of cognitive impairment does not meet criteria for delirium (e.g., clouding of consciousness is not a prominent feature); or, if delirium is present, criteria for dementia need to have been met on a prior examination when delirium was not present.
- There is no evidence of a co-morbid cause for the dementia.

Appendix B **UEL Research Registration Confirmation Letter**

The researcher's and signatory's contact details have been redacted in the following document.

SCHOOL OF PSYCHOLOGY
Dean: Professor Mark N. O. Davies, PhD, CPsychol, CBiol.
uel.ac.uk/psychology

UEL University of East London

[redacted]

Date: 05/05/2015

Student Number: [redacted]

Dear Lucy,

Registration as a Candidate for the University's Research Degree

I am pleased to inform you that the Research Degrees Subcommittee on behalf of the University Quality and Standards Committee, has registered you for the degree of Professional Doctorate.

Title of Professional Doctorate: Professional Doctorate in Clinical Psychology

Director of Studies: Matthew Jones Chester

Supervisor/s: Meredith Terlecki

Expected completion: According to your actual date of registration, which is **1st October 2014**, the registration period is as follows:

Minimum 18 months maximum 48 months (4 years), according to a full time mode of study.

Your thesis is therefore due to be submitted between:

1st April 2015 and 1st October 2018

I wish you all the best with your intended research degree programme. Please contact me if you have any further queries regarding to this matter.

Yours sincerely,

Dr Kenneth Gannon
School Research Degrees Leader
[redacted]

Stratford Campus, Water Lane, Stratford, London E15 4LZ
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POSITIVE ABOUT DISABLED PEOPLE

INVESTOR IN PEOPLE

Appendix C **Ethics Committee Documentation**

NOTICE OF ETHICS REVIEW DECISION

For research involving human participants
BSc/MSc/MA/Professional Doctorates in Clinical, Counselling and Educational Psychology

SUPERVISOR: Matthew Jones Chester **REVIEWER: David Harper**

STUDENT: Lucy Butler

Title of proposed study: Social cognition and HIV: exploring the profile of cognitive impairments in HIV-associated Neurocognitive Disorders (HAND)

Course: Doctorate in Clinical Psychology

DECISION *(Delete as necessary)*:

***APPROVED**

APPROVED: Ethics approval for the above named research study has been granted from the date of approval (see end of this notice) to the date it is submitted for assessment/examination.

APPROVED, BUT MINOR AMENDMENTS ARE REQUIRED BEFORE THE RESEARCH COMMENCES (see Minor Amendments box below)**:** In this circumstance, re-submission of an ethics application is not required but the student must confirm with their supervisor that all minor amendments have been made before the research commences. Students are to do this by filling in the confirmation box below when all amendments have been attended to and emailing a copy of this decision notice to her/his supervisor for their records. The supervisor will then forward the student's confirmation to the School for its records.

NOT APPROVED, MAJOR AMENDMENTS AND RE-SUBMISSION REQUIRED (see Major Amendments box below)**:** In this circumstance, a revised ethics application must be submitted and approved before any research takes place. The revised application will be reviewed by the same reviewer. If in doubt, students should ask their supervisor for support in revising their ethics application.

Minor amendments required *(for reviewer)*:

Major amendments required *(for reviewer):*

1

Appendix D **NHS (NRES) Provisional Approval Letter**

The researcher's and signatory's contact details have been redacted in the following document.

NHS
Health Research Authority
NRES Committee South Central - Hampshire A
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

02 June 2015

Miss Lucy Butler
[redacted]

Dear Miss Butler

Study title:	**Social cognition and HIV: Exploring the profile of cognitive impairments in HIV-associated Neurocognitive Disorders (HAND)**
REC reference:	**15/SC/0330**
Protocol number:	**n/a**
IRAS project ID:	**169576**

The Proportionate Review Sub-Committee of the NRES Committee South Central - Hampshire A reviewed the above application on 21 May 2015.

Provisional opinion

The Sub-Committee would be content to give a favourable ethical opinion of the research, subject to clarification of the following issues and/or the following changes being made to the documentation for study participants:

Participant Information Sheet (PIS)

1. *Please be more specific about the tests and short questionnaire and the potential of audio recording.*

2. *Please be more specific about the additional support services in case the study was to upset the participants.*

3. *Please also include the following sections:*

   A. *Who is organizing and funding the study?*
   B. *What if something goes wrong? This section should describe how any complaints will be handled and what compensation may be available in the event of anyone being harmed.*
   C. *Who has reviewed the study?*

The following is suggested wording:
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by _____Research Ethics Committee.

Research Ethics Committee established by the Health Research Authority

Consent form:

Please also include additional items in order to give the participants the opportunity to consent for their consultant to be informed about the results and for them to agree to take part in the study.

When submitting a response to the Sub-Committee, the requested information should be electronically submitted from IRAS. A step-by-step guide on submitting your response to the REC provisional opinion is available on the HRA website using the following link: http://www.hra.nhs.uk/nhs-research-ethics-committee-rec-submitting-response-provisional-opinion/

Please submit revised documentation where appropriate underlining or otherwise highlighting the changes which have been made and giving revised version numbers and dates. You do not have to make any changes to the REC application form unless you have been specifically requested to do so by the REC.

Authority to consider your response and to confirm the final opinion on behalf of the Committee has been delegated to the Chair.

Please contact REC Assistant, [redacted] if you need any further clarification or would find it helpful to discuss the changes required with the lead reviewer.

The Committee will confirm the final ethical opinion within 7 days of receiving a full response. A response should be submitted by no later than 02 July 2015.

Summary of discussion at the meeting

Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity

The Sub-Committee agreed that it would have been useful to see the additional support services listed in the PIS in case the study was to upset the participants (as was mentioned in the IRAs form).

Informed consent process and the adequacy and completeness of participant information

1. *The subcommittee noted that* PIS does not mention audio recording equipment but does in the IRAS.
2. The Sub-committee observed that, in the PIs it is mentioned that the consultant would receive a copy to help inform about the treatment but only with participants permission, if that is the case an item in the consent form will need to be included
3. The Sub-Committee noted that the PIS does not mention the number of questionnaire
4. The Sub-Committee did not found a summary of the tests the participants will be doing in the participant's information.
5. The Sub-Committee noted that participants are not informed of who have founded and organizing the study, neither there is mention of who had reviewed it.

Documents reviewed

The documents reviewed were:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance Certificate]		19 February 2015
Interview schedules or topic guides for participants [Interview Schedule Record Form]	Version 1	11 May 2015
IRAS Checklist XML [Checklist_18052015]		18 May 2015
Other [EQ Questionnaire]	Version 1	11 May 2015
Other [Second supervisor cv]	version 1	11 May 2015
Other [Insurance Certificate - Public Liability Certificate]		12 May 2015
Participant consent form [Consent Form]	Version 1	24 February 2015
Participant information sheet (PIS) [Participant Info Sheet]	Version 1	24 February 2015
REC Application Form [REC_Form_18052015]		18 May 2015
Research protocol or project proposal [Protocol]	Version 1	24 February 2015
Summary CV for Chief Investigator (CI) [CI CV]		24 February 2015
Summary CV for student [Student CV]		24 February 2015
Summary CV for supervisor (student research) [Supervisor CV]	Final	08 May 2015
Validated questionnaire [Social Stories Questionnaire]	Version 1	11 May 2015

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

None

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

15/SC/0330	**Please quote this number on all correspondence**

Yours sincerely

[redacted]

[redacted]
Chair

Email: nrescommittee.southcentral-hampshirea@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: [redacted]

Appendix E **NHS (NRES) Full Approval Letter**

The researcher's and signatory's contact details have been redacted in the following document.

NHS
Health Research Authority
NRES Committee South Central - Hampshire A
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 342 1381
Fax:0117 342 0445

18 June 2015

Miss Lucy Butler
[redacted]

Dear Miss Butler

Study title:	**Social cognition and HIV: Exploring the profile of cognitive impairments in HIV-associated Neurocognitive Disorders (HAND)**
REC reference:	**15/SC/0330**
Protocol number:	**n/a**
IRAS project ID:	**169576**

Thank you for your letter of 17th June 2015, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Mrs Maxine Knight, nrescommittee.southcentral-hampshirea@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance Certificate]	19th February 2015	19 February 2015
Interview schedules or topic guides for participants [Interview Schedule Record Form]	Version 1	11 May 2015
IRAS Checklist XML [Checklist_17062015]		17 June 2015
Other [EQ Questionnaire]	Version 1	11 May 2015
Other [Second supervisor cv]	version 1	11 May 2015
Other [Insurance Certificate - Public Liability Certificate]		12 May 2015
Participant consent form [Consent Form]	Version 2	11 June 2015
Participant information sheet (PIS) [Participant Info Sheet]	Version 2	11 June 2015
REC Application Form [REC_Form_18052015]		18 May 2015
Research protocol or project proposal [Protocol]	Version 1	24 February 2015
Response to Request for Further Information		
Summary CV for Chief Investigator (CI) [CI CV]	24th February 2015	24 February 2015
Summary CV for student [Student CV]	24th February 2015	24 February 2015
Summary CV for supervisor (student research) [Supervisor CV]	Final	08 May 2015
Validated questionnaire [Social Stories Questionnaire]	Version 1	11 May 2015

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

15/SC/0330	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

[redacted]

pp

Alternate Vice Chair
[redacted]

Email: nrescommittee.southcentral-hampshirea@nhs.net

Enclosures: *"After ethical review – guidance for researchers"*
Copy to: *Professor Neville Punchard*

[redacted]

Appendix F **Site A: Research Approval Letter**

The researcher's personal contact details, Trust logos, and specific Service details have been redacted in the following document.

[redacted] NHS

NHS Foundation Trust

Research & Development

[redacted]

[redacted]

[redacted]

2nd July 2015

Dear [redacted],

Re: Social Reasoning in People Living with HIV-Infection

R&D No: 1516

Thank you for sending all the relevant documents for [redacted] Trust Research and Development Approval of the above research study. As part of the Research and Development approval process we have conducted a site specific assessment for this study. I am happy to inform you that the Trust has approved the conduct of the study and that the Trust will indemnify against negligent harm that might occur during the course of this project.

The following main document/s has been received by R&D department as part of the approval process;

Research protocol or project proposal [Protocol] Version 1	24/02/2015
Participant consent form [Consent Form] Version 2	11/06/2015
Participant information sheet (PIS) [Participant Info Sheet] Version 2	11/06/2015

All other document/s you have sent in as part of the process has also been received.

I would like to draw your attention to the following conditions of the approval of this research project with which you must comply. **Failure to do so may result in the Trust withdrawing R&D approval which allows you to conduct this research project at [redacted] NHS [redacted].**

Untoward events - Should any untoward event occur it is **essential** that you complete a clinical incident form and write on the form '**R&D**'. Contact the R&D Office immediately and if patients or staff are involved in an incident you must also contact the Risk Manager on [redacted].

Status of Research - Inform us if your project is amended or if your project terminates early/requires an extension as well as informing the Research Ethics Committee. This is necessary to ensure that your indemnity cover is valid and also helps the office to maintain

Incorporating hospital and community health services, teaching and research

up-to-date records. A copy of any publications arising from the research should be sent to the R&D Office for use in the R&D Annual Report. Please be reminded that this hospital should be acknowledged in any publication.

Research Information - You will be required to complete a project update as required by the R&D Office to ensure that we have up to date information so that we can send accurate reports to the DoH and research networks. The project update form will be emailed or sent to you by the R&D Office.

Research Governance - As part of research governance, all investigators accessing identifiable personal information are required to comply with current data protection requirements.

Intellectual Property - If you believe that protectable intellectual property may arise from your research, please contact the [redacted] who will advise you on the proper course of action.

Monitoring of Studies – You must comply with the Trust's legal responsibility as host of this research project to monitor and audit the research to ensure that the Research Governance Framework and Good Clinical Practice (GCP) if applicable is being adhered too. Monitoring questionnaires will be sent to you and random audit visits will also take place across the trust and will be conducted following at least a seven day notice period. **Failure to respond to any of these monitoring or auditing requests may result in the Trust withdrawing your R&D approval to conduct this research at [redacted] NHS Foundation Trust.**

Please note that all NHS and social care research is subject to the DoH *Research Governance Framework.* If you are unfamiliar with the standards contained in this document, you may obtain details from the Trust R&D Office or from the DoH website (www.dh.gov.uk).

Please do not hesitate to contact [redacted], Research and Development Manager or me if you have any further questions.

Yours sincerely,

[redacted]

Director Research & Development

Appendix G **Site B: Research Approval Letter**

The researcher's personal contact details, Trust logos, and specific Service details have been redacted in the following document.

[redacted]

[redacted] NHS
NHS Trust

[redacted]

[redacted]

FINAL R&D APPROVAL

5th October 2015

Ms Lucy Butler
University of East London
[redacted]

Dear Lucy,

Protocol: **Social Cognition and HIV: Exploring the profile of cognitive impairments in HIV-associated Neurocognitive Disorders (HAND)**

ReDA Ref: **010833**
REC Ref: **15/SC/0330**

I am pleased to inform you that the [redacted] and [redacted] has approved the above referenced study and in so doing has ensured that there is appropriate indemnity cover against any negligence that may occur during the course of your project. Approved study documents are as follows:

Type	Version	Date
Protocol	1	24/02/2015
PIS	2	11/06/2015
ICF	2	11/06/2015
Interview Schedule Record Form	1	11/05/2015

Please note that all research within the NHS is subject to the Research Governance Framework for Health and Social Care, 2005. If you are unfamiliar with the standards contained in this document, or the [redacted] policies that reinforce them, you can obtain details from the [redacted] Management Office or go to:
http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962

You must stay in touch with the [redacted] Management Office during the course of the research project, in particular:

- If there is a change of Principal Investigator
- When the project finishes
- If amendments are made, whether substantial or non-substantial

This is necessary to ensure that your R&D Approval and indemnity cover remain valid. Should any Serious Adverse Events (SAEs) or untoward events occur it is **essential** that you inform the Sponsor within 24 hours. If patients or staff are involved in an incident, you should also follow the Trust Adverse Incident reporting procedure or contact the Risk Management Unit on [redacted].

[redacted]

Page 1 of 2

We wish you all the best with your research, and if you need any help or assistance during its course, please do not hesitate to contact the Office.

Yours sincerely

[redacted]

[redacted] Head of Research Resources

[redacted]

Appendix H **Site B: Scientific Peer Review Provisional Letter**

The researcher's personal contact details, Trust logos, and specific Service details have been redacted in the following document.

[redacted]

[redacted]

Lucy Butler

[redacted]

[redacted]

[redacted]

[redacted]

14th July 2015

Dear Lucy,

Study No: **206**

Study Title: **Social cognition and HIV: exploring the profile of cognitive impairments in HIV-associated Neurocognitive Disorders (HAND)**

Thank you for submitting this study to [redacted] Internal Peer Review Group. Reviewers raised a number of concerns and questions about the protocol & implementation plans within our service. Although we are in general supportive of the study, I am unable to give permission at this stage. Please respond to the comments below (summarised from all reviewer comments) by letter & revise your application form accordingly. Subject to satisfactory revisions, I am hoping to give permission within a short time frame.

- Who is the local lead for this study? Who is the supervisor?
- How will patients be identified?
- How will psychological issues which might emerge as a result of participating be addressed?
- Have we confirmed that there is space?
- How was sample size derived? CIs?
- What about confounding due to duration of HIV, co-existing morbidities, ethnicity?
- What about a comparator group with a different long term condition?
- Get names of the services correct before you submit documents to them!!!
- I really don't have much confidence that this will achieve very much given the above – it feels highly "exploratory" which is fine but these weaknesses need to be addressed in the protocol

- Provide rationale for the number of participants recruited.
- Participants might have questions, concerns about HIV and cognitive functioning. Consider how you might address such questions/concerns, and/or where you might need to refer them.
- No information is provided about methods for statistical analysis (2.5 "Appropriate statistical analysis will be used…")

I have the following concerns about this project:

- Recruitment plans: These are unclear. It is stated that, "Participants will be required to have diagnosis of HIV but not HAND." However, it is not clear who you wish to recruit as it seems that you are looking for participants with HAND and this potentially reads as if HAND is an exclusion criterion. How are participants to be identified? Are you looking

for individuals with symptoms of neurocognitive impairment (NCI) and /or for asymptomatic individuals? Antiretroviral treatment status is not mentioned and this may theoretically impact on NCI.

- Analysis: It is not clear how you plan to analyse your findings – are you going to compare symptomatic individuals with each of the 4 categories of NCI (ie. ANI, MCD, HAD, I-NOS as defined in methods)? If so, who are you comparing with – between NCI groups or against patients without HAND? The proposal is confusing as it states both, "Although not controlled for, HAND status will be identified and recorded at recruitment stage but also, "This will allow this information (ie HAND status) to be included in the analysis." Depending on how you plan to analyse, how will you ensure that you have adequate numbers of each? This may potentially require screening of large numbers of individuals at baseline.
- "Appropriate statistical analysis" – what analysis is this? Do you have a large enough sample to apply statistical analysis or would this be more appropriate as a descriptive study?
- "Is there any correlation between stage of HIV illness and social cognitive functioning?" There is no explanation of how stage of HIV is defined – NCI or otherwise?

- Ethics: It seems that you may be giving a diagnosis (ie. ANI, MCD, HAD, I-NOS) to individuals who may not previously have a HAND diagnosis or who may be asymptomatic. There needs to be consideration of how this will be managed and followed-up clinically and in terms of emotional and other support. These issues could potentially be addressed by recruiting from the specialist neurology / HIV clinic whereby patients will have already been referred with symptoms / concerns.

Yours sincerely,

[redacted]

Research Governance Lead for [redacted]

Appendix I **Researcher Response to Appendix H: Proposed Adjustments**

The following letter shows the researchers response to questions raised by the Scientific Peer Review, as shown in the previous Appendix item. The researcher's personal contact details, Trust logos, and specific Service details have been redacted to protect the anonymity of the participants.

ADDRESS DELETED

ADRESS DELETED

20th July 2015

Dear Dr X,

Study number: **206**

Study Title: **Social cognition and HIV: exploring the profile of cognitive impairments in HIV-associated Neurocognitive Disorders (HAND)**

Thank you for your letter dated 14th July 2015 in which you summarised the comments raised by the reviewers from the I&I Internal Peer Review Group for the aforementioned study. I am grateful to you and the reviewers for your time and detailed comments.

I hope this letter serves to adequately address and clarify the concerns and questions about the protocol & implementation plans of this research study within your service. I look forward to your response.

- "Who is the local lead/supervisor for this study?"

The local lead and on-site supervisor for the study with be Dr Alison Jones, Clinical Psychologist. The study will also be supervised off-site by experienced neuropsychologist Dr Matthew Jones-Chesters at the University of East London, who will both monitor the progress of the study as well as offer clinical supervision.

- "How will patients be identified?"

Neuropsychological assessments are routine practice at the Ambrose King Centre, and the service has a waiting list of patients waiting to receive this specific service. Potential participants will be identified from this waiting list. My research protocol involves conducting the same routine battery of tests that would be used in this clinical setting, with the addition of two extra questionnaires. I will therefore be able to provide the neuropsychological assessment to meet the identified clinical need, with the addition of two extra tests of social cognition in order to conduct my research. I will provide a neuropsychological report, setting out the client's strengths and weaknesses, and will include management and/or rehabilitation recommendations (subject to participant consent).

I have spoken to staff in the team about the practicalities of me identifying patients from this list who meet the study criteria. Suitability for participation will always be done in conjunction with the professional opinion of the senior clinician on site. I will liaise with Dr Alison Jones (Clinical Psychologist) and the team at the Ambrose King Centre to discuss which potential participants from the waiting list they feel may be appropriate for me to approach, and I will then contact the patient by phone and explain to them the study in line with the information provided in the Patient Information Form.

- "How will psychological issues which might emerge as a result of participating be addressed?"

The likelihood of participants feeling distressed after cognitive testing is very low. Any potential risks are discussed in the information letter to ensure transparency on behalf of the researcher and informed consent from the participant. For example, the participant information sheet states the potential of fatigue during the assessment, and the efforts to minimise this are outlined such as taking regular breaks, and organising the assessment over two days if necessary.

In addition to the aforementioned precautions, participants will be monitored by the researcher for signs of fatigue and/or frustration throughout the testing process. If necessary, breaks will be offered as will reminders of the participant's right to withdraw from the study. If anything of significant concern is evident throughout the performance (e.g. disorientation, unable to do a simple task) the clinical team will be informed immediately.

- "Participants might have questions, concerns about HIV and cognitive functioning. Consider how you might address such questions/concerns."

A verbal debrief at the end of testing will be provided to participants in further effort to minimise psychological harm and/distress to participants as well as make the process a potentially enjoyable rewarding and educational one in which to take part. In the verbal debrief the researcher will be able to answer any questions the participants may have about the content of the tests, and the participants will receive a neuropsychological report once the tests have been scored.

If the participant has any questions about their illness or cognitive functioning the researcher can signpost the participant to discuss these with their specialist care team, or, with the participants consent, chose to directly pass these concerns on behalf of the participant to the clinical team for further assessment and support. The researcher will also have to hand the contact details of two charity organisations which offer local non-directive support as well as confidential psychological support for the participant to take away with them and use in their own time should they wish.

The aforementioned details will look like this:

Support services for people living with HIV and/or AIDS

If you would like information or support regarding living with HIV or AIDs you can contact staff at Ambrose King Centre, or alternatively please find some information below about local charities you can access. If you have access to the internet you can find out more about these services online and contact them by email, or you can call the numbers below.

Terrance Higgins Trust *Tel: 0808 802 1221.*

Their number is free to call from all UK landlines and most UK mobiles and will not appear on your telephone bill. When you ring you'll hear a menu system which will give you options to: listen to recorded information, leave a message to be called back in another language, hold the line if you'd like to speak an adviser.

PositivelyUK *Tel: 0207 713 0444*

Their helpline is open from 10am-4pm, Monday to Friday. You can call to speak to one of their support team who are living with HIV themselves.

- "Have we confirmed that there is space?"

I have spoken with my on-site contact ***name deleted*** Chartered Clinical Psychologist at the service about the space and feasibility of my research being conducting with the service. It was felt that there was suitable clinical space in the service to facilitate the research in such a way that the research would not be burdensome or obstructive in any way to the existing clinical practice, but instead facilitative of an existing need for neuropsychological assessments as part of existing patients care package in the service.

- "Recruitment plans: These are unclear. It is stated that, "Participants will be required to have diagnosis of HIV but not HAND." However, it is not clear who you wish to recruit as it seems that you are looking for participants with HAND and this potentially reads as if HAND is an exclusion criterion. (Antiretroviral treatment status is not mentioned and this may theoretically impact on NCI.)"

The referral criteria for this study is that individuals must have diagnosed HIV infection, be able to understand spoken and written English, not require an interpreter, and have no active psychosis or substance use. A pre-existing diagnosis of HIV-associated neurological disorder (HAND) is welcome but not necessary due to the evidence that Asymptomatic Neurocognitive Impairment (the most common type of HAND) is asymptomatic and therefore likely under-diagnosed in services likes Ambrose King Centre where neuropsychological testing is not a mandatory. If many people with HAND are undiagnosed, only recruiting those with a diagnosis would severely limit the sample and risk making it more unrepresentative.

Given that participants will be identified off the waiting list of patients waiting for neurocognitive assessment, it follows that all potential participants will have some form of neurocognitive complaint which has warranted their referral onto the waiting list. As such, all participants will be assumed to have some cognitive impairment, whether it is formally diagnosed or not.

Antiretroviral treatment status and CD4 count will certainly be documented, but not controlled.

- "Are you going to compare symptomatic individuals with each of the 4 categories of NCI (i.e. ANI, MCD, HAD, I-NOS as defined in methods)? If so, who are you comparing with – between NCI groups or against patients without HAND?"

The primary focus of the research questions to observe the differences within a sample of individuals with HIV with varying levels of cognitive impairment, and since no data is intended to be manipulated, nor any trials or interventions offered, no control group was considered necessary.

Participants will be categorised into one of four types (ANI, MCD, HAD, INOS) for the initial purpose of demographic profiling only.

- "What about confounding due to the duration of HIV, co-existing morbidities, ethnicity?"

Previous research studies which have initially sought to recruit only participants with 'pure' neuro-cognitive difficulties and no other confounding variables have reported that they found that individuals such as these are very rare, particularly in the area of London (for example, Ireland, 2010). In such studies it has been necessary to change the initial exclusion criteria so that participants are not excluded based on co-morbidities or ethnicity, with the aim of both facilitating recruitment and encouraging a more representative sample. This is consistent with the literature which suggests that less than 10% of individuals with HAND are considered to have no co-morbidities (Heaton, Franklin, Clifford, Woods, & Rivera Mindt, 2009). As such, it was felt that controlling or excluding such criteria from the data set would risk not only restricting the sample size, but also reducing representative nature of sample to the identified clinical population.

Unlike other neurodegenerative disorders such as Alzheimer's, HAND is not invariably progressive and is therefore not an immutable diagnosis. Current literature reports mixed findings regarding the relationship between duration of HIV and severity of impairment, reporting that neurocognitive impairments can fluctuate over time regardless of duration of infection (Robertson et al., 2007), with longitudinal studies reporting 50% of those with HAND showing fluctuations in the degree of neurocognitive impairment. For this reason,

HIV/AIDs duration and severity will be noted but participants will not be excluded or included based on this factor.

In the development of this study I had initially planned to exclude participants with a diagnosis of Hepatitis C and current infections. However, following consultation with Dr Matthew Jones Chesters (off site supervisor) and Dr Alison Jones (on site supervisor if study is approved) it was agreed instead to drop these exclusion criteria for the reasons stated in the first paragraph of this section, as

it would significantly reduce the pool of potential participants to the point that the remaining pool become unrepresentative of the clinical reality.

- "What about a comparator group with a different long term conditions?"

A comparator group may serve to enhance the breadth of the study and the options of statistical analyses to analyse the data, but the additional input required to operationalise and implement this recommendation is unfortunately outside of the scope of this particular project due to the limited availability of time and resources.

- "Statistical analysis"

This study will employ a cross-sectional correlational cohort design (that is, a 'non-manipulation' study) and this will enable an exploration of a given number of variables within a given time frame within a representative group. The variables of particular interest are social cognition and executive function and their relationship to general cognitive functioning in a group of individuals with HIV. This approach was considered best to fit the research questions since the aim was to observe and explore relationships within this sample and no data it intended to be manipulated.

A single case series level of analysis will be used to enable a more detailed and descriptive analysis of the data and the individuals within the sample.

- "Ethics: It seems that you may be giving a diagnosis (i.e. ANI, MCD, HAD, I-NOS) to individuals who may not previously have a HAND diagnosis or who may be asymptomatic."

The site-specific assessment procedure required in order to give a diagnosis of HAND is not part of the project methodology and as such is not an outcome of participation in the study. If the basic cognitive assessment tools used in the methodology indicate an existing cognitive impairment requiring more depth assessment then this will be documented in the form of a Neuropsychological Report outlining cognitive strengths and weaknesses, rehabilitation recommendations and suggestions for further testing – with consent of the participant. Any necessary further assessment and care-planning will be managed within the specialist team in line with their operational policy, and the Clinical Psychologists in the team will be able to use my neuropsychological report as a baseline for further assessment and continuation of care within the service.

- "How was the sample size derived? CIs? / Provide rationale for the number of participants recruited. / Do you have a large enough sample to apply statistical analysis or would this be more appropriate as a descriptive study?"

To decide the sample size, consideration was given to a number of factors including the time taken to collect the data, the time frame of the study, the likely availability of people, the work time equivalent hours available for data collection, and the typical sample size in study of this type.

Given my plan for how participants would be identified (off a waiting list for patients awaiting neuropsychological tests) I would hope to obtain a broadly representative sample and the research methodology outlines a process of collecting data is labour-intensive which will limit sample size. Neuropsychological research frequently involves small Ns, and this is consistent with the numbers recruited for similar previous research projects which have been conducted with individuals with HIV in similar settings and with similar time restrictions.

In this instance, a power analysis is not appropriate as I am conducting a descriptive study and therefore not doing the type of analysis that requires one.

Appendix J **Site B: Scientific Peer Review Acceptance Letter**

The researcher's personal contact details, Trust logos, and specific Service details have been redacted in the following document.

[redacted]

[redacted]

Lucy Butler

[redacted]

[redacted]

[redacted]

23rd July 2015

Dear Lucy,

Study No: **206**

Study Title: **Social cognition and HIV: exploring the profile of cognitive impairments in HIV-associated Neurocognitive Disorders (HAND)**

Thank you very much for taking the time to address all the reviewers' comments so thoroughly. I am happy that you have responded to all issues and as such am delighted to provide approval for the study.

I wish you well with the research.

Yours sincerely,

[redacted]

Research Governance Lead for [redacted]

Appendix K **Participant Information Sheet**

The following document was used in both site A and site B. The text remained the same across sites but the logo and other identifiers changed depending on the site. NHS Trust logos and specific service details have been removed to protect the anonymity of the participants.

HIV Neuropsychology Research Study

Social reasoning in People Living with HIV-Infection

PARTICIPANT INVITATION and INFORMATION
V2: 11.06.2015

The purpose of this letter is to provide you with the information you need before deciding whether to participate in this research. My name is ***name deleted*** and I am the chief researcher. My contact details can be found below.

What is this research about?
This study aims to explore the impact that HIV infection may have on the way our brains work. Our brains are involved in numerous processes, including our ability to think, remember, judge, learn, and interact together as social beings. Different physical health conditions can affect our brains and therefore have an impact on how our brains perform on some of these skills.

What do I have to do?
You will complete a collection of short exercises which explore a wide range of skills and abilities like memory, language, visual-spatial ability and social skills. You will be asked to give verbal answers to questions asked by me, complete pen-and-paper exercises under timed conditions, and there will also be a questionnaire to fill in. These tests are quite common and are used routinely in other services as part of routine Neuropsychological evaluations.

You will be asked to complete:
- A questionnaire about social skills
- A set of short exercises for general skills like memory, language and visual-spatial skills
- A word-reading exercise
- Two exercises about social skills

The tests will take approximately 1.5 hours and you will be offered a break in the middle. If you prefer we can do two shorter assessments over two days. The tests which require verbal answers will be audio recorded to ensure your performance can be accurately scored.

Location
Testing will take place in one of the private rooms at … at a time and date agreed by you.

What will I gain from being involved?
Doing these tests can provide you with:
An enhanced understanding of your brain's strengths and weaknesses.
Information that will contribute towards your treatment plan and you and your health care professional better understand and treat your difficulties.

Who is organizing and funding the study?
The study was organized by myself and Dr Matthew Jones Chesters in collaboration with University of East London and **NHS Trust service deleted*,* as part of my doctoral thesis that will be submitted to the University of East London.

What will happen to the results?
We will write a summary of your test results, give you a copy of this, and if you wish discuss the results with you. The researcher will be unable to feedback immediately after testing as they will need to time to process your results.
You may also want your consultant (or other member of staff) to receive a copy to help inform your treatment but this will only be done with your permission.

Results from this research will be made anonymous and incorporated into a thesis which may be published in an academic journal in the future. No identifiable data about you will be included in any report or publication.

Will my study data and research participation be kept confidential?
All the information you provide for the purposes of the study will be anonymised, kept strictly confidential, and kept separately from personal information the service holds about you. Score sheets and consent forms will be stored in a secure location. Once the scores from your tests have been put onto the computer there will be no identifiable information which links you to the information. Confidentiality will only be broken if you tell us that you plan to harm yourself or somebody else. In such cases, we would discuss with you who would be best placed to help and tell people involved in your care.

Are there any risks involved?
Neither the questions nor procedures are in any way harmful. Sometimes, participants feel tired during or after the tests due to having concentrated for a longer time than normal, this is normal and can be reduced by taking regular breaks. You may also find yourself getting frustrated with certain tasks, this too is completely normal and I will be there to assist you.

What if something goes wrong?
You can direct any complaints to me or Dr Mark Finn Chair of the Research Ethics Committee at University East London (contact details below). In the unlikely event that anyone is harmed, the study is has indemnity cover from the University of East London.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by *NRES Committee South Central - Hampshire A* Research Ethics Committee.

Do I have to take part?
No. Your participation is voluntary. Should you choose not to participate, this will have no consequences for your relationship with staff at the service.

If you decide to take part but later change your mind, you are free to withdraw from the study at any time and your information will be deleted. However, the researcher reserves the right to use your anonymised data in the write-up of the study and any further analysis.

What happens now?
If you are happy to continue you will be asked to sign a consent form.

If you have any questions or concerns about how the study has been conducted, please contact me, Lucy Butler Trainee Clinical Psychologist, at **contact details deleted**

or

Chair of the School of Psychology Research Ethics Sub-committee **name and contact details deleted**

Support services for people living with HIV and/or AIDS

If you would like information or support regarding living with HIV or AIDs please find some information below about local charities. If you have access to the interest you can also find out more about these services online and contact them by email.

Terrance Higgins Trust Tel: 0808 802 1221.

Their number is free to call from all UK landlines and most UK mobiles and will not appear on your telephone bill. When you ring you'll hear a menu system which will give you options to: listen to recorded information, leave a message to be called back in another language, hold the line if you'd like to speak an adviser.

PositivelyUK Tel: 0207 713 0444

Their helpline is open from 10am-4pm, Monday to Friday. You can call to speak to one of their support team who are living with HIV themselves.

Instructions prior to appointment

How can I prepare for my evaluation? What should I bring?

- ✓ If you wear hearing aids or glasses, bring them with you.
- ✓ Take your medication(s) as you normally do, unless your doctor has told you otherwise.
- ✓ Give yourself plenty of time for travel, to find the location, and for parking.
- ✓ Make sure you eat something before you arrive so that you are comfortable until the lunch break.

Appendix L **Participant Consent Form**

The following document was used in both site A and site B. The text remained the same across sites but the logo and other identifiers changed depending on the site. NHS Trust logos and specific service details have been removed to protect the anonymity of the participants.

HIV Neuropsychology Research Study

Social reasoning in People Living with HIV-Infection

CONSENT FORM
V2; 11.06.2015

Date:
Participant Identification:

I confirm I have read and I understand the information sheet dated 11.06.2015 for this research study and have been given a copy to keep. I have had the opportunity to consider the information, ask questions, and have had these answered satisfactorily	
I understand that my involvement and data in this study will remain strictly confidential. I understand the limits to confidentiality e.g. times when confidentiality will be broken.	
I understand that my participation is voluntary and that I am free to withdraw at any time without giving reason and without it affecting my care. Should I withdraw, the researcher reserves the right to use my anonymous data in the write-up of the study and in any further analysis.	
I understand that my consultant will be informed of my participation in this study.	
I consent to my consultant being sent a copy of my results.	
I hereby freely and fully consent to participate in the study.	

_____	_____	_____
Participants Name	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Appendix M **Neuropsychology Test battery**

Table 8: Table of Neurocognitive Assessments

Cognitive Domain/Area of Assessment		Subtest
Premorbid Function		WTAR
Affect		Hospital Anxiety and Depression Scale (HADS)
Attention and Information Processing Speed		RBANS Digit Span Forward
		RBANS Coding
		*Trail Making Part A**
Immediate Memory		RBANS List Learning RBANS Story Learning
Delayed Memory		RBANS List Recall RBANS List Recognition RBANS Story Recall RBANS Story Recognition RBANS Design Recall
Language		RBANS Picture naming
		DKEFS Semantic Fluency
		WTAR
Visuo-Spatial Function		RBANS Line Orientation
		RBANS Figure Copy
Executive Function	**Word Generation – Verbal Fluency**	DKEFS word generation
	Word Generation – Semantic Fluency	DKEFS category generation
	Verbal Switching	DKEFS verbal switching
	Visual Switching and Sequencing	Trail Making Part A and Part B
	Visual Working Memory and Rule Detection	Brixton Test
	Verbal Working Memory	RBANS Digit Span Forwards RBANS Digit Span Backwards
Social Cognition	**Affective Explicit Mentalising/Affective ToM**	Social Stories Questionnaire
	Cognitive Explicit Mentalising/Affective ToM	Reading the Eyes in the Mind Test
	Empathy	Questionnaire of Cognitive and Affective Empathy

Appendix N **Conversion Table**

Table adapted from RBANS Published Normative Information

Table 9: Conversion Table showing Scaled Scores and Subjective Labels

%ile equiv	Scaled Score	Label
>98	**19**	**Very Superior**
	18	
	17	
91-97	**16**	**Superior**
	15	
	14	
75-90	**13**	**High Average**
	12	
50-74	**11**	**Average**
	10	
25-49	**9**	
	8	
10-24	**7**	**Low Average**
	6	
2-9	**5**	**Below Normal**
	4	
<2	**3**	**Impaired**
	2	
	1	**Very Impaired**

Appendix O **Correlational Analysis Matrix**

This table demonstrates how the measures of social cognition correlate with each other, as well as the other areas of (group-level) impairment, and demographic variables.

Table 10: Non-Parametric Bivariate Correlational Analysis Matrix

	WTAR	Age	HAD total	Education	List Total	Story Imm	Cat' Fluency	Figure Copy	RMET	SSQ	QCAE-CE	QCAE-AE
WTAR	1.000	.275	-.284	.741**	.331	.598*	.527*	.371	-.024	.387	.535*	-.021
Age	.275	1.000	.048	-.085	-.448	-.154	-.171	.061	-.062	-.121	-.106	.028
HAD	-.284	.048	1.000	-.370	-.241	.068	.005	.207	.383	-.482	-.462	.214
Education	.741**	-.085	-.370	1.000	.403	.618*	.476	.299	-.151	.444	.401	-.175
List Total	.331	-.448	-.241	.403	1.000	.652**	.730**	.390	0.010	.541*	.522*	.298
Story Imm	.598*	-.154	.068	.618*	.652**	1.000	.725**	.585	-.057	.237	.378	.226
Cat' Fluency	.527*	-.171	.005	.476	.730**	.725**	1.000	.554*	-.057	.237	.281	.226
Figure Copy	.371	.061	.207	.299	.390	.585	.554*	1.000	-.262	.328	.289	.107
RMET	-.024	-.062	.383	-.151	0.010	-.057	-.037	-.262	1.000	.013	-.304	-.042
SSQ	.387	-.121	-.482	.444	.541*	.237	.381	.328	.013	1.000	.684**	.098
QCAE-CES	.525*	-.106	-.462	.401	.522*	.378	.393	.289	-.304	.684**	1.000	.259
QCAE-AES	-.021	.028	.214	-.175	.298	.226	.093	.107	.167	.098	.259	1.000

*Correlation is significant at the 0.01 level (2-tailed).
**Correlation is significant at the 0.05 level (2-tailed).

Appendix P **Participant Characteristics Table**

Table 11: Table of Participant Characteristics

ID	Age	Sex	Years of Educat'n	Education	cART	CD	VL	WTAR	Ethnicity	HAD-A	HAD-D	Co-morbidities
1	57	M	13	UK	Y	575	1	11	White British	12	11	Paternal Alzheimer's
2	41	M	16	UK	Y	512	22174	12	Black British	12	10	
3	33	M	16	UK	N	587	42909	11	Black British	8	9	Non-cART
4	40	F	11	UGANDA	Y	529	1	7	Black African	7	10	Past PTSD
5	48	F	8	SOMALIA	Y	76	642167	9	Black African	9	18	Severe Depression
6	36	F	16	SPAIN	Y	441	88608	12	White Spanish	10	13	History of Postnatal Depression and mild Chrones Disease.
7	69	M	13	UK	Y	418	1	13	White British	8	11	Shingles
8	49	F	11	JAMAICA	Y	954	1	2	Black British	10	12	
9	41	F	6	KENYA	Y	594	1	1	Black African	17	12	Hypercholesterolaemia; Hysterectomy Severe Anxiety
10	42	F	11	PORTUGAL	Y	687	1	8	White Portuguese	14	14	Past Kaposi's Sarcoma.
11	49	M	19	UK	Y	869	1	13	Black British	11	13	
12	43	F	13	BARUNDI	Y	580	1	1	Black British	17	18	History of Trauma
13	48	M	13	UK	Y	704	1	11	White British	18	17	Poor sleep. Past Kaposi's sarcoma. Severe Anxiety
14	24	Male	15	SINGAPORE	Y	282	263	13	White Asian	13	14	
15	33	Male	11	UK	Y	720	1	8	White British	14	14	Severe adverse cART side effects to first regime
16	50	Male	13	UK	Y	806	1	12	White British	14	13	

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