Induction and HIV-associated neurocognitive disorders

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ABSTRACT

Antiretroviral medication has improved HIV-related prognosis. Yet HIV-associated neurocognitive disorders (HAND) have substantially increased, leading to decreased quality of life, increased illness severity and mortality. In the research literature, executive dysfunction (e.g. planning difficulties and cognitive inflexibility) has been identified as prominent in HAND, but there has been little analysis of the componential and qualitative aspects underpinning these deficits. Targeted and theory-driven neurorehabilition for HAND is limited due to the lack of this type of detailed information. This study aimed to explore whether induction, a key aspect of executive function, is impaired in HAND, and if so, the underpinning processes causing impairment.

Thirteen participants with HAND and thirteen HIV-negative participants were matched for gender, age, education and reading ability. The HAND population were assessed for current functioning, and compared to the control group on verbal and non-verbal tests of induction. Qualitative analysis was used to derive a componential scoring system for the Brixton Spatial Anticipation Test (non-verbal measure of induction) to qualitatively and quantitatively characterise performance in the HAND group compared to the non-clinical sample.

Results suggest that induction is impaired in HAND. However, initial rule detection appears spared. Processes such as slowed information processing, and lapses in attention and working memory affected induction across the HAND group. Other deficits appeared idiosyncratically: accordingly, no single *profile* of impairment was identified. This study showed that taking simple measures of executive function at face value does not provide an accurate description of individual performance in HAND. The results are interpreted in the context of a need for componential analyses of neuropsychological tests, generally in research and when interpreting scores in practice.

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LIST OF ABBREVIATIONS USED IN THE TEXT

ADC - AIDS Dementia Complex
ADLs - Activities of Daily Living
AIDS - Acquired Immune Deficiency Syndrome
ANI - Asymptomatic Neurocognitive Impairment
ART - Antiretroviral Therapy
BBB - Blood Brain Barrier
Brixton - Brixton Spatial Anticipation Test
cART - combined Antiretroviral Therapy
CD4 - CD 4+ T-lymphocyte cells
CHARTER - CNS HIV Anti-Retroviral Therapy Effects Research
CNS - Central Nervous System
DKEFS - Delis Kaplan Executive Function System
HAD - HIV-Associated Dementia
HADS - Hospital Anxiety and Depression Scale
HAND - HIV-Associated Neurocognitive Disorders
HIV - Human Immunodeficiency Virus
LD - Learning Disabilities
MND - Mild Neurocognitive Disorder
PLWH - People Living With HIV
PML - Progressive Multifocal Leukoencephalopathy
RBANS - The Repeatable Battery for the Assessment of Neuropsychological Status
SAS - Supervisory Attentional System
SIV - Simian Immunodeficiency Virus
sMRI – structural Magnetic Resonance Imaging
UK - United Kingdom
USA - United States of America
WAIS - Wechsler Adult Intelligence Scale
WCST - Wisconsin Card Sorting Test
WMS - Wechsler Memory Scale
WHO - World Health Organisation

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DEDICATION

This is dedicated to Vera Azarova.

You were with me every step of the way, and always will be.

1 INTRODUCTION

1.1 Literature search

A systematic literature search was conducted (August 2014 to May 2015) using EBSCO, PubMed, Science Direct and Scopus. Terms used were ‘HIV’, ‘HIV-associated neurocognitive disorders’, ‘cognitive impairment’, ‘executive function’, ‘concept formation’, ‘abstraction’ and ‘induction’. No time period was set. The reference list of each relevant article was examined to identify literature missed during the search.

1.2 HIV – History

Human immunodeficiency virus (HIV) is a highly infectious disease that came to the attention of medicine in the form of acquired immune deficiency syndrome (AIDS) in the early 1980s. From this time the disease has spread, quickly infecting almost 78 million people, killing an estimated 39 million of that number (UNAIDS, 2013). The history of HIV is associated with the politics of contagion and the influence of beliefs regarding moral behaviour on medicine, treatment and prevalence. The scope of which is too large to document here, therefore a brief summary will be presented.

1.2.1 The beginning of the pandemic

In 1981 an increasing number of previously healthy men in the United States of America (USA) contracted and quickly died from similar, treatment resistant opportunistic infections and cancers such as aggressive Kaposi’s sarcoma (Hymes et al., 1981) and Pneumocystis Carinii pneumonia (Friedman-Kien et al., 1981). The common factor amongst these men was their sexuality, leading medical professions to erroneously attribute the cause of death to a contagion only affecting men who had sex with men, naming it among other things, gay-

related immunodeficiency disease. Six months later intravenous drug users and haemophiliacs were also affected, shifting the understanding of the disease, and the name to AIDS (Centers for Disease Control, 1982). In 1983 two different research groups (Gallo et al., 1983; Barré-Sinoussi et al., 1983) purported to have discovered the causal substrate of AIDS. Following verification that these two findings described the same factor, HIV was named.

HIV exists in two forms; HIV-1 and HIV-2 (Kumar & Clark, 2012). They have 40% structural similarity but HIV-1 poses a greater threat, particularly HIV-1 group M, accounting for 90% of all infections to date (Taylor, Sobieszczyk, McCutchan & Hammer, 2008). HIV, irrespective of strain, is a lentivirus (a slow virus which takes time to exert its adverse effects on the host) meaning initial infection occurs without symptomatology. It was this delay that made identification of the link between HIV and AIDS so difficult in early research.

1.3 Transmission of the virus to humans

It is now generally accepted that HIV originated in non-human primates in sub-Saharan Africa in the form of Simian Immunodeficiency Virus (SIV). For example, HIV-1M links to the SIV carried by a subspecies of chimpanzees of south eastern Cameroon. SIV has been present for over 32,000 years (Sharp & Hahn, 2011) and is non-pathogenic to the primate host. In the late 19th or early 20th century SIV passed across the species barrier through zoonosis (WHO, 2007) mutating to HIV.

Hunter theory is the predominant explanation for cross-species transmission. It proposes that zoonosis occurred as early as the 1930s through bushmeat activities, contact with infected animal blood and excretions during hunting and meat eating. Serial passage theory (Marx, Drucker & Schneider, 2011) and colonial rule are thought to have escalated transmission to pandemic status. For example, colonialism led to labour camps and lowered immune systems making people more susceptible to any virus, lack of food meant animal meat made up

for scarce resources, and multiple needle use for medication and prostitution (provided to 'keep the workers happy') led to increased transmission (Timberg & Halperin, 2012; Giles-Vernick et al., 2013).

Other theories including the oral polio vaccine theory (which suggested that the live vaccine was created in infected primates leading to transmission during polio inoculation; Hooper, 1999) and conspiracy theory (suggesting HIV was created in a lab and designed as a weapon of genocide; Horowitz, 1997) have been considered but little evidence supports either approach (e.g. Sharp & Hahn, 2010).

Perhaps the most controversial theory to date is the Duesberg hypothesis (Duesberg & Rasnick, 1998) and AIDS Denialism Movement. The movement believes that HIV is a harmless passenger virus to the 'real' non-infectious cause of AIDS, which purportedly includes pharmaceutical and recreational drug use. Between 2000 and 2006, Thabo Mbeki, President of South Africa at that time, believing the Duesberg hypothesis rejected anti-retroviral medication in favour of garlic and other natural remedies leading to the deaths of up to 365,000 people (Chigwedere, Seage, Gruskin, Lee & Essex, 2008). Scientific evidence plus this loss of life has discredited this hypothesis.

1.4 HIV - Present day

1.4.1 Epidemiology

In 2013 the number of people living with HIV (referred to as PLWH from this point forward) globally was estimated at 34 million (UNAIDS, 2013), with 107,800 (95% confidence interval: 101,600 – 115,800) of those living within the United Kingdom (UK; Public Health England, 2014). Prevalence has decreased over the last decade thanks to initiatives including the Joint United Nations Programme on HIV/AIDS. In the UK diagnosis of new cases decreased from an estimated 8,000 per year between 1995 and 2005 (Health Protection Agency, 2012), to 6,000 per year in 2013 (Public Health England, 2014). While numbers are decreasing, the global burden of HIV remains high.

Epidemiological estimates must be interpreted with caution due to their inherent imprecision. This is further complicated in the case of HIV as many people live with the infection without being aware of their positive status; 24% of those estimated to be living with HIV in the UK in 2013 fell into this category (Public Health England, 2014).

1.4.2 Transmission

HIV is passed between individuals when infected bodily fluids (e.g. blood, semen and breast milk) make contact with the bloodstream, delicate mucous membrane, or skin lesion of an HIV-negative individual. Blood transfusion has the highest 'per-act' risk of HIV transmission, followed by mother-to-child transmission (Patel et al., 2014). Globally however, transmission is predominantly through intercourse (Kumar & Clark, 2012). The mucosal lining of the anus is more liable to tear than the vagina, making anal sex more risky in terms of transmission (Patel et al., 2014). This is reflected in the 2013 UK data, which reported that 54% of new cases were linked to men having sex with men and 45% to heterosexual sex (vaginal and anal sex). Only 1% of new cases linked to other routes of transmission including intravenous drug use, mother-to child transmission and exposure to contaminated blood products outside of the UK (Public Health England, 2014). Condoms, dental dams, needle exchanges, and in utero and postpartum antiretroviral medications have been shown to prevent transmission.

Transmission processes that include sex and drug use have led to stigma and discourses around HIV, including suggestions that those who contract it are in some way at fault and deserving of the disease, due to what is seen as morally questionable lifestyle choices and promiscuity. Research into the continuing spread of HIV implicates this kind of stigma and subsequent policy making, or lack of (e.g. Pisani, 2008).

Norman Fowler (2014), the medical health secretary in the UK at the time of the AIDS outbreak has addressed this topic specifically blaming continued transmission on the intolerance and prejudice of politicians, the media and society. For example, Russia and the USA do not use needle exchange programmes despite strong evidence of their effectiveness in preventing transmission. Furthermore, evidence suggests sex workers, who make up a large percentage of individuals vulnerable to HIV transmission, respond well to HIV prevention campaigns including distribution of free condoms and education around the necessities of their use. However, the USA will not fund such programmes and in some areas, including Los Angeles, possession of condoms counts as evidence of sex work. Additionally, stigma of HIV decreases likelihood of testing, and disclosure of an HIV-positive status, all of which increase risk of transmission.

1.4.3 Natural history of HIV

The natural progression of HIV post-infection is described as following three stages, unless interrupted by medical intervention (WHO, 2007):

1. Acute Response to HIV infection

Two to four weeks post-infection, extreme flu-like symptoms occur in 40-90% of individuals. At this stage blood tests do not detect HIV due to a lack of traceable antibodies in bodily fluids (95% of people 'seroconvert' within the first six months; WHO, 2004). Misdiagnoses are therefore often made, such as malaria.

Once in the body the virus replicates quickly and host CD4 counts start to decrease. At this time viral load in the blood and other bodily fluids can reach more than 1 million copies per millimetre. As a direct logarithmic relationship exists between viral load and transmission likelihood (Maartens, Celum & Lewin, 2014), this phase is a significant contributor to the spread of HIV as the individual is often unaware of their new status and therefore not exercising anti-transmission precautions

2. Asymptomatic HIV infection/clinical latency

Following the acute phase, host antibodies respond to the virus leading to slowed viral replication and an asymptomatic phase, which can last for a long period (WHO, 2004). Numbers of CD4 cells recover in this phase, however, the virus remains active within the lymph nodes.

Antiretroviral medication introduced at this time has been shown to improve survival rate. If untreated, the viral load will eventually increase again and the disease will progress.

3. HIV disease and AIDS

Once the CD4 cell count drops below 200 cells per cubic millimetre of blood, cell mediated immunity is lost and an individual is considered to have HIV disease or AIDS. Opportunistic infections (e.g. tuberculosis) and tumours (e.g. Kaposi's sarcoma) occur in this phase and can be fatal if untreated (McArthur, Steiner, Sacktor & Nath, 2010).

Increasing evidence suggests that HIV also attacks the central nervous system (CNS) leading to HIV-associated neurocognitive disorders (HAND), however the specific stage within which this occurs is unknown.

1.4.4 Pathology linked to natural history

Once inside the body HIV replicates and targets cells expressing the CD4 receptor and chemokine receptors, CCR5 and CXCR4; that is, cells responsible for cell-mediated immunity, particularly the CD 4+ T-lymphocyte cells (called CD4 cells from this point on) and monocytes and macrophages (CD 68+). CD4 cell depletion has been linked to complex mechanisms including non-inflammatory (e.g. activation of caspase 3, triggering apoptosis of infected and activated cells) and inflammatory processes (e.g. activation of caspase 1, leading to pyroptosis of non-productively infected bystander cells; Doitsh et al., 2014). Inflammatory mechanisms perpetuate further inflammation potentially accounting for a large proportion of lost T-cells. Following this the body produces antibodies, partially suppressing the virus. The virus then mutates, inhibiting the antibodies ability to

rid the body of HIV. This explains the asymptomatic latent phase. If un-medicated, viral load increases and the carrier progresses towards AIDS. Overall this suggests that the immune system takes centre stage in this disease, acting as a protective and pathogenic mechanism (Hong & Banks, 2015).

The existence of infected persons who are ‘elite controllers’ (those whose CD4 levels remain high irrespective of HIV infection and lack of medication) challenges the notion that HIV has a determined natural progression.

1.4.5 Treatment

Until recently HIV was seen as a ‘death sentence’. The first antiretroviral medications (developed in 1987) improved short-term prognosis but did not suppress viral mutation, leading to drug-resistant strains of the infection and limited long-term benefits (Ellis, Langford & Masliah, 2007). Subsequently, combination antiretroviral therapy (cART) was developed in 1996, creating the current gold standard of HIV management. Good adherence to cART is said to be effective in up to 70% of patients, decreasing viral load to undetectable levels allowing for recovery of CD4 cells and expectation of near normal life expectancy. Now over 75% of people over 50 living with HIV die of non-HIV related causes (Braithwaite et al., 2005).

During treatment low level latent infection resides in resting CD4 cells meaning disruption to medication causes re-emergence, proliferation and mutation of the virus leading to illness and drug resistance, only treatable with an alternative drug (Dahabieh, Battivelli & Verdin, 2015). As a result, medication regimens must be adhered to for life. Barriers to adherence include rare but significant side effects such as peripheral neuropathy, liver toxicity, lipodystrophy syndromes (Lucas & Nelson, 2015) and in rare cases death (Abers, Shandera & Kass, 2014).

The hunt for a ‘cure’ is ongoing, with scientists exploring the possibility of a functional (removing the negative effects of the virus, and detectable load from the blood) or sterilising cure (ridding the body of the virus in its entirety). Only one person has currently achieved sustained sterilisation, the ‘Berlin Patient’ (Hütter

et al., 2009). However the complex and high risk factors involved in his treatment, which included a CCR5-negative bone marrow transplant for leukaemia, have made this a difficult scenario to recreate (Cockerham & Hatano, 2014).

Future treatment may include gene therapy that creates HIV-resistant cells within the carrier. At present, gene therapy using modified human stem cells has proved efficacious within animal models (e.g. Bird, 2014; Barclay et al., 2014) and further work is being carried out to determine whether long term suppression or sterilisation of the virus can be achieved within humans.

1.4.6 HIV since cART

The advent of cART improved mortality rates. Yet it also altered the neurocognitive profile and incidence of HAND.

1.5 HAND

Prior to cART, severe cognitive impairment known as HIV-associated dementia (HAD), was noted in up to 15% (Underwood, Robertson & Winston, 2015) to 20% (Brew, 2001) of AIDS-defining illnesses (percentages depend on data source). These impairments were considered to be due to immunosuppression and opportunistic infection (e.g. toxoplasmosis), progressive multifocal leukoencephalopathy (PML), or structural neurologic disorders (e.g. brain tumours or strokes).

Since cART administration, HAD cases have decreased to approximately 1% (Heaton et al., 2011). However, mild to moderate neurocognitive disorders have increased and are being diagnosed in up to 50% of HIV-positive individuals (Robertson et al., 2007). As viral load and opportunistic infections are low in medicated persons, this suggests that HIV itself causes neurological impairment.

1.5.1 HAND Terminology

AIDS dementia complex (ADC; Navia, Jordan & Price, 1986) was the first term used to describe the cluster of neurocognitive symptoms (behavioural change, motor dysfunction and cognitive impairment) noted in some cases of AIDS-defining illness. The validity of ADC as a distinct syndrome was questioned (Catlan & Burgess, 1996), as was the dichotomous nature of the diagnosis, which potentially led those with mild cognitive impairment, and significant impairments, to become clustered within the same 'dementia' group.

To manage critiques, the American Academy of Neurology AIDS Task Force devised a classification system with two categories; HIV-associated dementia to represent those with more profound motor, behavioural and psychosocial deficits, and minor cognitive motor disorder for those less severely impaired. A further category, sub-syndromic neuropsychological impairment, was added in 1995 to categorise mild impairment without functional impact on activities of daily living (ADLs; Grant & Atkinson, 1995). Again, lack of specificity and inconsistent use of the categories (Griffin & Gerhardstein, 2010) led to criticism and subsequent revisions.

The current western diagnostic system of HAND is set out in the Frascati criteria (Antinori et al., 2007). Devised by the National Institutes of Health, the framework attempts to capture a spectrum of neurologic disease including the functional impact of impairment, range and complexity of presentations, available neuropsychological assessment and treatment protocols, as well as the effect of co-morbid conditions (Griffin & Gerhardstein, 2010). The framework's HAND subcategories are:

1. Asymptomatic Neurocognitive Impairment

30% of PLWH are thought to meet criteria for asymptomatic neurocognitive impairment (ANI), which describes mild neurocognitive impairment on standardised tests without significant impact on everyday functioning. Absence of functional impairment suggests that most would be unaware of any cognitive change. (McArthur et al., 2010).

The CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study, which monitored neurocognitive change in a cohort of 347 HIV-positive participants over 35 months via biannual neuropsychological assessment, found that ANI presented a two to six fold increased risk of progression to mild neurocognitive disorder (Grant et al., 2014). Subsequently it has been suggested that HIV-positive individuals be screened for ANI in order to tailor treatment appropriately and halt further progression. At this point, no treatment exists that would deter this progression as underpinning mechanisms of HAND remain unclear.

2. Mild Neurocognitive Disorder

20-30% of PLWH are thought to meet criteria for mild neurocognitive disorder (MND; Sacktor, 2002), which describes mild to moderate neurocognitive impairment (at least one standard deviation below normative data matched for age and education) in two or more domains plus change in daily functioning. MND is linked to reduced medication adherence, subsequent increased risk of cART resistance and mortality (McArthur et al., 2010).

3. HIV-associated Dementia

1% (Heaton et al., 2011) to 5% (McArthur, 2004) of PLWH are thought to meet criteria for HAD, which describes moderate to severe neurocognitive impairment (two standard deviations below normative data matched for age and education) in two or more domains plus marked functional impairment not explained by comorbidity or delirium. HAD is linked to increased mortality (Woods et al., 2009).

1.5.2 Critiques of the Frascati Criteria, diagnosis and HAND

The Frascati criteria and HAND are not without criticism. For example, functional impairment often depends on self-report measures. These can elicit false-positives and negatives due to exaggerated self-criticism and lack of insight (Heaton et al., 2010). Assessment of cognition is based on short screening measures or neuropsychological assessments, which have additional problems such as inappropriately matched normative data. Consequently, it has been suggested that clinical use of the Frascati criteria could lead to misdiagnosis in approximately 14% of PLWH (Nightingale et al., 2014).

Misdiagnoses have implications for costs of care, treatment regimen (as antiretroviral medication may be modified upon diagnosis of HAND), and anxiety and stigma for those misdiagnosed. This is of note as multiple groups including the Mind Exchange Working Group (2013) and The British HIV Association (2012) advocate for population wide screening of PLWH for HAND. This request seems understandable considering the link between ANI and MND, and HAND and life threatening complications. However, misdiagnosis and the lack of an available medicine that reliably prevents progression of ANI to MND makes the benefits of population wide screening debatable.

Repeated assessment suggests that cognition in PLWH generally fluctuates over time, and in both directions, i.e. improved functioning has been seen as often as deterioration (McArthur, 2004). Fluctuations in cognition may reflect instability in disease processes and viral replication, or limitations in the neuropsychological assessments measuring ability (Nightingale et al., 2014). The Frascati criteria do not reflect these changes, suggesting further concern for the classification system and misdiagnoses.

These arguments reflect criticisms levelled at the construction of diseases more widely. For example, Sontag (1991) discussed the necessity of deconstruction of mainstream discourses, which increase the suffering of the individual more than the disease process causing it. For example, she stated that labelling an individual as HIV-positive but asymptomatic was the same as saying someone was ill (but not yet aware) and awaiting death, without actual evidence that the definitive ending of all HIV cases was AIDS. Furthermore, she proposed that an HIV diagnosis itself created a stigma and fear that could contribute to cognitive or behavioural changes without actual pathology. Sontag wrote about HIV and not HAND. However, ANI maps closely onto her discussions, as evidence suggests it increases risk of further impairment without proof that this will happen to everyone. Diagnosis of ANI therefore suggests problems that may not yet be there but are ‘sure’ to come. The stigma and fear of diagnosis could cause changes subsequently misattributed to mild cognitive impairment.

Irrespective of specific diagnostic label or classification system, HAND has been linked to decreased quality of life, employment rate, life expectancy (Tozzi et al., 2007) and functional ability (Garvey, Yerrakalva, & Winston, 2009). At present no alternative for the criteria has been presented and therefore, bearing these criticisms in mind, this research worked with the notion of HAND based on this framework.

1.5.3 Neuropathology

The neuropathological mechanisms of HAND outlined here refer to primary (i.e. the direct effect of HIV on the CNS) and not secondary pathologies (i.e. opportunistic infections which further affect the CNS, including PML and lymphoma).

The process between initial HIV-1 infection and HAND starts when HIV-1 passes through the blood brain barrier (BBB) as either cell-free virus or within infected T-cells and monocytes (Hong & Banks, 2015). Inside the CNS the virus produces cytokines and other neurotoxic responses, destabilising the BBB allowing the virus to cross more freely (Hong & Banks, 2015). Cell death then ensues through infection of previously uninfected cells and production of proinflammatory cytokines including TNF and IL-1ß from infected monocytes and T-cells which activate further microglia, astrocytes, perivascular macrophages (cells tasked with initiating immune responses within the body when threat is encountered to protect it from further injury). Neurotoxic factors are then released, including inflammatory mediators and excitatory amino acids, disrupting neuronal function and leading to cell death. Cytokines in the blood, outside of the BBB may also act on CNS cells, further increasing inflammation and cell depletion (Hong & Banks, 2015).

HIV lacks specificity in terms of the neuronal forms it affects, unlike other kinds of neurodegeneration (e.g. Parkinson's targets nigrostriatal dopaminergic neurons). Instead diffuse damage occurs. However, pathogenic processes principally affect the basal ganglia, frontal cortex, hippocampus and white matter tract connections; preferentially affecting the fronto-striato-thalamo-cortical loops

(Thompson et al., 2005; Ellis et al., 2007). Neuroimaging, including structural Magnetic Resonance Imaging (sMRI) and diffusion tensor imaging, supports this explanation finding that subcortical brain regions are primarily affected, until later in the disease process when cortical areas may also be compromised (Lentz et al., 2009). Neurocognitive change and HAND also include ventricular enlargement, cerebral atrophy (Ances & Ellis, 2007), hypodensities and decreased diffusivity in white matter structures including frontal white matter and the corpus callosum (Leite et al., 2013), altered deep grey matter and subcortical regions (Valcour, Sithinamsuwan, Letendre & Ances, 2011).

1.5.4 Mechanisms of HAND in the cART era

HAND has increased despite cART's ability to decrease viral load to near undetectable levels (which would suggest the neuropathological mechanisms outlined above could not occur). Determining the mechanism through which HAND continues to occur is critical if it is to be attenuated. A direct mechanism of cART leading to HAND is unlikely to be found as not all PLWH receive this diagnosis. Also, in some cases length of time on cART is linked to improved learning and information processing speed (Giesbrecht et al., 2014). Mechanisms are therefore likely to be complex, as on one hand cART has increased problems, yet on the other it has helped cognition. The main theories proposed to date link to:

1. Irreversible pre-therapy damage to the CNS

HIV may create structural and functional changes prior to cART administration not ameliorated by medication, leading to cognitive impairment. For example, the nadir CD4 count (a measure of immunosuppression and cellular depletion prior to medication) is considered to be a useful measure to predict cognitive change (Ellis et al., 2011).

2. Persistence of HIV-related pathological processes

Pathological processes such as viral replication may continue in cART. For example, some ARTs do not cross the BBB suggesting the CNS (and cerebrospinal fluid if viral escape occurs; Hong & Banks, 2015) acts as a

reservoir for the virus, a place where ongoing damage can occur without suppression. The CNS therefore has longer exposure to HIV than before, which as the cohort of PLWH ages will only increase.

Research addressing this hypothesis has examined the efficacy of ART with high (compared to low) CNS penetration. The findings are patchy with some studies showing high CNS penetration gave increased benefit and protection from HIV (e.g. Vassallo et al., 2014), and others showing no benefit (e.g. Ellis et al., 2014), or increased neurotoxicity and risk of HAD (e.g. Caniglia et al., 2014).

The CNS immune response (started pre- or post-ART) to HIV is another process that may not be mediated by medication. Therefore inflammatory activity initiated to protect the body may become chronic (Gill & Kolson, 2014) causing vascular degeneration and CNS tissue damage (Heaton et al., 2011).

3. ART neurotoxicity

Some laboratory research suggests that ART may be neurotoxic and disrupts mitochondrial functioning (López-Armada et al., 2013). This indicates the medication itself may be damaging, leading to the kind of chronic inflammation seen in other neurodegenerative diseases (Underwood et al., 2015). However, to date, differentiating the effects of ART from other variables within clinical studies has been difficult.

1.5.5 Neuropsychological profile of HAND

Neurodegenerative HIV-related processes, while diffuse, link to specific profiles of cognitive impairment, which have changed since cART.

Pre-cART impairment was linked to slowed motor and information processing speeds. Now HAND also encompasses deficits in learning, memory and executive functioning (Heaton et al., 2011). Early stages are categorised by changes in motor functioning, speed and attention. As these areas decline further, difficulties with fine motor control, gait, short-term memory and mental slowing occur (Grant, 2008; Nath et al., 2008). Visuospatial functions appear to

remain relatively intact (Heaton et al 1995). However, only seven to ten percent of people with HAND are thought to present without additional comorbidities (Heaton et al., 2011), such as stroke or PML. Therefore, presentations may vary.

In response to known phenotypes, assessment for HAND covers domains including attention, information processing, motor skills, working memory, executive functions, language and memory (Cherner et al., 2007).

1.5.6 Assessment tools

As mentioned, there has been a drive to detect neurocognitive deficits in the early stages. Previously available brief screening tools have therefore been recruited and adapted to increase specificity for HIV-associated changes. For example, the Mini Mental State Examination (Folstein & Folstein, 1975), used as a screening tool for other types of cortical dementia (e.g. Alzheimer's), has been shown to lack sensitivity for HAND. Insensitivity may be due to lack of questions assessing subcortical regions linked to HIV damage, such as the prefrontal-striatal connections responsible for executive functions, working memory and information processing.

The HIV Dementia Scale was devised to assess subcortical functions, showing improved sensitivity and specificity when compared to similar brief measures (Power, Selnes, Grim & McArthur, 1995). Other specific measures, including the International HIV Dementia Scale (Sacktor et al., 2005) were devised, however they often lack sensitivity for mild impairment. The Montreal Cognitive Assessment, a generic measure for mild impairment has been shown to have good face validity for HAND sensitivity and highlights those needing further comprehensive assessment. However specificity and sensitivity of the tool varies across the literature (e.g. Brouillette et al., 2014; Janssen, Bosch, Koopmans & Kessels, 2015).

Neuropsychological assessment is used for multiple purposes including: creating a profile of cognitive difficulties; identifying cognitive strengths, weaknesses and subsequent appropriate support plans that build on skills to improve or maintain

day to day functioning; monitoring cognitive functioning over time possibly in line with disease progression and medication regimens; informing decision-making about care plan appropriateness, for example determining whether an individual can manage complex medication regimens (Grant, 2008; Woods et al., 2009). Therefore comprehensive neuropsychological batteries provide more in-depth profiles of individual performance than any brief diagnostic tool, subsequently improving sensitivity and specificity.

Problematically, neuropsychological assessment comprises multiple batteries and combinations of tests, rendering the available literature on HAND difficult to generalise as each paper utilises a different strategy. Furthermore, neuropsychological tests advertised as measuring specific domains (e.g. attention, information processing, working memory) require intact functioning of other domains. Therefore no test is completely 'pure', necessitating careful interpretation of results.

1.5.7 HAND and contributing factors

Multiple factors are suggested to influence the likelihood and severity of HAND. Much like research into other areas of HIV, findings are mixed. Pertinently, evidence documented thus far indicates HIV causes HAND in a percentage of cases. However, two recent investigations found that when demographic variables (including gender, age, schooling, co-morbidities) were controlled for, cognition did not differ significantly between HIV-positive and HIV-negative women (Manly et al., 2011), or men who have sex with men (McDonnell et al., 2014). From these cases, it was suggested that HIV-related decline might be overestimated when patient sample performance is compared to ill-matched normative data. These findings have not yet generalised to other studies. This does not invalidate their findings but may suggest other research has not had tight control over demographic factors. This needs to be considered when interpreting the following literature.

Gender

Until the late 1990's PLWH were mainly men. However, the millennium saw women become the fastest growing HIV population (Cohn, 2003). Current global distribution of HIV is shared almost equally between men and women, dependent on geographical location. For example, women make up approximately 57% of all PLWH in sub-Saharan Africa (UNAIDS, 2013), and only 32% of PLWH in the UK (Public Health England, 2014).

Due to the previous global and current local (western countries) overrepresentation of men, the majority of research carried out to date on HIV and its neurological sequelae has excluded women. Therefore biased data and norms may have been incorrectly generalised to both sexes (Faílde-Garrido, Alvarez & Simón-López, 2008). As a result, a small but growing literature has looked into gender differences in HIV and cognition with mixed outcomes.

Suggestions of a gender bias in HIV-related cognition have gone full circle over the last two decades. Early epidemiological studies suggested that women were more vulnerable to HAND, particularly in the pre-cART era, with more than double the number of cases of ADC diagnosed in women than men (Chiesi et al., 1996). Following cART, comparable rates were noted across genders in the USA (Robertson et al., 2004), Puerto Rico, Europe and Australia (Wojna et al., 2006). However, the recent CHARTER study (Heaton et al., 2010) found that women were up to three times more likely to experience deleterious effects of HIV (Albert & Martin, 2014).

Explanation for the discrepancy noted between genders, when noted at all, has been linked to biological aspects (such as difference in hormone levels, brain structure, body composition; Faílde-Garrido et al., 2008), increased intravenous drug use (Lopez, Wess, Sanchez, Dew & Becker, 1999) and mental health problems in women (Basso & Bornstein, 2000). More commonly however, it has been related to socio-political aspects of gender, such as the lower social status of women and their decreased access to education (e.g. Lopez et al., 1999; Maki & Martin-Thormeyer, 2009; Heaton et al., 2010) and protective services. For

example, differences in HAND prevalence across genders in Zambia were explained by sex-related social, financial and healthcare disadvantages affecting women's education, treatment availability and adherence (Hestad et al., 2012).

Aside from prevalence, little research has investigated the neuropsychological profile of HAND across genders. The limited research available suggests no significant difference in profiles. Outliers to this finding includes one study showing differences in verbal learning, delayed recall and working memory when HIV-positive men were compared to women matched for variables including disease stage (Maki et al., 2009). Another indicated a trend towards females experiencing higher rates of impairment (51.9% of males and 54.8% of females) than men particularly in psychomotor speed, attention and verbal memory, while men experienced more difficulty in visual memory, attention and abstract reasoning.

Age

In the next two decades, the majority of PLWH will be over 50 (Winston & Underwood, 2015). This is of particular concern as normal ageing processes lead to immunovirological deregulation (increased susceptibility to, and decreased ability to fight infection; Gardner, 1980), neural damage (Ernst & Chang, 2004), general comorbidities (e.g. cardiovascular disease) and mortality (Önen et al., 2010). Furthermore HIV is associated with accelerated ageing, with functional MRI finding blood oxygen level dependent responses in young HIV-positive individuals mirroring those found in HIV-negative individuals that are 15-20 years older (Ances et al., 2010). Therefore, accelerated decline and potentially synergistic effects of pathological processes may be expected.

It is unsurprising therefore that risk of HAND increases with age. With older adults at three-fold risk of HAND compared to young PLWH (Cherner et al., 2004; Valcour et al., 2004). Illustrating this, it was found that older PLWH had increased deficits in episodic (Sacktor et al., 2007) and prospective memory (Woods, Dawson, Weber, Grant & HIV Neurobehavioural Research Center Group, 2010), and executive functions including cognitive flexibility (Iudicello, Woods, Deutsch, Grant & HIV Neurobehavioral Research Program Group, 2012) than younger

PLWH. These age and HIV-related declines have been linked to disruption of ADLs, medication adherence (Hinkin et al., 2004), health-related quality of life (Doyle et al., 2012) and lower mood (Shimizu et al., 2011).

Education and cognitive reserve

Higher education level has been negatively correlated with onset of HAND (Heaton et al., 2015). This could suggest that education protects against HAND. Cognitive performance is generally improved by increased years of education as neuropsychological testing directly maps onto western educational procedures. Therefore, it is important not to conflate lower achievement in testing with a HAND diagnosis in those with lower educational experience, as this may be the influencing factor rather than HIV. Quality of education (purported to be measured by reading tests) is reported to be a more accurate measure of the exposure an individual had to learning than years of education, as teaching quality offered across the globe varies (Manly, Jacobs, Touraji, Small & Stern, 2002).

One explanation of education's protective ability is the cognitive reserve model (Stern, 2013). This states that higher reserve (quantified as prolonged education, higher IQ, reading skills and level of occupation) increases resilience to brain pathology through efficient pre-existing cognitive processes or ability to deploy alternative pathways. In short, it is thought that increased education leads to more complex, adaptable and available neural networks. This model suggests there will be a critical threshold of pathology past which functional impairment cannot be attenuated. The concept of cognitive reserve has been utilised in studies of HIV as many have linked higher reserve to improved outcomes (Heaton et al., 2015) and successful ageing (Heaton et al., 2015; Malaspina et al., 2011), and lower reserve to symptomatic HAND (Morgan et al., 2012).

Few have critiqued the notion of cognitive reserve within the neuropsychological literature. However, it is possible that the data upon which reserve models are based do not reveal a protective factor, but instead reflect the fact that people who perform well on neuropsychological measures pre-brain pathology, have further to fall to reach the impaired range.

Culture and Ethnicity

Lack of access to precautions and treatment has meant the majority of PLWH are found in sub-Saharan Africa. Despite this, most HAND-related research is carried out in western cultures making it difficult to understand the link between cultural variables and HAND. Furthermore, test resources that are culturally appropriate (i.e. that are in the relevant language, use culturally normative items and data) are limited in international settings such as in sub-Saharan Africa (Robertson, Liner & Heaton, 2009).

Assessment tools and normative data are rarely adapted to take cultural factors into account (Manly et al., 2011). For example, visual measures rather than verbal measures are found to have greater validity and reliability in rural China (Heaton et al., 2008). With normative data however, it has been suggested that even the 'most representative norms' do not include enough variance in factors such as intravenous drug use or mental health diagnoses to make the sample representative (Manly et al., 2011). Therefore even adapted norms must be considered fallible, and research to date needs careful interpretation.

International neuropsychological research varies. Robertson and colleagues (2009) reviewed the literature available on HIV, finding many papers showed similar prevalence and phenotype of HIV-related cognitive impairment across cultures, countries and strains (see Robertson et al., 2009 for full description). For example, a study in Cameroon found PLWH displayed impairment in executive functions, information processing speed, working memory and memory recall, matching the profiles noted in the USA (Kanmogne et al., 2010) and rural China (Cysique et al., 2007).

Other studies found differences between culture, ethnicity and HIV. For example, following adjustment for years in education and age, Manly and colleagues (2002) found that HIV-positive African-Americans had poorer neuropsychological outcomes than HIV-positive white Americans. However, this difference was lost after adjustment for scores on a reading test (the WRAT-3). The reading test may therefore be a better indicator of quality of education, and may account for cross-cultural differences. However, in 2011 it was suggested that variance in cognitive

scores between HIV-positive and HIV-negative individuals more significantly related to ethnicity and education than HIV status (Manly et al., 2011). The CHARTER study emulated this finding as 'Hispanic[1] ethnicity' was associated with higher rates of, and earlier progression to cognitive decline in HIV-positive individuals when compared to non-Hispanic white and non-Hispanic black Americans (Heaton et al., 2015).

Not expecting ethnicity-related findings, CHARTER explored possible reasons underlying their data. They highlighted the socio-political aspects of ethnicity, class and poverty within the USA. For example, people of Hispanic ethnicity have less access to health care and insurance (Adams, Kirzinger & Martinez, 2011; National Centre for Health Statistics, 2013), possibly leading to the finding that HIV-positive people of Hispanic ethnicity test (Chen, Gallant & Page, 2012; Dennis, Napravnik, Sena & Efron, 2011), obtain medical care for and initiate therapy (Turner et al., 2000) later than their American counterparts. Therefore it is possible that they are exposed to the disease for longer without knowing, accounting for discrepancies in the onset of HAND. Other factors such as housing, employment, education, and nutrition need to be investigated to identify whether these demographic variables explain the fluctuating findings in the literature regarding the impact of HIV on different cultures.

The literature is littered with examples from both sides of the debate on the relationships between most demographic variables, HIV and cognition. What is becoming clear however, is the effect of social position and access to resources (the lack of which can increase cognitive decline, decrease resilience or conversely lead to false-positives in HAND diagnoses).

Comorbidities

In the recent CHARTER study, neurocognitive impairment increased with the presence of comorbidities. Specifically, prevalence of HAND rose from 30% (of individuals with no substantial comorbidity) to 60% when mild contributing comorbidities were present and 80% when confounding comorbidities occurred.

[1] This is the terminology used within the CHARTER study.

These latter findings occurred irrespective of CD4 count and viral load (Sacktor & Roberts, 2014).

The main comorbidities investigated to date include Hepatitis C, substance misuse and mental health. Hepatitis C is shown to increase HAND through synergistic effects of the two illnesses which both target the CNS (e.g. Giesbrecht et al., 2014). Substance misuse has been described similarly, as most prescription and illicit drugs alter brain morphology, amplifying effects of HIV and subsequently HAND (e.g. Fama et al., 2011). Mental health has mainly been investigated in terms of its link to transmission rather than HAND. However, depression is known to affect motivation, verbal memory, executive functioning and motor performance (Castellon et al., 2006). Additionally, anxiety can affect processing speed, memory and cognitive flexibility during neuropsychological testing (Beaudreau & O'Hara, 2009), suggesting increased impairment would not be unusual.

It is not within the scope of this study to explore all risk factors fully. For a richer description of comorbidities and other risk factors see appendix A.

1.6 HAND and executive functions

HIV affects multiple areas of cognition but has been described as a primarily dysexecutive syndrome (Weber, Blackstone, & Woods, 2013). Therefore executive functions will be addressed in more depth here.

1.6.1 Executive Functions

Multiple theories on the theoretical underpinnings of executive functions exist (e.g. Luria, 1973; Stuss & Benson, 1986; Damasio, 1995). One major theory is the Supervisory Attentional System (SAS; Norman & Shallice, 1986). It suggests that in general, behaviour is determined by 'contention scheduling', activation of schemas that are overlearnt, automatic behaviours triggered by routine events,

(e.g. ‘wanting to clean’ could be a schema activated when observing dirty plates). However, when presented with novel stimuli, situations or danger the SAS, which governs contention scheduling and higher order processes, influences schema activation and suppression. It then adapts previous behaviours to determine and generalise new rules and ways of being.

Executive functions are summarised as higher cognitive processes which allow people to function in the world in a flexible, goal-directed, socially acceptable and effective manner. Lezak and colleagues (2012) separate these processes into two main categories: 1) concept formation, and 2) all other executive functions needed for goal-orientated behaviour.

Normal executive functioning depends on the integrity of areas commonly affected by HIV including the frontal cortex, basal ganglia and connecting pathways (Stuss & Levine, 2002). It is not surprising therefore that executive function deficits are considered central to HAND. At present there are studies to suggest all aspects of executive function are affected in HIV. Not all agree which are specifically affected, or to what extent. A far greater body of evidence explores executive functions linked to goal-orientated behaviour and therefore a summary of this research will be presented before exploring concept formation.

HAND and goal-oriented behaviour

Goal-oriented executive functions link to volition, planning, decision-making, decisive action and effective performance (Lezak, Howieson, Bigler & Tranel, 2012). They therefore include impulse control, planning, problem solving, fluency and working memory.

Executive functions receiving interest and research in HAND include impulse control and decision-making. Bechara’s (2007) gambling task has evidenced impulsivity and poor decision-making in a number of studies (e.g. Martin et al., 2004; Thames et al., 2012; Arentoft, Thames, Panos, Patel & Hinkin, 2013), specifically finding that PLWH chose larger, more immediate rewards instead of the gradually increasing smaller rewards chosen by HIV-negative individuals (Hardy, Hinkin, Levine, Castellon & Lam, 2006). Focused research into this area

may link to concerns that 'risky' decision-making may precede increased transmission of HIV. Planning has also been found to be impaired in HAND (e.g. Sahakian et al., 1995; Bartok et al., 1997; Cattie et al., 2012), in both symptomatic and asymptomatic individuals. These findings were replicated in assessment of functional abilities linked to social and activity planning using self-report measures (Benedict, Mezhir, Walsh & Hewitt, 2000).

Both letter and category fluency have been shown to be impaired in multiple verbal fluency tests (e.g. Iudicello et al., 2007, 2012). Verbal fluency impairments are considered the most frequently noted language deficit in HAND with up to 40% of PLWH estimated to experience these difficulties (Rippeth et al., 2004). These impairments increase further when a switching component is added (Iudicello et al., 2008), which is unsurprising as impaired attentional control and rigidity in HAND have been noted in the Intra-Extra Dimensional Set Shift (Giesbrecht et al., 2014), Wisconsin Card Sorting Test (Carter, Rourke, Murji, Shore & Rorke, 2003) and Trail Making Test Part B (Heaton et al., 1995; Reger, Welsh, Razani, Martin & Boone, 2002).

Furthermore, research looking into executive functions and disease stage have found spatial and verbal working memory impairments correlate with disease stage (e.g. Bartok et al., 1997; Martin et al., 2001), with fewer deficits noted in asymptomatic stages when measured using a computerised spatial working memory task (Grassi et al., 2014) and a visual vigilance task (Law et al., 1994). Difficulties with inhibition using the Stroop Color-Word Test (Tozzi et al., 1999; Hinkin et al., 1999) and sequencing through the WAIS-III Picture Arrangement (Melrose, Tinaz, Castelo, Courtney & Stern, 2008), are also demonstrated in late phases of HAND, however it is unclear at what stage these problems arise.

HAND and concept formation

Concept formation describes people's ability to categorise objects and events based on their common properties, and then generalise these findings to other areas (Lezak et al., 2012).

The Halstead Category Test has indicated deficits of category sorting within large samples of PLWH (Heaton et al., 1995; Grant et al., 1987), which increases with disease stage and is noticeable in medically asymptomatic phases (Grant et al., 1987). This test has subsequently been critiqued for oversensitivity and high levels of false-positives when testing patients with brain pathology (MacInnes, Golden, McFadden & Wilkening, 1983; Mitrushina, 2005; Larrabee, Millis & Meyers, 2008). Additionally, only one study has noted potential impairment in HAND linked to induction, a form of concept formation associated with recognising relationships, and rule acquisition and following (Johal, 2014). No further studies, known to the author, have focussed on this area. Therefore the literature on concept formation in HAND is limited.

1.6.2 Critique of the executive function literature

The evidence base

Problematically, all studies linking HAND to goal-orientated behaviour and concept formation are based on short-term trials; providing only a snapshot of functioning in those assessed. Therefore, findings may not generalize over time. Domains (such as attention control, inhibition, decision-making and planning) that have multiple studies with similar findings could be said to be well evidenced. Other executive functions have had less attention including concept formation. Less explored areas will need further research to establish the validity of the currently available findings. Furthermore, while there is a study to indicate impairment for each executive function, not all agree which is most impaired. For example, one paper evidencing deficits in attentional flexibility and decision-making did not find executive difficulties in other domains (Giesbrecht et al., 2014). Discrepancies across studies may reflect different neuropsychological batteries, small sample sizes and methodological problems, or may reflect challenges with the concept of executive functioning itself.

The concept of executive function

Neuropsychological evaluation of executive functions have been critiqued since the impairment noted in testing does not always map onto functional ability. Rabbitt (2004) discusses this and suggests domains may overlap in testing or cortically. For example, diffuse (sub)cortical regions involved in each executive function means you cannot always predict impairment based on anatomical location of lesions. Conversely, Rabbitt also notes that executive functions could be more specific than currently understood, affecting interpretation of the neuropsychological results. Finally, skills may be overlearnt and therefore resistant to damage based on individual abilities rather than disease specific processes.

These criticisms highlight the constructed nature of cognitive testing and neuropsychology. Specifically, executive functions are often discussed as discrete domains. However, they are concepts designed to capture functions and abilities expected of people in the modern world. The terminology does not represent a truth, but the current understanding and nomenclature used in order for professionals and others to communicate and measure phenomena appearing in clinics.

Underlying difficulties in executive function and HAND

Executive functioning relies on other intact abilities such as information processing and attention. This means qualitative analysis of clinical measures is needed to elucidate the multiple factors affecting performance on each test and may subsequently elucidate the factors Rabbitt (2004) referred to when discussing problems within the executive function literature. Significantly, little has been done to assess underlying processes of executive dysfunction in HAND (Woods et al., 2009), which is essential if we are to better understand the difficulties experienced by people, and target cognitive rehabilitation (Weber et al., 2013).

This is in contrast to the expanding literature on deficits underpinning language and memory problems in HAND. For example, Woods and colleagues (2014)

found that diminished attentional resources underpinned problems with events-based prospective memory in HAND, but that increased task importance afforded prioritisation of limited attentional resources. This suggested that disruption to medication regimens in HAND may link to the individual's inability to attend to, and remember events that need to be carried out in the future. Subsequently, focussing on the importance of cART adherence with patients has been put forward as a strategy to improve prospective memory for required medication-based actions (e.g. through use of rewards and reinforcement of beliefs regarding medication).

To the researcher's knowledge four studies to date have assessed and proposed mechanisms underlying executive functions impairment in HAND (verbal fluency is not included here as it is generally explored within language literature). Firstly, switching difficulties and fronto-striatal circuit damage have been suggested to underpin deficits in category fluency (Iudicello et al., 2008). Secondly, when depression and low mood are present in HAND they have been proposed to underpin 'risky' decision-making measured by the Iowa Gambling Task (IGT; Thames et al., 2012). This is purportedly due to depression's link with decreased cognitive flexibility, cognitive resources and responsiveness to reward and punishment. Thirdly, and conversely, Arentoft and colleagues (2013) constructed a novel outcome measure for the IGT to categorise strategy use within the task. They found that inability to develop a strategy (problem solve) underpinned difficulties with decision-making rather than 'risky' or impulsive behaviour. Finally, lack of efficiency and accuracy in problem solving and rule-bound control has been identified as underpinning planning deficits measured by the Tower of London task (Cattie et al., 2012).

These studies only used one task to investigate underlying deficits in each domain. Therefore, findings may pertain specifically to the task rather than cognitive domain, as it is hard to extrapolate other active neuropsychological abilities without a larger battery or other linked measure. They have also not yet been repeated, suggesting a necessary avenue for future research.

This current study was limited in terms of time and resources therefore one domain was selected in order to investigate underlying components affecting executive functions and address the gap in the literature regarding concept formation. This executive function is induction.

1.6.3 Induction

Central to human learning is the ability to detect relationships between events in our environment, and infer generalisable rules from abstract information (Holland, Holyoak, Nisbet, & Thagard, 1989). This ability, called induction or inductive reasoning, is often considered under the executive function, abstraction, and is a kind of multiple trial concept formation.

The currently accepted process of induction, specifically linked to inferring and following rules, is thought to occur across multiple stages: 1) instance gathering and temporary memory storage; 2) recognition, and hypothesis generation, of similarities and relationships between items; 3) integration of new and old inferences; 4) information gathering to confirm hypotheses and allow future generalization of rules (Crescentini et al., 2011). Impairment in any of these stages would lead an individual to experience difficulties learning novel or generalisable information without explicit, concrete guidance and rule giving from another individual or text; significantly affecting independence and ability to adapt to the environment.

1.6.4 Neuropsychological assessment of Induction

The neuropsychological assessment tool most widely used to quantify inductive ability, at least relating to visuospatial rule acquisition from abstract information, is the Brixton Spatial Anticipation Test (known as the Brixton from this point forward; Burgess & Shallice, 1996). The Brixton was developed based on the SAS theory of executive functioning. It was intended as an alternative for the Wisconsin Card Sorting Test (WCST; Grant & Berg, 1948) because the authors felt the SAS theory suggested the WCST utilised aspects (colour, shape and number) with salient relationships outside of the task, activating schema

previously learnt and affecting performance. The exact method of the Brixton's development is unclear as it is presented within its complete form in the initial paper, where it was utilised upon a group of 77 patients with anterior (frontal) or posterior (non-frontal) cerebral lesions.

The Brixton consists of 55 visual items. Each of which have a rectangle drawn in the centre with ten circular outlines inside. On each page one of the circles is coloured blue. The blue circle moves around as the pages turn according to a rule, which changes over time. The participant must infer the rule and tell the examiner where the blue circle will go next. They must also notice when the pattern has changed and acquire the new rule. The rule changes eight times utilising a total of six rules (see appendixes B-J for an example of each set and rule).

The test purports to be a more valid test of rule acquisition and following than the WCST as the rules relate solely to the presented cards, and no other stimuli needs to be previously understood. It is also suggested to be valid and reliable in terms of testing various patient groups, such as stroke, Korsakoff's psychosis and dementia types including Alzheimer's (Van Den Berg et al., 2009). Normative data is based on a sample of 118 hundred British participants (57 were males), whose ages ranged between 18 and 80. However, the norms are not age-stratified. This is problematic as older age (60 years plus) is a known predictor of poorer performance on the Brixton (Andrés & Van der Linden, 2000). Normative data has subsequently been made for older adults (Bielak et al., 2006), yet none exist for the younger population.

When used in an fMRI study investigating the neural correlates of induction it suggested that early stages of induction including rule search, acquisition and hypothesis generation are linked to activation in the mid-dorsolateral prefrontal cortex. Rule following has been linked to complex interactions in the temporal, motor, and medial/anterior prefrontal cortex. Activation in the frontopolar cortex has been noted throughout induction while a rule remains novel, switching off once a rule has been integrated and familiar (Crescentini et al., 2011). This was the first study to identify specific areas linked to induction and its stages, it was

also in line with previous findings that rule-guided behaviour depends on frontal, parietal, and temporal connections within the brain (Bunge, 2004; Bunge & Wallis, 2008).

As induction is a complex skill requiring multiple intact networks, it is vulnerable to impairment following brain injury of any kind. Furthermore, these frontal regions are disrupted within HIV, rendering this a potential target within the disease.

The Brixton does not possess a componential scoring system. Instead participants receive one overall score linked to performance, leaving it to others to consider underlying mechanisms during testing. In Johal's (2014) doctoral thesis looking at executive functions affected in HAND, the author hypothesised that impaired induction, as measured by the Brixton, possibly linked to disruption of working memory and complex attention, both skills required in the task. The author also noted that participants struggled to develop and adjust strategies to manage the ever-changing rules in the task. The study looked at performance across multiple cognitive domains of 16 PLWH and HAND, and did not use a componential analysis. Therefore little is known about this executive function, whether Johal's finding would be generalisable in other studies, or what underpins the impairment if it is indeed present in all experiencing HAND.

1.7 Justification

cART has decreased mortality rates and increased HAND, through a number of possible mechanisms not yet clearly understood. Neurocognitive impairment has led to decreased medication adherence and subsequent related illness, decreased employment rates, quality of life and ability to maintain independence. Even in its asymptomatic form HAND is considered to be a risk factor for ongoing problems. Vulnerability to HAND is also yet to be clearly understood but appears to link to populations already disadvantaged in terms of resources and access to health care. As the cohort of PLWH ages it is possible that the number of people

presenting to services with HAND will increase, creating increased need for effective treatment and related protocol. In order to meet this need greater detail is required regarding the profile of deficits linked to HAND, particularly the componential underpinnings of deficits present.

The current literature asserts that executive functions are affected, and while not all of it agrees which specifically, evidence suggests that no executive function is resistant, at least in the later stages of HAND. Furthermore, aside from category fluency, decision-making and planning, little has been done to investigate the underpinnings of executive dysfunction. This needs to be addressed if the future of HAND is to be improved. Induction is one such executive function of which little is known with relation to HAND. It appears to be affected but it is unknown in what way and why. Problematically, current neuropsychological assessment tools such as the Brixton do not possess the required scaling systems to make componential analysis of results routinely possible. Therefore, development of subscales which aid componential analysis are also imperative.

1.7.1 Aims

This study aimed to address some of the gaps in the current HAND literature, such as HAND profiles linked to induction and underlying qualitative deficits causing impairment if any was noted. In order to do this the author aimed to develop an assessment measure that could be added to the current Brixton scaling system, which aids componential analysis and could be utilised more widely in the future.

The literature has presented multiple, overlapping but not always coherent accounts of executive dysfunction in HAND profiles. Therefore impairment may be idiopathic and not represent a homogenous phenotype. If this is the case the research hopes to document this. Three research questions were identified at the start of the work and are as follows:

1. Is induction disrupted in HAND when compared to a non-clinical population?

2. If induction is affected, is there a profile of disruption on measures of induction in HAND or does it differ by person?

3. What underlying mechanisms do these deficits on measures of induction reflect?

2 METHODS

2.1 Epistemology

Epistemology is a branch of philosophy concerning itself with knowledge (Barker, Pistrang & Elliot, 2003). It questions the scope, reliability and validity of information people hold and believe to be true, through examination of the theoretical foundations upon which the information was sought or found (Willig, 2008).

The prevailing epistemological stance in contemporary scientific research is positivism. This asserts that logic and observation can lead us to truths about the world, its objects and phenomena (Willig, 2008). Therefore if something exists within the world it can be objectively verified by mathematics, the science of logical testing. For example, behaviourism was a major mode of positivist thought in the mid-20th century. Behaviourists studied only that which they could observe in others (i.e. their behaviour) and ignored, or denied the existence of, other postulated processes such as consciousness. Difficulties arose however as behaviourism was unable to continually predict and control others, which Trochim (2000) argues is the unspoken aim of positivist research. Therefore critiques have been raised that a positivist search for truth is reductionist, ignoring social and historical processes invisible to the eye but which may elucidate more reliable explanations.

Conversely, a social constructionist epistemology asserts that there is no such thing as an external reality or ‘one truth’, but multiple ‘truths’, derived and given credence and meaning through their social context. Social constructionism would therefore argue that the search for ‘facts’ is futile as each finding will depend on the historical, political and societal factors of the time, which could shift moment to moment, dependent on the relationship and subjectivity of the researcher and its subject (Gergen, 1985).

The current research will be carried out from a critical realist position, which could be described as taking aspects from each of the two epistemological stances mentioned. Critical realism postulates that a reality exists outside of human thought and that research can be scientific. However it notes that objective facts may never be attained, particularly without acknowledgement of historical and social narratives, human error, systemic bias (Mackay & Petocz, 2011), and the potential impact of unobservable events. Due to, what is believed to be, fallible research methodology a critical realist should make use of multiple measurements and observations, and acknowledge the inherent cultural, professional and personal biases of researchers involved, and acknowledge that all theory is revisable.

It is important to note that the aims and research questions used in this study more directly lend themselves to a positivist stance. However, a critical lens needs to be applied to research into this area in order to acknowledge multiple potentially immeasurable contemporary factors influencing neuropsychological research and HAND (e.g. socio-political factors), and the inherent biases of neuropsychological testing, devised, validated and continuously altered through western research. Therefore while this research aims for objectivity it is also critical of its methodologies and findings, using neuropsychological nomenclature with the understanding that this is the current accepted language through which findings can be discussed and shared.

2.2 Design

This was an exploratory study using mixed methodology. A quantitative cross-section correlational design was used, in addition to a cases-series analysis of individual profiles. A qualitative component was also used to explore induction-related responses pertaining to the Brixton. As no previous componential analysis of the Brixton indicating performance within the HIV-negative population exists, a control group was necessary to compare to the patient population’s performance.

Sample size was influenced by similar exploratory studies looking at, for example, sub cortical dementias (e.g. Abrahams et al., 2000). A power calculation was considered however the aim of the study was to explore effect size across and between groups, and sample size is described as relatively independent of the effect size (Clark-Carter, 1999). Furthermore, the study was constrained by time, resources and referral rate. Larger sample sizes are linked to more reliable, valid and powerful studies. Therefore the researcher aimed to acquire the largest sample size possible within the allotted constraints.

2.3 Ethical approval

Ethical approval was granted by the University of East London Ethics Committee (appendix K). For Mildmay UK, ethical approval was sought through the medical director and their committee. The service is not within the NHS and does not require IRAS/NRES ethical approval applications.

All participants were required to give personal, written consent (see appendix L). Within the patient group the service's consultant clinical psychologist provided assessment of capacity to consent. Written (see appendixes M and N) and verbal information about the study was provided to all potential participants to ensure informed consent. Information detailed that any choice made by the participant would have no bearing upon their clinical care. Should they decide to participate, their right to withdraw from the study at any time, without having to provide a reason and without impact on their medical care, was also clarified. Furthermore, confidentiality was explained (i.e. that following the assessment no identifiable information would be made available to anyone other than the researcher).

To ensure anonymity, participants were assigned participant numbers that were used throughout data entry, analysis and this write up. A word document linking the participant name and number was created and kept separately, only accessible with a password. In accordance with the Data Protection Act (UK Parliament, 1998) test sheets were stored in a locked NHS filing cabinet and will

be destroyed after five years.

2.4 Recruitment

Patients were recruited from Mildmay UK, a neurorehabilitation centre in London. Mildmay UK offers specialist multidisciplinary care to PLWH and HAND in an inpatient and day service setting. It is the only centre in Europe dedicated to HIV and HAND.

The HIV-negative control group was recruited through convenience sampling. Colleagues and contacts of the researcher were provided with the information sheet for the study and using a snowballing method others were informed. The control group was recruited to match, as closely as possible, the patient sample on a range of levels including age, years of education and premorbid IQ.

2.4.1 Inclusion and exclusion criteria

People referred to Mildmay UK present with varying medical and psychological conditions. To limit effects of confounding variables on neuropsychological performance, core inclusion and exclusion criteria were developed for participants irrespective of (criteria 1 – 3), and dependent on (criteria 4), group.

Inclusion criteria 1 - Demographics:

All participants were required to be between the ages of 18 and 65. The previously explained interplay between neuropsychological assessments, language and schooling meant participants were required to be fluent English speakers who had undertaken some formal education.

Inclusion criteria 2 - Medical comorbidities:

Participants were excluded if they held an active diagnosis of any illness known to acutely affect cognition, such as a urinary tract infection or hepatitis C. The patient group at Mildmay UK presented with multiple medical conditions affecting

cognition such as syphilis, toxoplasmosis, and tuberculous meningitis. The service's consultant clinical psychologist therefore assessed patient suitability case-by-case, considering the cognitive impact of physical health statuses. Patients' considered successfully treated for comorbid infections were invited to participate within the study. However, diagnoses linked to irreversible cognitive impairment or alteration (such as PML and CNS tumours) were excluded from the study.

Inclusion criteria 3 – Psychological factors:
Participants were excluded from the study if under the influence of illicit substances at the time of testing, or they presented with misuse-associated brain damage (e.g. Wernicke-Korsakoff's syndrome). They were also excluded if they had a 'psychotic illness' diagnosis, due to the impact this would have on functioning. Low mood and anxiety are common across the patient population within Mildmay UK. Therefore, case-by-case assessment of cognition and mood was carried out. If not deemed to impact functioning, low mood and anxiety alone did not stop inclusion into the study.

Little research exists to date linking learning disabilities (LD) to HAND, however a diagnosis of LD was an exclusion criteria due to the implications of LD on cognitive performance, and informed consent.

Inclusion criteria 4 – Factors linked to participant group:
For the patient group, inclusion criteria required an HIV-positive diagnosis and symptoms indicative of HAND. For the control group, patients were required to be HIV-negative.

2.4.2 Recruitment procedure

HIV-positive population
Upon admission to Mildmay UK the consultant clinical psychologist screens each patient. This enhanced selection of suitable participants as the current health status, and language ability of each inpatient was understood and monitored by

those in charge of recruitment selection.

Neuropsychological testing is part of the standard assessment and treatment protocol at Mildmay UK. Therefore once the patient was deemed suitable for assessment they were provided with information about the routine procedure. Information included length of standard assessment (estimated at 1 hour) and subsequent procedures such as interpretation of results, report writing and impact upon medical care. Next, the patient was informed of a potential study they could participate in, adding 45 minutes onto testing time. They were provided with the information sheet and given as much time as they needed to consider it. Time was also given for discussion of the study and any questions they wished to pose. If they then wished to participate they were asked to sign a consent form.

Control population

Once identified, potential participants were approached by email and sent the information sheet, details of the study such as assessment length (approximately 30 minutes) and consent form. They were given 24 hours, or longer if needed, to consider participation and questions they wished to have answered. A face-to-face meeting was set up for discussion of the study, before written consent was given.

2.5 Materials

The full test battery (see table 1) included measures of premorbid functioning and mood, current cognitive status and executive functioning, including two tests of induction. The HIV-positive group undertook the complete battery, while the control group only completed tests of premorbid functioning and induction.

2.5.1 Premorbid function

The ability to read irregular words is believed to be resistant to cognitive

impairment (Strauss, Sherman & Spreen, 2006) at least until the later stages of neurodegeneration. Performance on a test of irregular word reading is therefore thought to represent a snapshot of pre-impairment cognitive functioning. This is supposed as words cannot be read correctly through phonemic pronunciation and correct performance relies on previous knowledge of the word, rather than knowledge of grammatical rules. The test relies on normal reading skill development prior to impairment.

The *Wechsler Test of Adult Reading* (WTAR; Wechsler, 2001) is made up of 50 irregular words that participants have to read aloud and pronounce correctly, there is no time limit. Answers provided by participants are marked on a pass/fail basis. Overall scores are then compared to normative data to achieve an index function score. Normative data is based on a sample of 1,134 American and 331 British participants deemed to be representative through census data. The American sample, aged 16-64, were equally spread between men and women. Those over 64 were mainly female. The sample from the UK was also majority female.

2.5.2 Mood

Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983)

Participants are asked to rate themselves on fourteen items, seven linking to the symptoms of anxiety and seven to depression. A separate score is acquired for each of these constructs. Scores are stratified to identify 'suspicious cases' (a score of 8 or more) and 'safe cases' (a score of 11 or more). As anxiety and mood affect cognitive performance this was used to inform interpretation of the neuropsychology outcomes. Normative data is based on 810 male and 978 females ranging between 19-91 years in age (Crawford, Henry, Crombie & Taylor, 2001). Good reliability and validity has been shown for patients in hospital (Herrmann, 1997).

2.5.3 Current functioning

The *Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998)*

The RBANS has 12 subtests and assesses cognitive status in neurological disease and dementia, with good reliability and validity (Hodges, 2007). It was chosen for this study as Mildmay UK uses it in routine assessment, meaning clinical utility for the service and patient was maintained and that any patient opting out of the study still received standard care. Furthermore, the RBANS covers areas associated with HIV and other dementias, meaning differential diagnosis could be made if necessary (e.g. Alzheimer's). It is also relatively quick (approximate test length is 45 minutes) and easy to administer at the bedside of the participant (Lezak et al., 2012), which suits the assessment setting. Furthermore, employing a single battery for the majority of the assessment meant co-normed results enhancing comparability of test results.

The RBANS' normative data is based on a sample of 540 Americans ranging from 18 to 89 years old. The sample was 81% white American, 13% African American and 7% Hispanic Americans. RBANS subtests are discussed below, separated by cognitive domain:

1. Attention:

i) Digit Span Forward

To assess attention and short term stores, participants' are read number strings of increasing length that they must repeat back verbatim.

ii) Coding

To assess attention and information processing speed, participants are given a page with a printed key showing nonsense symbols paired with numbers. Below the key are continuous rows of symbols without their corresponding number. Participants need to identify the missing symbol, entering it into the boxes below as quickly as they can. 90 seconds are given for the task.

2. Immediate Memory:

i) List Learning

To assess verbal learning, participants are read a list of 10 unrelated words that they must try to recall. There are four trials of this task.

ii) *Story Learning*

To assess episodic memory, participants are read a story comprising 12 linked items, which they must repeat back with as much detail as they can recall. There are two trials to this task.

3. Visuospatial:

i) Figure Copy

To assess visuospatial perception and construction, participants are given a 10 component complex design that they must copy directly.

ii) *Line Orientation*

To assess visuospatial perception, participants are asked to identify the location of two lines presented to them, based on a key of 13 lines spreading across 180 degrees from a single origin. There are ten trials within this task.

iii) Figure Recall

Following a 20-minute delay, participants are asked to redraw as much as they remember from the Figure Copy task. This is a visuospatial memory task.

4. Verbal:

i) List Recall

Following a 20-minute delay, participants are asked to recall any words they remember from the List Learning task. This is a verbal memory task.

ii) List Recognition

Participants are read a list of 20 words and asked to identify words present in the initial List Learning task. Ten words originate in the List Learning task, the other ten are distracter items. This is a verbal memory task.

iii) Story Recall

Following a 20-minute delay, participants are asked to recall as much detail as

they can from the initial Story Learning task. This is a verbal memory task.

5. Language:

i) Picture Naming

In this naming-to-confrontation task participants must name the items presented in ten images.

ii) Semantic Fluency

To assess semantic fluency participants have to name as many items within a specific category as possible within 60 seconds.

2.5.4 Executive function

The RBANS misses certain important features of executive functioning. For example semantic fluency is assessed, but not letter fluency. Furthermore, visuospatial working memory and single or multiple trial concept formation are not assessed. Therefore additional measures were included:

1. Verbal fluency:

The Verbal Fluency Test (D-KEFS; Delis, Kaplan & Kramer, 2001).

Different aspects of verbal fluency are assessed across three stages.

i) Word generation and letter fluency: *Verbal Fluency Test*

This subtest assesses skills in word generation. Participants must generate as many words as possible within 60 seconds starting with a given letter, which changes across trials (‘F’, ‘A’, ‘S’). Successive words must not share the same prefix, be numbers, or names of people or places. The number of words generated that adhere to the rules makes up the final score.

ii) Category fluency: *Semantic Fluency Test*

This subtest assesses semantic retrieval strategies and word generation. Participants must generate as many words as possible within 60 seconds that link to a provided category, which changes across trials (‘animals’ and ‘boys names’). The number of words generated makes up the final score.

iii) Switching: *Switching test*

This subtest assesses ability to switch attention between tasks, and verbal fluency. Participants must switch between two given categories ('fruit' and 'furniture'), generating a word from each category each time they switch. They have 60 seconds. The number of words generated that fall into the two categories makes up one score. Another score counts the number of times the person accurately switches between categories.

Each score is compared to the DKEFS normative data. This data is based on a sample of 1,750 Americans whose ages range between eight and 89 and were considered to be representative of the American population in terms of ethnicity. Males and females are equally represented within the younger age groups, however, more females participated in the older age group.

2. Visual Working Memory:

Spatial Span (Wechsler Memory Scale – third edition [WMS-III]; Wechsler, 1997a)

This test assesses visuospatial short-term memory. A page with randomly positioned printed spots is presented to the participant. The assessor touches the spots in a sequence that increases in length over each trial. The participant must copy the pattern exactly in order to score points.

Normative data is based on a sample of 700 Americans, 78% white Americans, 53% female, all aged between 20 and 89 years of age.

3. Visual abstract reasoning:

Matrices Reasoning (Wechsler Adult Intelligence Scale - third edition [WAIS-III]; Wechsler, 1997b).

This is a visual test of single trial concept formation. Participants are presented with a series of figures that are linked through a discernable pattern on each item. One figure is missing and the participant must decide from a list of possibilities which figure completes the pattern.

4. Verbal abstract reasoning:

Similarities (WAIS-III; Wechsler, 1997b).

This is a verbal test of single trial concept formation. Participants are read two semantically linked words (for common objects or concepts). There are 19 pairs of words in total. The participant must explain the way in which the words are similar. Many words may seem dissimilar. It is the role of the participant to abstract the superordinate relationship of the two items.

Normative data for the WAIS-III is based on a sample of 2,450 adults considered to be representative of the US population in terms of ethnicity.

2.5.5 Induction

1. Visuospatial induction:

The Brixton Spatial Anticipation Test (Burgess & Shallice, 1996).

The Brixton is described within the introduction. The total number of errors made across the test comprises the overall score, which is then compared to normative data.

2. Verbal induction:

The Word Context Test (D-KEFS; Delis et al., 2001)

This test assesses verbal multiple trial concept formation and has nine trials. In each trial a mystery word is given and the participant must determine the meaning of the word. The mystery word is presented alongside an initial clue sentence, which hints at the meaning of the word. The participant must make a guess at the meaning of the word. Five clue sentences are given in total and the participant must continue to guess after each clue is given.

Scores include the total number of consecutively correct answers, repeated incorrect answers and ‘no/don’t know’ responses. Only consecutively correct is used within this study, and compared to the DKEFS’ normative data.

Table 1. *Neuropsychological test battery*

Test component	Cognitive Domain	Subtest
1. Premorbid functioning		WTAR
2. Mood		HADS
3. Current Functioning *RBANS	Attention	Digit Span Forward*
		Coding*
	Immediate Recall	List Learning*
		Story Learning*
	Visuospatial	Figure Copy*
		Line Orientation*
	Delayed Recall	List Recall*
		List Recognition*
		Story Recall*
		Figure Recall*
	Language	Picture Naming*
		Semantic Fluency
4. Executive Functioning	Verbal Fluency	DKEFS Verbal Fluency
		DKEFS Category Fluency
		DKEFS Switching
	Working Memory	WMS-III Spatial Span
	Abstract Reasoning	WAIS-III Matrices Reasoning
		WAIS-III Similarities
5. Tests of Interest	Induction	Brixton Spatial Anticipation Test
		DKEFS Word Context Test

2.6 Test Procedure

Prior to testing, all participants were interviewed to gain a general history. This covered the number of years they spent in education, occupational trajectory, languages spoken, health status and mood-related factors. Impairments potentially affecting performance, such as eyesight and motor control, were also discussed.

2.6.1 HIV group

All patients were tested in their hospital rooms. Medical information was gathered from medical files with permission of the participant. The full battery was administered following each test's protocol. A break was offered 45 minutes into testing to alleviate fatigue and ensure the required time had elapsed between immediate and delayed recall tasks. Verbal debriefing was offered immediately after assessment.

Participants were given feedback on their assessment scores through a brief written report, and verbal discussion if still on the ward following assessment. The summary included strengths, difficulties and recommendations. With consent, full reports were then sent to their HIV consultant and clinical nurse specialist.

2.6.2 Control group

Participants were tested in separate clinic rooms within Mildmay UK, or in the home of the participant. If at home it was ensured that quiet spaces were available where the test could be completed without distraction.

In addition to formal test procedures, extra information was gathered during the Brixton test in each group. For example, qualitative descriptions of participant behaviour were noted. Information included hesitation and verbal comments.

2.7 Analysis

2.7.1 Quantitative analyses

Data collected was scored through methodology set out in each test's respective manual, and raw and age-scaled scores (scaled scores and subjective ranges were based on Slick, 2006; see appendix O) were entered into the Statistical Package of Social Sciences version 20 (SPSS). The small sample size, and proportion of ordinal data, indicated the necessity of non-parametric tests in exploratory analysis when exploring data collected. SPSS procedures, bootstrapping and resampling were used to produce exact tests. This gave rise to exact significance values, indicating the proportion of times the results found within the data would be repeated if the test was run including all possible variations. Therefore no asymptotic p values are provided.

Correlational analyses were used to identify relationships across group characteristics, including age and language.

Case series analyses were used to identify patterns within individual profiles.

2.7.2 Qualitative/componential analyses

Experimental psychology has demonstrated the subcomponential facets of cognitive domains (Neisser, 1967), suggesting that all information processed passes various cognitive components and processes. Componential analysis is utilised in psychometric testing to create scoring systems (e.g. Delis, Squire, Bihrle & Massman, 1992) that identify these subcomponents and structural variables (items within a task where the component can be seen to occur and can then be quantified; Clark & Gardner, 1990). The tests are then scored based on these aspects. Additional reference testing (use of other neuropsychological tests) can be undertaken to identify other contributing variables in the componential analysis.

No componential scoring system exists for the Brixton. Instead people receive one total error score. However, Burgess and Shallice (1996) define three

separate features of error performance: perseveration, misapplication of strategy and bizarre. Little information exists to explain the exact characteristics of these errors and what it means to score under the category of misapplication of strategy, but a perseverative or bizarre answer may be more self-explanatory.

Other tests have validated componential scoring systems measuring similar domains. For example, the WCST derives a score for multiple areas (Heaton, Chelune, Talley, Kay & Curtis, 1993) including:

- number of categories completed,
- trials to complete first category,
- perseverative responses, perseverative errors,
- failure to maintain set,
- percent conceptual level responses,
- learning to learn.

Each scoring domain has a specific methodology, which can be followed by all using the test. Furthermore, the Brixton test involves visuospatial perception and short-term memory suggesting that aspects of these areas of cognitive functioning may be reflected in performance.

In order to derive componential analysis for the Brixton, the researcher noted qualitative information pertaining to performance on the task, such as comments made by the participant during testing. After collection, this data and the scored tests were explored for errors and styles of response arising across the test. Analysis was both deductive and inductive as the Brixton tests were coded in three stages for:

- error types outlined by Burgess and Shallice,
- error types outlined by the WCST system,
- any other themes or error types arising from participant's performance during testing and their score sheets. The researcher derived these codes.

Every answer given by a participant was analysed for performance strategy and resemblance to expected answers. Once a list of codes and structural variables (i.e. method through which this code was identified) was created, every test was re-marked to quantify the number of trials across which each theme arose. Codes were collapsed into overarching themes if it seemed they pertained to the same response type. These numbers were then entered into SPSS where they could be explored statistically. It should be noted that errors were thought to be operationalised aspects of the componential factors at play within the task, hence focussing on these aspects.

Tests within the full neuropsychological battery measured memory, visuospatial skills and single trial concept formation, all of which link to Brixton performance. These were cross-referenced with performance on tests of interest.

2.7.3 Participant Characteristics

Within the allotted timescale 15 HIV-positive patients met criteria for the study. One candidate declined neuropsychological assessment, both for routine medical care and the study. The other candidates consented to take part. One participant withdrew from the study after assessment, as he was unhappy with the results of his neuropsychological examination. Therefore 13 people made up the HIV-positive group. The control group was recruited to achieve a matched sample, therefore 13 controls were assessed leading to a total of 26 participants. Age, years of education and other demographic variables for each group are presented in Table 2 (full information is in appendixes P-Q)

Of all participants seven were female and 19 male, meaning an overrepresentation of males within the study and a significant difference between sexes, X^2 (1) = 5.538, exact sig. = .029. A chi-square test (see table 3) indicated that the male to female ratio was the same in the HIV and control population. A Mann-Whitney U test on participant data (see table 4) indicated the groups were well matched for age, years of education and reading ability (as assessed by the WTAR). While not significantly different, the control group scored slightly higher

on the WTAR, approximately one to one and a half scaled score points above the HIV group.

Table 2. *Participant characteristics*

	Group	Min	Max	Mean	SD
Age (Years)	**HIV***	38.0	65	51.38	8.91
	Control**	32.0	65	50.00	11.37
Education (Years)	**HIV**	6.0	21	14.08	3.66
	Control	8.0	18	14.15	2.97
WTAR	**HIV**	5.0	14	8.69	3.10
	Control	5.0	14	10.08	2.66
HADS Anxiety	**HIV**	2.0	12	6.69	3.199
	Control	-	-	-	-
HADS Depression	**HIV**	1.0	13	5.46	2.961
	Control	-	-	-	-
Recent CD4	**HIV**	24.0	400	178.69	122.296
	Control	-	-	-	-
Nadir CD4	**HIV**	17.0	308	111.15	85.737
	Control	-	-	-	-
Viral Load	**HIV**	40.0	511214	70436.62	144929.720
	Control	-	-	-	-
Years since diagnosis	**HIV**	0.5	24	10.153	9.233
	Control	-	-	-	-

*HIV group = 3 female, 10 male
**Control group = 4 female, 9 male

Table 3. *Correlational analysis of gender and language distribution across groups*

Group	Pearson's Chi-Square	Df	Exact sig. (2-sided)	Phi	Exact Sig.
Gender	.195	1	1.000	-.087	1.000
Language	.722	1	.673	-.167	0.673

Table 4. *Comparison of participant characteristics*

	Mann-Whitney U	Z	Exact Sig. (2-tailed)
Age (Years)	76.00	-.437	.677
Education (Years)	79.500	-.259	.810
WTAR (Scaled)	61.500	-1.187	.246

Table 5. *Effect of primary language on the WTAR and Word Context Test*

	Mann-Whitney U	Z	Exact Sig. (2-tailed)
WTAR (scaled)	39.00	-1.189	.242
Word Context Test (Scaled)	21.00	-2.392	.016

Primary language varied across participants but the ratio was not found to differ between groups (See table 3). In the HIV group, participants whose primary language was English were born in the UK (n=5), Kenya (n=1), Uganda (n=1) and Portugal (n=1). Participants whose primary language was not English, yet presented as fluent, were born in Ghana (n = 1), Nigeria (n = 1), Uganda (n=1) and Ethiopia (n=2). In the control group, participants whose primary language was English were born in the UK (n=9) and South Africa (n=1). Non-primary English speakers were from India (n=2) and Portugal (n=1).

The WTAR and Word Context Test were used across both groups and rely on English language and related-cultural knowledge. Therefore, a Mann-Whitney U test was carried out to explore the relationship between primary language and performance on these tests (see table 5). No concern was noted in terms of primary language and premorbid functioning. However, those whose primary language was English performed significantly better on the Word Context Test suggesting care must be taken when interpreting results based on this test.

Within the HIV group, 11 participants presented with comorbidities including previously diagnosed and treated tuberculosis (n = 2), syphilis (n=2) and C-Diff (n=1). Ongoing comorbidities included Kaposi's sarcoma (n=1) and pain conditions (n = 2). Three participants had previously been treated for depression and remained on medication, and two for substance misuse where treatment had been deemed successful. HADs scores indicated one person met criteria for depression and anxiety (participant 10), and one for anxiety (participant 7); neither of these were being treated for either condition. Within the control group only three participants presented with comorbidities: hyperthyroidism, a pain condition and diabetes.

Time since HIV-positive diagnosis, most recent CD4 count and nadir CD4 count were also collected and are presented in table 2. The most recent CD4 count for each participant depended on testing within the service. Therefore this cannot be relied upon as an accurate measure of illness stage.

3 RESULTS

3.1 Exploratory data analysis

Data were explored within SPSS, firstly to identify errors and secondly to determine distribution of variables and whether they met the assumptions required for parametric analyses. Boxplots and histograms were appraised for outliers and coding errors and any coding problems identified were corrected.

3.2 Exploratory analysis of cognitive functioning within HIV group

Both raw and age-scaled scores were reviewed in the initial exploration of cognitive data. Age-scaled data were used for final analysis, since it accounts for age-related variance in neuropsychological performance. However the Brixton lacks age-stratified norms; this must be noted when interpreting the following data. Descriptive statistics and the Kolmogorov-Smirnov (KS) test were used (see table 6) to explore the HIV-positive group's performance on the cognitive battery and assess whether distribution of scaled scores within the group matched age-scaled normative data (Mean = 10, SD = 3).

Inspection of mean age-scaled scores for each subtest within the HIV group indicates a profile of impaired functioning across all domains. Mean scores for the visuospatial RBANS tests (Figure Copy and Line Orientation) lie closer to the normative mean of ten. Additionally performance on Similarities, Matrices Reasoning and Spatial Span, while weaker than the visuospatial domain, also lie within one standard deviation of the normative mean.

KS results indicate that apart from Figure Copy and Line Orientation, which fell into the normative range, participants' scores were significantly lower than the normative sample on all tests of cognition. This is to be expected in an HIV-neurologically impaired population, where visuospatial processing is often found

to remain relatively intact. Although significantly different to normative data, KS scores indicated that performance on a few tests was less substantially impaired than others. Reported in order of increasing difference from the normative, these tests were Similarities, Picture Naming, Matrices Reasoning and the Brixton. Performance on these tasks link to visuospatial skill, language and single trial concept formation, skills required in the Brixton.

Table 6. *Descriptive statistics and distribution of current functioning in HIV group compared to normative data (Mean = 10, SD = 3)*

	Mean	SD	Min	Max	Kolmogorov-Smirnov	p
RBANS List Learning	4.31	2.529	1	9	2.479	.000
RBANS Story Learning	4.31	1.888	2	8	2.756	.000
RBANS Figure Copy	8.92	4.368	1	14	.887	.411
RBANS Line Orientation	8.62	4.134	3	15	1.214	.105
RBANS Picture Naming	6.77	4.604	1	12	1.613	.011
RBANS Coding	2.15	1.345	1	5	3.433	.000
RBANS Digit Forward	6.46	2.634	2	11	1.996	.001
RBANS List Recall	3.75	3.306	1	11	2.519	.000
RBANS Story Recall	4.08	2.712	1	9	2.433	.000
RBANS Figure Recall	6.33	2.387	3	11	2.337	.000
RBANS List Recognition	4.75	4.938	1	12	2.231	.000
DKEFS Letter Fluency	5.46	2.222	1	9	2.479	.000
DKEFS Category Fluency	4.00	3.109	1	9	2.418	.000
DKEFS Switching Total	3.69	3.881	1	12	2.722	.000
DKEFS Switching Accuracy	4.31	4.289	1	12	2.183	.000
WAIS Similarities	7.83	3.380	3	15	1.471	.026
WAIS Matrices Reasoning	7.33	2.309	4	12	1.723	.005
WMS Spatial Span	7.17	1.586	5	9	2.184	.000
Brixton	5.18	3.628	1	10	1.790	.003
DKEFS Word Context	3.85	3.262	1	11	2.722	.000

3.2.1 Contribution of executive function to HIV group Brixton performance

Multiple regression was used to compare the relative contribution of visuospatial perception (Figure Copy), visuospatial memory (Spatial Span) and verbal multiple trial concept formation (Word Context Test) to Brixton performance (see table 7). No significant relationship or predictive value was found for any predictor variable.

Table 7. *Multiple regression of predictor variables and Brixton performance*

Predictors	B	Std. Error	ß	t	Sig.
Figure Copy	-.222	.304	-.314	.728	.494
Spatial Span	-.305	.880	-.140	-.347	.740
Word Context	.421	.381	.425	1.103	.312

3.3 Group comparison - measures of induction

A Kolmogorov-Smirnov test was carried out on control group data to assess whether they performed within the normative range (see table 8). The results indicated that control group performance matched the normative distribution for the Word Context Test but not the Brixton. The distribution curve for the control group's Brixton performance was higher than the norm. This suggests visuospatial induction was superior to verbal-based induction within the control group. This needs to be taken into account when interpreting the following data.

Tables 9 and 10 present descriptive statistics and Mann-Whitney U test results for the HIV and control group on tests of induction. Two participants in the HIV group did not complete the Brixton due to reports it was too difficult for them to finish. Therefore percentages of correct answers out of total trials completed were calculated (see table 9) so as to include all participant data. Percentage scores are not adjusted for age and therefore must be interpreted with caution. The results (table 10) indicated that the control group scored significantly higher

on Word Context Test scaled scores, and Brixton scaled and percentage scores. The effect size (Z scores) for both tests were similar across tests also.

Table 8. *Descriptive statistics and distribution of Control Group performance on tests of Induction compared to normative data*

	Mean	SD	Min	Max	Kolmogorov-Smirnov	p
Brixton (scaled)	12.31	2.594	8	16	1.586	.013
Word Context (scaled)	11.23	2.651	7	16	1.055	.216

Table 9. *Descriptive statistics of performance on tests of induction for both groups*

	Group	Mean	SD	Min	Max
Brixton (Scaled)	HIV	5.18	3.628	1	10
	Control	12.31	2.594	8	16
Brixton (Percentage)	HIV	51.30	13.342	29	69
	Control	77.22	9.652	62	91
Word Context (Scaled)	HIV	3.85	3.262	1	11
	Control	11.23	2.651	7	16

Table 10. *Comparison of group performance on tests of induction*

	Mann-Whitney U	Z	Exact Sig. (2-tailed)
Brixton (Scaled)	9.500	-3.613	.000
Brixton (Percentage)	13.000	-3.674	.000
Word Context	8.000	-3.954	.000

3.4 Componential Analysis of Brixton performance

Qualitative appraisal of Brixton performance started during testing. Early on it became apparent that three areas could be coded separately when exploring the compiled data, to elucidate different aspects of performance across the groups:

- Assessment of performance across the Brixton as a whole exploring abilities expected by the task, including rule detection and switching to further rules (referred to as 'overview').
- Assessment of specific errors made (error-by-error) and underlying processes/strategies used to arrive at this answer (referred to as 'reasons underlying errors').
- Assessment of patterns of responding across the test, other themes not obviously noted as part of the test (referred to as 'anything else').

Themes and strategies that were coded consistently across tests were compiled into a scoring system through which all tests were re-marked (see Table 11). An example of the general Brixton scoring form is provided in appendix R, followed by an example of a completed Brixton test scored using the new componential system (appendix S). It was decided that codes should not go 'beyond the description' (Wittgenstein, 1958) of observed behaviour, to limit the level of interpretation necessary at this stage. Therefore, for example, 'misapplication of strategy' was not utilised, as 'reverting to a previous rule' appeared to better describe performance. Also 'bizarre' was not utilised as a final code as the participant may have utilised a strategy that was not observable to the researcher; instead the term 'no observable strategy' was used.

Table 11. *Codes noted in componential analysis and methods of measurement*

Themes and codes	How measured	Additional information
Overview		
1. Rule acquisition	Number of rules acquired out of 6	-
	Number of sets acquired out of 9	-
1a. Speed of rule acquisition (could also reflect speed of shift).	Number of trials taken to acquire rules in total	Add up all errors within a set until two consecutive correct answers indicate rule is acquired (if rule never acquired all trials within that set will be counted)
2. Shifting	Number of shifts achieved out of the 8 required in the test	-
3. Rule following - Set-loss	Number of times a set is lost after rule acquired	Add up all times an error is incurred part way through the set (this is the total).
3a. Reasons for set-loss	Set-loss due to participant anticipating rule change	Trials participant verbalized they expected the rule to change
	Set-loss due to participant not managing 1-10 shift or vice versa	On trials 11, 24, 27 & 30 the circle reaches the end of the line, add number of times error occurs on these trials.
	Set-loss due to participant reverting to 10-5 rule	On trials 24, 28, 30, 35, 37, 39 & 41 (after set 3), add up times participant reverts to this rule when another 10 or five is shown.
	Set-loss not accounted for by another observable reason	-
3b. Regaining set	Number of times they manage to regain set immediately after losing set	Add the number of times a set-loss if followed by a correct response.
Exploration at the single error level		
4. Total errors	Total number of errors	This is also the raw score
4a. Perseveration	Number of trials participant perseverates with the previous set rule after pattern changes	-
	Number of repeated answers	Add the number of times participant repeats answer. Does not include repetition of number 9 in rule 5 (set 8)
4b. Reverting to a previous rule	Number of times errors link to use of a previous rule	Guessing trialling previous rule (e.g. -1, +1, 10-5)
4c. 1-10 shift	Number of times errors link to 1 to 10 shift	This may be different to set-loss section as errors may not have led to set-loss.
4d. Response capture	Number of times error is the person saying the number on the page	Do not monitor this response in rule 5 (set 8)
4e. No observable strategy	Number of answers that have no strategy obvious to observer	-
Themes emerging linked to patterns of responses		
5. Monitoring	Number of trials participant did not realise the rule had changed and continued responding to previous rule and stimulus. Did not realise responses wrong.	If a pattern of responses occur which do not link to visual stimuli but to the participant's previous response (e.g. says 7, 8,9,10 when pattern changed after 7) add up these trials.
	Numbers of trials participant continues to use an incorrect strategy when visual stimuli indicate strategy is wrong.	If a pattern of incorrect strategy use occurs (e.g. using +1 strategy repeatedly with incorrect answers) add up number of trials after pattern initiated.

Table 12. *Descriptive statistics of performance on the Brixton test across groups*

Theme	Measure	Group	Mean	SD	Min	Max
1. Rule detection	**Rules acquired (out of 6)**	HIV	3.46	1.808	1	6
		Control	5.85	.376	5	6
	Sets acquired (out of 9)	HIV	5.31	2.658	1	9
		Control	8.85	.376	8	9
1a. Speed of acquisition	**Total trials to acquire rules**	HIV	25.36	10.122	12	39
		Control	10.38	5.268	4	18
2. Shifting	**Shifts achieved (out of 8)**	HIV	4.08	2.691	0	8
		Control	7.85	.376	7	8
3.Sets Lost	**Number of sets lost**	HIV	1.82	1.537	0	5
		Control	2.23	1.092	1	5
3a. Set-loss reasons	**No observable reason**	HIV	.64	.809	0	2
		Control	.23	.439	0	1
	Anticipation	HIV	.18	.405	0	1
		Control	.77	1.092	0	4
	1-10 shift	HIV	.64	.809	0	2
		Control	1.08	.494	0	2
	10-5 rule	HIV	.36	.505	0	1
		Control	.15	.376	0	1
3b. Sets regained	**Number sets regained**	HIV	.91	1.044	0	3
		Control	1.38	.650	1	3
4. Total Errors	**Total errors**	HIV	25.91	7.463	17	39
		Control	12.54	5.301	5	21
4a. Perseveration	**Perseveration with rule just finished**	HIV	6.18	9.837	0	33
		Control	2.54	1.984	0	6
	Repeated answers	HIV	3.00	2.324	0	7
		Control	.85	1.144	0	4
4b. Reverting previous rule	**Revert to previous rule**	HIV	6.09	3.081	0	11
		Control	5.69	2.594	3	10
4c. 1-10 shift	**1-10 shift**	HIV	.64	.809	0	2
		Control	1.46	.776	0	3
4d. Response capture	**Saying number on the page**	HIV	.31	.630	0	2
		Control	0	0	0	0
4e. No Strategy	**No observable strategy**	HIV	10.91	10.397	0	35
		Control	2.38	2.022	0	6
5. Monitoring	**Did not realise rule change/answer**	HIV	1.08	.954	0	4
		Control	.08	.277	0	1
	Continued incorrect strategy	HIV	4.64	5.732	0	20
		Control	2.25	2.050	0	7

3.4.1 Overview:

Descriptive statistics of the componential analysis are in table 12. As the control group scored significantly higher than the normative population it was noted that this should contrast sharply with the lower performance of the HIV group. Information pertaining to each code will be provided first, followed by control group performance, as this was gathered to create a benchmark of performance to which the HIV group could be compared.

1. Rule detection

The overarching theme 'rule detection' was based on three separate codes, rules acquired, sets acquired, and speed of acquisition. The Brixton requires detection of rules across 55 trials. There are six new rules to detect, two of which are repeated (one once, the other twice) to make up nine sets; therefore number achieved by participants was counted.

Speed of rule acquisition across the test was measured through the total number of trials (errors) taken to acquire each rule across all nine sets. If people acquired the rule immediately after the pattern shifted no trials were added to the count. If no rules had been acquired the total number could reach 54. An average speed across tests (i.e. total number of trials to acquire rule divided by number of rules) was not used due to variance in number of trials per set (ranging from 3 - 8).

All control group participants achieved the first rule and detected the majority of the 6 novel rules and 9 sets. These findings suggest excellent rule detection. Speed of acquisition was also quick as participants in the control group acquired the first rule in the first trial. As no other measure of this has been completed elsewhere, the number of trials taken to acquire all sets in this group was selected as the benchmark of 'good' within this study.

All members of the HIV group also achieved the first rule in the first trial, suggesting good rule detection at the simplest level. Subsequently however, they detected fewer new and repeated rules than the control group and their detection was slower. Acquisition speed could also represent facility in switching set.

2. Shifting

To achieve high marks in the Brixton, examinees must not only detect and follow rules but also shift (or switch) between new and old rules. Therefore the overarching theme of shifting was derived through the number of switches achieved across the test.

The control group achieved near perfect shifting, suggesting no difficulties. The HIV group achieved fewer shifts suggesting lower switching ability, and also displayed increased variance across the group. For example, one participant in the HIV group did not manage any switches, instead utilising the first rule across the entire test even though the visual stimuli indicated change was needed.

3. Set-loss

Occasionally, participants suddenly gave an incorrect answer after having shown they had managed to acquire and follow the set's rule. This was referred to as 'set-loss' and was based on five related codes. Four of these related to qualitative aspects of set-loss and one to regaining set. Specifically, one code linked to a pattern of set-loss arising when the circle reached an extremity (i.e. named the '1-10 shift' by the researcher, see appendix T for an illustrated example). Another code linked to times when participants were shown the circle in position ten (following set 3) and would erroneously revert to the 10-5 rule (see appendix D). Furthermore, some participant's pre-empted set-loss (coded as 'anticipation') by saying the rule was about to change and therefore they needed to change their answer. Other times 'no obvious reason' was noted, and was therefore coded as such.

In the control group, participants lost at least one set. The pattern of set-loss errors from most common to least common was the '1-10 shift', followed by 'anticipation', 'no obvious reason', 'reverting to the 10-5 rule'. This suggests set-loss occurs within the 'above-normal' population, at least within this study. Most commonly this occurred due to erroneous attribution of certain numbers as indicators of pattern change and anticipation of rule change. When set-loss did occur, they regained set immediately approximately half the time.

Slightly fewer sets were lost within the HIV group than the control group. As they achieved fewer sets overall the mean score may not be directly comparable. The pattern of set-loss errors followed: 'no obvious reason', '1-10 shift', then '10-5 rule' and finally 'anticipation'. The group also regained approximately half of all sets lost.

In order to compare the groups more directly, and adjust for number of sets gained in total, the proportion of sets-lost of sets-gained were calculated (table 13). Visual appraisal of the mean proportions indicate the HIV group lost a slightly higher percentage of acquired sets than the control group.

Table 13. *Proportion of sets gained that were subsequently lost*

	Group	Mean	SD	Min	Max
Sets lost out of sets gained	HIV	.29	.291	.00	1.00
	Control	.23	.115	.11	.55

Note. Max score of 1 indicates a participant losing all sets of sets gained.

Overall, it is hard to compare this section entirely. However, qualitatively it appears that set-loss may be normative, generally occurring through mechanisms other than spontaneously 'falling-off' task. In the HIV population spontaneous loss may explain set-loss slightly more frequently than in the control group.

3.4.2 Reasons underlying errors

In addition to ability to detect and switch rules, errors made by participants were explored and qualitatively interpreted. Error styles appeared to cluster under five main themes: 'perseveration', 'reverting to a previous rule', 'the 1-10 shift', 'response capture' and 'no observable strategy'. The Brixton total error score acts as the overall raw score, and the scaled scores based upon these numbers had already yielded a significant difference between these groups.

Error type 1. Perseveration

Perseveration was noted across all participants, in the form of utilising and not shifting from the rule used in a just finished set (participants applied the rule to whichever position the circle had moved to, code 1), and repeating the answer previously given (code 2 for this theme). Number of total trials where perseveration of a rule could occur, could total up to 33 times (if a participant used the same rule all the way through, they would be wrong 33 times because set 1 rule reappears in sets 4 and 6), while perseverative answers could occur 54 times.

Perseveration with the rule just finished, and repeated answers, occurred within the control group at a very low level. In the HIV group perseveration was higher for both aspects.

Error type 2. Reverting to a previous rule

It was often noted that participants would trial a previous strategy while trying to identify the new rule or attempting a guess, leading this to become an overarching theme. If the rule was not acquired, participants might keep trialling that rule or another. Rules that participants' trialled were most often the rules from set 1 (add one to the number on the page), 2 (remove one from the number on the page) and 3 (alternate between the numbers 5 and 10).

In the control group, reverting to a previous rule made up the main error type. In the HIV group this occurred a similar number of times, but due to the group's higher number of overall errors this did not constitute the majority of error types.

Error type 3. 1-10 shift

The '1-10 shift' caused changes in patterns of guessing across both groups as mentioned in the section 'set-loss'. This did not always cause people to lose set as it also occurred at times when the set had not been gained or was already lost. In the control group this error occurred slightly more than the HIV group.

Error type 4. Response capture

This was the least noted error type and did not occur in the control group. In the HIV group four people said the number of the circle on the page rather than predicting the future trajectory of the circle (within sets where the circle was continuously moving and not static).

Error type 5. No observable strategy

Answers were coded together if they did not link to another response type or, in no perceptible way, the stimulus array. In the control group this occurred at a low rate. This was however, the main error type within the HIV group.

3.4.3 Additional information about errors

Another feature of responding occurred across this test. This linked to participants' monitoring of the visual information presented. These were not included in the specific error types above as they were derived from consideration of patterns of responding. They were also considered to reflect an additional componential feature of executive functioning necessary for this task.

Monitoring

Monitoring comprised two codes. The first code described a pattern across tests that suggested participants had not noticed a rule change. This was deemed to occur when an individual's response continued on from their previous answers and did not link to the stimulus array on the test. For example, on occasion participants following rule 1 (circle moves forward by one on each trial) would state the position of the circle as moving from position 1 to 2, then 3, 4, 5, 6 and 7. Then as the set changed and rule 2 was required (circle moves backwards by one on each trial) the participant continued stating the circle will move to 8, then 9 and so on.

The second code linked to times when an incorrect strategy was repeated despite visual evidence that the strategy was not working. These two codes could have counted as perseveration but were located within monitoring as participants

generally verbalised their surprise after they realised the rule had changed. They would not then self-correct previous errors but would instead shift to a new, more appropriate, strategy.

Failure to monitor the stimulus array was low within the control group (only one participant failed to notice the rule shift - they self-corrected one trial later). Continuing with an incorrect strategy was slightly higher but still remained low.

The HIV group appeared to have difficulties with monitoring the stimulus and their answers within the task. For example, except for one participant, all participants failed to notice the shift in pattern at least once. Continuing with an unsuccessful strategy also occurred more often in the HIV group than the control group.

To summarise, multiple differences were noted between the groups suggesting that at the group level it was possible to identify components contributing to impaired performance in the HIV group, including slowed shifting, perseveration and reduced monitoring.

3.5 Individual Profile Analyses of Brixton performance

Individual case analysis, which allows exploration of within-group data, was used to identify whether a profile of deficits existed within the HIV group. Profile of performance for each participant was inspected and compared to the mean performance of the control group. Age and comorbidities were also considered when looking at profiles (see table 14). Bar charts for each participant are shown in figures 1-7.

Table 14. *Age and comorbidities present in the HIV group*

Participant	Age	Comorbidity
1	38	Treated TB. Depression treated with antidepressants.
2	46	None.
3	50	Treated TB. Depression treated with antidepressants.
4	58	Treated Syphilis.
5	65	Treated Syphilis.
6	49	NSTEMI. G6PD.
7	65	COPD. Kaposi's Sarcoma.
8	49	Treated C-Diff
9	56	None.
10	40	History of substance misuse.
11	61	HIV encephalopathy.
12	47	Back pain. Treated stomach ulcer.
13	44	Leg pain. Treated toxoplasmosis. History of substance misuse. Depression treated with antidepressants.

Figure 1. *Counts for the control group (mean) and HIV participants 1 - 2*

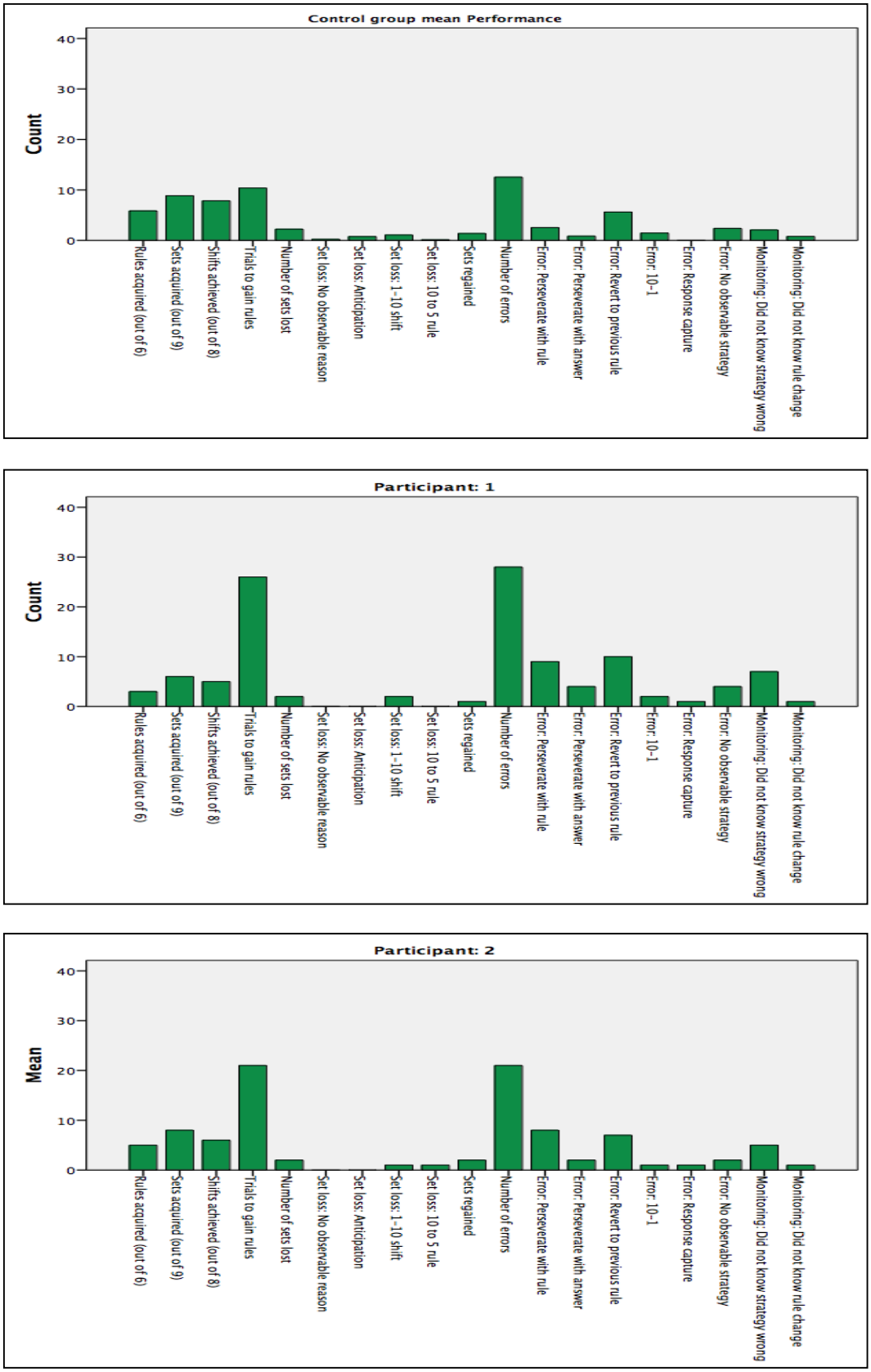


Figure 2. *Counts for the control group (mean) and HIV participants 3 - 4*

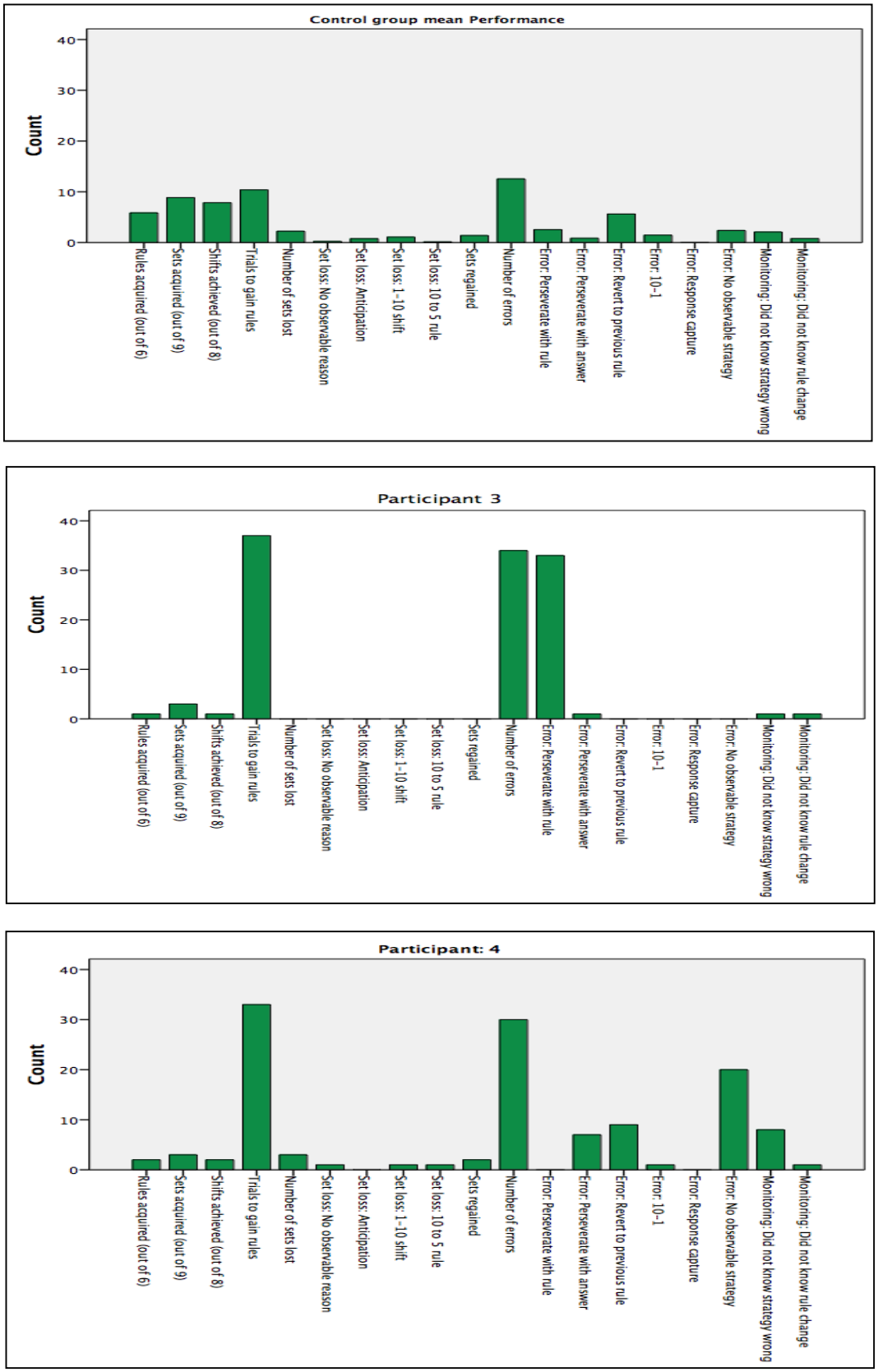


Figure 3. *Counts for the control group (mean) and HIV participants 5 - 6*

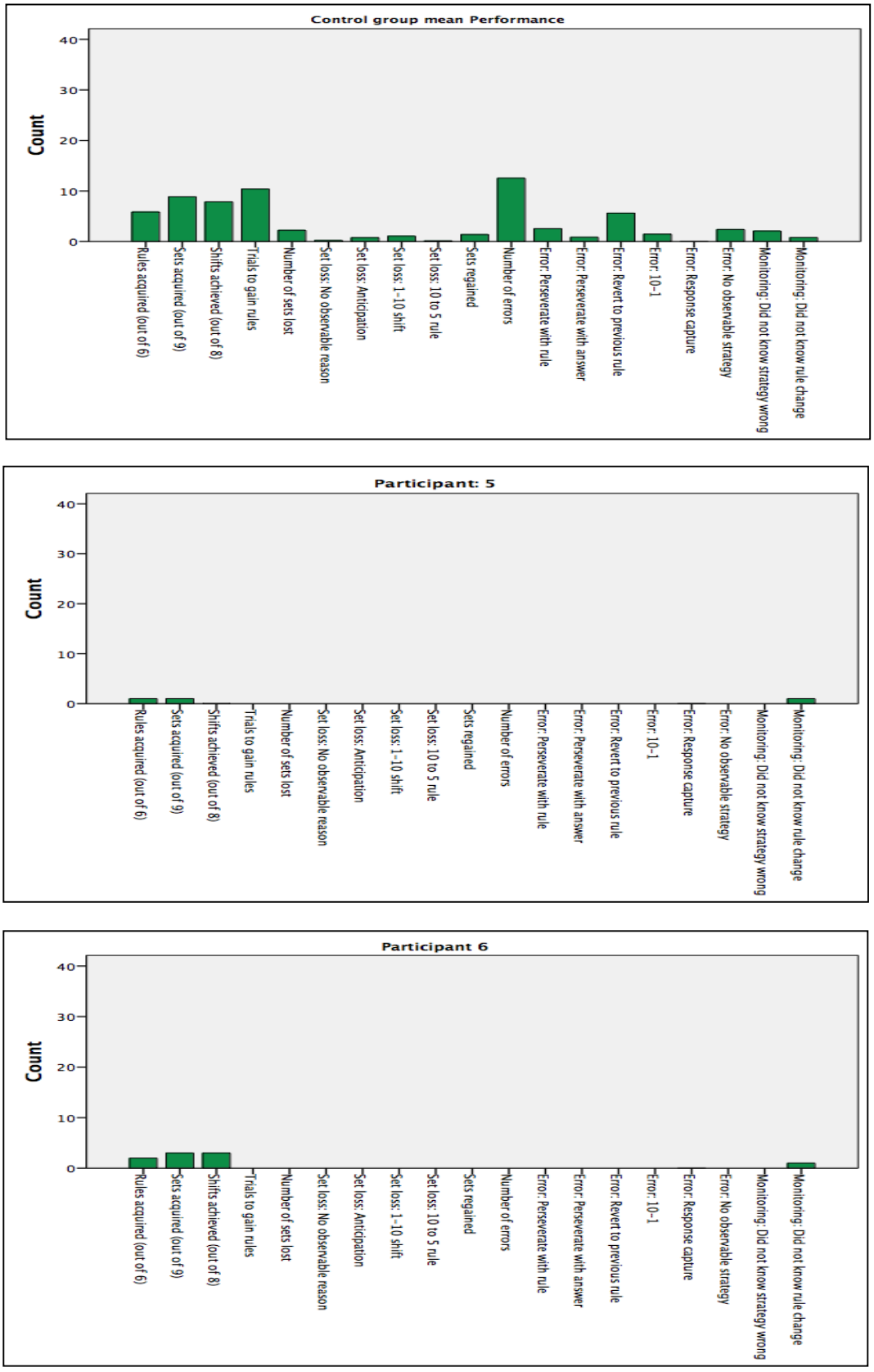


Figure 4. *Counts for the control group (mean) and HIV participants 7 - 8*

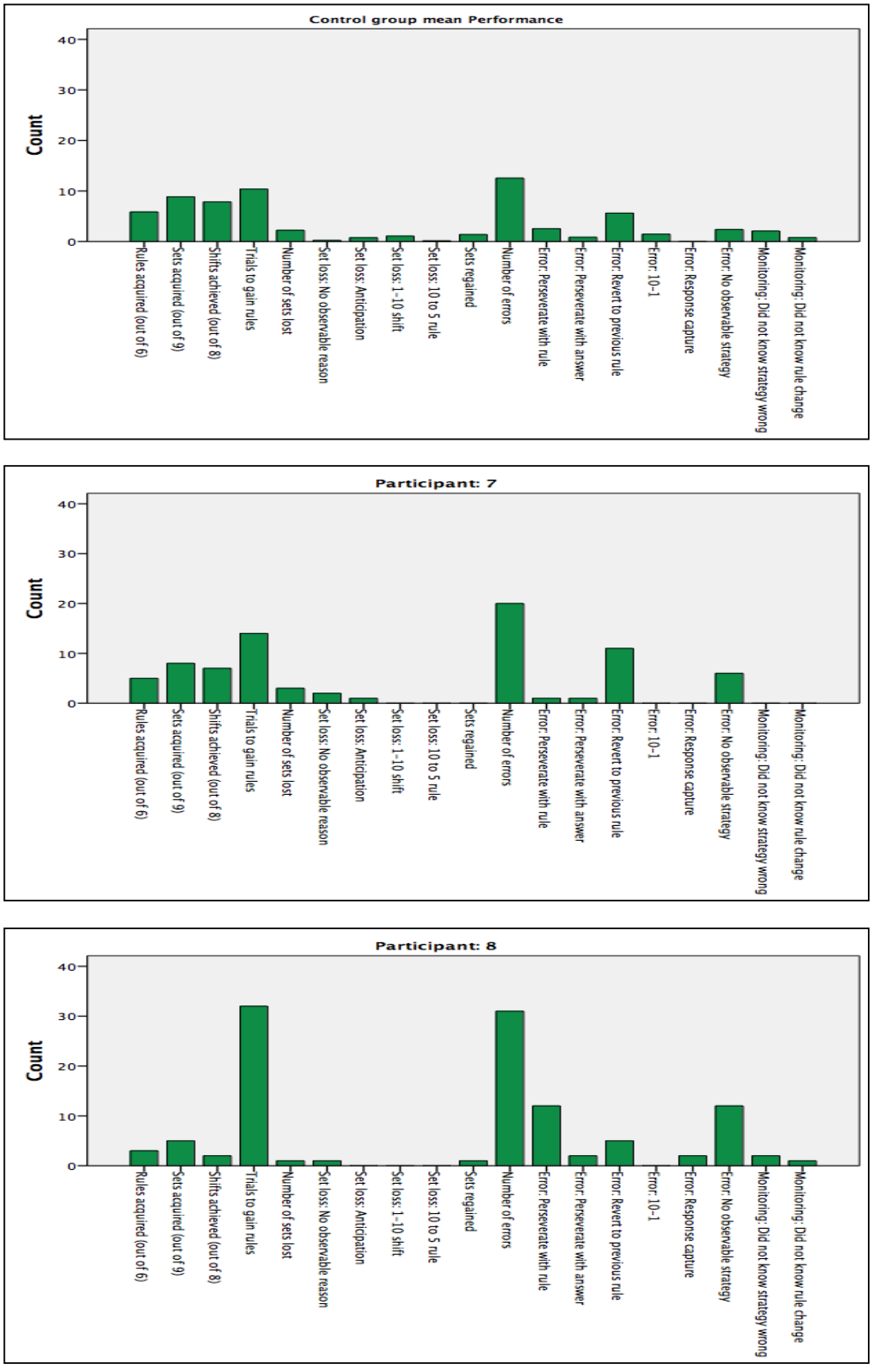


Figure 5. *Counts for the control group (mean) and HIV participants 9 - 10*

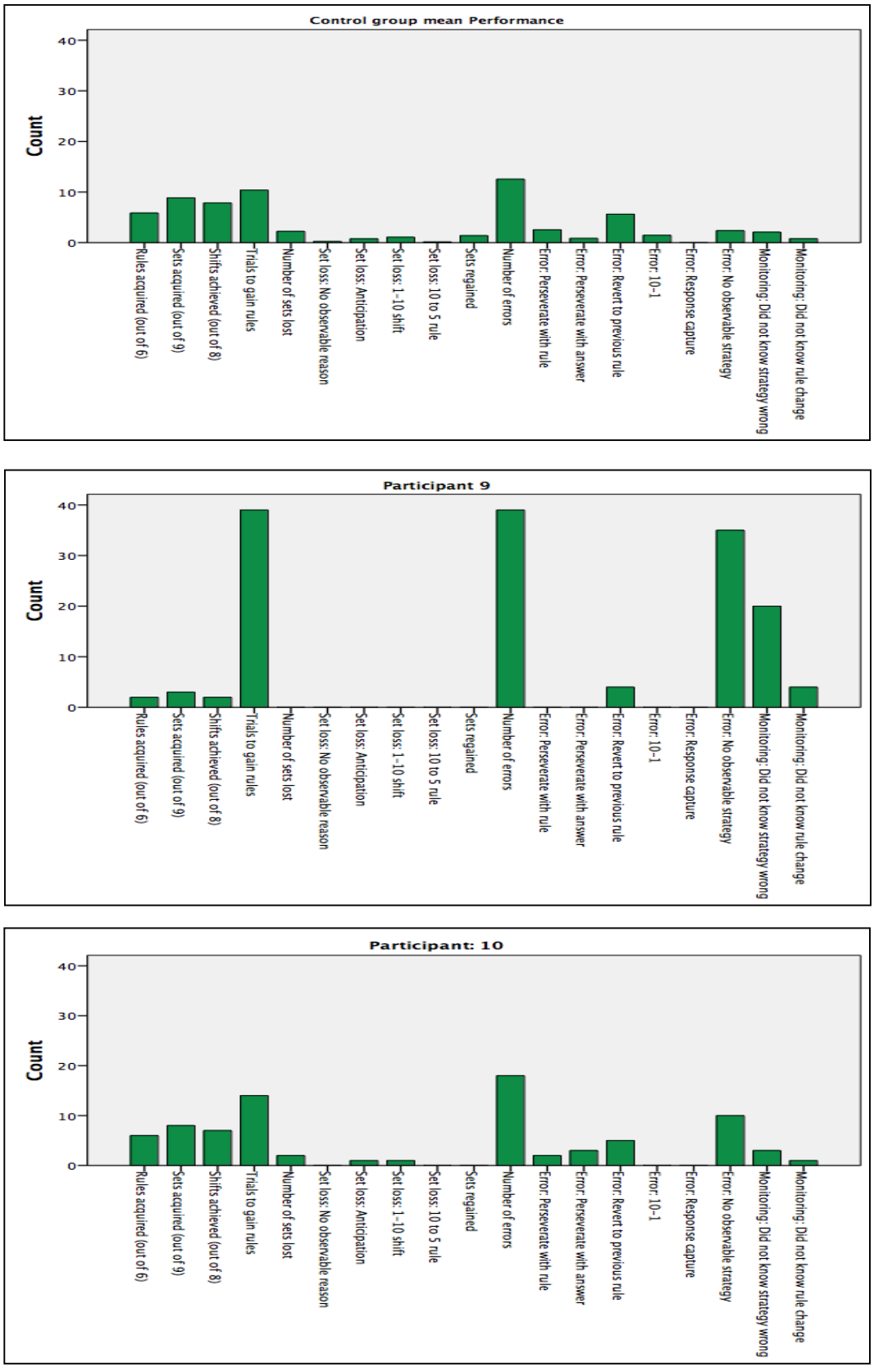


Figure 6. *Counts for the control group (mean) and HIV participants 11 - 12*

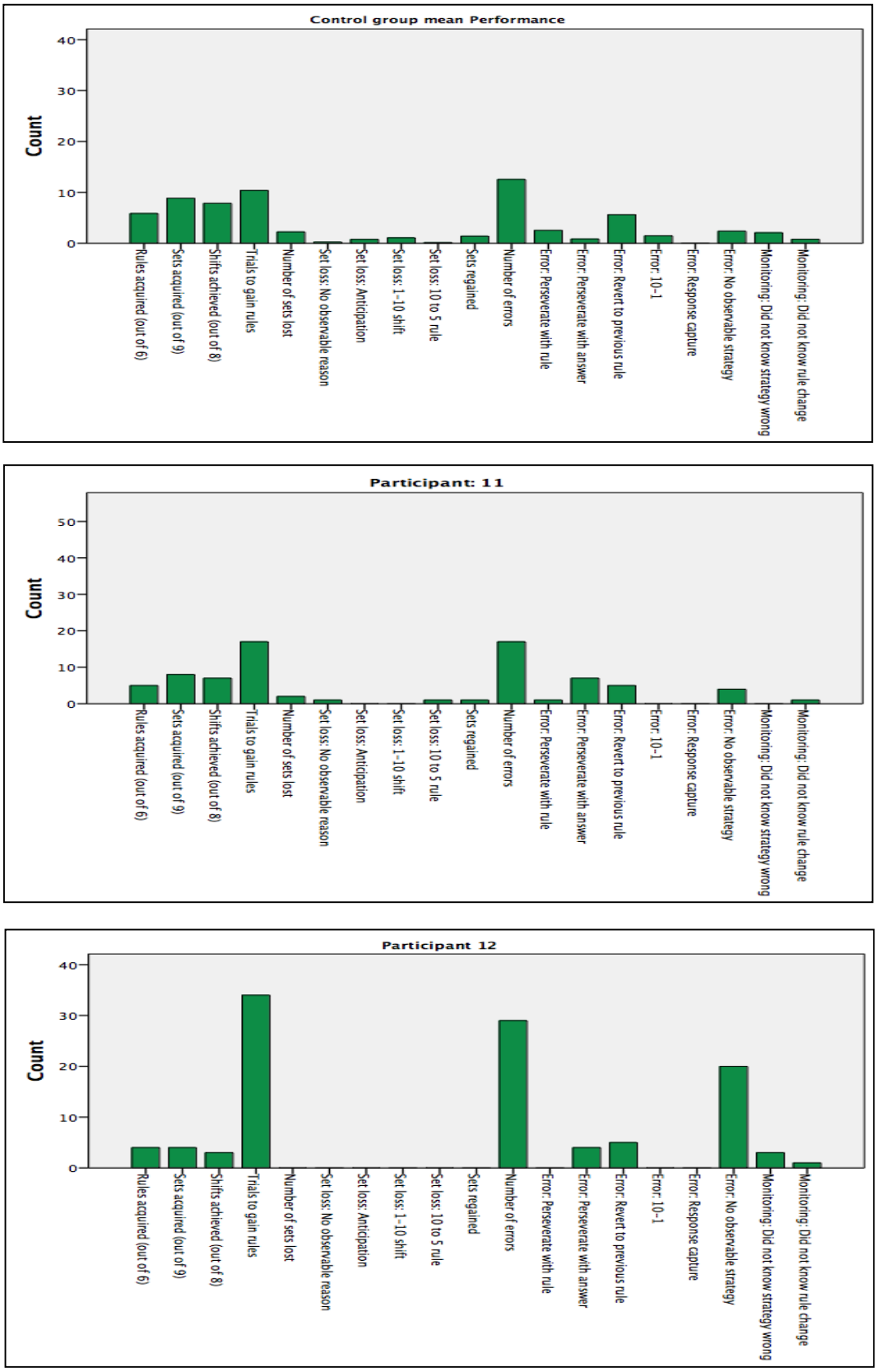
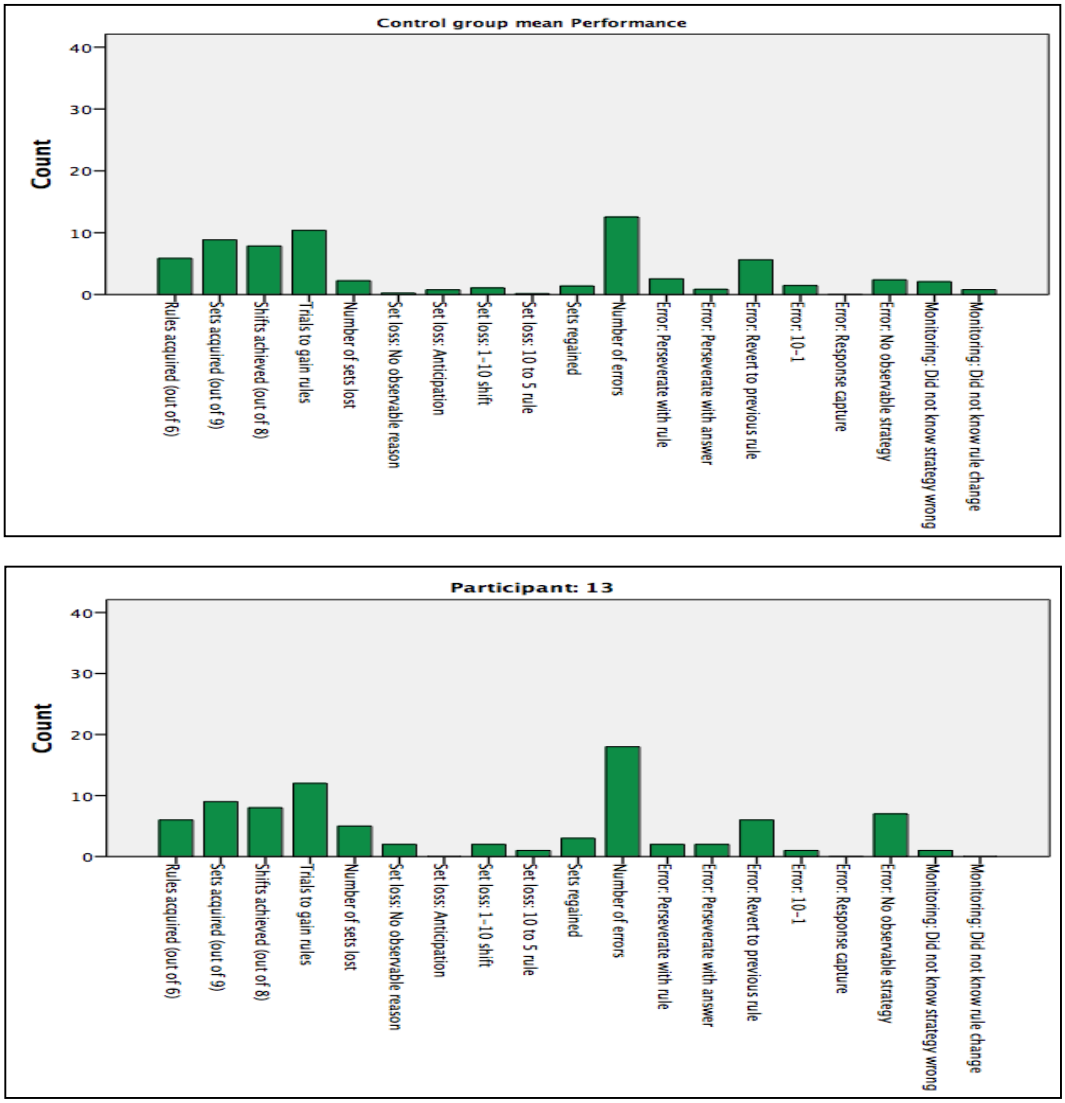


Figure 7. *Counts for the control group (mean) and HIV participant 13*



Inspection of individual profiles highlighted the variance in performance across the group. Participants 5 and 6 did not complete the task. The charts illustrate the number of sets they acquired of the proportion they managed. All other participants' data were completed. Despite the heterogeneity of counts and profiles, there were general themes across the participants' performance. The graphs indicate that:

1. Except for participant 13, the HIV group gained fewer rules and sets than the control group (mean). Participants 7, 10 and 11 performed close to the control group (mean) gaining one less rule and set. All other participants performed below this level.

1a. All participants took more trials to acquire rules than the control group (mean), suggesting slowed speed.

2. Except for participant 13, the HIV group all managed fewer shifts than the control group (mean). Participants 7, 10 and 11 were again closer to the control group (mean), managing one less switch than them. All others performed below that number.

3. No distinct pattern exists for set-loss since a wide level of variance was seen in participant profiles:

3a. Not all participants lost set in the HIV group, it occurred in 8 cases. There was no specific profile of loss consistent across all losing set. However, sets were mostly lost due to no observable reason and then the 1-10 shift, resembling the pattern found at the group level. Interestingly, those performing closer to the control group (participants 7, 10, 11, 13) lost at least 2 sets. Those who did not lose a set generally had an overall profile of impaired performance, for example in rules and sets acquired, and shifts attained (e.g. Participants 3 and 9).

3b. There did not appear to be a profile linked to regaining set. However, apart from participant 10, all participants who lost set regained at least one immediately.

4. Number of errors made was consistently higher in HIV individual profiles than the control group (mean), suggesting lower performance across the board. However the following was noted:

4a. Perseverating with a previous rule happened at least once across all participants apart from participants 4, 9 and 12 (whose profiles were predominantly made up of no observable strategy error types). However this did not always occur above the control group (mean).

4b. Except for participant 9, perseverating with a previous answer occurred in all individual profiles. Except for participants 3 and 7 (who had the same count as the control group) this occurred more frequently than the control group (mean).

Reverting to a previous rule, which occurred in all participants except participant 3, was consistently noted across the group, however, this was not always higher than the control group (mean).

4c. The 1-10 shift only caused errors in participants 1, 2, 4 and 13.

4d. Response capture only occurred in participants 1, 2 and 8.

4e. Except participant 3, who utilised the same rule throughout, errors with no observable strategy were consistently counted across all profiles more times in HIV participants than the control group (mean).

5. Aspects of performance linked to monitoring were common within the HIV group:

Except for participants 7 and 13, all had at least one trial where they had missed a rule change. HIV participants did not have consistently higher counts than the control (mean). However, within the control group only one participant had performed this kind of error, while in the HIV group this was noted in almost every individual profile.

Continuing with an incorrect strategy was not a consistent profile across the HIV group, however when it did occur the count was consistently higher than the control group (participants 1, 2, 4, 9, 10, 12).

In summary, there was not a distinct profile (observable when viewing individual summaries) that was consistent across all variables. However, some performance styles were consistent and seen across the group even when participants performance was less impaired.

With regard to age and comorbidity, no relationship was seen between either variable and performance profile. Two examples of this include: 1) participant 13 (who performed closest to the norm) presented with four comorbidities, and was 47 (near the mean age of the group); 2) Participant 11 who also performed close to the norm had one comorbidity but was 61 (the older end of the age range).

4 DISCUSSION

A plethora of evidence exists documenting executive dysfunction within HIV-positive populations diagnosed with HAND. Little exists, however, looking at the componential processes underpinning these deficits. This study aimed to address this research gap. Specifically, it aimed to investigate an aspect of executive functioning known as induction, or multiple trial concept formation; to assess whether it is impaired in HAND and furthermore, what mechanisms if any are responsible for decreased performance. This required quantitative and qualitative analyses of a well-known test of induction, and therefore production of a novel scoring system. Findings and their implications will be discussed within this chapter.

4.1 Summary of results

4.1.1 Participant related variables

Two groups of participants were recruited to this study, to create comparable subsets of individuals on tests of induction. The groups were well matched on demographic variables (age, gender, number of years in education and reading ability). Participants' age ranges and gender ratio mean the study's findings describe and relate most closely to cohorts of PLWH who are male and in the middle age ranges. Apart from gender, the other demographic factors controlled for in this study are known to contribute to neuropsychological test performance which suggests they should not be responsible for between group differences. Despite this, the control group, while not reliably different from the patient sample, showed a trend towards increased ability as measured by the WTAR.

Furthermore, in the HIV group there was an increased number of people not educated within the UK, or not brought up with English as first language (language was not reliably different across groups). Performance on the Word Context Test differed by primary language, suggesting these results need

cautious interpretation. This was not the case for the WTAR however, suggesting language was not responsible for differences seen. Therefore, exactly matched years of education but slightly differing reading ability may instead support the notion that years of education do not describe quality of teaching, making it a less accurate predictor of subsequent learning and ability (Manly et al., 2002). Alternatively, it could suggest that reading measures present terminology not relevant to people born outside of the culture in which it was developed. Finally, premorbid tests work on the notion that reading ability remains relatively spared during neurodegeneration. If reading ability was impaired in this group, premorbid functioning will not have been accurately represented in this study.

The HIV group

Viral load counts within the HIV group suggest a mix of illness severity within patients, however CD4 counts suggest high levels of immunosuppression and illness. For example, seven people would have met criteria for AIDS-defining illness (<200 CD4 cells per cubic millimetre of blood; Castro et al., 1993). Two patients were on the cusp of this (at 200) and all others clustered near this mark. The discrepancy between viral load and CD4 count suggests those with low viral load and low CD4 count (n=3) had been successfully treated at the viral level, but their CD4 had yet to replenish its numbers. This would indicate they were recovering. Therefore these findings will best illustrate performance of those considered medically unwell rather than those considered well with good viral load and CD4 count. Relationship between performance and illness related variables were not assessed, as counts were collected at varying distances from the testing day, suggesting they could be best used as rough guides to illness status rather than reliable variables.

Comorbidities were present in all patients except two within the group. While three were receiving treatment for low mood, two different participants were suggested to have high levels of anxiety and depression as measured by the HADS. These comorbidities should be considered when interpreting the reliability the findings.

General cognitive functioning within the HIV group was found to be impaired in all areas assessed within this study apart from visuospatial functioning. Impairments noted were distributed across the population in a way that differed from the normative population, suggesting impairments generalized across the group. These findings conform to literature indicating relative sparing of the visuospatial domain and related lobes in HAND (e.g. Heaton et al., 1995). It also suggests the sample are representative in terms of the population we hoped to assess. Patients were not further categorised into stage of HAND, in part due to the exploratory nature of the study but also due to the contentious nature of the categories.

4.2 Question 1. Is induction disrupted in HAND when compared to a non-clinical population?

4.2.1 Induction in the HIV group compared to normative data

Measures of concept formation, both single trial (Similarities and Matrices Reasoning) and multiple trial (Brixton and Word Context Test), were also impaired compared to normative populations in terms of average scores and the distribution of performance across the group. Induction requires attention and information processing, short-term memory storage and abstract reasoning. These abilities when assessed in the general battery were all reliably impaired however, single trial concept formation and visuospatial memory (spatial span) were relatively preserved when comparing performance to normative scores. When comparing distribution of performance in the HIV group to normative distributions, single trial concept formation remained relatively spared. Brixton performance was also relatively spared but to a lesser extent (visual multiple trial concept formation).

Multiple regression found there was no predictive value of visuospatial perception, working memory or verbal concept formation on Brixton performance. This suggests Brixton test scores reflect the Brixton's test properties alone. Lack of relationship between the Word Context Test and the Brixton is surprising, as

their shared assessment of multiple trial concept formation is not reflected in this result. This could mean Brixton performance was not due to participant's inductive ability. Alternatively, it could reflect the different qualities of the tests linked to language, cultural specificity, or another component suggesting the tests are philosophically linked but not reliably associated.

Overall, this data suggests that induction is affected in HAND and is not solely due to general impairment in functions known to contribute to induction. It does not suggest it is the most affected function however. It also indicates that concept formation is still possible within the group particularly when single instances are necessary to abstract relationships in information (i.e. all information needed to infer relationships is provided at one time). Visuospatial sparing in terms of perception may suggest induction would improve when linked to visuospatial information. However, the different tests of single trial concept formation did not illustrate this, with improved performance noted on the verbal test (Similarities) over visual (Matrices Reasoning).

4.2.2 Induction in the non-clinical population

In order obtain a matched sample, a cross-section of individuals were recruited to the control group. Overall their years in education and reading ability suggests the group represented a wide variety of people (i.e. with limited to high levels of education), akin to experience within the patient group, with their mean abilities falling within the average range. It was hoped they would represent an average to which the HIV group could be compared.

Only multiple trial concept formation was assessed within the control group. Following the model of inductive processes discussed in the introduction, which describes the necessary gathering of instances for real world inductive processes, multiple trial tests may more closely represent functional induction. This suggests it was acceptable to neglect single trial tests within this group. Verbal induction (Word Context Test) was within normal range in the control group, however visuospatial induction as tested by the Brixton was not. The

group instead performed above the norm on this test. Without further cognitive assessment of controls it is not clear what specific features led to this above-normal finding. Whatever the reason this was an unexpected finding and will have affected results.

4.2.3 Induction in HAND compared to a non-clinical population

The HIV group performed significantly below the non-clinical population on both tests of induction. This was not unexpected, as they had already been shown to perform below the normative average, while the control group performed at the norm on the Word Context Test and above the norm on the Brixton. Not all participants within the HIV group completed the Brixton, but adjustment for number of trials completed, and inclusion of the missing people, did not alter these findings. Within group, both the HIV-positive and control population performed less well on the verbal Word Contest Test than the visual Brixton. This may suggest a pattern of inductive strengths that was similar across groups, or may reflect divergent aspects of the tests used to quantify inductive ability, plus the primary language makeup of the groups.

The Word Context Test requires literacy, an understanding of the words used within the test and an intact verbal domain. It is also culturally specific. The first trial presented to participants, which comprises a practice run, has a final statement “a *sev* a day keeps the doctor away”. As the final clue sentence (of this trial) it is meant to be the most persuasive. Across both groups, some participants did not know this British proverb. This example will not have affected findings as it is not scored, however other trials may be considered similarly culturally specific.

The Brixton is meant to be less vulnerable to culture and literate abilities, implicating itself as a purer measure. Therefore cultural features of the Word Context Test may have led to both groups’ weaker performance on this test. This is illustrated by the finding that primary language and performance on this task were linked.

In summary, these findings indicate that both simple (single trial) and more complex (multiple trial) induction is impaired in a HAND population when compared to a non-clinical population and published normative data. However, participant variables such as primary language may have added to these findings.

4.3 Answering questions 2 and 3

To assess induction more intricately, another scoring system had to be devised that had a baseline measure upon which the HIV group could be compared.

4.3.1 A novel scoring system for the Brixton

The scoring system was derived through componential analysis, combined hypotheses about induction from previous systems (e.g. Burgess & Shallice, 1996; Heaton et al., 1993) and related literature. Additional themes arising in the performance styles and errors of the participants recruited were also added. The final measure did not map directly onto previous systems or known components of induction. For example, a measure of memory may have been expected, as it is known to underpin induction. However no discernible measure was found, and therefore no related code. Additionally, as previously stated error types described as bizarre, or due to misapplication of strategy (Burgess & Shallice, 1996) were not included in the final system.

The final system identified quantifiable components of the Brixton, such as ability to detect rules, speed, shifting, maintaining set and monitoring. Furthermore, errors (considered operationalisations of underlying components of the inductive process) were observed to fall into categories relating to perseveration, reverting to a previous rule, 1-10 shift, response capture and no observable strategy. The initial components (except speed) plus the error types, perseveration and response capture, directly map onto executive functions. That is, if you follow the

hypothesis that executive functions aim to help an individual identify and act towards a pre-defined goal. Moreover, aside from acquisition of the first rule within the test, all other components could be said to link to executive functions not directly considered as induction, linking instead to other functions necessary for ongoing induction in tests such as the Brixton. For example, the number of rules and sets detected, as well as the speed of acquisition, involve switching and ongoing attention.

This scoring system is idiosyncratically linked to this study. Two particular codes illustrate this point:

- Anticipation: People failed to maintain set for multiple reasons. The code 'anticipation' linked to participant's comments preceding behaviour change. This study did not ask participants to describe their strategies aloud, however people invariably did so. The qualitative nature of the study allowed documentation of verbalised behaviour, gaining deeper insight into examinees actions, but only during times of their choosing. This will have affected findings as those not speaking may have been marked differently. With this in mind, a think-aloud protocol (e.g. Davison, Vogel & Coffman, 1997) would have been well placed within this study to more clearly explain participant's performance.
- Response Capture: People within the HIV group were noted on occasion to respond with the number on the page rather than a number linked to the circle's trajectory. The control group did not err in this way, suggesting it as a phenomenon linked to this population.

Subsequently, it is not possible to say whether another population would have led to an alternative system, or whether another researcher would have reached a different conclusion. Some writers on qualitative analysis suggest that findings can only ever be linked to the context of the time in which, and the researcher by whom, they are created (Willig, 2013). They may also say this can be acceptable as long as it is acknowledged. Other qualitative researchers would disagree, stating that objectivity needs to be the aim from the outset, (e.g. through

triangulation or inter-raters; Denzin, 1970). Something akin to triangulation could be described here as multiple data sources were consulted prior to testing, to elucidate underpinning factors in induction. Irrespective of this, qualitative research is often used to identify information upon which subsequent larger studies and scales can be based (Curry, Nembhard & Bradley, 2009). Therefore, the inevitable subjectivity of qualitative research does not have to be considered problematic at this stage.

Another important reason for cautious interpretation is that, like the Brixton test itself, this scoring system has no related stratification to adjust for age related performance. The groups were well matched in terms of age, which goes some way to addressing this issue.

4.3.2 Non-clinical performance as measured by the scoring system

The control group was assessed to gain a baseline level of functioning, and hopefully provides an initial illustration of 'normative' performance styles.

Findings linked to this method of componential analysis suggest that high-level performance on the Brixton requires good concept formation, high speed detection and good switching abilities. The control group were considered to have both of these requirements due to the number of sets gained and the trials it took to gain them. Classification of performance as 'good' on components such as speed of acquisition was made post-hoc through comparison with HIV group scores, as no previous benchmark existed for these categories. Maintaining set is also required to achieve high marks within the test (as any other kind of performance increases error scores), however, all control group participants lost at least one set. This could indicate that set-loss is a normative phenomenon occurring within high scoring individuals with reasons linking more to erroneous attribution of specific items as predictors of pattern change than to spontaneous loss. Regaining set occurred approximately 50% of the time, equalling the benchmark set by this group as the norm in a non-clinical population.

The number of errors made on the Brixton inversely correlates with overall performance. In line with this the control group made low numbers of errors as compared to normative data, however multiple error types were made which suggests various kinds of inaccuracies are possible within induction and the Brixton. Reverting to a previous rule was the most common error type, followed by (to a lesser extent) continuing with the rule just finished, no observable strategy, misinterpreting the 1-10 shift and finally, perseverating with a previous answer. The number of trials across which these errors were made suggested good rule detection and following, with low levels of perseveration within the group.

Reusing a previous rule was the most common error response within the control group. This may suggest that reverting to a previous rule is a common strategy through which guesses at a new rule can be made when not enough instances have yet been acquired by the participant. During initial analysis there was a feeling that some guesses provided by participants were 'educated' and based on a reasonable, yet incorrect strategy. A code such as this required more tenuous interpretation than fitted the analysis. Potentially, trialling a previous rule for the first trial of a new set could represent this kind of strategy. In the WCST, Barceló (1999) found that 'normal' participants undertake trial and error processes to speed up rule detection. Barceló and Knight (2002) call these 'efficient errors' as they utilize recent contextual information to optimize set-shifting. This could be reflected in the performance documented here.

Furthermore, the group showed the importance of continuous monitoring of the stimulus array and their own performance. Ongoing monitoring was considered to be good in the control group as participants were rarely observed to miss a rule change (only one participant did this) or continue with an inappropriate rule, and self-corrected quickly when they noticed they had made an error. Again, categorization of an ability being 'good' (i.e. when linked to continuing with an incorrect rule) was labelled through their overall performance as 'above average' and their subsequent comparison to HIV group performance.

4.4 Question 2. If induction is affected, is there a profile of disruption on measures of induction in HAND or does it differ by person?

4.4.1 Profile of induction at the group level

Quantitative analysis of performance at the group level indicated that HIV participants showed impaired performance on the Brixton, suggesting impaired rule detection. However, when looking at performance at the componential level, all participants achieved the first rule, suggesting simple rule detection was relatively intact. Problems arose when individuals were expected to detect and change to further rules. Cognitive inflexibility may have attributed to this, as lower levels of rules were acquired post-first set, and less shifts were achieved than the control group. In terms of error types, perseveration was high, suggesting that people became stuck within set. When shifting and looking for new rules, the HIV group trialled previous rules in the same manner as the control group but gave much higher numbers of no observable strategy and perseverative answers.

Interestingly, the HIV group were less likely to monitor rule changes or their progress, leading to increased use of ineffective strategies. This suggests that simple rule detection is relatively spared (as backed by performance on single trial concept formation) at the group level. Problems occur when cognitive load is increased and the participant has to switch repeatedly. Failure in cognitive flexibility (shifting and perseveration), and self and environmental monitoring appear to be underpinning the majority of difficulties. Furthermore, the high number of no observable strategy errors suggests a facet of performance not yet understood.

4.4.2 Individual performance in the HIV group

Individual case analysis showed higher variance among the HIV-positive participants with some performing closer to the control group and others demonstrating more impairment. To measure this, individual profiles were compared to the control group mean for each component. Not all people in the control group will have performed equal to or better than the mean, but those

performing differently to the mean within the HIV group were defined accordingly (as better or worse than that number). Therefore, again, findings are tentative. To answer question 2, profiles will be discussed without detailed reference to mechanisms, as this pertains more to question 3.

Across the group, no consistent overall profile existed for all measured variables. No relationship was noted between age, comorbidity and performance profile either. However, two sub-profiles were noted in performance that linked to level of impairment (measured by overall performance on the Brixton). The first was noted across all participants including those performing closest to the non-clinical population (participants 7, 10, 11 and 13) and is therefore suggested to present a sub-profile of mechanisms impaired in HAND at the earlier stages of (inductive) dysfunction. This profile linked to consistently higher numbers (when compared to the control group mean) of:

1. Trials to acquire rules and sets[2]
2. Errors
3. No observable strategy error types
4. Perseverating with the previous answer

This suggests an early profile of impairment in HAND linked to speed of rule acquisition, and general and specific error types. As impairment in performance increased (as measured by overall score) there was another pattern relating performances to each other. This indicated lower:

5. Numbers of rules and sets acquired
6. Numbers of shifts achieved
7. Times they did not notice a rule or set change

This suggests that as impairment increases other components become disrupted,

[2] Number of rules and sets acquired were deemed not to be part of this initial profile, as participants 7, 10 and 11 scored so close to the control group mean.

further impairing inductive performance on the Brixton. These link to rule detection over time, shifting to a new rule or answer, and monitoring. These seven factors could act as a core profile of impairment in induction in HAND, which changes over time. However, other variables were seen (but not consistently) at the individual level such as response capture, and other types of set-loss and errors. Variability within the group suggests that each person may have their own idiosyncratic profile in addition to the profile mentioned here.

4.5 Question 3. What underlying mechanisms do these deficits on measures of induction reflect?

At the group level, mechanisms underpinning HAND were more clearly interpretable as they generalized across the group and linked to decreased performance in the majority of sections measured by the new system. The individual performance instead elucidated themes with individuals also showing their own profiles. Therefore mechanisms will first be discussed in terms of those seen across the group, then individually.

4.5.1 Mechanisms underpinning early impairment in induction

Simple rule detection – a spared mechanism

All HIV-positive participants gained the first rule of the Brixton within the first trial, suggesting that rule detection at its simplest does not underpin impaired performance on induction. This finding is tentative as a methodological issue with the Brixton test's practice section was noted during testing. Prior to initiation of the scored test, three pages are used to illustrate the test. These pages show the circle moving around following a 'plus one' rule (the circle moves forward one position every time the page turns), the same rule utilized in the first testable set of the Brixton. This may have confounded performance as people had been given chance to practice and identify this rule, which they subsequently applied when the test started. This hypothesis was evidenced as the first trial, which should be

a complete guess, was completed 100% accurately across all participants (irrespective of group). An alternative example pattern should be considered in future tests of the Brixton, and would be better used to validate the findings of this study.

Speed of rule acquisition

All HIV-positive participants were slower to acquire sets and rules, even those who managed to gain a (near) complete set. This could suggest underlying mechanisms of impairment linked to declined inductive processes. For example, that effective induction in HAND needs more trials for information to be gathered, stored and integrated. The cognitive component most closely related to this is information processing.

HAND is considered to be primarily subcortical, suggesting early impairment of information processing and attention. Slowed information processing has been suggested by Hardy and Hinkin (2002) to be the cardinal feature of HAND, and has been repeatedly demonstrated in tasks with and without motor demands (Woods et al., 2009). Becker and Salthouse (1999) suggest slowed processing may underpin neurocognitive abilities (in HAND) on tasks not expressly noted as 'speeded'. The findings within this study may reflect this literature, as induction and the Brixton task would not primarily be considered to have a speed-based component.

Information processing has been shown to decrease further in HAND when cognitive demand of a task increases, particularly when attention is divided (Martin et al., 1999). The Brixton requires high cognitive demand and controlled attention for set-shifting, suggesting information processing may indeed have been by slowed by task demand. In general, shifting ability will have affected the speed with which rules were acquired, making it difficult to extrapolate these two different components.

Errors

HIV-positive participants made more errors in general, with particular reference to errors with no observable underpinning strategy and perseveration. Increased

errors within the Brixton are traditionally associated with impaired induction. However, the scoring system devised within this study suggests error level may not solely link to induction. It is not possible to interpret the increased number of errors at the general level at this point, therefore more focus is given to the error type.

No observable strategy error type

Multiple factors need to be considered when interpreting the mechanisms underpinning the no observable strategy error type. Burgess and Shallice (1996) referred to errors like this as bizarre, as they "appear to arise from a preference which is not based on a rational response to the current task situation" (p. 253). They then link bizarre errors to the 'guessing behaviours' observed in another study (Miller, 1985) looking at cognitive risk-taking in anterior lesion patients. Guessing behaviour in that study was interpreted as impulsivity (Miller, 1985; Miller and Milner, 1985), an inability to prevent expression of the first answer to come to mind. Burgess and Shallice might subsequently name impulsivity as one of the mechanisms underpinning impaired performance in HAND.

However, lack of an observable strategy does not directly imply a bizarre answer or lack of rationale. For example, Nelson (1976) noted in the modified WCST that errors occurring in those considered 'above-normal' in intellect, which seem unusual, sometimes reflect elaborate strategies unobservable to the viewer. Therefore it is possible the group utilised reasonable strategies unknown to us. Conversely, this error type could reflect a lack of strategy (problem solving difficulties) within the group. Arentoft and colleagues (2013) defined impaired strategy development as the underpinning mechanism of 'risky' decision-making within HAND. Similarly, Cattie and colleagues (2012) linked decreased efficiency and accuracy in problem solving to planning difficulties in HAND. Further investigation, using a think-aloud protocol for example, would be required to elucidate which, if any, of the above mechanisms led to the increased level of this error type.

Perseveration

Perseveration was made up of two separate codes. HIV-positive participants showed a pattern of perseveration linked to one (repeated answers) but not the other (perseverating with a just finished rule). This suggests a discrepancy in the kinds of perseveration documented here.

Lezak and colleagues (2012) suggest two kinds of perseveration exist, which must be differentiated in order to understand the causal mechanism. The first type links to responses that continue with a previous strategy, reflecting an inability to terminate in-use strategies and shift to new ones, this directly links to cognitive inflexibility (Goldberg, 1986). The other error type links to repetition of a previous answer due to a lapse in attention and/or working memory. This lapse renders the person temporarily unable to move forward as they have lost the information driving their next step. It is possible Lezak's account describes the two kinds of perseverative responses noted within this study, with rule continuation reflecting cognitive rigidity, and answer repetition indicating attentional and memory based deficits.

The mechanisms underpinning the initial profile of impairment in HAND, linked to the Brixton, therefore probably links to lapses in attention (considered the hallmark of HAND; Morgan, Woods, Delano-Wood, Bondi & Grant, 2011) and working memory (both verbal and visual working memory are shown to be impaired in HAND; Martin et al., 1995, 2001). This reiterates Johal's (2014) suggestion that these may be two mitigating factors in inductive performance in HAND. However, perseveration linked to cognitive flexibility should also be considered when working with people clinically, as this also occurred within the group but did not constitute a consistent profile.

5.4.2 Mechanisms underpinning impairment in HAND as impairment progresses

Rule and set detection after first rule achieved

As overall performance scores decreased, participants acquired fewer total rules and sets than the control group. This could suggest impaired induction, although

rule detection at its simplest seemed intact. Interestingly, the most commonly acquired rules were those most closely relating to the first rule. For example, rule one sees the circle move forward one position every time the page turns. Rule two then sees the circle move backwards one position with each trial. These two were most commonly achieved. Sets four, five and six are repetitions of these rules. Then the rule in set nine switches between these rules. Again this was achieved slightly more often. Rules from sets three (the circle moves between position 10 and 5), seven (the circle moves between positions 10 and 4) and eight (the circle stays at position 9), those most different to the previously mentioned rules, were most often missed by the HIV-positive participants. This could suggest induction becomes less accomplished when rules become more abstract or differ substantially from the first acquired pattern. Moreover, decreased set detection may link to other components including cognitive flexibility.

Shifting sets

Within the HIV group those achieving comparatively lower scores also shifted between rules a lower number of times. This suggests lower cognitive flexibility may play a part in poorer performance as impairment increases. HIV-positive participants performed in the impaired range on both the switching subcomponents of verbal fluency verifying the suggestion that this is impaired within the group. At its most extreme, cognitive rigidity causes people to become stuck within one mode of functioning, as observed in the performance of participant 3 who utilized the first rule throughout the test.

This finding is not unusual as HIV is known to affect cognitive flexibility (e.g. Iudicello et al., 2013; Giesbrecht et al., 2014), and has been found to be the highest predictor and clinical indicator of poor performance on other tasks of executive functions, such as when using a gambling task to assess decision-making (Carter et al., 2003). Surprisingly, cognitive flexibility has not been found to reliably associate with real-life functional performance linked to decision-making (Iudicello et al., 2013). This may suggest that a test of real-life functioning in situations involving induction, not just neuropsychological batteries, could add another dimension to this study. For example, component counts linked to

induction could be correlated with aspects of the Árnadóttir OT-ADL Neurobehavioural Evaluation (A-ONE; Árnadóttir, 1990), to identify which aspects most closely link to lived experiences.

Monitoring

Within the HIV group, not noticing a rule change was more consistent than the monitoring code linked to utilizing an inappropriate strategy, and appeared to be part of a profile of impairment seen as Brixton-related performance decreased. This performance style was considered to reflect an inefficiency in continuous monitoring of, and responding to, the stimulus array. The concepts most closely linked to this in the neuropsychological literature are self-monitoring and metacognition.

Self-monitoring is integral to daily functioning, as the ability to perform a task is only as effective as an individual's ability to monitor and correct their performance (Lezak et al., 2012). Monitoring is linked to the integrity of prefrontal structures (Fleming, Huijgen and Dolan, 2012), damage to which has been shown to lead to two categories of deficits: those who do not perceive errors and therefore do not self-correct, and those who perceive the error but do nothing to correct it (known as pathological inertia; Lezak et al., 2012). The former concept may relate more to processes witnessed within this study as the HIV group changed behaviour once they perceived the rule change.

Metacognition, which links to the ability to think about thinking and have insight into oneself, overlaps with the idea of self-monitoring. The finding that approximately 50% of people with HIV lack insight into their cognitive difficulties (Weber et al., 2009) is thought to indicate metacognitive impairment in HAND. Therefore, this finding does not propose a new feature of HAND but suggests metacognitive and self-monitoring dysfunction may underpin poorer inductive performance.

Overall

To summarise, it appears that rule detection in its simplest form is spared. However across people with HAND, mechanisms such as slowed information

processing may slow the time it takes to induce rules, and lapses in attention and working memory may cause people to repeat previous answers. Furthermore, error types at this earlier stage suggest individuals may be impulsive, lack strategy or simply did not explain their performance. Once impairment increases, rule detection may become poorer and this could be caused by decreased cognitive flexibility, or error perception and monitoring.

4.5.2 Other mechanisms

At the individual level other components were noted to affect induction, dependent on the participant, for example, set-loss varied across participants. Moreover, when impairment as measured by Brixton performance was high, set-loss was low. Failure to maintain set has been described as an inability to perseverate. It can occur due to distractibility (disturbance by an external stimuli) or an internal process reflecting difficulty with self-control (Lezak et al., 2012). The latter point, also known as cognitive impersistence, occurs when an individual's focus has already moved to another area, or when they have lost interest, slowed down or given up. Set-loss occurred within each group, highlighting that it is not a pathological process by itself. However, it is interesting that it occurred less with poorer performance. This could be due to the lower number of sets acquired and therefore lost, or could reflect perseverative ability; a level of cognitive rigidity stopping people spontaneously losing set.

People lost set for multiple reasons within both groups. When occurring due to anticipation or another reason it may not link to an impaired mechanism, but to incorrectly interpreted visual signals. When occurring due to no observable reason, this could reflect higher levels of cognitive impersistence linked to attentional control, fatigue or boredom. Recruiting from an unwell population means fatigue is not improbable, especially as the Brixton was one of the later tests of a long battery. Furthermore, while neuropsychological literature does not generally explore the link between set-loss and (working) memory, it would make sense that those unable to hold information in mind whilst performing a task may, on occasion, lose set as they suddenly find themselves lost within the task at

hand. Each of these explanations could account for the kinds of set-loss seen in this study. Again, it would require a think-aloud protocol to accurately depict the real mechanisms underlying performance.

Response capture was another mechanism noted in some members of the sample. This kind of response suggests a failure in the executive functions necessary to keep you on task (Humphreys & Riddoch, 2000). It is similar to utilisation behaviour, a term used by Lhermitte (1983) to describe times when items and objects within the world captures an individual's attention causing them to act upon it despite other information suggesting this is not what is required.

4.6 Clinical Implications

To the authors knowledge this was the first study to directly investigate induction within HAND, and therefore also addresses feasibility of use of the Brixton within the HIV-positive population. Additionally, it was the first to explore the mechanisms underlying induction within this population. A number of implications are therefore discussed below.

1. It is possible to derive a componential scoring system for the Brixton
Findings within this study are tentative, and need replicating in order to assess the reliability and validity of the scoring system created here. However, it has shown the complexity of skills required for one test of executive function, and therefore, the lack of information gained from direct interpretation of single score measures of functioning (e.g. the Brixton). With this in mind, this study has shown it is possible to derive a componential scoring system for the Brixton, similar to that utilised in other tests such as the WCST. It has also shown that with this technique, consistent and meaningful data can be gathered explaining performance.

2. It is necessary to use componential scoring systems when working with HAND
An overall profile of HIV-related impairment linked to induction did not emerge.

Instead, themes arose that were also accompanied by other idiosyncratic difficulties. This serves to reiterate the need for componential analysis when utilising the Brixton. Therefore, clinicians should focus on creating, validating and/or utilizing a system such as the one devised in this study to understand the specific features of the clients seen.

3. Outcomes of componential analysis are needed to identify specific treatment targets

Induction is an important ability that is required for people to function independently within their environment. When induction breaks down people will become concrete, struggling to interpret patterns and rules within the environment and generalize them to other areas, or follow them without didactic teaching. Therefore, findings suggest this could occur within the population of people living with HAND, having significant implications for people's independence, especially at later stages. Moreover, the current study highlighted that induction of rules is not by itself problematic, but is further affected by a number of other skills.

Treatment should be based on the outcome of componential assessment. For example, building upon on the findings of this study people may need help at the early stages with:

- slowed information processing, through strategies such as increased time, repetition and chunking of information, increasing an individual's chance to take on information. InSight (Posit Science, 2012), a computerized training program aimed at improving processing speed could also be used.
- should errors with no observable strategy link to inhibition or problem solving deficits, structured environments should be used to support individuals. Breaking problems into manageable chunks, sequencing, routines, prompt and cues for behavioural organization should also be implemented.
- lapses in attention and working memory should be supported through

chunking tasks, use of cueing reminders, self-checking strategies and awareness of deficit training (e.g. through Sohlberg and Mateer's three stage approach; 1989)

As HAND progresses they may need help with:

- cognitive flexibility through behavioural support outlined above and selection of an appropriate care setting.
- meta-cognition and performance monitoring. Without support for this other strategies may be redundant as people with HAND may not be able to gain insight into the need for support.

In 2014, the National Institutes of Health awarded a grant to a researcher linked to the CHARTER study to investigate metacognition based therapy for HAND in Methamphetamine users (Casaletto, 2014). Therapy involves teaching monitoring and self-regulation skills (see Sohlberg & Turkstra, 2011, for more detailed information) and results have yet to be published.

4. Componential analysis and subscales are needed for other areas of functioning in HAND populations

Category fluency, decision-making, planning, and now induction have been investigated for their underlying mechanisms in HAND. Murji and colleagues (2003) suggested maintenance of executive functions in HAND should be a top priority in order to limit subsequent cognitive decline and preserve quality of life. In order to identify treatment targets, other executive functions and their related tests should be analysed to quantify each skill contributing to ability or impairment. For example, inhibition could be investigated through qualitative analysis of tests such as the Stroop Colour-Word Test (Stroop, 1935) or Hayling Test (Burgess & Shallice, 1997). The Hayling Test already possesses a componential scoring system, categorising scores based on initiation speed, inhibition ability and thinking time. It is therefore a viable test for future use.

5. More focus is needed on the cultural validity of neuropsychological tests
The relationship between primary language and the Word Context Test performance reiterates the need for language and culturally appropriate neuropsychological measures in order to avoid false-positives. It also suggests language fluency is not enough for a test to be considered applicable.

As HIV continues to spread around the world, more studies will emerge calling for entire culture specific batteries and norms. In the short term, culture fair tests such as the Brixton, which does not need language knowledge, may be a more realistic goal (Manly et al., 2011). However, the notion of 'culture fair' testing has been challenged as some believe neuropsychological assessment is inherently culturally biased (e.g. Siedlecki et al., 2010). Clinicians may have more flexibility to work idiosyncratically with people, altering their assessments to include wider psychological formulation not solely based on neuropsychological testing. This may be more difficult to manage within research however, where data requires matched norms, samples and batteries.

4.7 Critical review

4.7.1 Sample

Methodological rigour will have been affected by the sample size and limitations of the test materials utilized, meaning findings need to be interpreted with caution. A larger sample would have enhanced study validity and reliability, making results more generalisable to the wider population of people living with HAND. Recruitment and testing occurred within a limited time frame and the HIV-positive population was drawn from a single group at Mildmay UK, restricting what was possible. Furthermore, a sample of people with 'pure' HAND was not achieved, as patients within the service presented with high levels of comorbidity, such as infections and a history of substance misuse, all of which have their own potential cognitive sequelae.

Inclusion and exclusion criteria, and involvement of a non-study related

consultant to consider the impact of comorbidities on cognition aimed to improve selection of ‘suitable’ participants. Consultant inclusion was valuable due to the extensive knowledge brought in about each participant’s condition and also this field of research. Yet in hospital settings that are not the patient’s local medical centre, it is difficult to gain accurate histories, which suggests additional information may have been missed further affecting findings. This is particularly pertinent for those recently diagnosed with HIV yet appearing to have contracted the virus up to a decade ago, as little accurate information is available about disease progression. Therefore within these contexts, conclusions from this study are tentative at best.

Regarding comorbidities, the diversity within the study reflects the population-wide estimate of comorbidity prevalence in HAND (noted by Heaton et al., 2011). Additionally, exclusion of participants with comorbidities has been said to decrease ecological validity of research (Robertson et al., 2009) as it creates data not matching real-life situations. Excluding comorbidities may have decreased the ecological validity of the research, in addition to impeding recruitment. Furthermore, many comorbidities present within the sample are not well understood in terms of their link to cognition in HIV, post-treatment effects of toxoplasmosis for example. Further research would be needed to elucidate the effect of the comorbidities present within this study, and to pinpoint whether in fact these comorbidities obscure the findings or investigate the reality of the population in question.

Age, education, ethnicity and language ability varied across both populations, although all met criteria for inclusion and were considered fluent in English. The literature documenting the effects of ill-matched demographic variables, or lack of cultural specificity of neuropsychological research, is extensive. The majority of HIV group participants were born outside of the UK, therefore there are implications for the validity of results as measures are biased towards western cultures.

This was an exploratory study. In general, exploratory studies investigate whether specific phenomena occur under particular conditions in a given population and

can often incur similar limitations as those presented here. Larger scale secondary studies generally follow initial evidence that there is something to look for. Tentative findings in exploratory studies are therefore used as a base to guide subsequent research.

4.7.2 Test materials and battery

Assessing a cognitive domain or ability in a 'pure' way, through neuropsychological assessment, is hampered by the interplay between different abilities. For example, measures of memory necessitate language, attention and information processing. If one of these is affected, performance could erroneously suggest memory difficulties. The Brixton also cannot be said to be a pure measure, requiring attention and short term storage of previous trials shown. Careful interpretation of measures and comprehensive neuropsychological batteries can extrapolate certain factors arising in test performance, hence utilization of a full battery and multiple regression here. However, in general it can be difficult to state reliable conclusions about an individual ability from single tests.

One strength of this study is that componential analysis in some way addresses the lack of specificity of the Brixton test, as it looks to identify mechanisms at play within participants' performance. Furthermore, having taken the WCST scoring methodology (Heaton et al., 1993), and Burgess and Shallice's (1996) comments into account, some of the themes could be considered reliable purely due to their documentation across multiple literatures. However, as previously mentioned, one researcher carried out the qualitative analysis, suggesting the need for future repetition of the study with think-aloud protocol and potentially more researchers.

Sample size was small, but made smaller due to two people stopping the Brixton before completion. This has consequences for the findings but may also have methodological implications. The Brixton was the last test undertaken as it comprised part of the additional research battery. Therefore difficulties with completion may reflect test fatigue that was not addressed by breaks. The Brixton

was one of the tests with the longest duration, reasonably suggesting fatigue could be caused or exacerbated by this task. While all participants completed the Word Context Test, four HIV-positive patients gave the answer “don’t know” continuously, for up to the last five trials. Scores on this subtest could therefore also reflect exhaustion or decreased effort, rather than ability. An individual’s management of neuropsychological assessment provides information on cognitive ability. However, practical issues of testing unwell patients, such as test length, are well recognised. If this study were repeated the battery should be reassessed for necessity of each task, with a view to significantly decreasing test time. Otherwise, the measures of interest should be administered first to diminish the effects of fatigue.

The findings within this study suggest that multi-faceted impairments can be seen in HAND based on one single test of induction, the Brixton. Without a functional assessment of peoples ADLs it is hard to see how Brixton findings impact people’s lived-experience, particularly as the test materials do not closely map onto daily activities and situations.

Neuropsychological tests of executive function are often criticized for lack of verisimilitude (i.e. the level with which they resemble the real-life abilities they are supposed to test; Rai, 2014). However, Shallice (1988) argues that low verisimilitude is intentional, as most real-life activities become routine and possible to complete without cognitive engagement. Therefore neuropsychological tests generally present novel situations that necessitate on-the-spot formulation and implementation of new strategies. This suggests that Brixton performance may therefore predict real-life functioning.

Moreover, it could mean people with HAND may not display as impaired concept formation in routine areas of their life. As hospital settings can present a ‘novel’ environment, impairment documented here may overstate deficits experienced when at home or with known individuals. Conversely however, these tests were carried out in a quiet structured setting where participants are alerted to the requirements of the task at hand. In the ‘real-world’, multiple competing stimuli, such as noise and visuals, occur at the same time as people are expected to

complete tasks such as induction. If executive functioning is impaired in the way suggested within this study (where performance was seen to decrease as cognitive load increased), this would suggest impairment noted here may be an under-representation of real-life functional disruption.

4.7.3 Personal reflections

Research was carried out within an epistemology not commonly utilised in this field. There were times when it felt closer to positivist work as the quantitative methodology and neuropsychological battery mapped more closely onto this line of thought. However, inclusion of a qualitative element as well as reading linked to the socio-political aspects of HIV allowed more critical viewing of the test materials and literature gathered for the study.

The work documented here was rewarding in terms of gaining skills in neuropsychological assessment, research and componential analysis. Simultaneously, challenges on multiple levels raised interesting issues. For example, before embarking on this study I continuously considered the constructed nature of emotional wellbeing, but was surprised at the extent to which a medical condition so firmly rooted within positivist traditions could be influenced by societal and cultural beliefs. HIV and transmission related stigma has been repeatedly shown to disable international, national and local abilities to implement effective preventative strategies, and decrease the likelihood that someone would test for and disclose an HIV-positive status.

At the start of the project I had read articles and listened to talks that implicated inappropriate policy in the ongoing HIV pandemic, they also suggested that decreased fear of HIV due to available medication had led to decreased precautionary measures such as condom use (Pisani, 2010). Relating this to the Health Belief Model (Rosenstock, 1974) I queried whether increased information about the consequences of HIV could reinstate the necessity of prevention in people's minds, as well as inform appropriate treatment. However, over the course of the work I have shifted towards a belief that research focused at the

individual can be redundant if not accompanied by social and political awareness, challenging the status quo at the national level. Therefore, while more research needs to be carried out to validate the findings of this study, my future focus would be to campaign against stigma, and for ongoing preventative strategies at a wider level.

4.8 Future research

Throughout the discussion further research ideas have been mentioned and the main points, and some final ideas are summarised here.

1. Research to address shortcomings within this study:
This study used a smaller sample size than was hoped for, furthermore, results were affected by variance within the group such as comorbidities and primary language. A larger version of this study with less variance would elucidate more generalisable findings. Inclusion of additional visuospatial measures of multiple trial concept formation would also improve the findings, identifying which components link more to the Brixton test than induction per se. Of upmost importance would be inclusion of a think-aloud protocol.

2. Research to follow on from this study:
It would be interesting to further this research by looking at the functional links between induction and ADLs in people with HAND. For research to be useful and ethical it should do more than inform professionals about a disease. If a functional link could be highlighted it may mean more to the people the research intends to serve, as well as providing further exploration of induction as measured outside of the clinic.

Also, this study has shown the multiple aspects of performance underpinning induction in HAND. So far, category fluency, decision-making and planning have been explored componentially. Future research is needed to investigate other executive functions, including inhibition.

Further investigation into culturally acceptable assessment tools would create improved assessment, reflecting the diversity of PLWH. It would also clarify whether results within the literature pertain to HIV specifically, or to socio-political factors surrounding the disease and neuropsychological assessment.

3. Research to adapt the Brixton:

The Brixton would benefit from research leading to age-stratified norms for the younger population. Furthermore, it is necessary to create a validated componential system for the Brixton that can be utilised in clinical settings and in research. Repetition of componential analysis methods utilised in this study with multiple researchers would highlight reliably agreed upon criteria. Wider populations would need to be drawn from, particularly non-clinical samples, to identify generalisable performance styles. Larger scale multiple regression of components outlined in the new system could identify those important for performance on the test (Clark & Gardner, 1990).

Brixton based componential analysis could be carried out in other cognitive impairments, including Parkinson's disease (as Parkinson's affects motor and cognition, similar to HIV) and frontal lobe damage or dementia (as this also affects cognition, especially executive functioning). This could be used to triangulate impairment styles, answering whether profiles emerge that directly link to disorder, or whether Brixton performance is always idiosyncratic (similar to performance seen in this study).

Finally, some neuropsychological tests contain subtests to control for contributing factors. For example, the DKEFS Trail Making Test (Delis et al., 2001) has subtests to assess general speed, sequencing and switching separately. To improve componential analysis, a visuospatial short-term memory test could be built into the Brixton test, to account for perceptive and memory components affecting performance. This could be done using the same basic stimulus array used within the Brixton. For example, examinees could be shown a pattern, then asked to point to it on a separate page three seconds later.

4. General research:

One conclusion from this study is the necessity of componential scoring systems to understand the complexity of individuals' performance. Scales need to be created for tests not already using them (e.g. WAIS-III and WAIS IV tests such as Similarities and Matrices Reasoning) for use across all, not solely HIV-related, clinical and patient settings.

4.9 Conclusion

This study highlights the complexity of executive functions within a non-clinical and clinical population, which is often ignored within neuropsychological measures since basic test scores are often taken at face value. Through an attempt at addressing this, it became clear that like other cognitive domains (except visuospatial domains), induction is impaired in HAND. Multiple factors are responsible for this rather than rule detection alone. This appears to be the first study documenting mechanisms underpinning induction within this population and suggests that rule detection at its simplest may be spared. However, difficulties occur if cognitive demand is increased. Information processing, lapses in attention or working memory, and other mechanisms (either impulsivity, problem solving deficits or another unknown variable) appear to comprise initial deficits in induction. Secondary deficits affecting induction arise as the disease progresses or performance on the Brixton decreases, they include cognitive rigidity and monitoring difficulties. However, performance was not exclusively consistent.

Clinically, this implies that wider testing is required, including componential analysis. This is important not only to test these findings but also to document individual idiosyncrasies that affect the type of treatment most appropriate for each person presenting with difficulties linked to HAND.

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6 APPENDIXES

APPENDIX A. Information on HAND, comorbidities and risk

Hepatitis C

Hepatitis C viral infection (HCV) is a blood-borne virus diagnosed in 55-90% of HIV-positive intravenous drug users (IDUs). Alone HCV replicates in the CNS leading to neuropsychological consequences. When co-occurring with HIV infection, HCV is thought to have additive effects on cognitive impairment (e.g. Giesbrecht et al., 2014) leading to further impaired learning, speed, recall ability and problem solving (Cherner et al., 2005). Furthermore, in a study looking at the relationship between HIV, hepatitis C, substance use and HIV disease measures (e.g. current and nadir CD4, HIV RNA, duration of infection), hepatitis C was the most consistent predictor of poor cognitive performance (Devlin et al., 2012). However, one study found HCV did not contribute to neurocognitive impairment, when HCV had no associated liver damage (Clifford et al., 2015). As HCV is usually passed through IDU, substance use will also affect the findings of research carried out on HCV and HIV.

HAND and substance use

Drugs, both legal and illicit, are known to have significant deleterious effects on neurochemistry. Therefore it is not unexpected that poorer neurocognitive outcomes have been found in PLWH who use any of the following: alcohol, methamphetamine, opioids, Ecstasy/MDMA and other ‘club’ drugs (Kennedy & Zerbo, 2014).

An example of this is alcohol, which affects cerebellar, prefrontal structures and the limbic system leading to cognitive impairment over time (Sullivan & Pfefferbaum, 2014). Together HIV and alcoholism have been shown to have synergistic effects. Leading to increased severity of HIV symptoms (Heinz, Fogler, Newcomb, Trafton & Bonn-Miller, 2014) and impairment in reaction times, verbal reasoning, visuospatial perception and episodic memory, causing impairments far greater than seen in individuals with either HIV infection or alcoholism alone (Fama et al., 2011).

It must be noted that drug use is often accompanied by lower socio-economic status, nutrition, education levels, and higher rates of head injury, other neurological compromise and psychiatric disorders (Durvasula & Hinkin, 2006). Each of which confounds research carried out in the area. It would therefore be hard to extrapolate the effect of each of these variables.

Mental health

A higher prevalence of mental health diagnoses is found in PLWH than in the general population. For example, estimates suggest 4-23% of PLWH (Cournos & McKinnon, 1997) also live with a diagnosis of schizophrenia (compared to 0.87 in the general population; Perälä et al., 2007), and that PLWH are two to three times more likely to have a diagnosis of depression (Tucker, Buram, Sherbourne, Kung & Gifford, 2003).

A reciprocal relationship has been suggested to exist between HIV and diagnosed mental health problems. Specifically, poor mental health has been linked to increased risk of transmission and transmission linked to decreasing psychological wellbeing. Furthermore, disruption of cART adherence has been linked to poor mental health, which increases risk of further illness and mortality (Anand, Springer, Copenhaver & Altice, 2010).

As with all areas of HIV another study noted the inverse. The study followed HIV-negative people with and without diagnosed mental health conditions over a two year period, finding that people with a serious mental health diagnosis were 23% less likely to become HIV-positive than those with good mental health (Prince, Walkup, Akincigil, Amin & Crystal, 2012). However, this study only included what it determined to be a serious condition (i.e. bipolar disorder or schizophrenia), and placed people with anxiety and depression in a different group.

Suggestions exist that different mental health diagnoses have cognitive sequelae. Schizophrenia is thought to impair executive functioning (Angelino & Treisman, 2008) while depression has been linked to deficits in motivation, verbal memory, executive functioning and motor performance (Castellon et al., 2006).

Additionally, anxiety is thought to affect speed, memory and switching ability (Beaudreau & O'Hara, 2009). Therefore, it may be expected that HIV and mental health could have an additive effect. However, extrapolating the effect of either would be difficult.

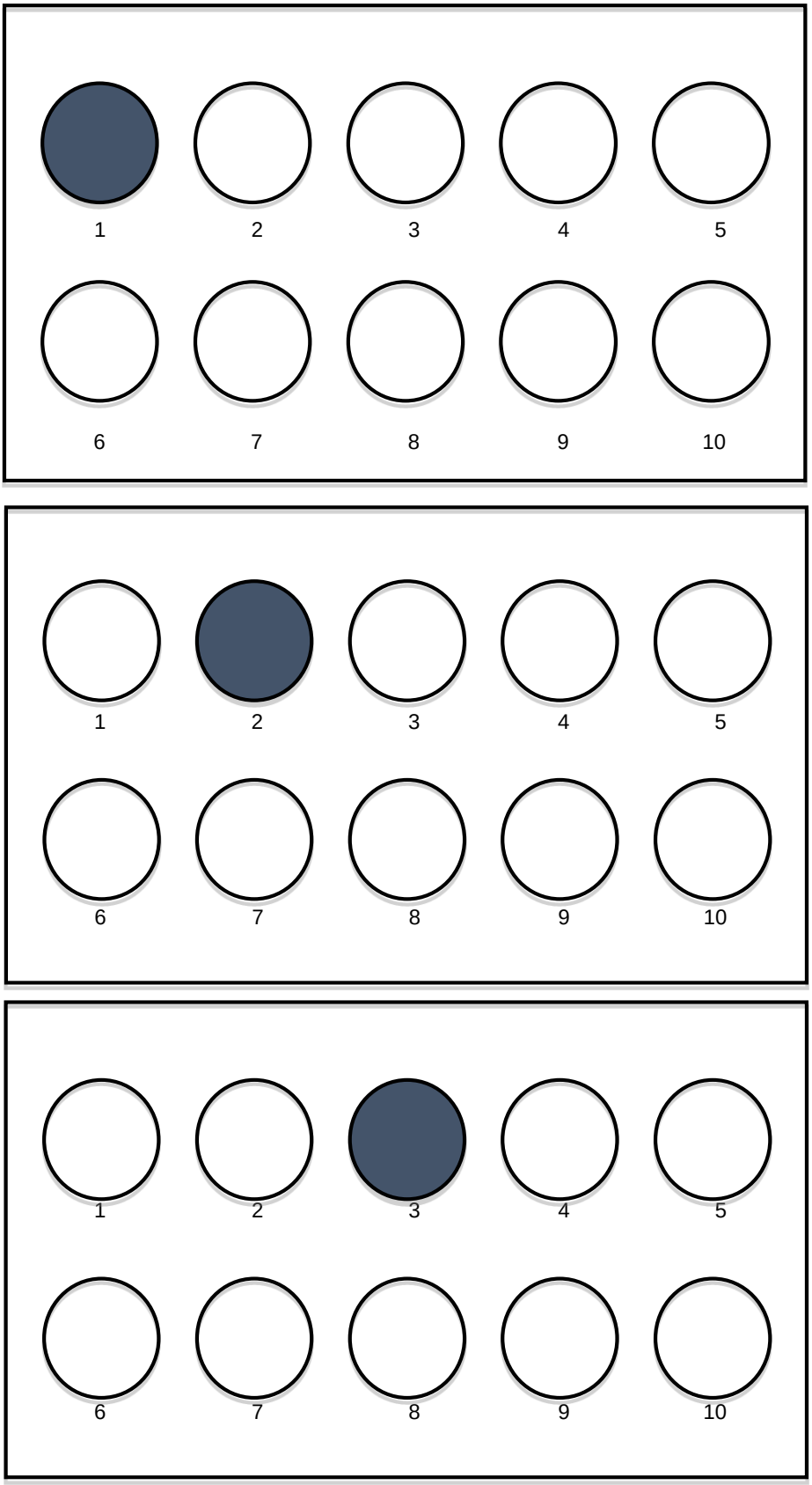
Little research exists investigating mental health and HAND. Depression and anxiety has been linked to higher rates of HAND in men (Micali, Zirilli, & Abbate, 2011). However, the CHARTER study found no relationship between depressed mood and neuropsychological HIV sequelae (Heaton et al., 2015). No specific research looking at HAND and schizophrenia has been carried out to the author's knowledge.

The directionality of the effects, when found at all in the literature, is not clear. Furthermore, the validity and reliability of the mental health constructs (schizophrenia, depression and anxiety) have been questioned (e.g. Rapley, Moncrieff & Dillon, 2011) putting the reliability of the mental health and HIV research into question. In line with previous comments regarding socio-demographic aspects people with mental health diagnoses experience stigma and are positioned at lower levels of society (Wilkinson & Pickett, 2010) suggesting these factors may also be at play.

Other

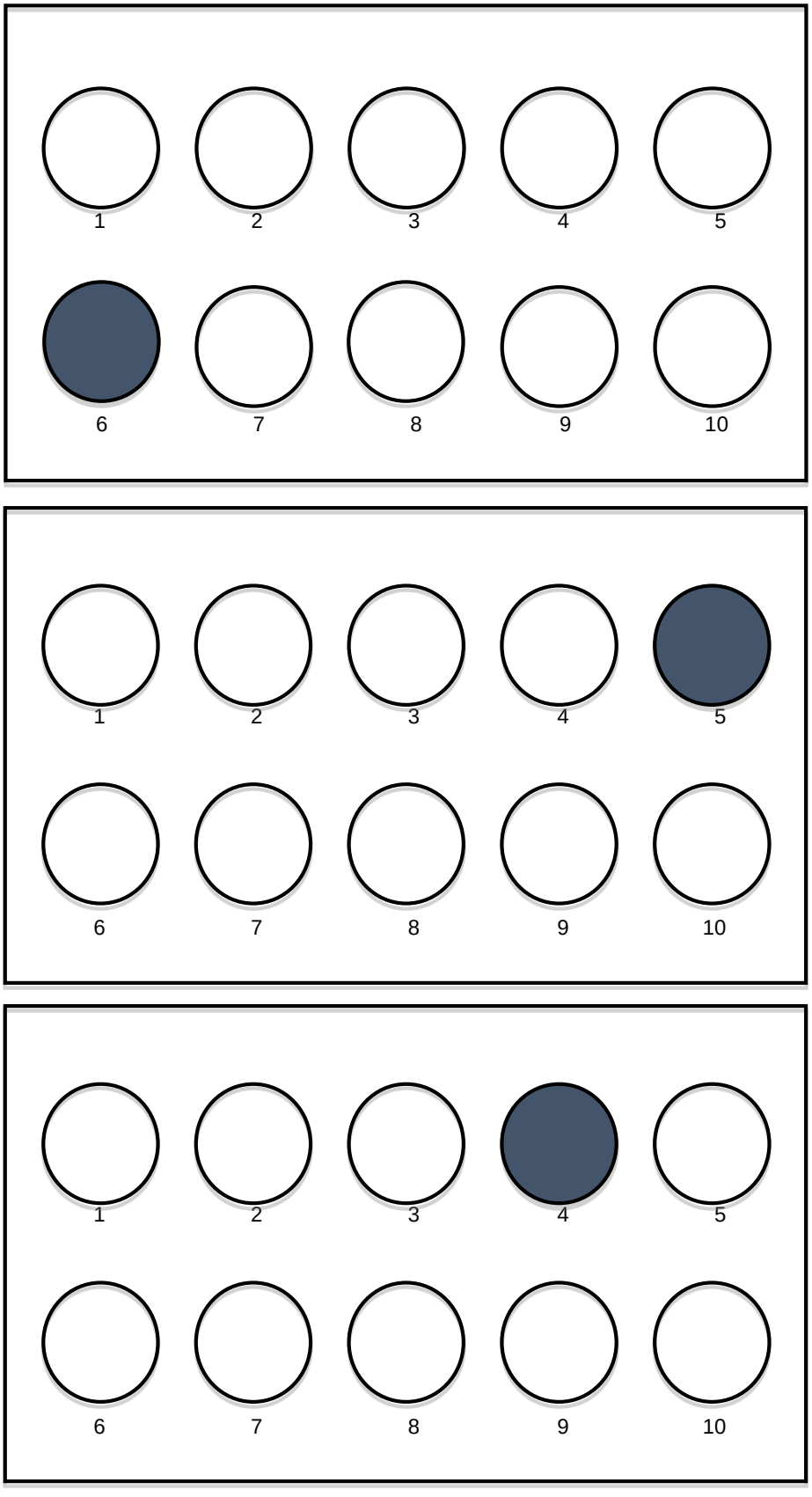
Other factors influencing HAND include genetic factors. For example, The APOE ε4 allele has been associated with HAD, but links to mild and moderate HAND are unclear (Kallianpur & Levine, 2014). Inactive lifestyles have also been postulated to link to HAND. The directionality of this claim is unclear as, while it is possible that activity protects against decline, it is also possible that better/worse neurocognitive functioning instead leads people to be more/less inclined to be active (Fazeli et al., 2014).

APPENDIX B. Example of Brixton set 1 (rule 1): circle moves forward 1 position[3]



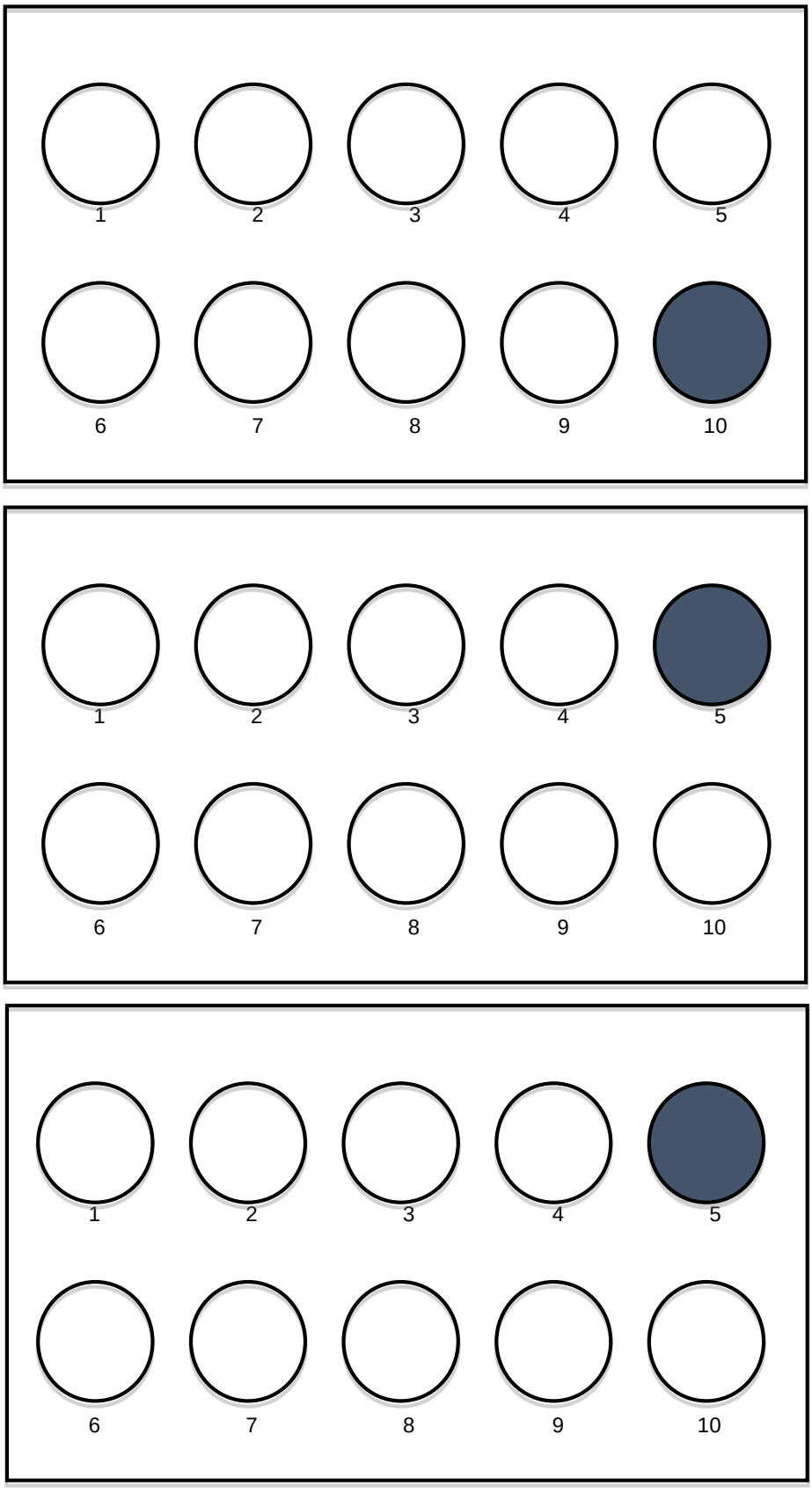
[3] Shown across three different stimulus arrays (each rectangle represents a new array/page).

APPENDIX C. Example of Brixton set 2 (rule 2): circle moves back 1 position[4]



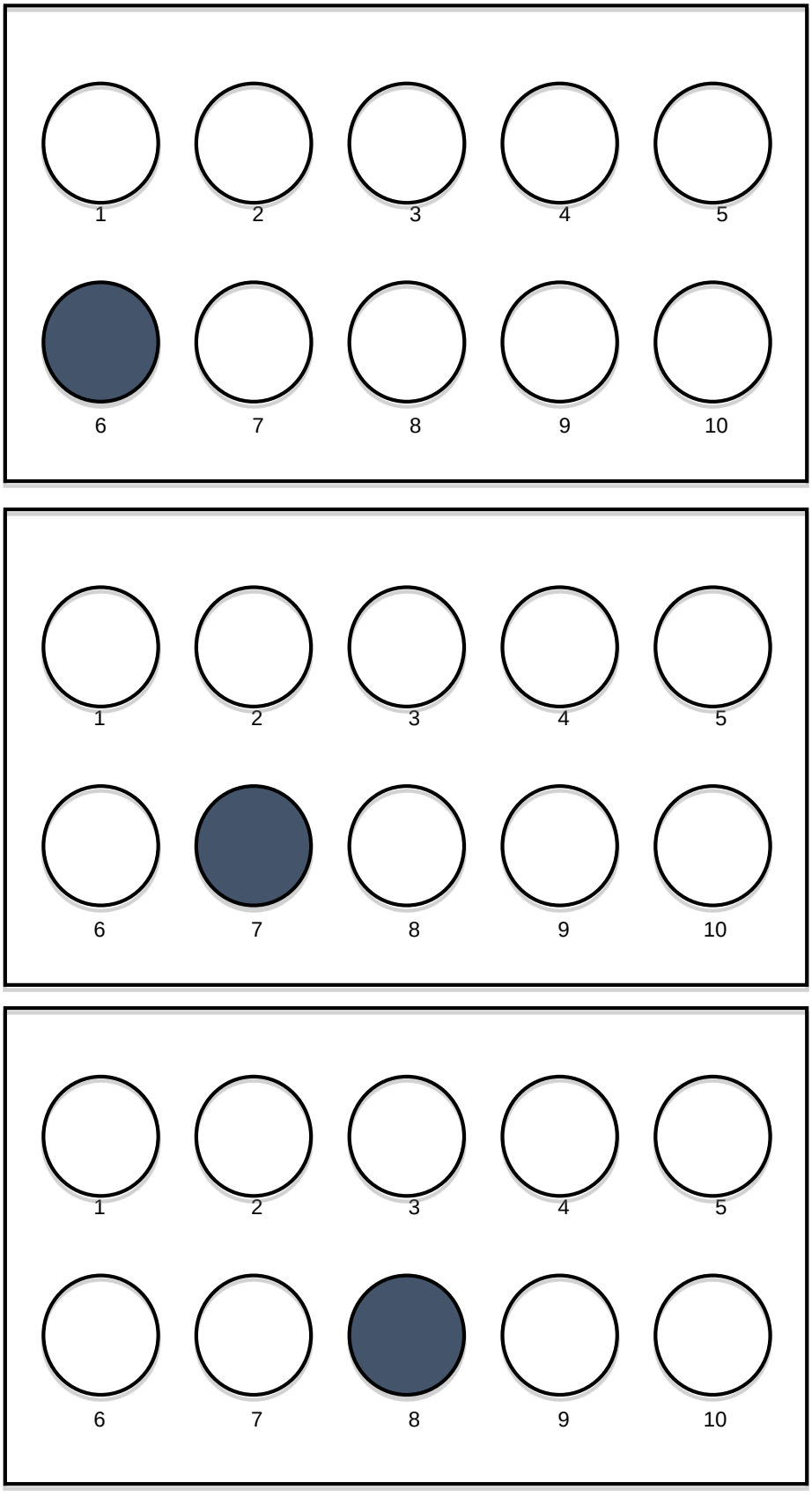
[4] Shown across three different stimulus arrays (each rectangle represents a new array/page).

APPENDIX D. Example of Brixton set 3 (rule 3): circle alternates between 10 & 5[5]



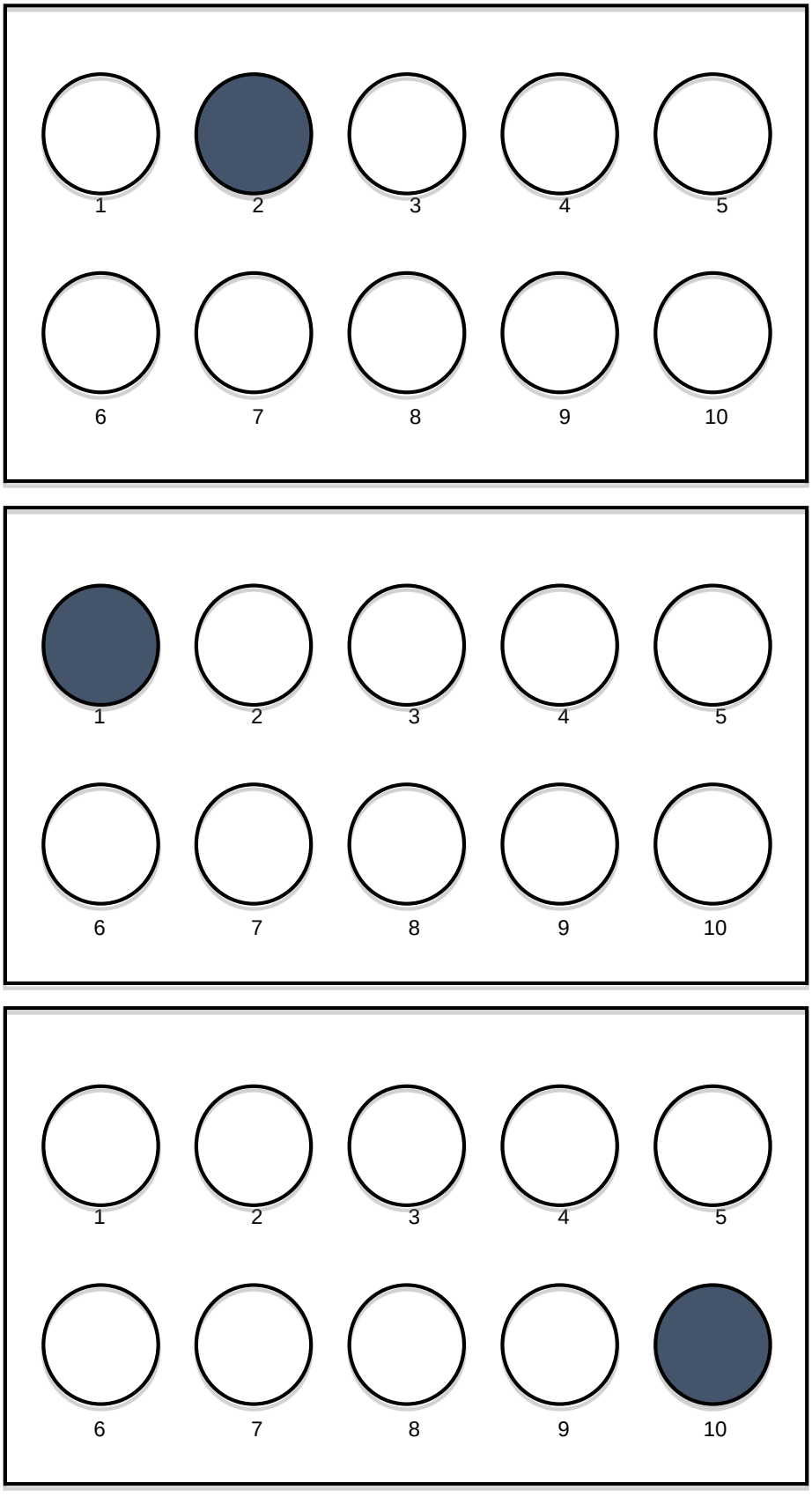
[5] Shown across three different stimulus arrays (each rectangle represents a new array/page).

APPENDIX E. Example of Brixton set 4 (repeat rule 1): circle moves forward 1[6]



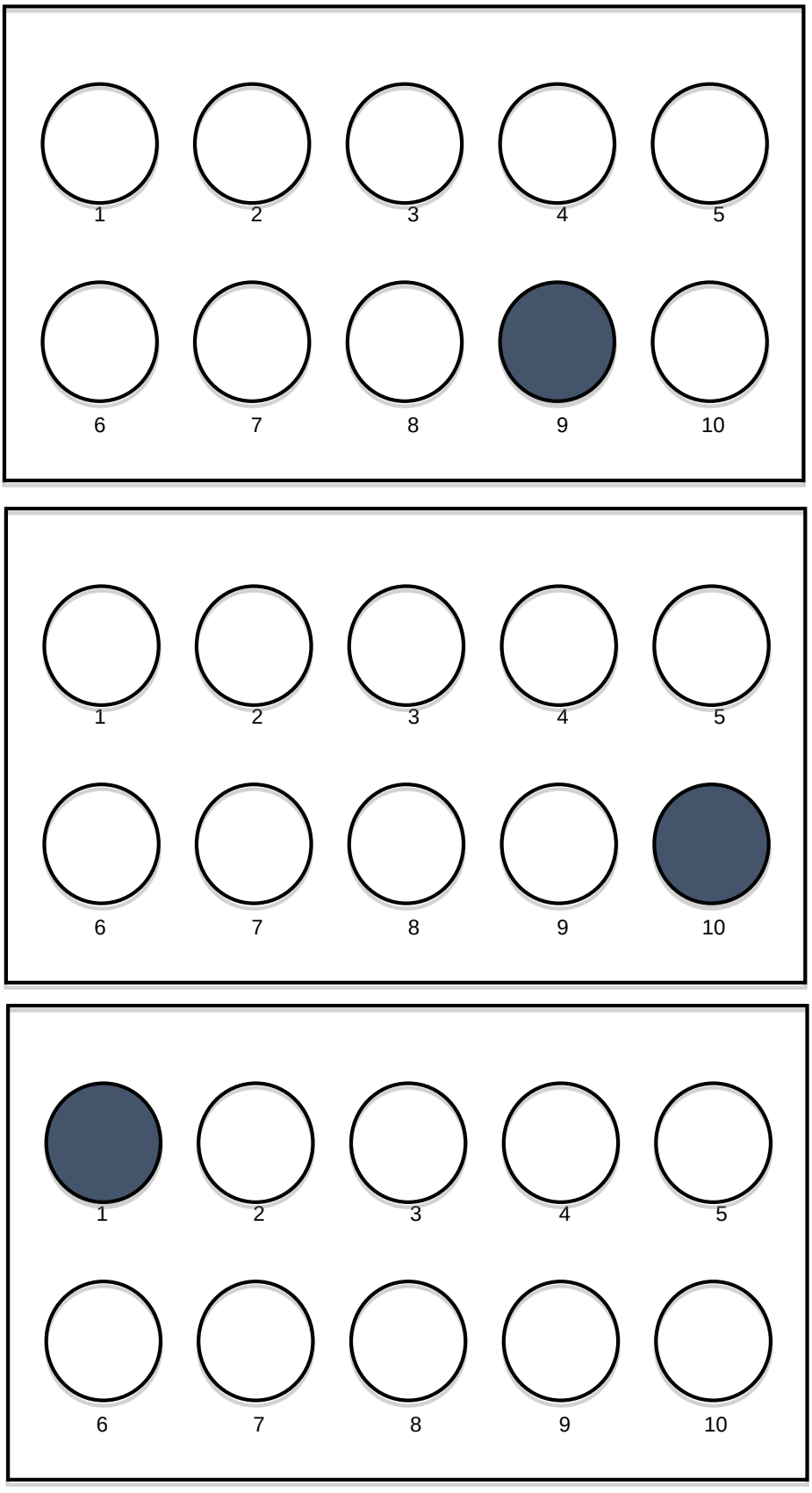
[6] Shown across three different stimulus arrays (each rectangle represents a new array/page).

APPENDIX F. Example of Brixton set 5 (repeat rule 2): circle moves back 1[7]



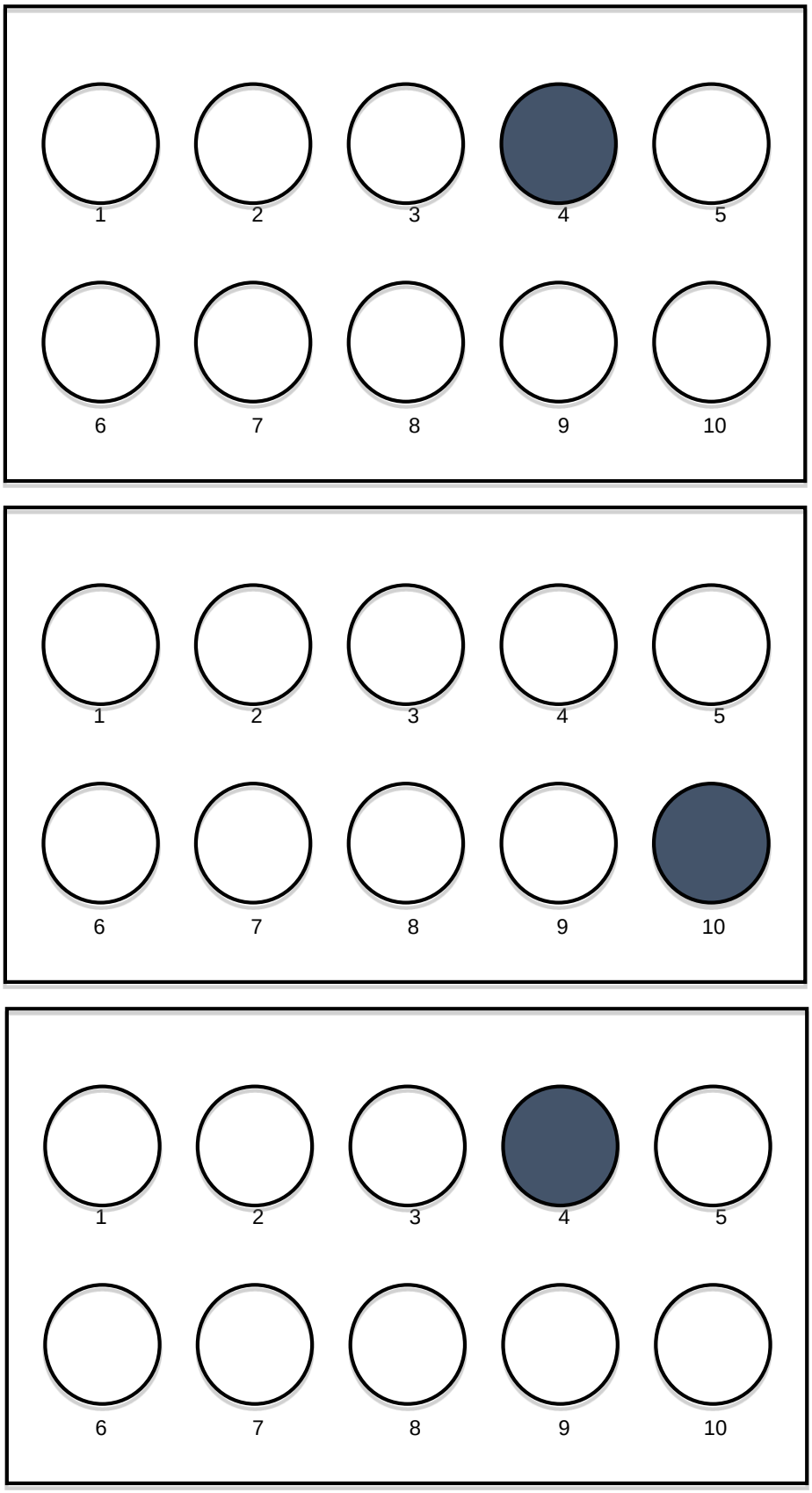
[7] Shown across three different stimulus arrays (each rectangle represents a new array/page).

APPENDIX G. Example of Brixton set 6 (repeat rule 1): circle moves forward 1[8]



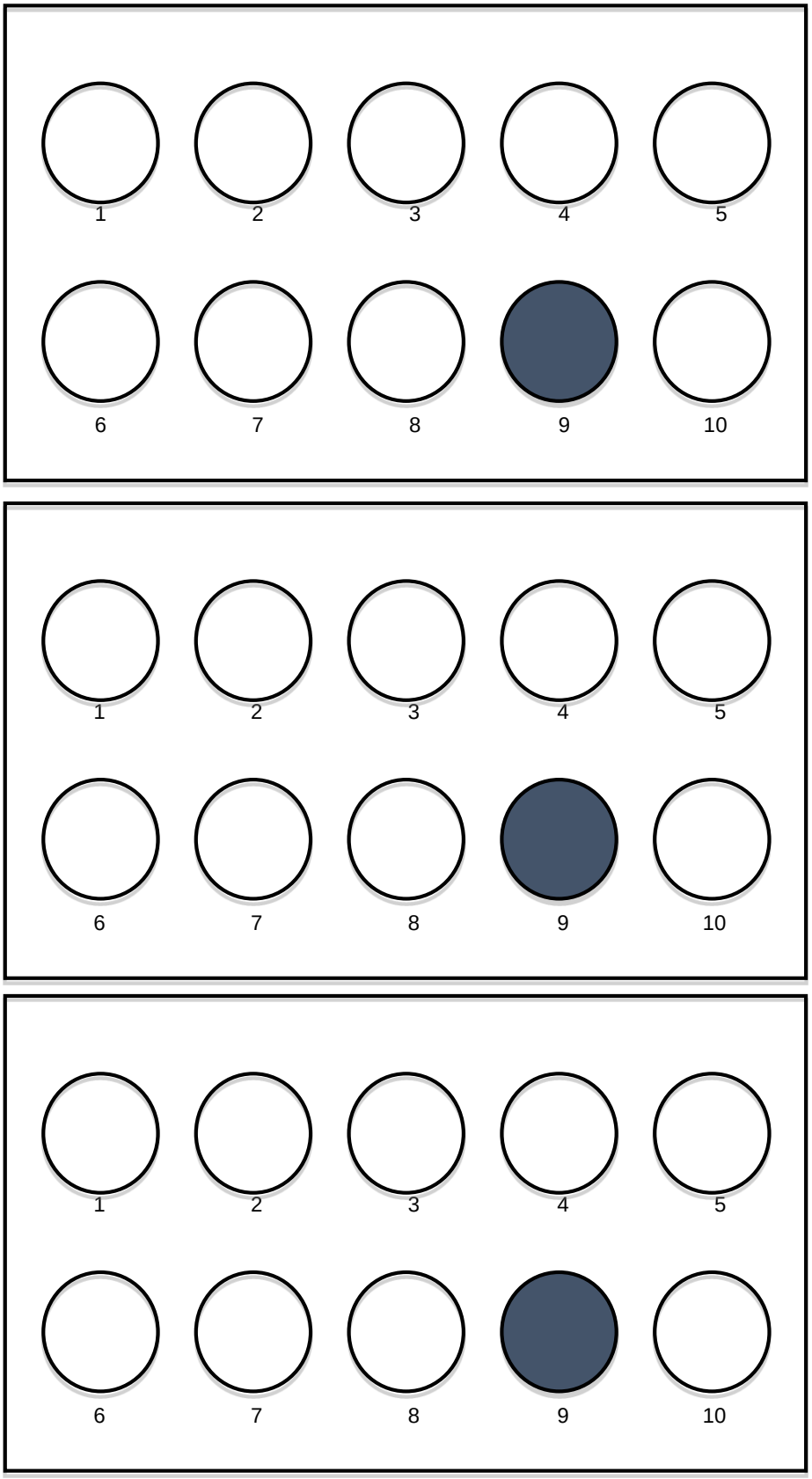
[8] Shown across three different stimulus arrays (each rectangle represents a new array/page).

APPENDIX H. Example of Brixton set 7 (rule 4): circle alternates between 10 & 4[9]



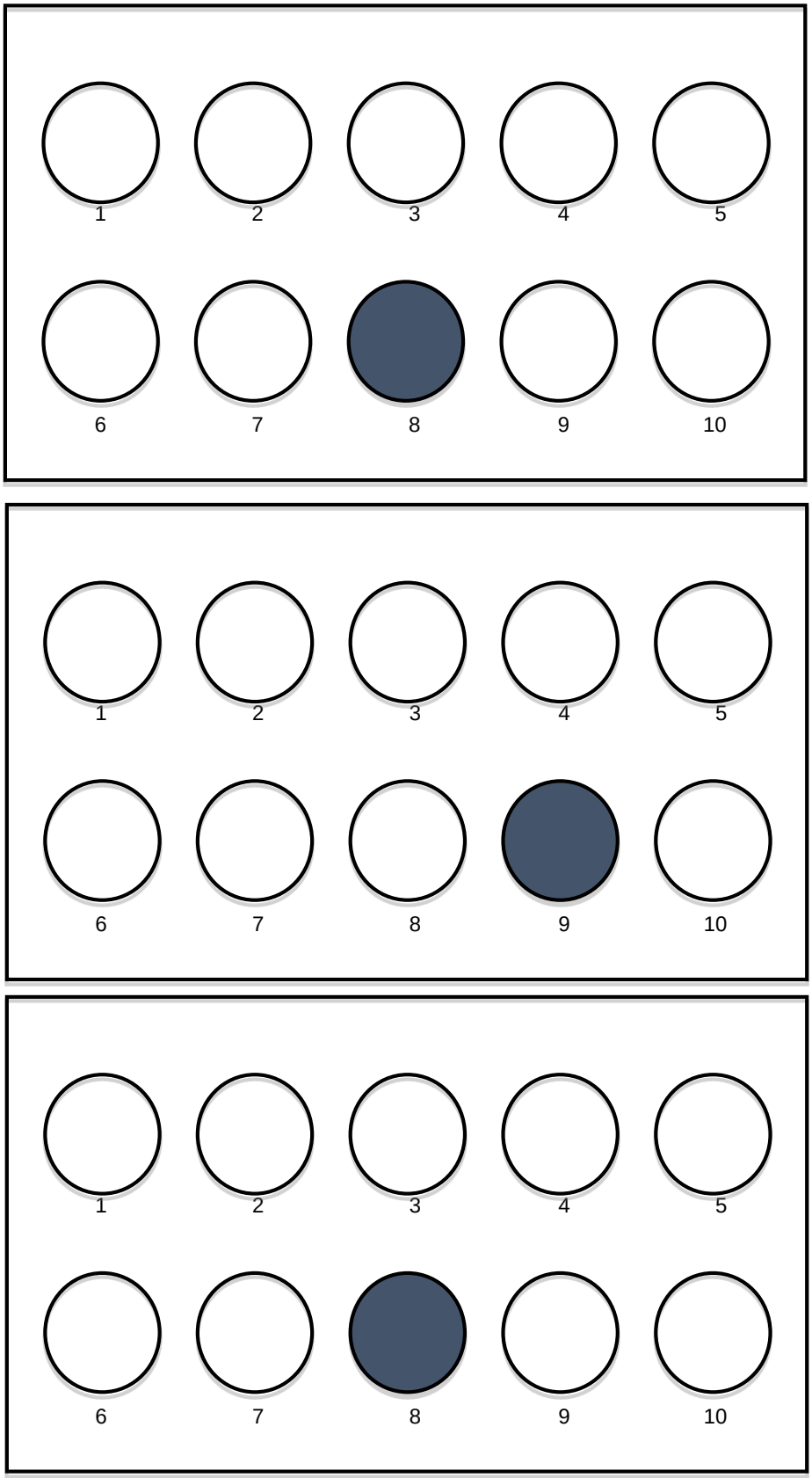
[9] Shown across three different stimulus arrays (each rectangle represents a new array/page).

APPENDIX I. Example of Brixton set 8 (rule 5): circle stays in position 9[10])



[10] Shown across three different stimulus arrays (each rectangle represents a new array/page).

APPENDIX J. Example of Brixton set 9 (rule 6): circle alternates between 8 & 9[11])



[11] Shown across three different stimulus arrays (each rectangle represents a new array/page).

APPENDIX K. UEL Ethical approval and checklist

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

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

School of Psychology

Professional Doctorate Programmes

To Whom It May Concern:

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

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

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

Yours faithfully,

Dr. Mark Finn

Chair of the School of Psychology Ethics Sub-Committee

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

ETHICAL PRACTICE CHECKLIST (Professional Doctorates)

SUPERVISOR: Matthew Jones Chesters **ASSESSOR:** Davide Rivolta

STUDENT: Sophie Inchley Mort **DATE (sent to assessor):** 01/07/2014

Proposed research topic: Induction and HIV-associated Neurocognitive Disorders

Course: Professional Doctorate in Clinical Psychology

1. Will free and informed consent of participants be obtained? YES
2. If there is any deception is it justified? N/A
3. Will information obtained remain confidential? YES
4. Will participants be made aware of their right to withdraw at any time? YES
5. Will participants be adequately debriefed? YES
6. If this study involves observation does it respect participants' privacy? NA
7. If the proposal involves participants whose free and informed consent may be in question (e.g. for reasons of age, mental or emotional incapacity), are they treated ethically? NA
8. Is procedure that might cause distress to participants ethical? NA
9. If there are inducements to take part in the project is this ethical? NA
10. If there are any other ethical issues involved, are they a problem? NA

APPROVED

YES		

MINOR CONDITIONS:

REASONS FOR NON APPROVAL:

Assessor initials: DR Date: 01 July 2014

RESEARCHER RISK ASSESSMENT CHECKLIST (BSc/MSc/MA)

SUPERVISOR: Matthew Jones Chesters **ASSESSOR:** Davide Rivolta

STUDENT: Sophie Inchley Mort **DATE (sent to assessor):** 01/07/2014

Proposed research topic: Induction and HIV-associated Neurocognitive Disorders

Course: Professional Doctorate in Clinical Psychology

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

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

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

APPROVED

YES		

MINOR CONDITIONS:

REASONS FOR NON APPROVAL:

Assessor initials: DR Date: 1st July 2014

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

APPENDIX L. Consent form (both groups)

CONSENT FORM
UNIVERSITY OF EAST LONDON

CONSENT FORM

Title of Project: Componential analysis of induction and executive function in HIV associate neurocognitive disorders

Name of Researcher: Sophie Inchley-Mort

Please initial all boxes

1. I confirm that I have read and understand the information sheet for the above stud I have had the opportunity to consider the information, ask questions and have h these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that all information collected in this study will remain strictly confidential. Only the researcher(s) involved in the study will have access to identifying data. It has been explained to me what will happen once the research study has been completed. ☐

4. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of person taking consent	Date	Signature

APPENDIX M. Participant information (HIV Group)

PARTICIPANT INVITATION LETTER
UNIVERSITY OF EAST LONDON

INFORMATION SHEET

Title of Project: Componential analysis of induction and executive function in HIV associate neurocognitive disorders

Name of Researcher: Sophie Inchley-Mort

Who am I?

I am Sophie and I am a clinical psychology trainee at the University of East London. My email address is [redacted]

What is this about?

I am doing a study that looks at the effect of HIV infection on people's ability to think, learn and follow new information. Finding out about this will improve our understanding of the impact of HIV on the brain and on daily living skills. It will also help us know how to give better care, and make better interventions for people with HIV in the future.

What does the study involve?

If you decide that you would like to be involved you will be invited to complete a set of psychological tests which look at different types of abilities, such as attention, problem solving and memory. Some of the tests involve verbal questions and responses and others will be pen and paper exercises. In total, the tests will last approximately 90 minutes and you will be able to have a break in the middle. If you change your mind you can withdraw from the study at any time. If you do, any information that you have given will not be used.

What happens to the information we collect?

Any information that you give to us for the study will be kept confidentially. All names and identifiable information will be removed and kept separately from the information that the service holds about you.

What happens to the results of the study?

The results that come from this research will be written up in a doctoral thesis that will be submitted to the University of East London. The write up may also be published in an academic journal in the future to help increase understanding of

HIV and its effect on the brain. No identifiable information of any participant will be included in either report.

What will happen afterwards?

Before, during, and after the assessment session I will be there to answer any questions or concerns you have about the study.

What should I do if I have any questions now?

If you have any questions about the study you can contact me on:

Email address: [redacted]

Or

Dr Matthew Jones Chesters (Clinical Psychologist/tutor at the University of East London) on:

Email address: [redacted]

Thank you

Sophie Inchley-Mort

Trainee Clinical Psychologist

APPENDIX N. Participant information (Control group)

PARTICIPANT INVITATION LETTER
UNIVERSITY OF EAST LONDON

INFORMATION SHEET

Title of Project: Componential analysis of induction and executive function in HIV associate neurocognitive disorders

Name of Researcher: Sophie Inchley-Mort

Who am I?

I am Sophie and I am a clinical psychology trainee at the University of East London. My email address is [redacted]

What is this about?

I am doing a study that looks at the effect of HIV infection on people's ability to think, learn and follow new information. Finding out about this will improve our understanding of the impact of HIV on the brain and on daily living skills. It will also help us know how to give better care, and make better interventions for people with HIV in the future. I am also collecting information from people without HIV infection so that I can compare the results between the two groups and see what changes following HIV infection.

What does the study involve?

If you decide that you would like to be involved you will be invited to complete a couple of psychological tests which look at different types of abilities, such as attention, rule detection and memory. Some of the tests involve verbal questions and responses, and others will be pen and paper exercises. In total, the tests will last approximately 15-20 minutes. If you change your mind you can withdraw from the study at any time. If you do, any information that you have given will not be used.

What happens to the information we collect?

Any information that you give to us for the study will be kept confidentially. All names and identifiable information will be removed and kept separately from the information that the service holds about you.

What happens to the results of the study?

The results that come from this research will be written up in a doctoral thesis that will be submitted to the University of East London. The write up may also be published in an academic journal in the future to help increase understanding of HIV and its effect on the brain. No identifiable information of any participant will be included in either report.

What will happen afterwards?

Before, during, and after the assessment session I will be there to answer any questions or concerns you have about the study.

What should I do if I have any questions now?

If you have any questions about the study you can contact me on:

Email address: [redacted]

Or

Dr Matthew Jones Chesters (Clinical Psychologist/tutor at the University of East London) on:

Email address: [redacted]

Thank you

Sophie Inchley-Mort

Trainee Clinical Psychologist

APPENDIX O. Scaled scores and subjective labels (adapted from Slick, 2006)

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

APPENDIX P. Table of Participant Characteristics (HIV Group)[12]

No.	Age	Sex	Ethnicity	Is Primary language English?	Education (years)	Year Diagnosed (nadir CD4)	CD4	Viral Load
1	38	F	Kenyan	Yes	12	2014 (130)	24	450
2	46	M	White British	Yes	16	2007 (308)	310	122
3	50	F	Ethiopian	No	14	1997 (100)	340	1200
4	58	M	White British	Yes	21	2013 (140)	239	Unknown
5	65	M	Ghanaian	No	14	2014 (200)	200	133000
6	49	M	Nigerian	No	14	2012 (50)	50	97000
7	65	M	White British	Yes	15	1998 (138)	200	<40
8	49	M	Ugandan	No	12	1993 (Unknown)	194	167655
9	56	M	Ugandan	Yes	18	2007 (17)	178	101
10	40	M	Portuguese	Yes	13	2001 (Unknown)	36	Unknown
11	61	M	White British	Yes	11	2014 (47)	92	97000
12	47	F	Ethiopian	No	17	2004 (37)	400	1300
13	44	M	White British	Yes	6	1990 (60)	60	Unknown

[12] Comorbidities for each participant are presented in table 14

APPENDIX Q. Table of Participant Characteristics (Control Group)

No.	Age	Sex	Ethnicity & Country of Birth	Is Primary language English?	Education (years)	Additional Information
14	48	M	White British	Yes	15	None
15	54	M	Indian	No	8	None
16	43	M	White British	Yes	14	None
17	41	F	White British	Yes	18	None
18	55	F	White British	Yes	15	Thyroid problem
19	47	M	South African	Yes	15	None
20	65	M	Portuguese	No	17	Pain condition
21	40	F	Indian	No	17	Diabetes
22	65	M	White British	Yes	10	None
23	36	M	Black British	Yes	17	None
24	64	M	White British	Yes	12	None
25	60	F	White British	Yes	14	None
26	32	M	White British	Yes	12	None

APPENDIX R: Example of the Brixton Spatial Anticipation Test scoring form

Figure 8. Scoring section of the Brixton (from Burgess & Shallice, 1997)

Item	Ans	Resp	Score	Item	Ans	Resp	Score	Item	Ans	Resp	Score
1	-			**21**	*8*			**41**	*4*		
2	*3*			**22**	*9*			**42**	*9*		
3	*4*			**23**	*10*			**43**	*9*		
4	*5*			**24**	*1*			**44**	*9*		
5	*6*			**25**	*2*			**45**	*9*		
6	*7*			**26**	*3*			**46**	*9*		
7	*4*			**27**	*10*			**47**	*9*		
8	*3*			**28**	*9*			**48**	*9*		
9	*2*			**29**	*8*			**49**	*9*		
10	*1*			**30**	*1*			**50**	*8*		
11	*10*			**31**	*2*			**51**	*9*		
12	*9*			**32**	*3*			**52**	*8*		
13	*10*			**33**	*4*			**53**	*9*		
14	*5*			**34**	*5*			**54**	*8*		
15	*10*			**35**	*4*			**55**	*9*		
16	*5*			**36**	*10*						
17	*10*			**37**	*4*						
18	*5*			**38**	*10*				TOTAL ERRORS		
19	*10*			**39**	*4*						
20	*7*			**40**	*10*						

Information about columns on the score sheet
Item column shows the trial number
Ans column is the correct answer needed to score correctly on the trial
Resp column is where the actual answer of the participant is inserted
Score column is where the answer is marked correct or incorrect.

Information about trials and sets[13]:
Set 1 = trials 1-6
Set 2 = trials 7-13
Set 3 = trials 14- 19
Set 4 = trials 20- 26
Set 5 = trials 27-29
Set 6 = trials 30-34
Set 7 = trials 35-41
Set 8 = trials 42- 49
Set 9 = trials 50-55

[13] Rules used in each set are described in Appendixes B – J.

APPENDIX S: Example of marking using the novel scale on the Brixton Spatial Anticipation Test

Figure 9. Completed Brixton score sheet (answers are hypothetical)

Item	Ans	Resp	Score	Item	Ans	Resp	Score	Item	Ans	Resp	Score
1	-	2	-	21	8	8	✓	41	4	4	x
2	3	3	✓	22	9	9	✓	42	9	8	x
3	4	4	✓	23	10	10	✓	43	9	10	x
4	5	5	✓	24	1	5	x	44	9	9	✓
5	6	6	✓	25	2	2	x	45	9	4	x
6	7	7	✓	26	3	3	✓	46	9	2	x
7	4	8	x	27	10	2	x	47	9	5	x
8	3	3	✓	28	9	10	x	48	9	5	x
9	2	2	✓	29	8	10	x	49	9	1	x
10	1	1	✓	30	1	1	✓	50	8	8	✓
11	10	6	x	31	2	2	✓	51	9	9	✓
12	9	9	✓	32	3	3	✓	52	8	8	✓
13	10	10	✓	33	4	3	x	53	9	9	✓
14	5	5	✓	34	5	4	x	54	8	8	✓
15	10	10	✓	35	4	4	✓	55	9	9	✓
16	5	5	✓	36	10	10	✓				
17	10	10	✓	37	4	4	✓				
18	5	5	✓	38	10	10	✓	TOTAL ERRORS			19
19	10	10	✓	39	4	4	✓				
20	7	1	x	40	10	5	x				

Overall scores:
Sets gained = set 1, 2, 3, 4, 6, 7, 9 (7 sets out of 9)
Rules gained = 1, 2, 3, 4, 6 (5 rules out of 6)
Trials to acquire sets= 13
Sets lost = 2, 4, 7 (3 lost)

Error Key:	**Count**
Green = set-loss due to 1-10 shift (also in this error due to 1-10 shift)	1
Pink = set-loss, reverting to 10-5 rule	1
Purple = set-loss, anticipation (participant verbalised)	1
Red = regained set	2
Grey = response capture	2
Pale blue = error type, no observable strategy	4
Dark green = perseverate with previous answer	3
Black = perseverate with previous rule	2
Yellow = monitoring error, did not realise rule change	1

APPENDIX T. Example of the 1-10 shift

When the circle reaches position 1 during set 2 (circle moves backwards by 1) it then moves to position 10 (see below). However in some cases, people who had already acquired the set would state that the circle was going to move to position 6 or another position which did not follow the set 2 rule. This also happened when the circle was in position 10 and was meant to move to position 1.