Frontal lobe dysfunction, as measured by the Frontal Systems Behavioural Scale, in the context of HIV infection and heavy episodic drinking

Dissertation

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Declaration

I, Everhardus Johannes Smith, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. This work has not been published prior to registration for the MMed in Psychiatry degree.

Signed: …Signed by candidate…

Date: 29/11/2020

Table of contents

Abstract

Background: The frontal lobe of the human brain is integral in regulating behaviour. Behavioural disturbances such as apathy, disinhibition, and dysexecutive function are well-known consequences of frontal lobe pathology, leading to significant impairment. Heavy episodic drinking (HED) and HIV are common conditions that impair the frontal lobe, with disinhibition frequently being seen in people with HED, apathy in HIV positive patients and both HIV and HED leading to executive dysfunction. There is a paucity of research on the interplay between HIV and HED and how this impacts behaviour associated with frontal lobe dysfunction. The Frontal Systems Behaviour Scale (FrSBe) is a questionnaire designed to measure problematic behaviour associated with frontal systems impairment. It has been used in a range of clinical populations. It consists of a total score and three subscale scores, namely apathy (Scale A), disinhibition (Scale D) and executive dysfunction (Scale E). This tool is easy to administer and has the potential to provide clinically useful information that could guide management of patients with these conditions.

Aim: As a first step to knowing more about the complex interplay between HIV and HED and its effects on frontal lobe function, the aim of this study was to determine the relationship between HIV status, HED and frontal-systems behavioural dysfunction (impulsivity, apathy, and executive dysfunction) as measured by the FrSBe.

Methods: Participants for this quantitative, cross-sectional, and analytical study were recruited from the Nolungile Clinic in Khayelitsha, Cape Town. They were grouped according to their HIV- and HED status. Relevant demographic and clinical data were obtained. Participants completed the Substance Abuse and Mental Illness Symptoms Screener (SAMISS) questionnaires and the FrSBe self-report measure that was translated into isiXhosa. Both measures were scored and the FrSBe raw scores were converted to T-scores.

Results:

A total of the 99 participants met the inclusion criteria, of which 25 were in the HED only group, 22 in the HIV+ only group, 26 in the dual group, and 26 were in the control group. The mean age (SD) of the sample was 37.92 (8.8) years. There was a statistical difference between groups for the total drinking score on the SAMISS ($p < 0.001$). The viral load in the comorbid group was significantly higher than in the HIV only group (Mann-Whitney $W = 229$, $p = .011$). No other clinical variable demonstrated statistical significance (Table 4). The only statistically significant difference ($p = 0.046$) in unadjusted mean total FrSBe scores was between HED only and HIV only groups, with the HED group having relatively higher scores. There were statistically significant differences in adjusted means for the FrSBe disinhibition subscale scores between the groups (p =

0.005), but there were no statistically significant differences for either the FrSBe apathy subscale scores (p = 0.827), or for the FrSBe executive dysfunction subscale scores (p = 0.024). Disinhibition scores were significantly greater in both the dual group (p = 0.026) and the HED only group (p = 0.018), compared to the HIV only group. Clinically significant deficits, as defined by the FrSBe (converted T-score >= 65), were present on the FrSBe Total Score in 29 of the participants. On the apathy subscale score, 36 participants had clinically significant (T-score >= 65) deficits, 14 had deficits on the disinhibition subscale, and 34 had on the executive dysfunction subscale. There were no statistically significant differences in the proportion of participants with clinically significant deficits between groups for any FrSBe scores.

Conclusions:

This study shows that people with HED have more dysfunctional behaviour associated with frontal system impairment and are more disinhibited. HIV status does not appear to influence frontal system behaviour. These finding needs to be interpreted with caution as the study FrSBe was administered in isiXhosa, in which it has not been validated, and no normative data was available for the study population. Future studies validating the FrSBe in a South African context and deriving normative data for South African populations would be a first step into developing the FrSBe into a clinically useful tool. This could, in turn, potentially lead to improved care and treatment in these conditions by identifying specific impairments and problematic behaviours as targets for intervention.

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List of tables

List of figures

Abbreviations

AUDIT	Alcohol Use Identification Test
AUDIT-C	AUDIT alcohol consumption questions
AUQ	Alcohol usage questionnaire
BDI-II	Beck Depression Inventory-II
cART	Combined antiretroviral therapy
FHS	Faculty of Health Sciences
FLOPS	Frontal lobe personality scale
GSH	Groote Schuur Hospital
HREC	Human Research Ethics Council
HRQoL	Health-related quality of life
I-ADLs	Instrumental activities of daily living
TFLB	Timeline FollowBack Questionnaire
UCT	University of Cape Town

Glossary of terms

Frontal disinhibition	Frontal disinhibition results from damage to the orbitofrontal area of the frontal lobe. Aspects of the basal forebrain and medial frontal lobe are also involved. This usually results in behavioural disinhibition as manifested by impulsivity, impaired judgment, and an inability to delay gratification, and may include emotional reactivity and increased energy (Scott & Schoenberg, 2011).
Frontal lobe	The anterior one-third of the brain represents the frontal lobe, which is positioned superior to the temporal lobe and anterior to the parietal lobe. It lies above the lateral fissure and anterior to the central sulcus (Guido, 2011).
Frontal systems	The frontal lobe contains five parallel frontal-subcortical circuits that connect the frontal lobe to deep brain structures and link functionally similar areas of the brain (Alexander et al., 1986). These circuits are defined and named according to their site of origin in the frontal lobe or according to their function. These five circuits are known as the motor circuit, oculomotor circuit, dorsolateral prefrontal circuit, orbital frontal and anterior cingulate circuits (Tekin & Cummings, 2002).
Heavy episodic drinking (HED)	This is defined as six standard drinks (a standard drink equals 14 grams of alcohol) per occasion on at least a weekly basis for a year (Bauer & Ceballos, 2014; Míguez-Burbano et al., 2014).
Instrumental activities of daily living (I-ADLs)	This refers to complex activities related to independent living in a person's community (e.g., managing medication and finances) (Mlinac & Feng, 2016).
Impulsivity	Acting or done without forethought (*Oxford Dictionaries*, 2019).

Chapter 1
Introduction and literature review

Introduction

The human frontal lobe, including its parallel subcortical neuronal circuits, plays an integral part in behaviour. Therefore, direct frontal lobe dysfunction, or indirect disruption of the frontal-subcortical circuits, may be associated with behavioural disturbances. Dysfunction in the dorsolateral prefrontal circuit typically manifests with executive functioning impairment, whereas anterior cingulate circuit dysfunction is typically associated with abnormal motivational states. Orbitofrontal circuit impairment often presents as personality change (Tekin & Cummings, 2002).

Frontal behavioural dysfunction is relevant in a clinical setting as the associated symptoms pose a threat to personal autonomy and increase the burden of care on families and society at large (Stout et al., 2003). Disinhibition increases risky behaviour and results in increased risk for adverse sequelae, while apathy and executive functioning impairment has been shown to impact instrumental activities of daily living (I-ADLs) negatively (Gorman et al., 2009; Kamat et al., 2012; Karzmark et al., 2012). Apathy has also been shown to be negatively associated with combined antiretroviral therapy (cART) adherence in particular (Gorman et al., 2009; Kamat et al., 2012).

In South Africa, human immunodeficiency virus (HIV) infection and heavy episodic drinking (HED) are highly prevalent (*Global Report: UNAIDS Report on the Global AIDS Epidemic*, 2010; Shield et al., 2013; World Health Organization et al., 2018), and both have been associated with frontal lobe dysfunction. For example, apathy and executive dysfunction are often apparent in HIV-positive patients (McIntosh et al., 2015). Furthermore, frontal lobe dysfunction both predisposes individuals to and results from harmful alcohol use (Khanna et al., 2017; Meil et al., 2016). Little is known about the interplay between HED and HIV on frontal lobe dysfunction and behavioural sequelae. In a resource-constrained setting, such as South Africa, a behavioural measure that is accurate, easy to use, and quick to administer would have potential clinical value. The identification of problematic behaviour could reveal therapeutic targets and improve the clinical management of patients.

Frontal lobe dysfunction has been measured with neuropsychological testing, imaging, and behavioural measures. However, these are time-consuming, resource-intensive, and abnormalities on imaging do not necessarily correspond to functional impairment. Behavioural measures, including the use of the Frontal Systems Behaviour Scale (FrSBe), are potential alternatives.

The FrSBe was developed to identify and quantify disordered behaviour associated with damage to the frontal systems of the brain. The scale measures executive dysfunction, disinhibition, and apathy. It has been used to measure behavioural dysfunction in a range of clinical patient populations, such as different dementia types, traumatic brain injury, as well as movement-, demyelinating- and substance use disorders (Carvalho et al., 2013; Grace & Malloy, 2001; Stout et al., 2003).

To our knowledge, no studies have used the FrSBe to measure disordered behaviour amongst individuals with HIV and HED. Therefore, the aim of this study was to determine the relationship between HIV status, HED, and frontal-systems behavioural dysfunction (impulsivity, apathy, and executive dysfunction) as measured by the Frontal Systems Behavioural Scale (FrSBe).

Literature review

Frontal lobe function in health and disease

The frontal lobe makes up the anterior portion of the brain and includes five frontal-subcortical circuits (Alexander et al., 1986). These are defined and named according to their site of origin in the frontal lobe or according to their function. These five circuits are known as the motor circuit, oculomotor circuit, dorsolateral prefrontal circuit, orbital frontal, and anterior cingulate circuits (Tekin & Cummings, 2002).

The frontal lobe of the human brain has long been known to play a significant role in human behaviour (Miller & Cohen, 2001). The motor and oculomotor circuits are primarily involved in motor function. In contrast, the dorsolateral prefrontal circuit, orbital frontal circuit and anterior cingulate circuit are involved in executive functioning, social behaviour, and motivational states respectively (Alexander et al., 1986; Alexander & Crutcher, 1990). These parallel frontal-subcortical circuits link areas of the cortex to subcortical structures. They are also thought to mediate coordination between regions in the brain that are functionally similar through open afferent and efferent connections (Alexander & Crutcher, 1990; Tekin & Cummings, 2002).

Dysfunction in these circuits, either in the cortex or subcortical structures, can lead to a range of disturbances in behaviour and other neuropsychiatric effects. The specific fallout depends on the circuit or circuits affected by the pathology (Duffy & Campbell, 1994). For example, patients with impaired dorsolateral prefrontal cortex circuits present with executive functioning impairment, as evidenced by impaired reasoning and mental inflexibility (Duffy & Campbell, 1994). Executive functioning impairment has also been linked to a worsening ability to perform I-ADLs (Karzmark et al., 2012). Furthermore, orbitofrontal circuit pathology typically results in personality change. Marked emotional lability with disinhibition is often noted in this type of impairment. This often manifests as irritability and explosive outbursts (Tekin & Cummings, 2002). Social functioning impairment is often seen as well, with inappropriate responses to social cues. Impaired empathy and judgement are also common in these cases (Tekin & Cummings, 2002). Anterior cingulate circuit lesions are known to lead to apathy (Kamat et al., 2012; Tekin & Cummings, 2002). Apathy manifests on a spectrum ranging from decreased motivation to akinetic mutism, in cases with bilateral lesions to the anterior cingulate (Harding, 2011; Tekin & Cummings, 2002). The aetiology of frontal-subcortical circuit dysfunction is multiple and varied, but evidence has shown that both HIV and alcohol use is strongly associated with impairment in these circuits with resulting behavioural and cognitive manifestations.

Impact of HIV and HED on frontal lobe function

In the South African context, both harmful alcohol use and infection with HIV are highly prevalent. Although both are associated with multiple comorbidities that warrant clinical attention (Heaton et al., 2010), a key concern relates to their effects, alone and in conjunction, on frontal systems and its resulting sequelae, the detrimental effect on treatment adherence in particular (Dux & Lee-Wilk, 2018; Gorman et al., 2009).

HED as a cause of frontal lobe dysfunction

South Africa has a high prevalence of harmful alcohol use and heavy episodic drinking (HED) (Shield et al., 2013; World Health Organization et al., 2018). HED, commonly referred to as ‘binge’ drinking, is defined variably in the literature. For the current study, HED is defined as drinking at least six standard drinks (a standard drink equals 14 grams of alcohol) per occasion on at least a weekly basis for the past three months (Bauer & Ceballos, 2014; Míguez-Burbano et al., 2014). Of all provinces of South Africa, the Western Cape appears to have the highest prevalence of HED (16.3%; 95% CI 7.4-11.1), as determined by the Alcohol Use Identification Test (AUDIT) in a random population sample (Peltzer et al., 2011; Shield et al., 2013).

The relationship between alcohol and frontal-striatal circuits is complex and bi-directional. Impulsivity and disinhibition are both known to be risk factors for alcohol misuse, with alcohol being linked to executive function impairment (Meil et al., 2016). Individuals with alcohol use disorders have been shown to have impaired insight and decreased awareness of their problem. More severe alcohol use is linked to more impairments in awareness (Verdejo-García & Pérez-García, 2008). Harmful alcohol use may therefore occur in a behavioural context of increased impulsivity, dysexecutive functioning and impaired insight. Frontal lobe dysfunction could both increase the risk of problematic alcohol use as well as result from it.

It is widely accepted that problematic alcohol use has several deleterious effects on the brain and cognitive function. There is growing evidence that alcohol use also causes frontal lobe dysfunction. There is some evidence that repeated cycles of bingeing and withdrawal that characterise binge drinking might be particularly harmful to the brain (Hunt, 1993). Executive functioning is particularly impaired (Galandra et al., 2019; Khanna et al., 2017). Although some research has examined these impairments with different forms of cognitive testing (Khanna et al., 2017), very few studies have assessed the behavioural sequelae of harmful alcohol use in general, and in the context of HED specifically.

HIV as a cause of frontal lobe dysfunction

South Africa has the largest total number of HIV infections in the world (*Global Report: UNAIDS Report on the Global AIDS Epidemic*, 2010). HIV is a neurotrophic virus, which means that the neuropsychiatric manifestations of HIV, both cognitive and behavioural, are common and varied. HIV infection is also associated with lower health-related quality of life (HRQoL) (Kamat, Woods, et al., 2016). Apathy remains one of the common neuropsychiatric behavioural symptoms in people living with HIV (Castellon et al., 2000; Cole et al., 2007; McIntosh et al., 2015). Executive dysfunction on cognitive testing has also been well documented in this group (Fellows et al., 2014; Walker & Brown, 2018; Witten et al., 2015).

Complex interplay between HED and HIV

It has been shown that higher prevalence rates of alcohol consumption and alcohol use disorders are found in HIV infected populations than in the general population (Hahn & Samet, 2010; Heaton et al., 2010; Kader et al., 2014). In a study by Kader et al. (2014), done at HIV clinics in Cape Town, South Africa, 37% of the 1503 patients in the study indicated hazardous/harmful drinking. A causal effect between alcohol and HIV incidence has also been demonstrated (Rehm et al., 2017). Impaired decision-making has been implicated in this complex relationship between alcohol and HIV, with alcohol linked to worsened outcomes in HIV (Hahn & Samet, 2010; Rehm et al., 2017). Compound adverse effects of comorbid alcohol and HIV on cognition and executive functioning has also been demonstrated (Fama et al., 2016; Newman, 2014). Rothlind et al. (2005) reported additive adverse effects on neuropsychological functioning in patients with both HIV and heavy active alcohol use. These researchers postulated that executive functioning and heavy drinking might mediate health-related behaviours in HIV-positive patients because executive functioning difficulties and heavy alcohol use were associated with lower levels of self-reported medication adherence in their HIV-positive sample. It is, therefore, essential to understand the role the brain and the frontal lobe play in this patient population.

Behavioural measures of frontal lobe function

There are multiple ways of testing frontal lobe function in the context of HIV or alcohol use. For example, numerous studies have used cognitive neuropsychological testing (Foster et al., 2015; Robbins et al., 1998). Other studies have used imaging techniques (Pal et al., 2012). However, these are time-consuming, resource-intensive, and abnormalities on imaging do not necessarily correspond to functional impairment. Behavioural measures, including the use of the Frontal Systems Behaviour Scale (FrSBe), are potential alternatives.

The FrSBe, previously referred to as the frontal lobe personality scale (FLOPS) (Grace et al., 1999), was published in its current form in 2001. It encompasses three subscales, namely, apathy (Scale A); disinhibition (Scale D), and executive dysfunction (Scale E). It has an informant and a self-report scale of which only the latter was completed in this study. The FrSBe was designed to measure behaviours in populations with neurological impairments and is the only measure of frontal lobe functioning that is based on a theoretical construct (Carvalho et al., 2013; Grace & Malloy, 2001; Stout et al., 2003).

Tests that measure executive functioning directly through neuropsychological testing, or indirectly through relevant behaviours such as the FrSBE, are clinically useful. They have the potential to predict how well patients perform instrumental activities of daily living (IADLs), such as managing their finances, and fetching their own medication (Karzmark et al., 2012). Karzmark et al. (2012) conducted a study with a sample of patients referred for neuropsychological testing with primarily neurologic diagnoses at a university medical centre. The executive dysfunction subscale of the

FrSBe, as completed by a family member, was found to be a more important predictor of IADLs than the two self-regulating measures, apathy and disinhibition subscales. The FrSBe has the potential to identify specific problematic behaviours that lead to impairment in IADLs. These behaviours could become targets for patient-specific therapeutic action. Overall, this means that the use of the FrSBe might improve patient management and outcomes.

FrSBe in alcohol and HIV

It is well established that poor inhibitory control and trait impulsivity are risk factors for alcohol misuse (Weafer et al., 2015). In a recent study by Meil et al. (2016), FrSBe self-report disinhibition scores emerged as a unique predictor for binge drinking frequency. There appear to be no studies that have examined the effects of HED on FrSBe scores in an HIV population.

In acute and early HIV infection, significantly higher levels of current apathy and executive dysfunction have been demonstrated than controls, but not greater disinhibition as self-reported on the FrSBe (Kamat, Doyle, et al., 2016; Kamat et al., 2012). Higher apathy scores on the FrSBe self-report are known to correlate with impairment in IADLs in patients living with HIV. Apathy was also strongly associated with decreased mental and physical HRQoL in these patients (Kamat, Woods, et al., 2016).

Rationale

This literature review has shown that both HIV and alcohol use can have deleterious consequences for frontal lobe function. However, there appears to be a lack of data available regarding the effects of an interplay between HED and HIV infection on the frontal systems of the brain. There is also a paucity of research on how HIV and alcohol influence the behavioural manifestations of frontal lobe syndromes in these population groups, especially in areas of executive functional impairment, apathy, and disinhibition. To our knowledge, no studies have used behavioural measures, such as the FrSBe, to quantify frontal lobe dysfunction and its behavioural sequelae in HIV-positive individuals with comorbid HED. The FrSBe might be a quick and useful tool for understanding behavioural challenges in patients, especially in low resource settings. This information has the potential to inform changes in patient management strategies which, in turn, could reduce the morbidity and mortality associated with these conditions. Therefore, as a first step to knowing more about the complex interplay between HIV and HED and its effects on frontal lobe function, the focus of the current study will be to use the FrSBe self-report to assess executive dysfunction, disinhibition, and apathy in patients with HIV and HED.

Research question

What is the relationship between HIV status, heavy episodic drinking (HED), and frontal-systems behavioural dysfunction (impulsivity, apathy, and executive dysfunction) as measured by the Frontal Systems Behavioural Scale (FrSBe)?

Aims and objectives

The aim of this study is to determine the relationship between HIV status, heavy episodic drinking (HED), and frontal-systems behavioural dysfunction (impulsivity, apathy, and executive dysfunction) as measured by the Frontal Systems Behavioural Scale (FrSBe). To achieve this aim, the following objectives were identified:

1) To provide a profile of heavy episodic drinkers in an HIV population by conducting descriptive analyses of demographic and clinical data, including frontal systems behaviour.

2) To determine whether HIV status and/or HED contribute to differences in FrSBe scores

Hypotheses

1) Participants with both HED and HIV+ will have higher Total FrSBe scores than in either group alone
2) Participants will display different patterns of behaviour based on their HIV and HED status. We hypothesise that:
    a) Disinhibition will be more pronounced in people with HED,
    b) Apathy will be more pronounced in people with HIV,
    c) Both HED and HIV will negatively impact executive function.

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Chapter 2
Publication-ready manuscript

The following manuscript has been prepared for submission to the *Journal of the Neurological Sciences*. The journal's aims and scope, as well as author guidelines, are given in Appendix C.

Exploring frontal lobe function in heavy episodic drinkers and persons living with HIV in South Africa by using the Frontal Systems Behavioural Scale

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Exploring frontal lobe function in heavy episodic drinkers and persons living with HIV in South Africa by using the Frontal Systems Behavioural Scale

Abstract

Background: There is a paucity of research on the interplay between HIV and Heavy episodic drinking (HED) and how this impacts behaviour associated with frontal lobe dysfunction.

Aim: To determine the relationship between HIV status, HED and frontal-systems behavioural dysfunction as measured by the Frontal Systems Behaviour Scale (FrSBe).

Methods: Participants were recruited from a primary health clinic in Cape Town. They were grouped according to their HIV- and HED status. Participants completed the Substance Abuse and Mental Illness Symptoms Screener (SAMISS) questionnaires and the FrSBe self-report measure.

Results: A total of the 99 participants were included, of which 25 were in the HED only group, 22 in the HIV+ only group, 26 in the dual group, and 26 were in the control group. The HED group had significantly higher total FrSBe scores ($p = 0.046$) than the HIV only group. There were statistically significant differences in FrSBe disinhibition subscale scores between the groups ($p = 0.005$). Disinhibition scores were significantly greater in both the dual group ($p = 0.026$) and the HED only group ($p = 0.018$), compared to the HIV only group.

Conclusions:

Persons with HED reported more global frontal system impairment and are more disinhibited than those without. HIV status does not appear to influence frontal system behaviour. These findings need to explored in larger samples, using prospective designs in order to better understand the implications.

Introduction

The human frontal lobe, including its parallel subcortical neuronal circuits, plays an integral role in behaviour. Therefore, direct frontal lobe dysfunction, or indirect disruption of the frontal-subcortical circuits, may be associated with behavioural disturbances. Harmful alcohol use is associated with frontal lobe dysfunction, and the relationship between alcohol and frontal-striatal circuits is complex and bi-directional. Frontal lobe dysfunction could both increase the risk of problematic alcohol use as well as result from it. Individuals with alcohol use disorders have been shown to have executive function impairment (Galandra et al., 2019; Khanna et al., 2017; Meil et al., 2016), impaired insight, and decreased awareness of their problem with more severe use being linked to more impairments in awareness (Verdejo-García & Pérez-García, 2008). Harmful alcohol use may therefore occur in a behavioural context of increased impulsivity, dysexecutive functioning and impaired insight.

Furthermore, HIV infection is also known to have deleterious consequences for frontal lobe function. HIV is a neurotrophic virus, which means that the neuropsychiatric manifestations of HIV, both cognitive and behavioural, are common and varied. Executive dysfunction on cognitive testing has been well documented in HIV-positive patients (Fellows et al., 2014; Walker & Brown, 2018; Witten et al., 2015). Of particular concern are the compound adverse effects of comorbid alcohol and HIV on cognition and executive functioning (Fama et al., 2016; Newman, 2014; Rothlind et al., 2005).

Although both are associated with multiple comorbidities that warrant clinical attention (Heaton et al., 2010), a key concern relates to their effects, alone and in conjunction, on frontal systems and its resulting sequelae, the detrimental effect on treatment adherence in particular (Dux & Lee-Wilk, 2018; Gorman et al., 2009). This is particularly concerning in the South African context where both harmful alcohol use and HIV infection are highly prevalent. South Africa has a high prevalence of harmful alcohol use and heavy episodic drinking (HED) (Shield et al., 2013; World Health Organization et al., 2018). The Western Cape province appears to have the highest prevalence of HED (16.3%; 95% CI,7.4-11.1) (Peltzer et al., 2011; Shield et al., 2013). South Africa also has the largest total number of HIV infections in the world (Global Report: UNAIDS Report on the Global AIDS Epidemic, 2010). It is therefore important to understand the effects of the interplay between HED and HIV on frontal lobe function in the South African setting, which could inform patient management strategies and improve patient outcomes.

The effects of HIV and alcohol use on frontal lobe function have been assessed separately, usually through cognitive testing (Khanna et al., 2017) and imaging. However, there is a paucity of research on the interplay between HED and HIV infection on the frontal systems of the brain or how either or both influences the behavioural manifestations of frontal lobe syndromes in at-risk population groups. Both cognitive testing and imaging are time-consuming and resource intensive. Abnormalities on imaging do not necessarily correspond to functional impairment. In a resource-constrained setting, such as South Africa, a behavioural measure that is accurate, easy to use, and quick to administer would have immense clinical value. Behavioural measures, including the use of the Frontal Systems Behaviour Scale (FrSBe), are potential alternatives

The Frontal Systems Behaviour Scale (FrSBe) was designed to measure behaviours in populations with neurological impairments and is the only measure of frontal lobe functioning that is based on a theoretical construct (Carvalho et al., 2013; Grace & Malloy, 2001; Stout et al., 2003). The scale measures executive dysfunction, disinhibition, and apathy. It has been used to measure behavioural dysfunction in a range of clinical patient populations, such as different dementia types, traumatic brain injury, movement-, demyelinating- and substance use disorders (Carvalho et al., 2013; Grace & Malloy, 2001; Stout et al., 2003).

To our knowledge, no studies have used the FrSBe to measure disordered behaviour due to frontal lobe dysfunction amongst individuals with both HIV and HED. This information has the potential to inform changes in patient management strategies which, in turn, could reduce the morbidity and mortality associated with these conditions. Therefore, as a first step to knowing more about the complex interplay between HIV and HED and its effects on frontal lobe function, the aim of this study was to determine the relationship between HIV status, HED and frontal-systems behavioural dysfunction (impulsivity, apathy and executive dysfunction) as measured by the FrSBe.

Methodology

Study design

This study forms part of a larger prospective study (reference no. 003/2015; Health Research Ethics Council, University of Cape Town) which aims to determine the neurocognitive and neuroimaging effects of HED in HIV-positive individuals. In the parent study, 120 participants were recruited for baseline testing between 2015 and 2018, of which 99 completed the Frontal Systems Behavioural Self-Report Scale. The Informant Scale was not completed due to financial and time constraints. The current quantitative, cross-sectional, and analytical study used relevant demographic and clinical data obtained as part of the parent study.

Study setting

All participants were recruited from the Nolungile Community Health Centre, which is situated in Khayelitsha, an urban informal settlement within the City of Cape Town metropole (Western Cape, South Africa). According to the most recent census the total population of Khayelitsha was 391741 in 2011, of which 51.1% were female and 48.9% male. The largest population group in Khayelithsa at this time were Black African (98.6%), and 90.5% spoke isiXhosa as their first language. People living in formal dwellings constituted 44.6% of the population, with only 34.6% having running water. The combined monthly household income of approximately a third (32.1%) of the population is less than R9601, of which 18.8% had no income (*Statistics South Africa*, 2011).

Study population

Eligible participants were aged between 18-65 years (inclusive) and had at least seven years of formal schooling. Cannabis users that had stopped using 30 days or more prior to the screening session could be included in the study. The Mini-International Neuropsychiatric Interview (MINI) and Beck Depression Inventory-II (BDI-II) were used to screen for mental illness. Persons with active depression, recent (12-month) substance use other than alcohol, and severe mental illness were excluded. Other research exclusion criteria included central nervous system diseases such as Wernicke's encephalopathy, head injury with loss of consciousness exceeding 30 mins, and treatment with psychotropic medication. Women of child-bearing age who indicated that they were pregnant or who could not confirm that they had menstruated within the last couple of months were also excluded in order to minimize the cognitive effects of pregnancy-associated hormonal fluctuations.

A total of 99 participants were recruited into one of four groups determined by HIV and heavy episode drinking (HED) status. The four groups were the control group (HED-, HIV-), HED only group (HED+, HIV-), HIV only group (HED-, HIV+), and the dual diagnosis group (HED+, HIV+).

HIV diagnosis

Participants with HIV were required to have had a positive diagnosis of HIV infection made by using two independent rapid HIV test kits. The ELISA test was used to reconcile two discrepant rapid test results. HIV+ individuals were also required to be either antiretroviral treatment (ART) naïve or have received one month or less of ART.

Drinking status

Drinking status was confirmed using the 3-month Timeline Follow Back (TFLB) Questionnaire at the baseline visit at Groote Schuur Hospital. To be included in the HED+ group, participants were required to report drinking at least six standard drinks per occasion once per week. No limits were set on the maximum frequency. A standard drink is defined as containing 14 grams of alcohol. To avoid many exclusions due to inconsistent drinking patterns, participants could have a 2-week period (maximum) on the TLFB where they did not meet the 6-drink criterion. Participants in the HED+ group were also required to score 4-5 on the first three items of the Substance Abuse and

Mental Illness Symptoms Screener (SAMISS), which is closely modelled on the commonly used AUDIT-c screen for hazardous drinking. An attempt was made to ensure an equal proportion of men and women within each group.

Data collection

Upon initial screening at Nolungile clinic, brief demographic (age, gender, years of education) and socioeconomic status questionnaires were administered to all participants. Following screening and recruitment, participants underwent further testing at the Department of Psychiatry and Mental Health at Groote Schuur Hospital (Cape Town, South Africa). Testing included administration of the Frontal Systems Behavioural Scale (FrSBe) and Substance Abuse and Mental Illness Symptoms Screener (SAMISS) questionnaires. A Xhosa version of the Frontal Systems Behavioural Scale (FrSBe) was developed by following the standard translation procedure, in which translation from English into isiXhosa, and back-translation was performed using home-language Xhosa speakers. This version was administered to all patients by an isiXhosa-speaking research assistant to minimize the effect of a language barrier on the outcome. A neuro-medical examination by a psychiatrist was also performed for most patients. When no psychiatrist or medical officer was available the exam was omitted. CD4 count and HIV viral load were assayed using blood samples obtained from most participants either during screening or at the follow-up visit closest in time to initial screening.

Frontal Systems Behavioural Scale (FrSBe)

The FrSBe was developed to measure and quantify behaviours associated with frontal lobe impairment (Grace & Malloy, 2001). It is a 46-item behaviour rating scale consisting of three subscales to assess three behavioural domains. The domains are apathy/akinesia (Scale A, 14 items), executive dysfunction (Scale E, 17 items), and disinhibition/emotional dysregulation (Scale D, 15 items) (Stout et al., 2003). Each item is rated on a 5-point Likert Scale (1=Almost never – 5=Almost Always), with some items being reverse scored (Grace & Malloy, 2001).

The participants' degree of dysfunctional behaviour, as measured by the FrSBe, are interpreted by using T-scores, provided in the FrSBe manual (Grace & Malloy, 2001). These are linear transformation of the raw scores obtained in their normative sample. T-scores on the total scale, and each of the subscales, were calculated in such a way that the distribution of scores has a mean of 50 and a standard deviation of 10. The normative data and T-scores were stratified by gender, age, and educational level by the authors of the FrSBe (Grace & Malloy, 2001). T-scores for both the total score, as well as each of the subscale scores, on the FrSBe of 60-64 are regarded as borderline impairment, and 65-130 are considered to be clinically significant.

Substance Abuse and Mental Illness Symptom Screener (SAMISS)

The Substance Abuse and Mental Illness Symptom Screener was developed in the USA to screen for mental disorders and substance abuse in people that have HIV (Whetten et al., 2005). A 13-item and a 16-item version were developed (Pence et al., 2005), of which the latter was used in this study. The 16-item SAMISS questionnaire consists of a substance abuse module (questions 1-7) and a mental illness module (questions 8-16). Questions 1-3 look at alcohol specifically (Pence et al., 2005). Pence et al. demonstrated a 75% specificity 86% sensitivity for substance abuse in a cohort of people living with HIV in North Carolina, USA(Pence et al., 2005). The SAMISS is known to be reliable (Breuer et al., 2012) and valid in a South African setting with the alcohol component having a specificity of 85% and a sensitivity of 94% (Breuer et al., 2014).

Data analysis

Continuous variables were summarized as means with standard deviations (SD), while nominal variables were summarized as counts and percentages. One-way multivariate analysis of covariance (MANCOVA) was used to determine whether there were significant differences in the FrSBe subscale scores between the different participant groups, after controlling for the effects of age and gender.

Linearity was tested for by making use of scatterplot matrices, which showed no indication of non-linear relationships between each pair of dependent variables within each group of the independent variable, nor between the continuous covariate and the dependent variables within each group of the independent variable. The assumption of linearity was therefore met. There was homogeneity of regression slopes, as assessed by the interaction term between HIV/HED group and age not being significant, $F(9, 214) = 0.518$; $p = 0.861$. There was also a homogeneity of variances and covariances, as assessed by Box's M test, $p > 0.001$. There were no univariate outliers in the data, as assessed by no standardized residuals being greater than ± 3 standard deviations. There were also no multivariate outliers, as assessed by Mahalanobis distance ($p>0.001$). The residuals were approximately normally distributed, as assessed through the visual inspection of Normal Q-Q Plots.

One-way analysis of covariance (ANCOVA) was used to test for the main effects of group status on the FrSBe total scores, after controlling for differences in age and gender. There was a linear relationship between age and FrSBe total scores, as assessed by visual inspection of a scatterplot. There was homogeneity of regression slopes as the interaction term was not statistically significant, $F(3, 90) = 0.323$; $p = 0.809$. Standardized residuals were approximately normally distributed, as assessed by the visual inspection of Normal Q-Q Plots. There were homoscedasticity and homogeneity of variances, as assessed by visual inspection of a scatterplot and Levene's test of homogeneity of variance ($p = 0.744$), respectively. There were no outliers in the data, as assessed by no cases with standardized residuals greater than ±3 standard deviations A Bonferroni correction was applied to reduce the risk of inflated positive findings due to multiple comparisons between the groups where post-hoc testing was conducted.

Pearson's chi-square (χ^2) test of independence (or the Fisher's exact test where appropriate) was used to test for differences in the proportion of individuals in each group with clinically significant (T-score >= 65) deficits in self-reported frontal cortical systems functioning, as well as apathy, disinhibition, and executive dysfunction.

Spearman's correlations were used to test for a relationship between total drinking scores, FrSBe subscale scores, or FrSBe total scale scores and CD4 count and viral load.

The Kruskal-Wallis test, the non-parametric equivalent of the ANOVA was used test for differences between the groups in proportion of females, education, age, and SAMISS scores.

The non-parametric Mann-Whitney test was used to compare clinical characteristics between participants classified as impaired on the FRsBe, using the published normative tables and a T-score threshold of 65 and greater.

A power analysis, using the Cohen et al. (1988) conventions for a moderate effect size, was run.

The R statistical computing platform (version 3.6.3, R Core Team, 2020) and the Statistical Package for the Social Sciences (SPSS) version 24 software were used for all statistical analyses. Statistical significance was set at $p<0.05$.

Ethics considerations

Ethical approval for this sub-study was obtained from the by University of Cape Town's Faculty of Health Science Human Research Ethics Council (reference no. 515/2019; Appendix A).

Participation in the parent study was voluntary, and all participants provided written informed consent. All data were anonymised to ensure the privacy and confidentiality of participants' personal information, with each participant assigned a unique identifier.

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of 99 participants are summarised in Table 1. The sample consisted of 41 (41.4%) males and 58 (58.6%) females. The mean age (SD) of the sample was 37.92 (8.8) years. Of the 99 participants, there were 25 in the HED only group, 22 in the HIV+ only group, 26 in the dual group, and 26 were in the control group. There were no statistically significant differences between the groups in terms of gender, age, or years of education.

Table 1: Demographic and clinical characteristics of participants (N=99).

Variable	Overall (N=99)	Groupings based on HIV and HED status				Test	*p*-value
		HED only group (n=25)	HIV only group (n=22)	Dual group (n=26)	Control group (n=26)		
Gender, n (%)							
Male	41 (41.40)	11 (44.0)	8 (36.36)	13 (50.00)	9 (34.62)	$\chi^2 = 1.586$	0.663
Female	58 (58.60)	14 (56.0)	14 (63.64)	13 (50.00)	17 (65.38)		
Mean age (SD), years	37.92 (8.84)	37.20 (10.08)	39.09 (8.71)	36.27 (7.71)	39.27 (8.90)	$\chi^2 = 2.124$	0.547
Mean years of education (SD)	10.57 (1.34)	10.4 3 (1.33)	10.47 (1.30)	10.93 (1.00)	10.55 (1.61)	$\chi^2 = 1.164$	0.762
SAMISS drinking score (SD)	9.08 (5.44)	14.39 (1.80)	4.42 (1.39)	14.35 (2.62)	3.96 (1.46)	$\chi^2 = 63.110$	< 0.001
HIV Viral Load [log (copies/mL)] (SD)	Not measured	Not measured	8.00 (2.45)	9.98 (2.16)	Not measured	W = 229	0.011*
CD4+ (cells/mL] (SD)	Not measured	Not measured	403.00 (248.77)	345.11 (257.88)	Not measured	W = 157.5	0.382

*indicates statistical significance at p<0.01

There was a statistically significant difference between groups for the total drinking score on the SAMISS ($\chi^2 = 63.11$; $p < .001$). Notably, the viral load in the comorbid group was significantly higher than in the HIV only group (Mann-Whitney W = 229), with a p-value of 0.011. There were no differences between these groups in CD4 count (W = 157.5, p = 0.382).

CD4 counts, were available for 39 of 48 HIV+ participants and ranged from 23-1095 (mean 376.28, SD 251.351). HIV VL [log (copies/mL)] were available for 35 participants and ranged from 4.663 to 13.566 (mean 11.243, SD 12.078).

Power Analysis

We calculated a power of 0.73 to detect a moderately-sized difference in the total score between the dual and single diagnostic groups (hypothesis 1). These findings are therefore somewhat underpowered and should be interpreted with caution. This hypothesis should be retested as part of primary research and using a larger sample size. Additionally, for hypothesis 2 we calculated a power of 0.92 which signifies that this study was suitably powered to detect a moderately-sized effect when comparing all 4 groups on the total or subscale scores.

The effect of HIV/HED on FrSBe total scores

The mean FrSBe scores for each group of participants are summarised in Table 2 and Figure 1. Results of a one-way ANCOVA showed that there was a statistically significant difference in mean total FrSBe scores between groups ($p = 0.023$), after adjusting for age and gender differences. The Bonferroni post-hoc test showed that the only statistically significant difference (p = 0.046) in unadjusted mean total FrSBe scores was between HED only and HIV only groups, with the HED group having relatively higher scores compared to the HIV only group. There were no other statistically significant pairwise comparisons.

Table 2: The effect of HIV/HED on FrSBe scores.

Mean FrSBe Scores (SD)	**Overall**	**Groupings based on HIV and HED status**			
		HED only group	**HIV only group**	**Dual group**	**Control group**
Apathy subscale	31.14 (5.77)	31.24 (6.24)	30.36 (5.09)	31.31 (6.86)	31.54 (4.85)
Disinhibition subscale	27.08 (7.02)	29.44 (6.14)	23.77 (6.3)	29.00 (8.73)	25.69 (5.19)
Executive dysfunction subscale	38.44 (8.34)	40.80 (9.25)	34.64 (7.73)	40.15 (7.74)	37.69 (7.65)
Total scale	96.67 (17.84)	101.48 (17.80)	88.77 (16.98)	100.46 (19.80)	94.92 (14.58)

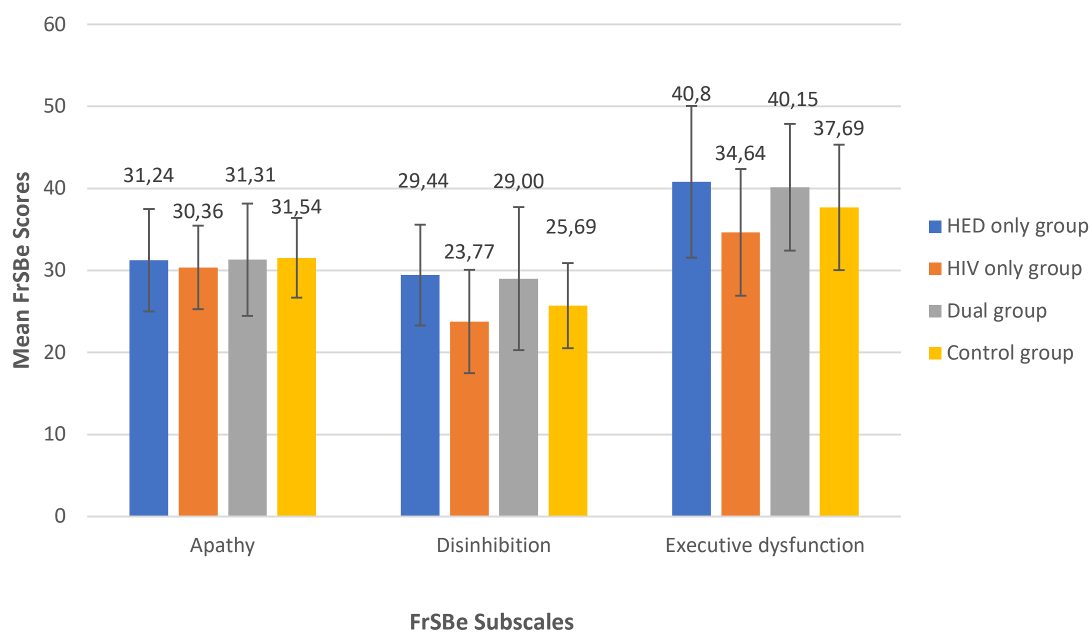

Figure 1: The effect of HIV/HED on FrSBe scores

In terms of FrSBe sub-scales, one-way MANCOVA showed there were statistically significant differences between groups after controlling for age and gender. Follow-up univariate one-way ANCOVAs were performed, where Bonferroni adjustment was made such that statistical significance was accepted when $p < 0.0167$. There were statistically significant differences in adjusted means for the FrSBe disinhibition subscale scores between the groups ($p = 0.005$), but no statistically significant differences in the adjusted means between the groups for either the FrSBe apathy subscale scores ($p = 0.827$), or for the FrSBe executive dysfunction subscale scores ($p = 0.024$).

Bonferroni post-hoc tests showed that compared to the HIV only group, disinhibition scores were significantly greater in both the dual group ($p = 0.026$) and the HED only group ($p = 0.018$).

Clinically significant deficits as measured by FrSBE scores

Clinically significant deficits, as defined by the FrSBe manual (converted T-score >= 65), were present on the FrSBe Total Score in 29 of the participants (Table 3). On the apathy subscale score, 36 participants had clinically significant (T-score >= 65) deficits, 14 participants had deficits (T-score >= 65) on the disinhibition subscale, and 34 had on the executive dysfunction subscale. There were no statistically significant differences in the proportion of participants with clinically significant deficits between groups for any FrSBe scores.

Table 3: Number of individuals with clinically significant impairment (based on FrSBe scores.

FrSBe scale	Overall (N=99), n (%)	Groupings based on HIV and HED status, n				χ^2	*p*-value
		Control (n=26)	Dual (n=26)	HED only (n=25)	HIV only (n=22)		
Total score	29 (29.3)	8	8	10	3	4.042	0.257
Apathy score	36 (36.4)	10	9	10	7	0.432	0.935
Disinhibition score	14 (14.1)	3	6	4	1	3.594	0.309
Dysexecutive score	34 (34.3)	11	8	11	4	4.461	0.216

Discussion

This study assessed the impact of HIV and HED on frontal-systems behavioural dysfunction (apathy, disinhibition, and executive dysfunction), as measured by the FrSBe. Our findings suggest that people with HED have more dysfunctional frontal systems behaviour and are more disinhibited, as demonstrated by higher scores on the FrSBe when compared to people with HIV.

Participants with HED, both in the HED-only and dual groups, scored higher on the disinhibition subscale of the FrSBe. This was expected as disinhibition is known to be associated with HED, but previous studies did not show a clear association between HIV and raised FrSBe disinhibition scores (Kamat, Doyle, et al., 2016; Kamat et al., 2012). Disinhibition is an established risk factor for alcohol misuse (Weafer et al., 2015), and Meil et al. (2016) demonstrated that FrSBe Disinhibition scores are a predictor of HED.

The higher FrSBe scores in the HED-only group compared to the HIV-only group seems to indicate more disordered behaviour and greater overall impairment in the former group. A possible explanation for the discrepancy in the degree of self-reported impairment between the groups might be selection bias for higher impairment in the HED group. Participants with alcohol misuse that qualified for the HED-only group might be particularly impaired because a pattern of bingeing and withdrawing is known to have a significant harmful effect on the brain (Hunt, 1993). The HIV-only group possibly selected for a less severe degree of illness. Neurocognitive and behavioural sequelae of HIV infection are most evident in those patients who have been infected for longer (Kamat, Doyle, et al., 2016). Selecting HIV+ participants with less than a month of ARV-exposure likely resulted in selecting people that have had the disease for a shorter period, in a lesser severity, with less neurocognitive damage compared to more chronic HIV which has been inadequately treated (or even untreated), still commonly observed in South Africa.

No significant differences were found between HED groups and controls on the apathy or executive dysfunction subscale, findings which are in keeping with those of Meil et al. (2016). The HIV groups, as compared to the others, also did not demonstrate statistically significant differences on these two subscales. This is unlike previous studies that showed higher apathy and executive dysfunction subscale scores in HIV positive people when compared to controls (Kamat, Doyle, et al., 2016; Kamat et al., 2012). The absence of findings could potentially be due to any one of several reasons. Firstly, the small sample size could be the cause or a contributing factor. Secondly, the FrSBe has not been validated in the South African context. Furthermore, even though every effort was made to ensure a valid translation of the FrSBe to isiXhosa, the questions might not have been sensitive enough to pick up apathy and executive dysfunction in our context, while being more sensitive in picking up disinhibited behaviour associated with HED.

Higher viral loads were found in the dual group compared to the HIV-only group, as expected. This was similar to findings by Baum et al. (2010) who demonstrated that high alcohol intake was associated with HIV disease progression, independent of ARV use.

The SAMISS total drinking scores were higher in the drinking groups than in the non-drinking groups, as expected. The drinking groups had similar scores, with the mean SAMISS score being somewhat higher in the HED-only group than the dual group. This, together with the small sample size, might explain in part why the HED-only group had statistically significant higher unadjusted total FrSBe scores than the HIV-only group, but the dual group did not.

Unexpectedly the dual group did not have significantly higher total FrSBe scores. Executive dysfunction subscale scores were also not significantly higher in the dual group. This might also be explained by the small sample size, where subtle differences between groups could not be resolved. Alcohol use is known to be associated with impairment in insight (Verdejo-García & Pérez-García, 2008), which might lead to under-reporting of deficits on this self-report measure.

There were no statistically significant differences between the four study groups when comparing participants that had clinically significant impairment to those that have not when using the FrSBe definition of a converted T-score >= 65. This might be explained by our sample differing significantly from the one used to derive normative data and develop the T-score conversion tables. Without these the FrSBe has been shown to give high numbers of false positives is some instances (Grace & Malloy, 2001).

Limitations and strengths of the study

A limiting factor of our study is that only the self-rating part of the FrSBe scale was completed, and no objective measurement of these behaviours was obtained. Cognitive dysfunction is associated with under-reporting of functional deficits on self-reported measurements in people living with HIV, which may impact the scale (Thames et al., 2011). It is known that individuals with alcohol use disorders have decreased awareness of their problem, with more severe use being linked to more impairments in awareness (Verdejo-García & Pérez-García, 2008). The self-report scale of impairments in different behavioural domains might, therefore, underestimate the severity and explain the absence of positive findings in some of the groups and subscales.

The study made use of secondary data which limited the sample size, and some clinical information was not available for all patients. Another limitation was the study design. A cross sectional study design does not lend itself to the investigation of causality.

South Africa is a diverse country consisting of people with multiple languages, ethnicities, and cultures. There are also vast differences in socioeconomic status and schooling. All these factors limit the generalisability of this study, which was conducted at one site in the Western Cape, to the greater South African context.

Both HIV and HED leads to progressively more impairment as these conditions progress. This cross-sectional study assesses data available from a single time-point. This is a limitation because both HIV and HED are dynamic diseases in which impairment fluctuates. Therefore, this study is unable to detect any time-dependent fluctuations in the behavioural sequelae of HIV and alcohol.

This study explored the relationship between HIV, alcohol, frontal lobe function, and the behavioural manifestations thereof in a low resource, South African setting. It is a first step in expanding the existing knowledge base on these highly prevalent conditions with significant morbidity and developing an accurate behavioural measure for this context.

Conclusion

From this study, it appears that people with HED have more dysfunctional behaviour associated with frontal system impairment and are more disinhibited compared to people with HIV. HIV status does not appear to influence frontal system behaviour. These finding needs to be interpreted with caution as the FrSBe was administered in isiXhosa, and no normative data was available for the study population.

Future studies validating the FrSBe in a South African context and deriving normative data for South African populations would be a first step into developing the FrSBe into a clinically useful tool. This could, in turn, potentially lead to improved care and treatment in these conditions by identifying specific impairments and problematic behaviours as targets for intervention.

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Appendix A – Ethics approval

Appendix B – Additional Tables

Table 4: Effect of clinical variables on FrSBe Scores

FrSBe scale	Clinical Variable								
	CD4			Viral load			Total drinking scores		
	N	Correlation coefficient	*p*-value	N	Correlation coefficient	*p*-value	N	Correlation coefficient	*p*-value
Total scale	39	0.144	0.383	35	0.173	0.319	83	0.308	0.005*
Subscales:									
Apathy	39	0.146	0.376	35	0.069	0.693	83	0.160	0.148
Disinhibition	39	0.119	0.472	35	0.237	0.171	83	0.298	0.006*
Executive dysfunction	39	0.143	0.385	35	0.139	0.426	83	0.315	0.004*

*indicates statistical significance at p<.05

Appendix C – Instructions for authors