Neuropsychiatric symptoms and emotional processing in HIV

Facial emotional processing in HIV infection: relation to neurocognitive and neuropsychiatric status

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Abstract

**Objective:** To examine facial emotional processing in HIV+ individuals and its relation to neurocognitive performance, neuropsychiatric symptomatology and immune status.

**Method:** Participants included 85 HIV+ individuals (82 males, 2 females) and 25 age-comparable HIV- individuals (22 males, 3 females). Participants underwent The University of Pennsylvania computerised neuropsychological facial emotion test battery, standardised neuropsychological testing, neurobehavioral questionnaires, a semi-structured psychiatric interview and assessment of independence in activities of daily living.

**Results:** Relative to HIV- controls, HIV+ individuals showed a mild difference for recognition of sadness ($p= 0.02, d = 0.43$), discrimination of happiness ($p= 0.02, d = 0.52$) and speed of recognition for fear ($p= 0.04, d = 0.37$). HIV+ individuals with HIV-associated neurocognitive disorder (20% had HAND) had abnormal emotional facial recognition ($p=.04; d=.59$), and slower recognition facial expressions of negative expressions ($p<.01; d= .63-.83$) as well as poorer discrimination of happy facial emotions ($p<.003, d=.83$). Apathy, depression, reduced independence in activities of daily living and HIV biomarkers were not associated with reduced facial emotion recognition in the HIV+ group.

**Conclusions:** Clinically stable HIV+ individuals show a mild level of emotional processing reduction that is dissociated from neuropsychiatric complaints. Individuals with HAND showed moderate to large emotional processing abnormalities, particularly for the timely recognition of negative expressions (fear; sadness and anger). These findings warrant a more
comprehensive and dynamic evaluation of emotional processing in HIV infection and an investigation of the integrity of the fronto-basal-amygdala circuits.

**Keywords:** HIV, Neuropsychiatry, Depressive Disorder, Apathy, Cognitive Impairment
Introduction

1.1. HIV-1 associated neurocognitive disorders

HIV-1 (human immunodeficiency virus type-1) infection is associated with neurocognitive complications in 30-50% of people, depending on the stage of the disease (Robertson et al, 2007). HIV-associated neurocognitive disorder (HAND) is a subcortical neurological disorder characterized by fronto-striatal cognitive impairment, behavioural disturbance, and motor dysfunction. The disorder can progress from asymptomatic neurocognitive impairment (ANI) to HIV-associated mild neurocognitive disorder (MND) to HIV-associated dementia (HAD) (Antinori et al., 2007). HAND is less fulminant due to the advent of combined antiretroviral therapy (cART). Improved medication options and adherence have effectively reduced the incidence of the disease and reversed cognitive disturbances in many individuals, yet HAND prevalence persists in the cART era mainly because HIV+ people are living longer (Cysique & Brew, 2009).

1.2. Common neuropsychiatric conditions associated with HIV-1 infection

Symptomatic HIV+ individuals are at an increased likelihood of experiencing a major depressive episode (MDE) when compared with asymptomatic HIV+ individuals and healthy subjects. A recent Australian study found that rates of depression (on a screening measure) were higher in HIV + men than HIV– men (32.0% and 21.4.0% respectively, $p< 0.02$) (Mao et al, 2008) and that HIV- gay and bisexual men suffer a higher rate of major depressive disorder (MDD) (17%) compared with the general American adult population (9.5%) (Henneman, 2007). This is important considering that in Australia men who have sex with
men account for 64% of newly diagnosed HIV infections and they also represent the majority of those with chronic HIV infection (Australia Annual Surveillance report, The Kirby Institute, 2011). Other research indicates that men who did not identify as being either homosexual or heterosexual experienced an increased risk of meeting criteria for major depression (Mao et al, 2008). In HIV+ populations, MDD is associated with increased rates of self-reported cognitive complains, but not with impairment on standardised neuropsychological (NP) tests (Cysique et al, 2007).

Apathy refers to diminished motivation that leads to a reduction in goal related thoughts, actions and emotional responses (Marin, 1991). Apathy has been historically recognized as an important clinical feature of HAND (Castellon, Hinkin & Myers 2000). Several studies (Tate, Paul, Flanigan, Tashima, Adair, Boland, Cohen, 2003; Paul, et al 2005; Cole et al, 2007) have found increased prevalence of apathy in HIV+ individuals (median rate 26%). In contrast to depressive symptomatology, apathy has been associated with declines in cognitive performance (Tate et al, 2003), thus providing evidence that apathy may be more robustly associated with fronto-subcortical dysregulation and potentially a better marker of HAND.

1.3. Emotional processing

Emotional recognition is considered to play a significant role in healthy psychological functioning and is of critical importance when interpreting the expressions of others to successfully engage in everyday communication (Williams & Gordon, 2007, Ekman, 1993, Fridlund, 1991, Mineka & Cook, 1993). A majority of literature supports the notion that facial expression of emotion occurs in the same way regardless of race or culture (Ekman, 1980; Izard, 1980). Six facial expressions consistently occur when emotion is aroused across
both literate and non-literate cultures. These facial expressions include anger, disgust, fear, happiness, surprise and sadness (Ekman, 1972). One of the most accepted neuroanatomical models of emotion processing proposes three interacting systems (Dagleish, Dunn & Mobbs, 2009). The striatal complex and the basal ganglia are thought to be associated with primitive emotions such as anger and fear, while the thalamus, hypothalamus, hippocampus, cingulate cortex, amygdala and prefrontal cortex are theorized as having a key role in augmenting primitive emotions and elaborating social emotions. The model also proposes that the prefrontal cortex is responsible for integrating emotion with cognition. The measurement of emotion perception through facial expressions is popular because of the universality of facial emotions (Ekman, 1972) and practicality in both clinical and research settings. For the current study, we selected The Face and Emotion Recognition Tasks of the University of Pennsylvania Computerized Neuropsychological Test Battery (PennCNP, Gur et al, 2001). It is a computerized battery based on facial expressions that has important advantages in the context of HIV infection. It allows precise measurement of reaction time (RT) and accuracy measures, includes faces that are historically recent and includes a multi-procedural assessment of emotional processing (i.e., recognition, discrimination and emotional acuity).

1.4. Emotional processing, depressive disorders and apathy

Research has shown that mood disorders are associated with abnormalities in the way emotional stimuli are perceived, responded to and stored in memory (Leppanen, 2006). Studies investigating emotional processing in patients with MDD have found biases in attention toward stimuli which was congruent with their current mood (Murphy et al, 1999) such as preferentially attending to sad facial expressions over simultaneously presented neutral facial expressions (Gotlib, Kasch, Traill, Joormann, Arnow & Johnson, 2004). In
addition, individuals with MDD have been shown to demonstrate a bias away from the identification of happy or mildly happy facial expressions (Surguladze et al, 2004). There is also evidence to suggest that emotional processing abnormalities in mood disorders may be related to abnormalities in those neuroanatomical regions associated with emotional processing (Phillips, Drevets, Rauch & Lane, 2003). Post-mortem pathological studies of MDD patients have revealed volume reductions and substantially reduced glial density and glia/neuron ratio in the amygdala (Bowley, Drevets, Ongur & Price, 2002) and various regions of the prefrontal cortex (Phillips et al, 2003). To the best of our knowledge there have been no studies investigating the contribution of apathy as observed in subcortical disorders and emotional processing capacities.

1.5. Emotional processing in disorders with subcortical pathology

The recognition of facial emotions has been found to be impaired in disorders with fronto-striatal pathology, including Parkinson’s disease (PD) (Lewis, Dove, Robbins, Barker & Owen, 2003) and Huntington’s disease (HD) (Lange, Sahakian, Quinn, Marsden & Robbins, 1995). However findings have varied. For example, it has been reported that recognition of anger and fear is disrupted in medicated individuals diagnosed with PD, while recognition of fear, anger, disgust and sadness is impaired in unmedicated individuals with PD (Sprengelmeyer et al, 2003). Furthermore, individuals with PD were impaired in recognising anger and surprise, and overall, were less accurate at identifying emotional expressions when compared with healthy controls (Clark, Neargarder & Cronin-Golomb, 2008). Marked impairments have been found in the recognition of anger, fear and disgust from facial and vocal expressions in patients with manifest HD (Calder et al, 2010), while others have shown that disgust is most adversely affected in HD (Montagne et al, 2006). This variation in results
may be explained by the wide variety of protocols used to study emotions, the clinical advancement of the population studies, cognitive state and inconsistency in controlling for depression and apathy.

1.6. The current study: newly investigating emotional processing in HIV-1 infection

Despite strong evidence from anatomical, neuroimaging and clinical studies (in PD and HD for example) that preservation of subcortical-frontal circuits is central for adequate emotional processing, there has been no systematic study of emotion processing in HIV-1 infection. To the best of our knowledge only one study by Clark and colleagues (2010) has been published. This study found preliminary evidence of facial recognition impairment (i.e., fear). However, as discussed in a subsequent section of this paper, the neurocognitive status of participants was not adequately examined, rendering the finding difficult to contextualise.

The aim of the current study was to determine whether clinically stable HIV+ individuals exhibit facial emotional processing deficits and how those may be related to neuropsychiatric changes, NP performance and impairment, as well as traditional HIV disease markers. Based on the previous literature pertaining to emotional processing, it was hypothesised that overall facial emotional processing would be mildly to moderately impaired in HIV+ individuals when compared to age-comparable HIV- controls. Severe emotional processing dysfunction was not anticipated as the group under investigation was clinically stable and free of other major neurological and psychiatric confounds (except for MDD). It was expected that emotional processing impairment would involve the recognition, discrimination and acuity of negative emotions (fear, anger or sadness), while recognition, discrimination and acuity of neutral and happy emotions would be similar to the HIV- group. Apathy, but not depression was hypothesised to be associated with worse facial emotional processing difficulties. It was
also predicted that facial emotion processing difficulties would be associated with poorer performance on standard NP tests, HAND diagnosis and decrease in IADL. Finally, nadir CD4 cell count was expected to be associated with worse facial emotion processing, as a history of immune compromise (indicated by nadir CD4 cell count) is known to be a risk factor for cognitive deterioration.
Methods

2.1 Participants

Between June 2009 and August 2011, 85 HIV+ individuals and 25 HIV- individuals aged 45 years old and above were enrolled into a prospective study investigating the effects of HIV infection on the brain in middle-aged persons. The HIV+ participants were recruited through the HIV and Neurology Clinics at St Vincent’s Hospital, Sydney, New South Wales. Potential participants were screened on the Immunology and Infectious Diseases department HIV outpatient database for the following eligibility criteria: at least 45 years old and stable on their cART for at least six months, nadir CD4 equal to or below 350, HIV duration equal to or greater than five years. Among those screened, 50% agreed to participate in the study. HIV- controls were recruited via advertising in the metropolitan area of Sydney and across St. Vincent’s Hospital and University of New South Wales campus. To meet eligibility criteria, control participants were required to be HIV-negative on an ELISA test within the past three months.

2.2. Criteria for exclusion

Participants were excluded from the study based on the following criteria: having a history of non-HIV related neurological disorders or psychiatric disorders on the psychotic axis (e.g., schizophrenia); current alcohol/substance use disorders (within 12 months of study enrolment); a history of loss of consciousness (greater than 30 minutes); being non-proficient in English. English proficiency was assessed with a custom made English proficiency questionnaire assessing bilingualism, current English proficiency and frequency of use. Four
HIV+ and two HIV- participants had English as a second language but were assessed as proficient in English. Participants were not excluded on the basis of current depressive complaints or past substance use disorders (predating study entry by 12 months). Heavy use of marijuana was set as an exclusion criterion, but not recreational use as it would exclude many HIV+ individuals. Individuals with Hepatitis C (HCV) were included only if successfully treated (active HCV was excluded based on positive HCV RNA).

2.3 Materials and Apparatus

2.3.1 Standard Neuropsychological testing

Assessment of psychological functioning was obtained through self-report measures, as well as a semi-structured clinical interview using the following instruments: the Beck Depression Inventory –II (Beck 1996), the IADL Scale (Heaton et al, 2004a), the Patients Assessment of Own Functioning Inventory (PAOFI; Chelune, Heaton & Lehman, 1986), the Frontal Rating Systems Behaviour Scale (FrSBe) (Grace & Molloy, 2001), and the Electronic Mini International Neuropsychiatric Interview (eM.I.N.I) (Sheehan et al, 1998). Assessment of cognitive functioning was obtained via use of standardised neuropsychological measures that have been shown to be sensitive to HAND (Table 6 in the Appendix; Carey et al., 2004).

2.3.2 The University of Pennsylvania Computerized Neuropsychological Test Battery (PennCNP) version 2, face and emotion tasks.

The PennCNP battery is a computerized web-accessible program (https://penncnp.med.upenn.edu) assessing several aspects of emotional processing based on five basic facial expressions (happy, sad, anger, fear, and neutral) which are gender and ethnicity balanced. Each sub-test yields an accuracy measure and a speed of response
measure (RT) (Gur et al, 2001). The default battery also includes a motor practice task for the participant to familiarize themselves with the computerised setting and a facial memory test. For the purpose of this study we report results on the three emotion subtests. In the Penn Emotion Recognition Task, participants are shown a series of 40 faces, one at a time, and asked to determine what emotion the face is showing (happy, sad, anger, fear or no emotion). In the Penn Emotion Discrimination Task, participants are shown 40 pairs of faces, one at a time. For each pair the participant must decide whether one of the faces represents stronger intensity or whether they are equally emotional. Finally, in the Penn Emotional Acuity Test, participants are presented with 40 faces, one at a time. Faces are comprised of 5 happy, 5 sad and 10 neutral faces. Participants are asked to rate the emotional valence of the expression on each face using a seven-point scale: very sad, moderately sad, somewhat sad, neutral, somewhat happy, moderately happy, and very happy

2.3.3 Biomedical Measures

Plasma and Cerebrospinal fluid (CSF) collection: All HIV+ participants had a standard venipuncture within three months of the NP testing. Eligible and consenting HIV+ participants (n = 35) also had a lumbar puncture. St. Vincent’s Hospital pathology laboratory used standard assays to determine plasma CD4 T-cell counts and HIVRNA as well as CSF HIV RNA.

2.3.4 Ethics

The study protocol was approved by Macquarie University, St. Vincent’s Hospital and the University of New South Wales ethics committees. All participants signed an informed consent prior to study participation.
2.4 Procedure

After providing written informed consent, participants completed a detailed demographics and medical history questionnaire, the eMINI and the self-report measures. Participants were subsequently administered the standardised NP test battery and the PennCNP. The average testing duration was 2 hours. The standard NP testing was conducted by research assistants/students who had completed or were currently undertaking their Master of Clinical Neuropsychology (EF, TL and DM) under the supervision of a senior neuropsychologist (LAC). All measures were administered and scored according to standard procedures. Using published normative data (Heaton et al, 2004b) raw scores were converted to demographically corrected T-scores in order to minimize the influence of age, education, sex and ethnicity (Caucasians versus other). T-scores were transformed into a Global Deficit Score (GDS, see Carey et al., 2004 for details). Deficit scores on all tests were then averaged to create the GDS. A GDS greater than or equal to 0.5 has typically been used as a cutoff (Carey et al, 2004) and indicates that, on average, an individual is at least mildly impaired in no less than half the tests in the battery.

2.5 Data Analysis

2.5.1 Facial emotions processing

Data from the PennCNP were inspected for normality of distribution. The RT data was log_{10} transformed. The accuracy data did not present a strong departure from normality except in the case of the happy emotion recognition task, for which a non-parametric statistic was used (the Wilcoxon Test) to compare the HIV- and HIV+ groups. In accordance with recommendations for exploratory analyses, effect sizes were computed in addition to p-values
to determine meaningful effects for the emotion processing data (Lipsey & Wilson, 2001). We used a slightly modified effect size classification compared to the “conventional rule of thumb” initially prescribed by Cohen (1988): .00-.39 was considered small, .40-.79 medium and >.80 large. This approach was chosen because reliance on the p-value in exploratory studies may lead to inflated Type II errors (Zakzanis et al., 2001), and experiment-wise corrections may not represent the best analytical inference for exploratory studies (Bender & Lange, 2001). Also, it should be noted that while our study had an exploratory component, specific hypotheses were tested. And those were tested using only comparisons that yielded a $d \geq 0.40$ or $p<.05$ two-tailed on the emotion tasks. This consequently unselected many uncalled analyses. Effect sizes were computed using the effect size determination program (Lipsey & Wilson, 2001).

2.5.2 Neurocognitive performance and emotional processing

To determine the neurocognitive predictors of facial emotion processing in the HIV+ group compared with the HIV- group, a series of regression models were developed. These regression models utilized the global mean T-score as the predictor for the Penn recognition and discrimination subtests that were reduced in the HIV+ group. For each model, an interaction term (in addition to the single group and T-score effect) was tested (group*T-score) to determine if the HIV+ group displayed a statistically significant difference from the control group in how neurocognitive functioning predicted emotion processing. Based on the significant results ($p<.05$), we investigated which specific cognitive domains were associated with reduced emotional processing. In addition, t-tests were used to compare those with a diagnosis of HAND and those deemed to be cognitively normal on the relevant emotional tasks.
2.5.3 Neuropsychiatric profile, complaints, and emotion processing

To determine the neuropsychiatric predictors of emotion processing in the HIV+ group versus the HIV- group, a series of regression models were developed using the total BDI-II score and the FrSBe apathy score (after illness). For each model, an interaction term (e.g., group*apathy) was tested in addition to the single group and neuropsychiatric effect. This was done in order to determine if the HIV+ group displayed a statistically significant difference from the controls in how neuropsychiatric functioning predicted emotion processing. Moreover, to determine the clinical significance of reduced emotional processing in the HIV+ group, a t-test was used to compare individuals for whom the IADL had significantly declined with individuals for whom the IADL was stable. Lastly, HIV+ individuals with little to no complaints on the PAOFI were compared with individuals who had mild to high complaints (low to no complaints = PAOFI ≤5, mild to high complaints = PAOFI ≥ 5).

2.5.4. Demographic characteristics and emotion processing

Pearson correlation analyses for age and education were conducted separately in the HIV-group and HIV- group. Gender was not examined due to insufficient number of women. Because of the relatively small sample size in the control group, we report correlations greater than $r=.30$ independently of the $p$-value. In the HIV- group, greater age was correlated with longer RT for the fear recognition ($r=.37$), a higher level of education was correlated with a more accurate recognition of sadness ($r=.47$). In the HIV+ individuals correlations were very small (age and education: $r=.07$). Therefore corrections for demographics were not used systematically. Rather we reported whether the corrections
yielded different results or not. Statistical analyses were conducted using the statistical package JMP 9, 2009 SAS Institute Inc.
Results

Demographic and clinical characteristics of the HIV- and HIV+ groups are presented in Table 1 and laboratory and treatment characteristics of the HIV+ group are presented in Table 2.

3.1: Neurocognitive functioning in the HIV+ group versus the HIV- group

The HIV+ group performed worse than the HIV- group on overall NP performance (global mean T-scores, \( p<.0009; d = 0.60 \)). In particular, the HIV+ had poorer performance in the domains of mental flexibility and attention/working memory (see Table 3).

3.2: Neuropsychiatric and complaints profiles in the HIV- and HIV+ groups

All types of complaints and neurobehavioral symptoms assessed were significantly greater in the HIV+ group as compared to the HIV- group on self-report questionnaires, with the exception of symptoms of disinhibition (see Table 4). Based on the semi-structured clinical interview 8.8% had MDE or dysthymia (past two years) and 10.8% had recurrent MDE in the HIV+ group versus 0% in the HIV- group.

3.3: Facial emotions processing differences by HIV status and by HAND status

Comparisons between the HIV- group versus the entire HIV+ group are presented in Table 5. In summary, the speed for the recognition of fearful faces was slower in the HIV+ group (\( p=0.04; d=0.37 \)). HIV+ individuals were poorer at identifying sad expressions (\( p=0.02; d=0.43 \)) and at discriminating between the intensity of happy expressions (\( p=0.02; d=0.52 \)).
Having HAND (note there was an exact match between the GDS conventional definition: GDS\(\geq\)0.5, and the application of the HAND Antinori et al., 2007 criteria) was associated with poorer overall emotional facial recognition (29.50, SD=3.60 versus 31.5, SD= 3.30; \(p=.04; d=.59\)). This was driven by a deficient recognition of fear (5.70, SD=1.3 versus 6.40, SD=1.6; \(p=.07, d=.54\)) and sadness (5.50, SD=2.0 versus 6.20, SD= 1.4; \(p=.21 d=.45\)). Although this did not reach statistical significance in these sub-sample analyses, effect sizes were medium. In addition to a slower recognition of the facial expression of fear (\(\log_{10} RT=3.65, SD=0.20\) versus 3.50, SD=0.19; \(p<.005, d=0.78\)), HAND was associated with a slower recognition of anger (\(\log_{10} RT=3.51, SD=0.19\) versus 3.40, SD=0.15; \(p<.03, d=.69\)), slower recognition of happiness (\(\log_{10} RT=3.36, SD=0.12\) versus 3.29, SD=0.11; \(p<.03, d=.63\)) as well as sadness (\(\log_{10} RT=3.51, SD=0.14\) versus 3.40, SD=0.13; \(p<.007, d=.88\)) when compared to cognitively normal HIV+ individuals. HAND also had poorer discrimination of happy faces (8.28, SD=3.94 versus 11.30, SD= 3.52; \(p<.003, d=.83\)) when compared to cognitively normal HIV+ individuals.

3.4: Neurocognitive performance and emotional processing reductions

A lower global neurocognitive performance was associated with worse discrimination of happiness in the HIV+ group \([R^2 = 0.22, F(3,109), p<.001]\); interaction effect: estimate = -0.25, 95% CI [-0.40; -0.09]; \(\beta=-.35, p<.002\). Moreover, there was a trend for a slower recognition of fear as a function of lower neurocognitive performance that was specific to the HIV+ group \([R^2 = 0.11, F(3,108), p<.005]\); interaction effect: estimate = 0.007, 95% CI [-0.001 - 0.015], \(\beta=.20, p <.08\).

When considering which specific cognitive domains predicted emotional processing in the HIV+ group, we found that lower performance in the domains of mental flexibility \([R^2 =
.076, $F(1,82), p=.01$; estimate = -0.008, 95% CI [-0.014 - -0.002], $\beta=-.26.5, p=.01$, speed of information processing [$R^2 = .076, F(1,82), p=.01$; estimate = -0.007, 95% CI [-0.013 - -0.002], $\beta=-.27.5, p=.01$] and motor functions to a lesser extent [$R^2 = .054, F(1,82), p<.04$; estimate = -0.006, 95% CI [-.010 - -0.0004], $\beta=-.24, p < .04$] were associated with a slower RT for fear. Lower performance in the domains of speed of information processing [$R^2 = .17, F(1,83), p < .0001$; estimate = 0.21, 95% CI [0.11 – 0.31], $\beta=.41, p < .0001$], motor functions [$R^2 = .08, F(1,83), p<.009$; estimate = 0.13, 95% CI [0.33 – 0.22], $\beta=.28, p < .009$], and mental flexibility [$R^2 = .11, F(1,83), p<.002$; estimate = 0.18, 95% CI [.07 - 0.29], $\beta=.33, p<.002$] were associated with poorer discrimination of happy faces.

3.5: Neuropsychiatric profile, complaints and emotional processing reductions

There were no statistically significant associations between emotional processing difficulties and increased complaints of depression and apathy in the HIV+ group compared to the HIV- group. Furthermore, there were no differences on the capacity to recognise and discriminate emotions between HIV+ individuals who had current MDE, recurrent MDE, or dysthymia ($p>.70$). There were no statistically significant associations between IADL and emotional processing difficulties in the HIV+ group. Results were similar for cognitive complaints on the PAOFI. Results did not change when demographic factors were included in the analyses.

3.6: HIV disease markers and emotional processing reductions

We found no significant correlations between the nadir CD4 or the current CD4 and reduced emotion processing. Results were similar when AIDS status or when the presence of AIDS-defining illnesses were considered. Results did not change when demographic factors were included in the analyses.
Discussion

In a clinically stable group of middle-aged HIV+ individuals we found: 1. No substantial abnormalities in the overall recognition of basic facial emotions, but a mild reduction for the recognition of sad facial expressions and the discrimination of happy facial expressions. 2. With the exception of fear recognition, speed of emotional processing was not reduced. 3. Global and domain specific NP deficits partially explained the reduced performance in the discrimination of happy expression. 4. When considering HAND classification, we found that HAND was strongly associated with lower emotional processing capacities, especially where speed of recognition for negative expressions was concerned. 5. Depression and apathy, IADL and HIV disease biomarkers were not associated with emotional processing reductions.

The hypothesis that overall facial emotional processing would be mildly to moderately impaired in the HIV+ individuals compared to age-comparable controls was partially supported, with the current study providing some new insights into the issue. Firstly, there was evidence of a mild deficit at the HIV+ group level. Further, among all negative emotions tested, the recognition of sad expression recognitions yielded mildly reduced performance in the HIV+ group, while anger and fear were normally recognised. The only other study that has examined emotional processing in HIV+ individuals (Clarke et al., 2010) also found evidence of mild impairment in emotion recognition abilities in HIV+ individuals. In contrast to the current study, impairments were dominated by difficulties recognising fear (see below for further discussion). Importantly, Clark (2010) reported no basic facial identification deficits in HIV+ individuals. These results are supported by findings from the current study.
in which the recognition of neutral faces was normal and consistent between our two groups, indicating that faces are a reliable medium to study emotional processing in HIV infection.

Speed of recognition for the facial emotions was similar between the two groups for all emotions, with the exception of fear, which was mildly reduced. This is a new and valuable finding, considering how speed of information processing (as measured by RT) is known to be a reliable marker of HIV-related neurocognitive impairment (Hardy & Hinkin, 2002). Moreover, it seems to support the findings of Clark et al. (2010) showing a specific involvement of this facial expression recognition in HIV infection. The fact that we found this to be true for the speed of recognition but not the accuracy may reflect that our patients were overall clinically stable with a relatively low rate of HAND, as discussed further below.

In the current study, we newly demonstrated that the ability to discriminate between levels of happiness intensity was specifically altered in the HIV+ group as a function of neurocognitive performance. This interaction between serostatus and NP performance suggests that this specific task may require a higher demand on cognitive abilities that are usually affected in HIV infection (Cysique, Maruff & Brew, 2006).

Interestingly, when comparing HAND versus HIV+ participants classified as cognitively intact, we found that emotional processing was moderately abnormal in persons with HAND for overall facial expression recognition and largely abnormal for the speed of facial recognition. This result lends support to the fact that the mild reduction observed in the entire group may reflect early abnormalities that are amplified with the development of clinically meaningful forms of cognitive impairment. This would be supported by the fact that recognition of the fear expression is not impaired when all HIV+ are concerned, but is found to be impaired in neurocognitively impaired HIV+ persons (lending support to the finding of
Clark et al, 2010). Further, the strength of these effects suggests that despite the use of American norms, the majority of HIV+ persons meeting criteria for HAND were correctly classified as impaired. However, the development of Australian norms remains necessary to avoid underestimation of impairment, particularly in high functioning individuals.

It was hypothesised that apathy but not depression would be associated with worse facial emotional processing. This hypothesis was not supported, with the results failing to reveal any statistically significant associations between emotional processing difficulties and increased rates of depressive symptoms in the HIV+ group. Due to our stringent selection criteria, it is possible that the lack of significant findings may have resulted from the limited severity of neuropsychiatric complaints in the HIV+ group. Furthermore, symptoms of depression and apathy were moderately correlated in both groups (r=>.50) warranting the development of a sensitive tool to reliably assess apathy in HIV infection. Similarly, there were no significant associations between self-reported IADL and emotional processing difficulties in the HIV+ group. As the overall level of emotional processing reduction was mild, it is possible that IADL and cognitive complaints did not reach statistical significance. However, we also found that IADL was highly correlated with depressive complaints (r=.52; p<.0001) and mildly correlated with global neurocognitive performance (r=-.22; p<.02) suggesting that IADL was partially influenced by self-report bias. More objective IADL instruments are therefore needed to more reliably assess associations with emotional processing reductions.

The final hypothesis that nadir CD4 count would be associated with poorer facial emotion processing was not supported. Clarke et al (2010) found a correlation between current CD4 counts and anger recognition abilities, suggesting that some of the HIV+ individuals had poor
CD4-T cell recovery. However, the clinical significance of this finding is unclear given that anger was not differentially recognised between their HIV+ and HIV- groups.

From the current findings, there are neuroanatomical hypotheses for emotional impairment in HIV infection that could be tested in future studies, particularly in relation to the early target of HIV in the frontal and limbic areas of the brain. fMRI BOLD studies have shown that activation of the left amygdala is associated with the perception of sad facial expressions (Adolphs et al, 2002) and bilateral activation of the amygdala is associated with the perception of fear facial expressions (Adolphs et al, 2005). Extensive work (LeDoux, 1995) has demonstrated that intact amygdala function is needed for timely fear processing, suggesting that the slower response to fear facial expression may involve the amygdala in HIV+ persons, particularly those with HAND. Importantly, research has also indicated that the amygdala is implicated in the regulation of complex attentional functions (i.e., mental flexibility, working memory, sustained attention and speed processing) associated with impaired emotional processing (Vuilleumier & Pourtois, 2007) and is thought to occur via a regulatory loop between the amygdala, the prefrontal cortex and the basal ganglia. This may help explain why we found evidence of a reduced capacity in discriminating or quickly recognising facial expressions as a function of lower neurocognitive performance and HAND. Because HIV-related brain injury is thought to affect fronto-striatal regions (Pfefferbaum et al., 2009), it would be of relevance to test whether striato-frontal circuits in connection to the amygdala are also disrupted early in the disease process and across the HAND spectrum.

The present study had several limitations. First, the sample size of the control group was smaller than the clinical group, which could have led to a loss of power. However, to improve
the interpretation of the data independently of power, effect sizes were provided. Because we focused on results involving magnitude of effect > d=.40 to balance between Type I and Type II errors, we were able to identify both mild to moderate and large emotional processing deficits. The use of more stringent cut-offs may have resulted in important, yet mild effects being ignored. The ability to recognise disgust was not examined because it was not part of the PennCNP. Disgust has been found to be impaired in other forms of subcortical disorders such as HD (Sprengelmeyer et al, 2003) and should therefore be investigated in future HIV studies. Finally, our study represents the exploratory phase of a larger project. As such, these current results would need to be further tested in a longitudinal design.
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Table 1

Demographic characteristics in the HIV+ and HIV- groups

<table>
<thead>
<tr>
<th></th>
<th>HIV-</th>
<th>SD</th>
<th>HIV+</th>
<th>SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>25</td>
<td>-</td>
<td>85</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.68</td>
<td>5.97</td>
<td>55.40</td>
<td>6.93</td>
<td>0.23</td>
</tr>
<tr>
<td>Education</td>
<td>15.16</td>
<td>2.64</td>
<td>13.98</td>
<td>2.90</td>
<td>0.06</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>12.00% (3/25)</td>
<td>-</td>
<td>2.35% (2/85)</td>
<td>-</td>
<td>0.04</td>
</tr>
<tr>
<td>% Caucasian</td>
<td>92.00%</td>
<td>-</td>
<td>94.00%</td>
<td>-</td>
<td>0.70</td>
</tr>
<tr>
<td>FSIQ</td>
<td>114.91</td>
<td>7.56</td>
<td>111.53</td>
<td>10.51</td>
<td>0.09</td>
</tr>
<tr>
<td>HIV Risk groups (%MSM)</td>
<td>-</td>
<td>-</td>
<td>85%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Currently Employed</td>
<td>72%</td>
<td>-</td>
<td>58%</td>
<td>-</td>
<td>0.19</td>
</tr>
<tr>
<td>% HCV+</td>
<td>4.00 (1/25)</td>
<td>3.50% (3/85)</td>
<td>0.91</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean SD otherwise notified

MSM: Men who have sex with men

FSIQ: Predicted Full scale IQ as determined by the NART.

Ethnicity: In control group – 1 Asian-Australian; 1 Middle-Eastern/Mediterranean Australian
In HIV+ group: 1 Asian-Australia, 1 Indigenous-Asian Australian, 2 Middle-Eastern/Mediterranean Australian, 1 South American Australian. All but one had secondary education in English, and this participant had secondary education in Spanish and had lived in Australia for 30 years.


**Table 2**

HIV disease and laboratory characteristics in the HIV+ group

<table>
<thead>
<tr>
<th>Disease characteristics</th>
<th>HIV+ group</th>
<th>IQR¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated HIV duration (Median years)</td>
<td>20.80</td>
<td>16.46-25.56</td>
</tr>
<tr>
<td>% AIDS</td>
<td>72%</td>
<td>-</td>
</tr>
<tr>
<td>% AIDS Defining Illness</td>
<td>44%</td>
<td>-</td>
</tr>
<tr>
<td>Nadir CD4 (Median)</td>
<td>180</td>
<td>58.5 – 277.5</td>
</tr>
<tr>
<td>Current blood CD4 (Median)</td>
<td>552</td>
<td>357.75 - 720</td>
</tr>
<tr>
<td>% Plasma HIV RNA (undetectable)</td>
<td>98%</td>
<td>-</td>
</tr>
<tr>
<td>% CSF HIV RNA (undetectable) ²</td>
<td>97%</td>
<td>-</td>
</tr>
</tbody>
</table>

¹. IQR: Inter-quartile range

². N=31 who had CSF lumbar puncture

Undetectable: HIV RNA assay with a limit of detection at 50 copies/mL.

HCV: Hepatitis C Virus (Note that all HCV+ individuals were not HCV active as per criteria of inclusion/exclusion)

The majority of patients reported a high to very high level of adherence as confirmed by a high level of plasma viral load undetectability.
Table 3

Domain mean T-scores, and overall prevalence of neurocognitive impairment in the HIV– and HIV+ groups

<table>
<thead>
<tr>
<th>Domains (T-scores)</th>
<th>HIV –</th>
<th>SD</th>
<th>HIV+</th>
<th>SD</th>
<th>P</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>52.88</td>
<td>4.99</td>
<td>49.72</td>
<td>5.35</td>
<td>0.009</td>
<td>0.60</td>
</tr>
<tr>
<td>Mental flexibility</td>
<td>55.08</td>
<td>4.49</td>
<td>51.38</td>
<td>6.92</td>
<td>0.002</td>
<td>0.57</td>
</tr>
<tr>
<td>Verbal generativity</td>
<td>53.17</td>
<td>8.16</td>
<td>50.67</td>
<td>8.99</td>
<td>0.19</td>
<td>0.28</td>
</tr>
<tr>
<td>Verbal Learning</td>
<td>49.64</td>
<td>12.21</td>
<td>44.59</td>
<td>11.12</td>
<td>0.07</td>
<td>0.44</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>48.92</td>
<td>12.39</td>
<td>44.67</td>
<td>11.29</td>
<td>0.13</td>
<td>0.35</td>
</tr>
<tr>
<td>Motor-coordination</td>
<td>50.75</td>
<td>7.75</td>
<td>47.84</td>
<td>8.41</td>
<td>0.11</td>
<td>0.35</td>
</tr>
<tr>
<td>Speed of Information Processing</td>
<td>52.18</td>
<td>6.69</td>
<td>50.26</td>
<td>7.40</td>
<td>0.22</td>
<td>0.26</td>
</tr>
<tr>
<td>Attention/Working Memory</td>
<td>55.66</td>
<td>7.28</td>
<td>51.68</td>
<td>8.07</td>
<td>0.02</td>
<td>0.50</td>
</tr>
<tr>
<td>GDS</td>
<td>0.12</td>
<td>0.19</td>
<td>0.28</td>
<td>0.37</td>
<td>0.006</td>
<td>0.47</td>
</tr>
<tr>
<td>Overall Neurocognitive impairment</td>
<td>4.00%</td>
<td>-</td>
<td>20.00%</td>
<td>-</td>
<td>0.05</td>
<td>-</td>
</tr>
</tbody>
</table>

GDS: Global Deficit Score (GDS≥0.5)

Some domain T-scores were above the mean of 50 in the controls. The differences between the control and HIV+ group are likely to be accurate estimate of performance difference; however the classification of impairment may have been underestimated by the use of American norms. Reasons for a suboptimal correction could include factors such as universal healthcare and indirect impact on brain aging,
possible educational differences for similar levels of education and lifestyle factors. In the absence of Australian-specific norms, we have used a robust and sophisticated normative approach from another English speaking country.
Table 4

Independence in Activities of Daily Living, cognitive complaints, depressive and frontal system behavioural symptomatology in the HIV+ and HIV- groups

<table>
<thead>
<tr>
<th></th>
<th>HIV-</th>
<th>SD</th>
<th>HIV+</th>
<th>SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IADL summary score</td>
<td>0.28</td>
<td>0.54</td>
<td>1.00</td>
<td>1.49</td>
<td>0.0004</td>
</tr>
<tr>
<td>% IADL significant decline 1</td>
<td>4.00%</td>
<td>-</td>
<td>24.71%</td>
<td>-</td>
<td>0.02</td>
</tr>
<tr>
<td>Cognitive Complaints PAOFI 2</td>
<td>1.76</td>
<td>1.88</td>
<td>4.30</td>
<td>5.14</td>
<td>0.0003</td>
</tr>
<tr>
<td>BDI-II total score 3</td>
<td>3.00</td>
<td>4.09</td>
<td>8.36</td>
<td>7.87</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clinically significant depression 4</td>
<td>0.00%</td>
<td>-</td>
<td>15.29%</td>
<td>-</td>
<td>0.04</td>
</tr>
<tr>
<td>FrSBe Total after 5</td>
<td>50.00</td>
<td>8.00</td>
<td>64.00</td>
<td>12.00</td>
<td>0.004</td>
</tr>
<tr>
<td>FrSBe apathy after</td>
<td>50.00</td>
<td>11.60</td>
<td>65.00</td>
<td>19.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FrSBe disinhibition after</td>
<td>50.00</td>
<td>11.50</td>
<td>54.00</td>
<td>14.00</td>
<td>&lt;.25</td>
</tr>
<tr>
<td>FrSBe executive dysfunction after</td>
<td>50.00</td>
<td>10.30</td>
<td>65.00</td>
<td>17.60</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

1. IADL significant change: Independence in Activities of Daily Living: self-report of at least 2 or more decrease in the capacity to perform IADL.

2. PAOFI: Personal Assessment of Own Functioning Inventory total score

3. BDI-II: Beck Depression Inventory-II total score.

4. BDI-II clinically significant: A cut off of >17 was used to define clinically significant levels of depression (Beck et al, 1996).
5. FrSBe: Frontal System Behaviour Scale T-scores (Higher T-scores represent worse symptoms). HIV+ individuals also completed the FrSBe before and after the illness and there was a significant increase in their total Frontal symptoms self-report ($p<.0001$) between before and after the illness (defined as AIDS or within the last five years for the purpose of this study). This represented a worsening of FrSBe symptoms equivalent to 7 point T-scores (57 vs. 64), and was due to changes reported for both apathy and executive functions.
### Table 5

Pennsylvania Computerised Emotion Battery results in HIV – and HIV + groups

<table>
<thead>
<tr>
<th></th>
<th>HIV-</th>
<th>SD</th>
<th>HIV+</th>
<th>SD</th>
<th>p</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recognition total correct (0-40)</td>
<td>32.12</td>
<td>3.28</td>
<td>31.08</td>
<td>3.31</td>
<td>0.17</td>
<td>0.31</td>
</tr>
<tr>
<td>Recognition total Log(_{10}) RT</td>
<td>3.39</td>
<td>0.11</td>
<td>3.39</td>
<td>0.12</td>
<td>0.96</td>
<td>0.00</td>
</tr>
<tr>
<td>Recognition Anger correct (0-8)</td>
<td>4.44</td>
<td>1.53</td>
<td>4.09</td>
<td>1.43</td>
<td>0.32</td>
<td>0.24</td>
</tr>
<tr>
<td>Recognition Anger Log(_{10}) RT</td>
<td>3.44</td>
<td>0.17</td>
<td>3.43</td>
<td>0.17</td>
<td>0.78</td>
<td>0.06</td>
</tr>
<tr>
<td>Recognition Fear correct (0-8)</td>
<td>6.52</td>
<td>1.69</td>
<td>6.23</td>
<td>1.56</td>
<td>0.45</td>
<td>0.18</td>
</tr>
<tr>
<td>Recognition Fear Log(_{10}) RT</td>
<td>3.46</td>
<td>0.14</td>
<td>3.53</td>
<td>0.20</td>
<td>0.04</td>
<td>0.37</td>
</tr>
<tr>
<td>Recognition Happy correct (0-8)</td>
<td>7.72</td>
<td>0.54</td>
<td>7.88</td>
<td>0.32</td>
<td>0.11</td>
<td>-</td>
</tr>
<tr>
<td>Recognition Happy (Log(_{10}) RT)</td>
<td>3.27</td>
<td>0.10</td>
<td>3.30</td>
<td>0.11</td>
<td>0.23</td>
<td>0.28</td>
</tr>
<tr>
<td>Recognition Neutral correct (0-8)</td>
<td>6.76</td>
<td>1.39</td>
<td>6.81</td>
<td>1.43</td>
<td>0.87</td>
<td>0.03</td>
</tr>
<tr>
<td>Recognition Neutral Log(_{10}) RT</td>
<td>3.46</td>
<td>0.21</td>
<td>3.41</td>
<td>0.16</td>
<td>0.23</td>
<td>0.29</td>
</tr>
<tr>
<td>Recognition Sad correct (0-8)</td>
<td>6.68</td>
<td>0.99</td>
<td>6.06</td>
<td>1.57</td>
<td>0.02</td>
<td>0.43</td>
</tr>
<tr>
<td>Recognition Sad Log(_{10}) RT</td>
<td>3.39</td>
<td>0.13</td>
<td>3.43</td>
<td>0.14</td>
<td>0.28</td>
<td>0.29</td>
</tr>
<tr>
<td>Discrimination Happy correct (0-20)</td>
<td>12.60</td>
<td>3.63</td>
<td>10.66</td>
<td>3.79</td>
<td>0.02</td>
<td>0.52</td>
</tr>
<tr>
<td>Discrimination Happy Log(_{10}) RT</td>
<td>3.73</td>
<td>0.18</td>
<td>3.73</td>
<td>0.17</td>
<td>0.92</td>
<td>0.00</td>
</tr>
<tr>
<td>Discrimination Sad correct (0-20)</td>
<td>13.64</td>
<td>2.48</td>
<td>12.83</td>
<td>2.60</td>
<td>0.16</td>
<td>0.31</td>
</tr>
<tr>
<td>Discrimination Sad Log(_{10}) RT</td>
<td>3.70</td>
<td>0.17</td>
<td>3.70</td>
<td>0.15</td>
<td>0.96</td>
<td>0.00</td>
</tr>
<tr>
<td>Acuity test total correct (0-40)</td>
<td>26.04</td>
<td>4.75</td>
<td>27.36</td>
<td>4.64</td>
<td>0.23</td>
<td>0.28</td>
</tr>
<tr>
<td>Acuity test total Log(_{10}) RT</td>
<td>3.40</td>
<td>0.15</td>
<td>3.38</td>
<td>0.15</td>
<td>0.57</td>
<td>0.13</td>
</tr>
</tbody>
</table>
Happy trials were analysed with non-parametric statistic as the distribution was skewed (Wilcoxon Test); therefore no effect size was computed.

For the PENN emotional acuity test, none of the sub-cores were significantly different between groups ($p>.30$).
**Appendix**

**Table 6**

**Neuropsychological test battery**

<table>
<thead>
<tr>
<th>Cognitive domains</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental flexibility</td>
<td>TMT B time in seconds</td>
</tr>
<tr>
<td></td>
<td>DKEFS CWI tests (inhibition &amp; switching subtests) time in seconds</td>
</tr>
<tr>
<td>Verbal generativity</td>
<td>COWAT (Letter FAS) total correct</td>
</tr>
<tr>
<td></td>
<td>Semantic verbal fluency (Animal Category) total correct</td>
</tr>
<tr>
<td>Verbal learning/memory</td>
<td>HVLT-R – total learning and delayed recall</td>
</tr>
<tr>
<td>Motor coordination</td>
<td>Grooved pegboard dominant and non-dominant hand</td>
</tr>
<tr>
<td>Speed of information</td>
<td>TMT A time in seconds</td>
</tr>
<tr>
<td>processing</td>
<td>WAIS-III Digit-symbol Coding total correct</td>
</tr>
<tr>
<td></td>
<td>DKEFS reading test time in seconds</td>
</tr>
<tr>
<td>Attention/ working memory</td>
<td>WAIS-III Letter-number sequencing total correct</td>
</tr>
<tr>
<td></td>
<td>WAIS-III Spatial span total correct</td>
</tr>
</tbody>
</table>


For individuals of non-English speaking background, this was substituted with the Colour Trails Test (D’Elia, Satz, Uchiyama & White,
1996); Delis Kaplan Executive Function System (DKEFS) Colour-Word Interference (CWI) Test: (Delis et al., 2001); Controlled Oral Word Association Test, Letter and semantic fluency (Benton, Hamsher & Sivan, 1994).