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Deficient Emotion Processing is Associated with Everyday Functioning Capacity in HIV-associated Neurocognitive Disorder

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Abstract

Objective: Emotion processing has received little research focus in HIV, but emerging evidence suggests that abilities such as facial affect discrimination may be features of HIV-associated neurocognitive disorder (HAND). The present study hypothesized that individuals with HAND would evidence an emotion processing deficit relative to cognitively unimpaired individuals with HIV and seronegative comparison participants on a task assessing these abilities. Moreover, it was expected that this deficit would be significantly associated with social aspects of everyday functioning.

Method: To explore these hypotheses, 37 HIV+ individuals with HAND, 46 HIV+ without HAND, and 38 HIV-seronegative comparison participants were administered the CogState Social Emotional Cognition Task (SECT) and the UCSD Performance-based Skills Assessment-Brief (UPSA-B).

Results: Results revealed that the HAND group was more likely to have impaired accuracy and slower reaction time relative to the comparison groups on the SECT task. In fact, individuals with HAND were almost 10 times more likely to be impaired on emotion processing accuracy than HIV+ without HAND. Among individuals with HIV, accuracy (but not reaction time) was independently related to a functional capacity measure tapping social ability, but not to a similar measure without a social component (UPSA-B Communication and Finances subscales, respectively).

Conclusions: These results suggest that disruption of emotion processing may be an important feature of HAND that has clinical value as an independent predictor of real-world activities that involve social components. Future research should prospectively investigate this relationship, which may inform of intervention strategies for improving everyday functioning.

Keywords: Social cognition; Emotion; Theory of mind; Everyday functioning; Social functioning

Introduction

In the era of combination antiretroviral therapy (cART), it is estimated that approximately 30%–50% of individuals infected with HIV meet criteria for an HIV-associated neurocognitive disorder (HAND; Heaton et al., 2011), which has an annual incidence rate of approximately 10%–15% (e.g., Bhaskaran et al., 2008). HAND is the neurobehavioral hallmark of HIV-associated neuropathologies, which are diverse in both their neurobiology (Everall et al., 2009) and brain networks affected, but tend to be most prevalent in the frontostriatal circuits (e.g., Ellis, Calero, & Stockin, 2009). The neuropsychological profile of HAND is also heterogeneous (e.g., Dawes et al., 2008), but executive functions, attention/working memory, information processing speed, episodic memory, and motor skills are the most commonly impaired domains (Woods, Moore, Weber, & Grant, 2009). HIV-associated neurocognitive impairment can adversely affect different aspects of everyday functioning (Heaton et al., 2004), including vocational outcomes (van Gorp, Baerwald, Ferrando, McElhiney, & Rabkin, 1999) and automobile driving (e.g., Marcotte et al., 1999). HAND is also associated with suboptimal health behaviors, such as

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medication non-adherence (Hinkin et al., 2002) and poorer retention in care (Jacks et al., 2015), as well as lower health-related quality of life (e.g., Parsons, Braaten, Hall, & Robertson, 2006).

Altered emotional and social functioning have received much less empirical attention in HIV disease as possible features of HAND, particularly syndromic HAND in which everyday functioning is compromised. Given that emotion processing is an integral part of our everyday social lives (Darwin, 1872/1965), it may offer an avenue for investigation into functioning abilities with social components. Recognizing the emotions of others and utilizing this information to respond appropriately is a key aspect of fruitful communication (e.g., Fridlund, 1991). Typically measured via tests of facial affect recognition (though less frequently measured as nonverbal communication such as emotional prosody), the ability to identify emotions in others is a widely studied aspect of social cognition across many bodies of literature with typically robust results in clinical populations (e.g., Parkinson's disease, Narme et al., 2013; traumatic brain injury, Genova et al., 2015). Moreover, the facial expression of basic emotions is viewed as pan-culturally universal (Ekman, 1972) and it lends itself to easy study in laboratory settings (Lane, Moore, Batchelor, Brew, & Cysique, 2012). The neural systems that support overall emotion processing are diverse (e.g., Fusar-Poli et al., 2009), including multiple frontal cortices, the basal ganglia, and the amygdala, which are regions that are also preferentially affected by HIV-related neuropathologies (e.g., Ances, Ortega, Vaida, Heaps, & Paul, 2012; Becker et al., 2011; Küper et al., 2011). Thus, it is reasonable to expect that emotion processing deficits could be a feature of HAND (Clark et al., 2015). In fact, social cognition is one of the six central cognitive domains that comprise diagnoses of HIV-associated neurocognitive disorders as defined by the latest edition of the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; American Psychiatric Association, 2013). However, we know little about the nature, extent, and functional relevance of emotion processing deficits in the context of HIV disease.

While the literature on the effects of HIV on emotion processing is still developing, early studies have provided important insights. As a group, HIV+ persons show moderately slower response times and reduced accuracy identifying and discriminating amongst facial emotional expressions (Gonzalez-Baeza et al., 2014; Heilman et al., 2013; Lane et al., 2012; Lysaker et al., 2012), with several of the studies finding specific effects for processing negative emotions such as sadness (Gonzalez-Baeza et al., 2014) and fear (Baldonero et al., 2013; Clark et al., 2015; Clark, Cohen, Westbrook, Devlin, & Tashima, 2010), which may be related to lower anterior cingulate cortex volumes (Clark et al., 2015). The HIV literature has not revealed consistent associations between emotion processing and mood, demographics, or traditional markers of disease severity in HIV (Baldonero et al., 2013; Clark et al., 2010; Heilman et al., 2013; Lane et al., 2012). With regard to neurocognitive correlates of emotion processing in HIV, verbal memory has been associated with facial emotion recognition (Baldonero et al., 2013), and psychomotor speed and cognitive flexibility are associated with both reaction time to fear and happiness discrimination (Lane et al., 2012). Although most studies did not specifically include HAND in their analyses, there is preliminary evidence that individuals with HAND may be particularly susceptible to deficits in facial emotion processing. In a series of uncontrolled secondary analyses, Lane and colleagues (2012) reported medium-to-large effect sizes for HAND in emotion processing accuracy and response times for both positive and negative emotions (including fear). In contrast, Baldonero and colleagues (2013) did not observe a disproportionate effect of HAND in HIV, as evidenced by secondary analyses showing that HIV+ individuals with and without HAND (i.e., Asymptomatic Neurocognitive Impairment) had comparable deficits in facial emotion recognition in relation to seronegatives. Thus, a prospective, case-controlled study of emotion processing in a well-characterized group of individuals with HAND (i.e., HAND diagnosis based upon a well-validated, comprehensive battery of neuropsychological tests that can also support correlate analyses) may help to clarify these conflicting findings.

The clinical relevance of emotion in HIV disease is supported by data from other neuropsychological populations, which suggest that this cognitive function may be a unique predictor of social functioning and capacity. For example, in the schizophrenia literature, several studies have found that emotion processing had a relationship with social functioning (Hooker & Park, 2002; Pan, Chen, Chen, & Liu, 2009; Poole, Tobias, & Vinogradov, 2000), or was a mediator between cognitive and social functioning (Addington, Saeedi, & Addington, 2006). To date, we are aware of only two studies examine the association between emotion processing and everyday functioning in HIV disease. Clark and colleagues (2010) reported that errors in identifying anger showed moderate univariate correlations with self-reported difficulties in intimate social relationships, specifically with maintaining a feeling of social connectedness. By way of contrast, Lane and colleagues (2012) reported that performance on a comprehensive battery of emotion processing was not associated with a self-report measure of general ADLs in HIV disease. Thus, HIV-associated difficulties in emotion processing may be particularly sensitive to the social aspects of everyday functioning. Additionally, performance-based measures of the capacity to perform daily activities are known to be particularly sensitive to functioning difficulties in HAND (Blackstone et al., 2012), and as such they may have greater utility than self-report approaches in identifying and describing the relationship between emotion processing and everyday functioning.

The current study therefore sought to determine the affect of HAND on emotion processing using a standardized, clinical social cognition measure. It was hypothesized that HAND would be associated with moderate deficits on measures of emotion

processing speed and accuracy as compared to HIV+ individuals without HAND and HIV− comparison participants. In addition we aimed to estimate the unique contribution of HIV-associated facial emotion processing deficits to real-world functional capacity as measured by a well-validated performance-based measure. It was hypothesized that after controlling for overall level of neurocognitive impairment and other relevant disease factors, deficits in emotion processing would be associated with poorer functional capacity on a task with strong social demands (i.e., communication), but not with performance on a parallel functional task with minimal social demands (i.e., finances).

Methods

Participants

One-hundred-twenty-one participants were enrolled from ongoing studies at a neuroAIDS research center, whose recruitment sources included local HIV clinics and community-based organizations. Exclusionary criteria included a severe psychiatric diagnosis (e.g., schizophrenia), neurological condition (e.g., seizure disorder, stroke, closed head injury with loss of consciousness greater than 15 min), or active illicit drug (assessed via positive urine toxicology) or alcohol (assessed via Breathalyzer) use. Substance use disorder within 30 days of the evaluation, as assessed by Composite International Diagnostic Interview (CIDI, version 2.1; World Health Organization, 1998), also served as a study exclusion criterion. Medmira rapid tests were used to establish HIV serostatus. Using the parent center's comprehensive assessment of medical, psychiatric, and neuropsychological information (see details in the Classification of HAND section.), HAND was categorized in accordance with Frascati research diagnostic criteria (Antinori et al., 2007). The three primary study groups of interest were: HIV– ($n = 37$), HIV+ without HAND (HAND–; $n = 46$), and HIV+ with HAND (HAND+; $n = 38$).

Classification of HAND

Study participants' clinical functioning was comprehensively characterized as part of the larger study. The neurocognitive batteries used to derive HAND classifications were constructed utilizing Frascati criteria (Antinori et al., 2007). The seven domains (and their component parts) tested were: (a) processing speed (WAIS-III Digit Symbol, Weschler, 1997; Trailmaking Test Part A, Reitan & Wolfson, 1985; and CogState reaction time on the detection and identification subtests); (b) attention/working memory (PASAT-50, Gronwall, 1977; and CogState accuracy on the one-back and two-back substests); (c) learning (CogState accuracy on one-card learning; HVLT-R Total 1–3, Brandt & Benedict, 2001; and BVMT-R Total 1–3, Benedict, 1996); (d) memory (CogState accuracy on continuous paired associates; HVLT-R Delayed Recall, Brandt & Benedict, 2001; and BVMT-R Delayed Recall, Benedict, 1996); (e) verbal fluency (letter/FAS and animals, Delis, Kaplan, & Kramer, 2001); (f) executive functions (Trailmaking Test Part B, Reitan & Wolfson, 1985; WCST-64 perseverative responses, Heaton, 1993; and Iowa Gambling Task total, Bechara, 1994); and (g) motor (Grooved Pegboard Test dominant and non-dominant hands, Kløve, 1963). Following a well-validated method described previously (Carey et al., 2004), a Global Deficit Score (GDS) was derived from T-scores (converted from relevant raw scores adjusting for demographics). A categorization of global neurocognitive impairment was then determined using a GDS cutpoint of ≥0.5 to classify HAND. Among HIV+ participants, 45% of individuals were classified with HAND, which were further classified into diagnostic categories based on absence vs. presence of everyday functioning impairment and degree of neurocognitive impairment (Antinori et al., 2007): 15 persons with Asymptomatic Neurocognitive Impairment (ANI), 20 with Minor Neurocognitive Disorder (MND), and 3 with HIV-associated Dementia (HAD). Consistent with our exclusion criteria (see Participants section) and the Frascati HAND criteria, participants with significant medical, neurological or psychiatric conditions known to affect cognition were not included so that the effects of HAND were not confounded.

Social Emotional Cognition Task (SECT)

The Social Emotional Cognition Task (SECT), a subtest of the CogState (www.cogstate.com), is a computer-administered task designed to assess emotional processing aspects of social cognition. This task has been validated as a measure of social cognition in controls and schizophrenic patients using the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT)-Managing Emotions task from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery (with a correlation of 0.45 for controls and 0.59 for schizophrenia; Pietrzak et al., 2009) and as a measure of facial affect recognition in traumatic brain injury (with a correlation of approximately 0.4 relative to two valid and reliable facial affect recognition tasks; Yim, Babbage, Zupan, Neumann, & Willer, 2013). The task entails 48 trials, and each trial

shows an array of four images that convey emotion for 15 s. The images are displayed as computerized faces or as sets of eyes. Participants were asked to use a computer mouse to select one of the four images in the array that was different from the others on each trial, but no guidance as to the nature of the difference was given (i.e., instructions read "tap the odd one out."). Some trials of this task involve discriminating between facial affect presentations of different emotions (e.g., neutral vs. fear) and others require discriminating between intensities of facial affect for the same emotion (e.g., mild fear vs. extreme fear). There were also control items in which four sets of neutral eyes were shown depicting eye gaze direction (no emotion displayed), and one pair of eyes was looking in a different direction than the other three sets. Both speed of response and accuracy were measured for each trial. The CogState program performs computerized scoring that yields a mean reaction time score (raw) and an arcsine-corrected accuracy score. For the accuracy score, age corrections were applied using CogState Normative Data (www.cogstate.com), and these scores were then converted into T-scores for ease of interpretation. A cutpoint of one standard deviation below the mean ($T < 40$) was used to define mild impairment, which is consistent with a well-validated standard approach (Carey et al., 2004). One prior study has examined SECT in the context of HIV, and a possible effect of HAND was detected in posthoc analyses (i.e., Lane et al., 2012).

UCSD Performance-based Skills Assessment-Brief (UPSA-B)

The UPSA-B (Mausbach, Harvey, Goldman, Jeste, & Patterson, 2007) is a measure of daily functional capacity utilizing performance on analogs of real-world tasks developed via factor analysis as shortened form of a previous measure (Patterson, Goldman, McKibbin, Hughs, & Jeste, 2001). The UPSA-B has been validated in multiple populations, including schizophrenia and bipolar disorder (Mausbach et al., 2010). This shortened form of the UPSA takes approximately 15 min to complete and covers two domains: Communication and Finances. In the Communication subscale tasks, the participants were supplied with a telephone and asked to role-play various tasks, most of which involve using communication skills for eliciting information from or to relaying information to another person; these tasks include retrieving a phone number from Information, dialing a phone number from memory, responding to an emergency, and leaving a detailed message with hospital staff regarding rescheduling an appointment. One point is given for each correctly completed aspect of the nine subtasks, for a raw score ranging from 0 to 9. The Finances subscale involved participants using supplied currency to count out a certain amount, make appropriate change, and properly fill out a check to pay a bill. A point is earned for each correctly completed aspect of the 10 subtasks (with two points for the change-making task), for a raw score ranging from 0 to 11. The raw score totals for each subscale are converted to a percentage correct (total points/total possible points) and then multiplied by 50 to get the total subscale scores (maximum score = 50). Our analyses used these raw subscale scores, which are not adjusted for demographic characteristics.

Clinical Characterization

Information on estimated duration of HIV infection, AIDS status, nadir and current CD4 counts, current cART regimen, plasma levels of HIV RNA, and hepatitis C infection was gathered via neuromedical exam, history, and phlebotomy/labs. Presence of current and lifetime mood and substance use disorders were assessed via the CIDI.

Data Analysis

An examination of potential covariates from demographic and clinical characteristics was undertaken using ANOVA or X^2 tests, as appropriate. These included age, education, gender, ethnicity, degree of cognitive impairment (measured by GDS), current and lifetime major depression, current and lifetime generalized anxiety, lifetime substance abuse/dependence, and hepatitis C. To be included as a covariate in our analyses, a factor was required to (1) differ significantly between the three study groups and (2) demonstrate a significant relationship with one of the cognitive or functional tasks of interest. The effects of HAND on the SECT and UPSA-B variables were assessed using Wilcoxon rank sums tests. The associations between SECT and the UPSA-B measures were examined using simultaneous linear regression in the HIV+ group, with a critical value of $p < .05$. All statistical analyses were performed with JMP version 11.2.

Results

As seen in Table 1, the three groups were generally similar on demographic factors, with the exception of a greater proportion of men in HIV+ groups, $X^2 = 8.7$, $p = .01$. HIV+ participants were also more likely to have had a diagnosis of Major

Depressive Disorder at some point in their lives, $X^2 = 16.0$, $p = .003$. These factors were not included as covariates, as neither was significantly related to the measures of interest ($ps > .10$). There were no differences between the groups on history of GAD, history of substance use disorder, or hepatitis C infection ($ps > .10$). In comparing HIV+ groups with and without HAND, there were no differences on HIV clinical characteristics ($ps > .10$) with the exception of detectable viral load, $X^2 = 3.9$, $p < .05$, which was not related to any primary outcome of interest. Significant group differences were observed in the expected directions on the UPSA outcome measures, including the Communication and Finances subscales, and are shown in Table 2.

HAND Effects on SECT and UPSA-B

No significant effect of HAND group was observed on SECT accuracy as a continuous variable ($p > .10$). However, using a standard cutpoint of 1 *SD*, a significantly higher proportion of HAND+ subjects were impaired on SECT accuracy relative to HAND– (no participants in the HIV– group were impaired, and therefore a Fisher's Exact Test was conducted between the HAND+ and HAND– groups), $X^2 = 5.4$, $p = .04$ (see Table 2 for proportion impaired in each group). No demographic, psychiatric, cognitive (i.e., HAND severity), or standard HIV disease factors differed between the SECT impaired and unimpaired groups. In the HAND group, SECT accuracy was significantly correlated with the memory domain ($r = .4$, $p < .05$), and correlations with all other domains were non-significant ($ps > .05$). There was also a significant between-group effect of HAND on SECT reaction time ($p < .001$, $\eta^2 = .11$), with the HAND+ group being slower than both HAND– ($p = .003$, $d = .78$) and HIV– ($p < .001$, $d = .74$) groups (see Table 2 for average reaction times by group). In the HAND group, SECT reaction time was significantly correlated with the information processing speed domain ($r = .4$, $p < .05$) only (all other $ps > .05$).

Table 1. Descriptive characteristics of the sample

Demographics	HIV– ($n = 37$)	HAND– ($n = 46$)	HAND+ ($n = 38$)
Age (years)	44.3 (12.9)	46.59 (9.52)	43.95 (10.52)
Education (years)	13.9 (2.3)	14.13 (2.64)	13.08 (2.01)
Sex (% female)*	32%	9%	13%
Ethnicity (% Caucasian)	59%	63%	53%
Psychiatric & substance use			
Current/Lifetime** Major Depressive disorder (%)	3%/24%	2%/58%	5%/68%
Current/Lifetime Generalized Anxiety disorder (%)	8%/14%	0%/7%	8%/21%
Lifetime Substance Use Disorder (%)	49%	66%	71%
HIV/medical characteristics			
Duration of HIV infection (months)	—	8.73 [3.42, 22.2]	13.02 [5.09, 19.34]
AIDS status (%)	—	55%	54%
Nadir CD4 (cells/μl)	—	220.5 [81.5, 354.75]	199 [22, 326.5]
Current CD4 (cells/μl)	—	676 [438, 854]	622 [321, 855.5]
cART status (% prescribed)	—	89%	89%
HIV Plasma RNA (% undetectable)*	—	91%	79%
Hepatitis C (% positive)	15%	11%	13%

Note: *$p < .05$, **$p < .01$. Data presented as Mean (standard deviation) and Median [IQR] unless otherwise noted. HAND = HIV-associated neurocognitive disorders. cART = combination antiretroviral therapy.

Table 2. Cognitive performance of the sample

	HIV– ($n = 37$)[a]	HAND– ($n = 46$)[b]	HAND+ ($n = 38$)[c]	Group contrasts
Global Deficit Score (GDS range 0–5)	0.2 [0, 0.77]	0.11 [0.06, 0.28]	0.83 [0.61 1.29]	—
SECT				
Accuracy % Impaired*	0%	2%	17%	—
Mean reaction time (ms)**	3.52 (0.12)	3.53 (0.08)	3.60 (0.1)	a, b < c
UPSA-Brief				
Finance*	45 [41, 47.5]	45 [41, 50]	45 [36, 45]	c < b
	43.5 (5.1)	45.5 (3.9)	40.8 (8.7)	
Communication**	33 [28, 44]	39 [33, 44]	33 [28, 39]	a, c < b
	35.6 (8.5)	38.4 (9.7)	33.7 (8.0)	

Notes: *$p < .05$, **$p < .01$. Data presented as Mean (standard deviation) and Median [IQR] unless otherwise noted; SECT = CogState Social Emotional Cognition Task. UPSA-Brief = UCSD Performance-Based Skills Assessment-Brief. UPSA-Brief omnibus group differences and group contrasts were based on Wilcoxon rank sum tests.

SECT and Social Communication in HIV

The overall model predicting UPSA Communication from SECT accuracy (percent impaired) in the HIV+ group (including both HAND– and HAND+, with GDS impairment as a covariate because of the significant effect of HAND on SECT accuracy percent impaired) was significant ($F(2, 83) = 5.4$; adjusted $R^2 = 0.1$; $p = .007$). Within that model, SECT accuracy ($b = -8.0$, 95% CI [–15.1, −0.9], $p = .03$) but not GDS impaired ($b = -3.5$, 95% CI [−7.4, 0.4], $p = .08$) was a significant independent predictor. Although the overall model predicting UPSA Finance was also significant ($F(2, 83) = 5.6$; adjusted $R^2 = 0.1$; $p = .005$), only GDS impaired was a significant independent predictor ($b = -4.4$, 95% CI [−7.3, −1.5], $p = .004$), whereas SECT accuracy was non-significant ($b = -1.9$, 95% CI [−7.2, 3.4], $p = .5$). There was no difference in the pattern of results when the continuous SECT accuracy variable replaced the percent impaired dichotomous variable. When SECT reaction time replaced accuracy in the above models, there were no significant effects of reaction time on either UPSA Communication or Finance ($ps > .10$).

Discussion

Little is known about the frequency of impairment in social cognition and its functional correlates in the context of HIV and HAND, and the importance of this research question is underscored by the role of social cognition role in diagnosing neurocognitive disorders in the DSM5. The present study demonstrated that emotional processing aspects of social cognition were deficient in individuals with HAND. Specifically, the HAND group was significantly slower and less accurate in choosing a target item (i.e., faces or eyes) that differed from three others in an array in terms of the nature or intensity of the emotion displayed. Notably, using a standard cutpoint for impairment (i.e., 1 *SD* below the mean), individuals with HAND were nearly 10 times (odds ratio) more likely to be impaired in their facial affect discrimination accuracy than, HIV+ individuals without HAND. Moreover, accuracy on this task was significantly associated with everyday tasks involving interactions with others (i.e., UPSA Communication), which is evidence of the real-world affect of social cognition deficits in individuals with HAND.

The effect of HAND on emotional processing observed in the present study is notable in several ways. The effect was independent of clinicodemographic factors, including education, lifetime mood or substance abuse disorders, and HIV clinical characteristics, which increases the rigor of the interpretation that deficient emotional processing was a feature of HAND in this study. This finding is broadly consistent with prior studies showing moderate deficits in facial affect recognition in HIV disease (Baldonero et al., 2013; Clark et al., 2010, 2015; Heilman et al., 2013; Lane et al., 2012) and supports a particular effect of HAND on emotional processing (Lane et al., 2012). Additionally, the current HAND effect on emotion processing was demonstrated using a computerized clinical task (i.e., SECT from CogState), results of which have not previously been reported in HIV to date. These findings suggest that emotion processing should be explored prospectively in future studies of HAND.

Although the SECT measure from the CogState is described and validated in the literature as a measure of social cognition, and more specifically as a measure of emotion identification (i.e., facial affect recognition), it is possible that it is a hybrid measure of social cognition that also taps affective theory of mind. Specifically, affective theory of mind is another type of emotion processing ability in which an individual infers the emotional state of another person. It is differentiated from simple emotion identification or discrimination by the fact that the inference is based on restricted information (e.g., facial emotion expression shown by eyes only rather than a complete face) or the context of the situation (Mitchell & Phillips, 2015). Some items of the SECT measure show only eyes as stimuli, suggesting that these items may better map onto affective theory of mind abilities. Affective theory of mind has not yet been explored in HIV, but deficits have been observed in disease populations with broadly similar cognitive profiles as HIV, including Parkinson's disease (Poletti, Vergallo, Ulivi, Sonnoli, & Bonuccelli, 2013). Future studies should explore affective theory of mind in the context of HIV to investigate a potential HAND effect on this domain of social cognition as well. Studies with a full battery of social cognition measures may also seek to examine the validity of the SECT with regard to established theory of mind measures, and to compare its sensitivity to HAND against tests that more purely measure facial affect recognition or theory of mind.

The present study also investigated the correlates of emotion processing measures in HAND. The interpretation of the association between SECT reaction time and speed of information processing is somewhat straightforward given that the pace of an individual's response to the target in the arrays would clearly be anchored to his or her information processing ability. Moreover, responses times would be expected to be slower when processing stimuli that present a challenge, such as the emotion processing stimuli did within the HAND group. SECT accuracy was significantly associated with memory, and yet there is no memory component to performance on this task. A possible interpretation of this association involves the prefrontocorticolimbic circuits that are preferentially affected by HIV disease. Social cognition ability is most often broadly attributed to medial prefrontal regions (Amodio & Frith, 2006), but emotion recognition, particularly for fear, has been shown to involve the

amygdala (Adolphs, 2002). Altered amygdala volume has been reported in HIV (Clark et al., 2015), and recent evidence shows an effect of HIV on the hippocampus that was associated with memory impairment (Maki et al., 2009). As such, the significant correlation between SECT and memory in this study may reflect the effect of HIV on limbic structures. This notion is additionally supported by the idea that emotion recognition (and discrimination) are more implicit/automatic types of social cognition tasks, which are hypothesized to rely more upon limbic structures, as opposed to explicit/deliberative, which draws from prefrontal regions (Forbes & Grafman, 2010). However, in a recent study of emotion recognition ability in HIV, increased amygdala volume observed in HIV+ individuals was not associated with poor fear recognition performance, whereas a significant association was observed for anterior cingulate volume (Clark et al., 2015), which is consistent with the explanation that medial prefrontal cortex functions support social cognition. Since the memory domain comprised recall and not recognition tasks, it could be that the strategic aspects of searching for and retrieving previously encoded information, which is reliant upon prefrontal cortex functions, is driving the association between memory and emotion processing in this study. If this were the case, it would be expected that the learning domain, which is also affected by strategic processes, would also be associated with the emotion processing outcome. While an association between emotion processing and learning was observed in a prior study (Baldonero et al., 2013), there was not a similar correlation revealed in the present data. Future studies should prospectively investigate the cognitive correlates of emotion processing in HIV to fully explore these associations.

A particularly novel aspect of this study was demonstrating that laboratory measures of emotional processing were moderately related to everyday functional capacity in HIV disease, which showed a specific association with a communication task involving social functioning skills. Specifically, the ability to accurately discriminate emotions (potentially combined with the ability to take the emotional perspective of another person, or theory of mind) was significantly related to accuracy on a performance-based task in which participants were asked to reschedule a medical appointment, contact emergency services, and utilize municipal telephone directory assistance. Notably, these findings were specific to the communication task and no relationship was observed between emotion processing and a performance-based functional task without an overt social component (e.g., properly counting out change and paying a bill by check), which instead was more strongly related to global neurocognitive functioning. These associations between emotion processing and communication were observed for accuracy but not reaction time on the emotion processing task. It is possible that in emotion processing, accuracy is more important than speed in relation to functional social capacity because competently navigating social interactions is more reliant on having correct information more so than one's speed of processing that information. Importantly, the association between emotion processing accuracy and communication/social capacity was independent of global neurocognitive impairment, thereby supporting the incremental ecological relevance of social cognition as a predictor of social functioning ability in HIV disease.

The present study had some limitations. We did not observe the expected pattern of UPSA-B scores such that the HAND– group would perform comparably to the HIV– group, and that the HAND+ group would perform significantly more poorly than both of these comparison groups. Importantly, the HIV− group was not a true control group in that they had similar levels of exposure to typical HIV comorbidities that increase risk for cognitive deficits (e.g., depression, substance use) as the HIV+ individuals, which may partly explain why they did not exhibit significantly higher levels of UPSA-B performance relative to the two HIV+ groups. In fact, is not uncommon for studies with a 3-group design that separates HIV+ individuals on HAND status to yield a high-functioning HIV+/HAND– group. Relatedly, it is our interpretation of the findings that the HAND– individuals did not have unusually high UPSA-B scores, but rather that sampling produced scores were that were slightly lower than expected in the HIV− group. As a result, we believe that the difference between the two HIV+ groups (i.e., HAND– and HAND+) on the UPSA-B was likely valid. Moreover, our main analyses (i.e., linear regression models conducted in the HIV+ group only) examining social cognition as a predictor of everyday functioning as measured by the UPSA-B are also likely valid and meaningful despite the counterintuitive pattern of UPSA-B performance across all three study groups.

Due to the nature of the emotion processing task, we were not able to examine specific emotions, which would be important because prior research has shown identification of certain emotions (typically negative emotions) to be more difficult than others. If a specific emotion were more related to our findings, then we would have a better idea of the neurological underpinnings of our observed effects. Additionally, although the task had control items in the form of differentiating gaze direction, it lacked other relevant control items that could rule out the contribution of visuospatial difficulties capable of interfering with the ability to select a correct response in someone who has intact emotion processing ability. Further, the task was for discrimination of emotion (i.e., requiring the participant to indicate which facial affect display is different from the others), but not recognition; a participant need not be able to identify the specific emotion in order to respond correctly. Ideally, it would be preferable to have data on both discrimination and recognition (broken down by emotion), in both accuracy and response time for each. This would enable a more robust analysis of the specific emotion processing dysfunctions related to social functional ability. Nor could we separate the facial emotion discrimination trials from the affective theory of mind trials, which would have allowed us to comment on whether an affective theory of mind deficit is noted in HAND. With the present data we can only infer a HAND effect on affective theory of mind based on performance on a hybrid task. Nevertheless, given

that the SECT task detected a signal in HAND, a single task that taps multiple emotion processing measures may be particularly sensitive and thereby have greater clinical utility. In a similar vein, we have a single measure of social functional capacity. Future work might include a more comprehensive assessment of social functioning, for example including information on social networks, interpersonal effectiveness, and social quality of life, as well as traditional measures of everyday functioning (e.g., self-reported activities of daily living). Moreover, the relationship between emotion processing and health-related activities may be particularly important in this population because effective communication is needed to successfully navigate multiple aspects of healthcare interactions, and emotions are known to be an important factor in health-related decision-making. Recent evidence showing an association between emotion processing (as measured by the SECT) was significantly associated with measures of health literacy (Morgan et al., 2015), which supports this research direction.

In conclusion, among individuals with HIV, HAND is associated with a disruption in emotion processing, which in turn is an independent predictor of social functional capacity. Given its increased importance in the DSM5, social cognition, and emotion processing in particular, should see increased attention in future research to investigate the extent to which it aids in the diagnosis of HAND. If a robust relationship between emotion processing and HIV/HAND emerges, these findings will inform interventions for improving social cognition and many aspects of everyday functioning.

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Conflict of Interest

None declared.

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References

Addington, J., Saeedi, H., & Addington, D. (2006). Facial affect recognition: A mediator between cognitive and social functioning in psychosis? *Schizophrenia Research*, *85*, 142–150.

Adolphs, R. (2002). Neural systems for recognizing emotion. *Current Opinion in Neurobiology*, *12*, 169–177. doi:10.1016/S0959-4388(02)00301-X.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: Author.

Amodio, D. M., & Frith, C. D. (2006). Meeting of minds: The medial frontal cortex and social cognition. *Nature reviews. Neuroscience*, *7*, 268–277. doi:10.1038/nrn1884.

Ances, B. M., Ortega, M., Vaida, F., Heaps, J., & Paul, R. (2012). Independent effects of HIV, aging, and HAART on brain volumetric measures. *Journal of Acquired Immune Deficiency Syndromes*, *59*, 469–477. doi:10.1097/QAI.0b013e318249db17.

Antinori, A., Arendt, G., Becker, J. T., Brew, B. J., Byrd, D. A., Cherner, M., et al. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*, *69*, 1789–1799.

Baldonero, E., Ciccarelli, N., Fabbiani, M., Colafigli, M., Improta, E., D'Avino, A., et al. (2013). Evaluation of emotion processing in HIV-infected patients and correlation with cognitive performance. *BMC Psychology*, *1*, 3. doi:10.1186/2050-7283-1-3.

Bechara, A. (1994). *Iowa Gambling Task*. Lutz, FL: Psychological Assessment Resources.

Becker, J. T., Sanders, J., Madsen, S. K., Ragin, A., Kingsley, L., Maruca, V., et al. (2011). Subcortical brain atrophy persists even in HAART-regulated HIV disease. *Brain Imaging and Behavior*, *5*, 77–85. doi:10.1007/s11682-011-9113-8.

Benedict, R. H. B. (1996). *Brief Visuospatial Memory Test-Revised (BVMT-R)*. Lutz, FL: Psychological Assessment Resources, Inc.

Bhaskaran, K., Mussini, C., Antinori, A., Walker, A. S., Dorrucci, M., Sabin, C., et al. (2008). Changes in the incidence and predictors of human immunodeficiency virus-associated dementia in the era of highly active antiretroviral therapy. *Annals of Neurology*, *63*, 213–221.

Blackstone, K., Moore, D. J., Heaton, R. K., Franklin, D. R., Woods, S. P., Clifford, D. B., et al. (2012). Diagnosing symptomatic HIV-associated neurocognitive disorders: Self-report versus performance-based assessment of everyday functioning. *Journal of the International Neuropsychological Society*, *18*, 79–88. doi:http://dx.doi.org/10.1017/S135561771100141X.

Brandt, J., & Benedict, R. H. B. (2001). *Hopkins Verbal Learning Test-Revised (HVLT-R)*. Lutz, FL: Psychological Assessment Resources, Inc.

Carey, C. L., Woods, S. P., Gonzalez, R., Conover, E., Marcotte, T. D., Grant, I., et al. (2004). Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. *Journal of Clinical and Experimental Neuropsychology*, *26*, 307–319.

Clark, U. S., Cohen, R. A., Westbrook, M. L., Devlin, K. N., & Tashima, K. T. (2010). Facial emotion recognition impairments in individuals with HIV. *Journal of the International Neuropsychological Society*, *16*, 1127–1137. doi:10.1017/S1355617710001037.

Clark, U. S., Walker, K. A., Cohen, R. A., Devlin, K. N., Folkers, A. M., Pina, M. J., et al. (2015). Facial emotion recognition impairments are associated with brain volume abnormalities in individuals with HIV. *Neuropsychologia*, *70*, 263–271. doi:10.1016/j.neuropsychologia.2015.03.003.

Darwin, C. (1965). *The expression of the emotions in man and animals*, *Vol. 526*). Chicago, IL: University of Chicago Press. (Reprinted from 1872).

Dawes, S., Suarez, P., Casey, C. Y., Cherner, M., Marcotte, T. D., Letendre, S., et al. (2008). Variable patterns of neuropsychological performance in HIV-1 infection. *Journal of Clinical and Experimental Neuropsychology*, *30*, 613–626. doi:10.1080/13803390701565225.

Delis, D. C., Kaplan, E., & Kramer, J. (2001). *Delis-Kaplan Executive Function System (D-KEFS)*. San Antonio, TX: Psychological Corporation.

Ekman, P. (1972). Universal and cultural differences in facial expression of emotion. In Cole J. R. (Ed.), *Nebraska symposium on motivation*, *Vol. 19*, pp. 207–283. Lincoln, NE: University of Nebraska Press.

Ellis, R. J., Calero, P., & Stockin, M. D. (2009). HIV infection and the central nervous system: A primer. *Neuropsychology Review*, *19*, 144–151. doi:10.1007/s11065-009-9094-1.

Everall, I., Vaida, F., Khanlou, N., Lazzaretto, D., Achim, C., Letendre, S., et al. (2009). Cliniconeuropathologic correlates of human immunodeficiency virus in the era of antiretroviral therapy. *Journal of Neurovirology*, *15*, 360–370. doi:10.3109/13550280903131915.

Forbes, C. E., & Grafman, J. (2010). The role of the human prefrontal cortex in social cognition and moral judgment. *Annual Review of Neuroscience*, *33*, 299–324. doi:10.1146/annurev-neuro-060909-153230.

Fridlund, A. J. (1991). Evolution and facial action in reflex, social motive, and paralanguage. *Biological Psychology*, *32*, 3–100.

Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., et al. (2009). Functional atlas of emotional faces processing: A voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *Journal of Psychiatry & Neuroscience*, *34*, 418.

Genova, H. M., Rajagopalan, V., Chiaravalloti, N., Binder, A., Deluca, J., & Lengenfelder, J. (2015). Facial affect recognition linked to damage in specific white matter tracks in traumatic brain injury. *Social Neuroscience*, *10*, 27–34. doi:10.1080/17470919.2014.959618.

Gonzalez-Baeza, A., Perez-Valero, I., Carvajal-Molina, F., Bayon, C., Montes-Ramirez, M., Bernardino, J. I., et al. (2014). Facial emotion processing deficits in long-term HIV-suppressed patients. *Journal of the International AIDS Society*, *17*, 19664. doi:10.7448/IAS.17.4.19664.

Gronwall, D. M. A. (1977). Paced auditory serial-addition task: A measure of recovery from concussion. *Perceptual and Motor Skills*, *44*, 367–373.

Heaton, R. K. (1993). *Wisconsin Card Sorting Test – Computer version 4*. Lutz, FL: Psychological Assessment Resources.

Heaton, R. K., Franklin, D. R., Ellis, R. J., McCutchan, J. A., Letendre, S. L., LeBlanc, S., et al. (2011). HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: Differences in rates, nature, and predictors. *Journal of Neurovirology*, *17*, 3–16. doi:10.1007/s13365-010-0006-1.

Heaton, R. K., Marcotte, T. D., MINDT, M. R., Sadek, J., Moore, D. J., Bentley, H., et al. (2004). The impact of HIV-associated neuropsychological impairment on everyday functioning. *Journal of the International Neuropsychological Society*, *10*, 317–331.

Heilman, K. J., Harden, E. R., Weber, K. M., Cohen, M., & Porges, S. W. (2013). Atypical autonomic regulation, auditory processing, and affect recognition in women with HIV. *Biological Psychology*, *94*, 143–151. doi:10.1016/j.biopsycho.2013.06.003.

Hinkin, C. H., Castellon, S. A., Durvasula, R. S., Hardy, D. J., Lam, M. N., Mason, K. I., et al. (2002). Medication adherence among HIV+ adults. Effects of cognitive dysfunction and regimen complexity. *Neurology*, *59*, 1944–1950.

Hooker, C., & Park, S. (2002). Emotion processing and its relationship to social functioning in schizophrenia patients. *Psychiatry Research*, *112*, 41–50.

Jacks, A., Wainwright, D., Salazar, L., Grimes, R., York, M., Strutt, A. M., et al. (2015). Neurocognitive deficits increase risk of poor retention in care among older adults with newly diagnosed HIV infection. *AIDS*, *29*(*13*), 1711–1714.

Kløve, H. (1963). *Grooved Pegboard*. Lafayette, IN: Lafayette Instruments.

Küper, M., Rabe, K., Esser, S., Gizewski, E. R., Husstedt, I. W., Maschke, M., et al. (2011). Structural gray and white matter changes in patients with HIV. *Journal of Neurology*, *258*, 1066–1075. doi:10.1007/s00415-010-5883-y.

Lane, T. A., Moore, D. M., Batchelor, J., Brew, B. J., & Cysique, L. A. (2012). Facial emotional processing in HIV infection: Relation to neurocognitive and neuropsychiatric status. *Neuropsychology*, *26*, 713. doi:10.1037/a0029964.

Lysaker, P. H., Ringer, J. M., Buck, K. D., Grant, M., Olesek, K., Leudtke, B. L., et al. (2012). Metacognitive and social cognition deficits in patients with significant psychiatric and medical adversity: A comparison between participants with schizophrenia and a sample of participants who are HIV-positive. *Journal of Nervous and Mental Disease*, *200*, 130–134. doi:10.1097/NMD.0b013e3182439533.

Maki, P. M., Cohen, M. H., Weber, K., Little, D. M., Fornelli, D., Rubin, L. H., et al. (2009). Impairments in memory and hippocampal function in HIV-positive vs HIV-negative women. *Neurology*, *72*, 1661–1668. doi:10.1212/WNL.0b013e3181a55f65.

Marcotte, T. D., Heaton, R. K., Wolfson, T., Taylor, M. J., Alhassoon, O., Arfaa, K., et al. (1999). The impact of HIV-related neuropsychological dysfunction on driving behavior. *Journal of the International Neuropsychological Society*, *5*, 579–592.

Mausbach, B. T., Harvey, P. D., Goldman, S. R., Jeste, D. V., & Patterson, T. L. (2007). Development of a brief scale of everyday functioning in persons with serious mental illness. *Schizophrenia bulletin*, *33*(*6*), 1364–1372.

Mausbach, B. T., Harvey, P. D., Pulver, A. E., Depp, C. A., Wolyniec, P. S., Thornquist, M. H., et al. (2010). Relationship of the Brief UCSD Performance-based Skills Assessment (UPSA-B) to multiple indicators of functioning in people with schizophrenia and bipolar disorder. *Bipolar disorders*, *12*, 45–55.

Mitchell, L. C., & Phillips, L. H. (2015). The overlapping relationship between emotion perception and theory of mind. *Neuropsychologia*, *70*(Apr), 1–10. doi:10.1016/j.neuropsychologia.2015.02.018.

Morgan, E. E., Iudicello, J. E., Cattie, J. E., Blackstone, K., Grant, I., Woods, S. P., & HIV Neurobehavioral Research Program (HNRP) Group. (2015). Neurocognitive impairment is associated with lower health literacy among persons living with HIV infection. *AIDS and Behavior*, *19*(*1*), 166–177.

Narme, P., Mouras, H., Roussel, M., Duru, C., Krystkowiak, P., & Godefroy, O. (2013). Emotional and cognition social processes are impaired in Parkinson's disease and are related to behavioral disorders. *Neuropsychology*, *27*, 182–192. doi:10.1037/a0031522.

Pan, Y. J., Chen, S. H., Chen, W. J., & Liu, S. K. (2009). Affect recognition as an independent social function determinant in schizophrenia. *Comprehensive Psychiatry*, *50*, 443–452. doi:10.1016/j.comppsych.2008.11.003.

Parsons, T. D., Braaten, A. J., Hall, C. D., & Robertson, K. R. (2006). Better quality of life with neuropsychological improvement on HAART. *Health and Quality of Life Outcomes*, *4*. 10.1186/1477-7525-4-11.

Patterson, T. L., Goldman, S., McKibbin, C. L., Hughs, T., & Jeste, D. V. (2001). UCSD Performance-based Skills Assessment: Development of a new measure of everyday functioning for severely mentally ill adults. *Schizophrenia Bulletin*, *27*, 235–245.

Pietrzak, R. H., Norman, T., Piskulic, D., Maruff, P., & Snyder, P. (2009). A comparison of the CogState Schizophrenia Battery and Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Battery in assessing cognitive impairment in chronic schizophrenia. *Journal of Clinical and Experimental Neuropsychology*, *31*, 848–859. doi:10.1080/13803390802592458.

Poletti, M., Vergallo, A., Ulivi, M., Sonnoli, A., & Bonuccelli, U. (2013). Affective theory of mind in patients with Parkinson's disease. *Psychiatry and Clinical Neurosciences*, *67*, 273–276. doi:10.1111/pcn.12045.

Poole, J. H., Tobias, F. C., & Vinogradov, S. (2000). The functional relevance of affect recognition errors in schizophrenia. *Journal of the International Neuropsychological Society*, *6*, 649–658.

Reitan, R. M., & Wolfson, D. (1985). *The Halstead-Reitan Neuropsychological Test Battery: Theory and clinical interpretation*. Tucson, AZ: Neuropsychology Press.

van Gorp, W. G., Baerwald, J. P., Ferrando, S. J., McElhiney, M. C., & Rabkin, J. G. (1999). The relationship between employment and neuropsychological impairment in HIV infection. *Journal of the International Neuropsychological Society*, *5*, 534–539.

Weschler, D. (1997). *The Weschler Adult Intelligence Scale – Third Edition (WAIS-III)*. San Antonio, TX: The Psychological Corporation.

Woods, S. P., Moore, D. J., Weber, E., & Grant, I. (2009). Cognitive neuropsychology of HIV-associated neurocognitive disorders. *Neuropsychology Review*, *19*, 152–168. doi:10.1007/s11065-009-9102-5.

World Health Organization. (1998). *Composite International Diagnostic Interview (version 2.1)*. Geneva, Switzerland: World Health Organization.

Yim, J., Babbage, D. R., Zupan, B., Neumann, D., & Willer, B. (2013). The relationship between facial affect recognition and cognitive functioning after traumatic brain injury. *Brain Injury*, *27*, 155–161. doi:10.3109/02699052.