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Brain volumetric studies reveal that human immunodeficiency virus (HIV) infection is associated with significant changes in several neural regions, including enlargements in the amygdalae, which are small subcortical structures located deep within the left and right temporal lobes that contribute to social behavior. Research on healthy individuals has shown a positive correlation exists between amygdalae volumes and social network size. However, there is evidence that larger amygdalae volumes are associated with increased psychiatric difficulties. The present study investigated the relation of amygdalae volumes and activation to social network size in HIV patients. It was predicted that HIV participants would demonstrate amygdalae enlargement and hyperactivity, and that this would correlate with reduced social interactions. The Social Network Index (SNI), a self-report measure that assesses involvement in eight social domains, was administered to 14 HIV positive (HIV) and 7 healthy control (HC) individuals. The psychological profiles of the groups were characterized using several self-report questionnaires, measuring current stress levels, mood, rates of interpersonal difficulties, and alexithymia. High resolution anatomical magnetic resonances images (MRI), obtained using a 3-Tesla scanner, were used to quantify amygdalae volumes. Participants viewed black and white images of angry and fearful faces, stimuli known to elicit robust amygdalae activation, as part of a functional MRI paradigm. The HIV and HC groups did not significantly differ on measures of social functions, amygdalae volumes, or amygdalae activation. In both groups, trend level correlations were observed between increased left amygdala volume and social network size. We also observed a significant correlation between right amygdala activation and social network complexity in the HIV group; however, these correlations were not significant in the HC group. Taken together, our results indicate that in HIV patients, greater amygdalae volumes and activation in response to highly potent social stimuli were associated with a higher degree of social interaction. These data have high clinical significance in that they provide preliminary evidence that individuals with HIV demonstrate a similar relation between social functions and amygdalae structure/function, as has been previously shown in HC samples. Studies with larger samples are needed in order to investigate these preliminary findings further.

Human immunodeficiency virus (HIV) is a disease that attacks specific blood cells, CD4 T cells, which protect the body against diseases (Centers for Disease Control [CDC], 2006). The CDC estimates that approximately 1.1 million people are living with HIV in the United States (CDC, 2011).

Second to the lungs, the brain is the most frequently affected organ in HIV patients (Masliah, DeTeresa, Mallory, & Hansen, 2000) and frontal-subcortical regions are particularly susceptible to the disease (Becker, J. T. et al., 2011; Wiley et al., 1999). Volumetric studies reveal significant brain changes in individuals with HIV, particularly in the amygdalae, which are small subcortical structures that lie deep within the temporal lobes (Clark et al., 2012). An extensive body of literature suggests that the amygdalae play a crucial role in social behavior (Cremers et al., 2011), as well as emotion recognition, particularly negative emotions, such as fear, anxiety, and aggression (Becker, B. et al., 2012; Garrett, 2011). The amygdalae are also active in recognizing emotional facial expressions – a role that is essential to normal social judgment. In a study by Adolphs, Tranel, & Damasio (1998), three individuals with complete bilateral (i.e., both sides of the brain) amygdalar damage were asked to judge faces of unfamiliar people on the basis of two attributes that are relevant to real-world social interactions: trustworthiness and approachability. All three participants judged the faces as more trustworthy and more approachable than control participants. Patients with bilateral amygdalae damage due to Urbach-Wiethe syndrome, a rare recessive autosomal disease which results in calcification (i.e., hardening of soft tissue due to the build-up of calcium salts) of anterior medial temporal lobe structures (Hamada et al., 2002; Hofer, 1973) also demonstrate deficits in the recognition of fearful faces and decreased social network size and complexity when compared to control participants (Becker, B. et al., 2012). Taken together, these findings suggest that damage to the amygdalae negatively impacts our ability to judge facial expressions, which could potentially further interfere with social interactions.

Some researchers have suggested that the amygdalae are most sensitive to ambiguity. Lloyd and Kling (1991) found that stimuli that predicted threat some of the time, as in a partial reinforcement schedule, produced greater amygdalae responses in squirrel monkeys than those stimuli that consistently predicted threat. Our day-to-day lives tend to have some level of ambiguity. As a result, researchers have suggested that there is a strong relationship between amygdalae function and activation and successful navigation of our social environments (Buchanan, Tranel, & Adolphs, 2009).

Volumetric research on the amygdalae has deepened our understanding of the active role these structures play in mediating social behavior, although findings vary across populations. Increased amygdalae volumes have been observed in children with autistic spectrum disorder (ASD) and have been implicated as a contributing factor in the social and communication deficits displayed by this population (Kim et al., 2010; Schumann, Barnes, Lord, & Courchesne, 2009). Cremers et al. (2011) found that the volume of the right amygdala positively correlated to healthy participants' levels of extraversion. Other research in healthy individuals has indicated that a positive correlation exists between amygdalae volumes and neuropsychiatric function, as indexed by measures of social network size (Bickart et al., 2010). Here, social network refers, for example, to an individual's friends, family members, neighbors, colleagues, peers. Individuals with larger amygdalae volumes had larger, more complex social networks. Kanai, Bahrami, Roylance, and Rees (2012) found that the grey matter density of the amygdalae positively correlated with the size of individuals' real-world social networks and their online social networks.

The present study was conducted to investigate whether there is an association between amygdalae volume and activation and social network size in individuals with HIV. In the present study, social network is defined as a social construct. The term refers to the collection of relationships maintained by an individual. Since individuals with HIV tend to demonstrate larger amygdalae volumes, it is of interest to determine if this volumetric abnormality correlates with social network size. Gaining a better understanding of the relationship between amygdalae volume and social network size could have important implications for the rehabilitation of individuals with HIV. This current project precedes a more involved study that will assess these effects in a larger population. Based on Bickart's (2010) findings, we predicted a positive correlation between amygdalae volume and social network size in the healthy groups. Based on data indicating that in patient populations enlarged, hyperactive amygdalae are associated with a greater degree of neuropsychiatric difficulty (Clark et al., 2012; Malykhin et al., 2012) we also hypothesized that HIV participants would demonstrate increased amygdalae enlargements and hyperactivity, and that these changes would correlate with reduced social functions.

METHODOLOGY

Participants. The study included 14 HIV-positive (HIV; 5 women, 9 men, M_{age} = 48.43 years, SD_{age} = 9.53 years) and 7 HIV-negative healthy control (HC; 2 women, 5 men, M_{age} = 55.14 years, SD_{age} = 8.51 years) individuals. HIV participants were recruited from a pool of participants currently enrolled in an ongoing longitudinal HIV aging study at Brown University. HIV participants did not have any comorbid psychiatric disorders known to alter amygdalar volume and function. HC participants were acquaintances of HIV participants and individuals recruited from the community. All participants scored within the normal range on the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975), indicating the absence of dementia and were fluent in English. The majority of the participants had already been recruited and screened based on a variety of criteria prior to the start of data collection for this study. The participants were well-matched on basic demographic variables and significantly differed only on number of years of education ($p < .05$). A variety of measures were administered to assess mood and perceived stress in the two participant groups. All participants completed the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988), the Center for Epidemiologic Studies-Depression Scale (CES-D; Radloff, 1977), the Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983), the Inventory of Interpersonal Problems (IIP; Horowitz, Alden, Wiggins, & Pincus, 2000), and the Toronto Alexithymia Scale (TAS; Bagby, Parker, & Taylor, 1994). These measures assessed anxiety, depression, perceptions of current stress in the month before testing, interpersonal difficulties and maladaptive relationship behavior, and alexithymia (i.e., difficulty identifying and describing one's own feelings) respectively. The HIV and HC groups did not differ on these measures (all p-values>.05).

Potential participants were excluded based on the following criteria: 1) history of significant pre-existing brain disease or injury; 2) previous and/or current central nervous system (CNS) infections; 3) current post-traumatic stress disorder (PTSD) diagnosis; 4) history of chronic psychiatric illness involving psychosis (e.g., schizophrenia); 5) mental retardation; 6) drug and alcohol dependence within the past six months; 7) positive urine drug screen at time of testing; 8) MRI contraindications (e.g., pregnancy, claustrophobia, MR non-compatible implants). Approval for using these assessment tools had been obtained from the Miriam Hospital's Institutional Review Board. All participants gave informed consent and were financially compensated for their time.

Measures and Procedures

All participants completed several psychological questionnaires that measure social network size, perceived stress levels, and mood. After answering the questionnaires, all participants completed an fMRI task.

Social Network Assessments. The Social Network Index (SNI; Cohen et al., 1997) is a 23-item self-report measure that assesses participation in eight social domains (e.g., family, professional, academic, volunteer). The SNI is arranged into a series of coupled questions. The first question asks if the respondent has a particular relationship and the second question asks if they communicate with the people in that particular relationship at least once every two weeks. For example, the second question on the SNI asks about the number of children a person has. Respondents answer by checking a line next to the correct number ranging from zero to seven or more. Question 2a asks about the number of children the participant communicates with in person or by phone at least once every two weeks. The same response key used in the previous question is supplied. If a respondent indicates that he/she have no children on question 2, he/she would skip question 2a and answer question three. The majority of the questionnaire is arranged in this format.

The SNI provides three sub-scales: (1) Number of High Contact Roles, (2) Social Network Size, (3) Number of High Social Domains. Each measures separate aspects of sociability. A high contact role is a social role in which the respondent has regular contact (i.e., at least once every 2 weeks) with at least one person. For example, if a participant is a parent who has regular contact with his/her children, they would qualify for that high contact role. Social network size is determined by calculating the total number of people with whom the respondent has regular contact. The number of high social domains is meant to reflect the complexity of the respondent's social network, and measures the number of different network domains in which a respondent is active.

Brain Imaging

Magnetic Resonance Imaging (MRI) – Amygdalae Volumetrics: Structural images of the brain were obtained using a 3-Tesla scanner (Siemens TIM Trio; Siemens, New York, NY). High-resolution T1-weighted MPRAGE images were acquired in the sagittal view.

Measures of whole-brain and amygdalae volumes (both on the left and right sides of the brain) were acquired via the Individual Brain Atlases using Statistical Parametric Mapping Software (IBASPM). Individual brain volumes were segmented into gray matter, white matter, and cerebrospinal fluid and normalized via nonlinear registration to the MNI 152 template. Volume estimates were calculated for each parcellation as well as for total intracranial volume. Participants' amygdalae volumes were determined in cm^3. Brabec et al. (2010) estimate that the anatomical volume of the amygdalae in normal healthy adults ranges from 1.24 cm^3 (SD = 0.14) to 1.63cm^3 (SD = 0.2).

Functional MRI (fMRI) Task – Amygdalae Activation

We administered an emotional paradigm known to elicit a robust response in the amygdalae. Participants viewed black and white images of angry and fearful faces and completed the five task conditions shown in Figure 1. While in the scanner, the participant gave their answer to the task by pressing the corresponding button on a button box. Our analyses focused on the Observe condition, as it is known to produce the most robust amygdalae response. Analyses of Functional NeuroImages (AFNI) software was utilized to conduct fMRI analyses.

Examples of FMRI Task Conditions

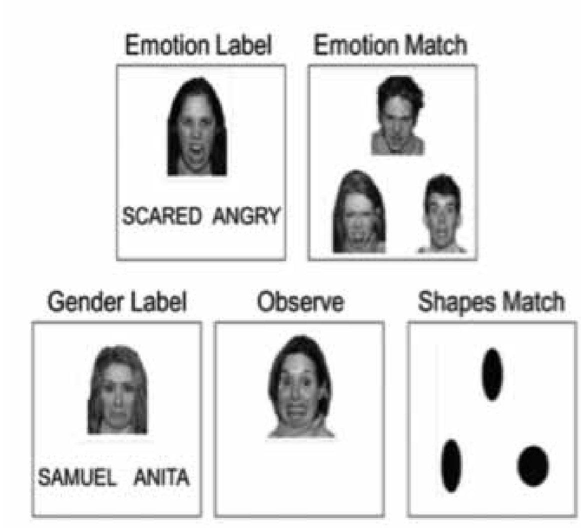

Figure 1. This figure displays the conditions of the FMRI faces task. All of the faces shown in the various conditions displayed anger or fear because these two emotions are known to illicit the most robust amygdala response. With the exception of the label headings, this is what the participant would have seen.

Results

Social Network Assessments

The HIV and HC groups did not differ on the three subscales of social functioning as assessed by the SNI. These subscales included number of high contact roles, t(19)= 0.79, p=0.44, social network size, t(19)=0.95, p=0.35, and number of high social domains, t(19)=1.04, p=0.31.

Amygdalae Volumetrics:

Amygdalae volumes in the HIV and HC groups did not significantly differ (left: t[19]=.29, p=.77; right: t[19]=.27, p=.79).

fMRI – Amygdalae Activation

We observed a significant activation of the left and right amygdalae during the Observe condition across groups (left: t[19]=3.38, p<.01; right: t[19]=2.60, p<.02); however, we did not find significant differences in amygdalae activation between groups in this condition (left: t[18]=.66, p=.52; right: t[18]=.71, p=.48;Figure 2).

SNI Correlations with Amygdalae Volumes

Across the HIV and HC groups, we observed a trend level correlation between left amygdala volumes and high contact roles (r[21]=.33, p=.07; one-tailed) as well as social network size (r[21]=.33, p=.07; one-tailed; Figure 3). No significant correlations were found between the HIV and HC groups on these measures (high contact roles: z=.20, p=.84; network size: z=.15, p=.88).

Amygdalae Activation Across Conditions

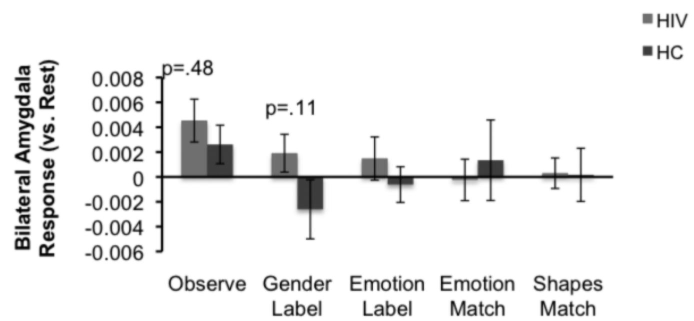

Figure 2. The graph presents the levels of bilateral amygdalae response in both groups according to the conditions in the FMRI task. We observed significant activation of the left and right amygdalae during the Observe condition across groups; however, there were no significant differences in amygdalae activation between groups in this condition. In both the HIV and HC groups, the right and left amygdala were most active when observing angry and fearful faces.

SNI Correlations with Amygdalae Activation

We observed a significant correlation between right amygdala activation and number of high social domains in the HIV group (r[13]=.69, p<.01; Figure 4). This correlation was at a

Correlations between Left Amygdala Volume and SNI Subscales Across Groups

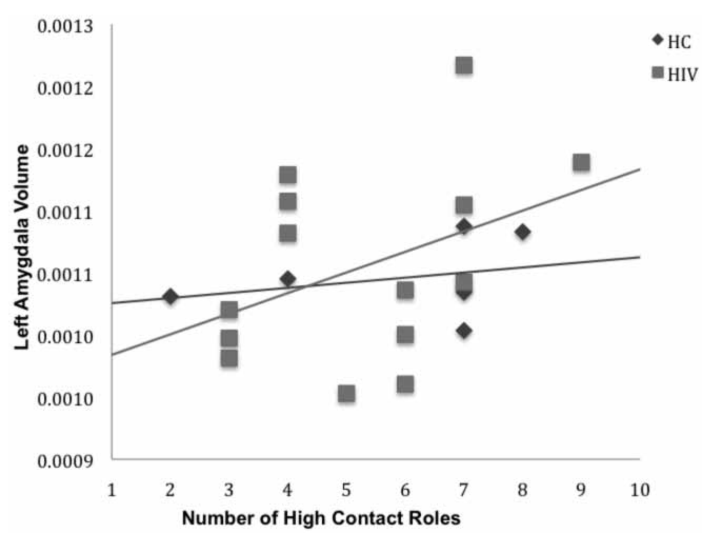

Figure 3. The graph shows that across groups there was a trend level correlation between left amygdala volumes and number of high contact roles as measured by the SNI. The correlation is not significant, but an increase in left amygdala volume is associated with an increase in participants' numbers of high contact roles.

Correlations between Left Amygdala Volume and SNI Subscales Across Groups

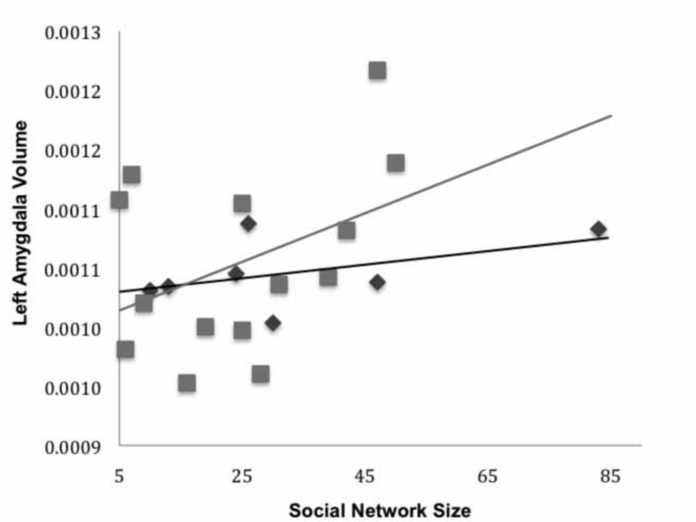

Figure 3b. The graph shows that across the groups there was a trend level correlation between left amygdala volumes and social network size as measured by the SNI. The correlation is not significant, but an increase in left amygdala volume is associated with an increase in the size of participants' social networks.

trend level for the left amygdala (r[13]=.50, p=.08). These correlations were not significant in the HC group (right: r[7]=.42, p=.35; left: r[7]=.22, p=.63). To validate our findings of a relationship between right amygdala activation and social function, we examined the relation between amygdalae activation

Correlations between Right Amygdala Activation and Number of High Social Domains in HIV Group

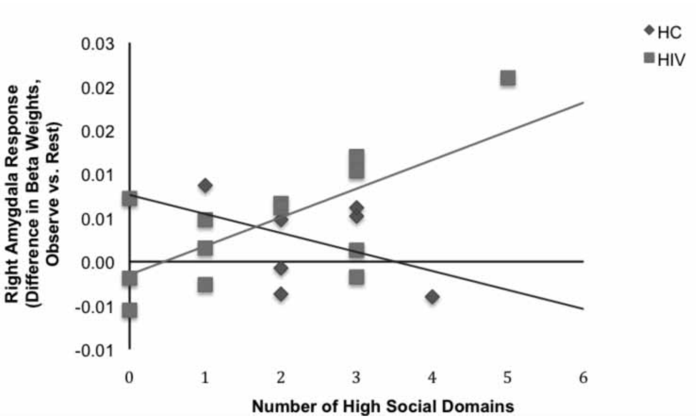

Figure 4. FMRI data analysis presented a significant correlation between right amygdala activation and number of high social domains in the HIV group. This correlation was at a trend level for the left amygdale. These correlations were not significant in the HC group.

and interpersonal problems as measured by the IIP, and found that across both groups, greater activation was associated with reduced levels of interpersonal problems (r[20]=.63, p<.01).

Discussion

Based on Bickart's (2010) findings, we anticipated that we would see a positive correlation between amygdalae volume and social function in the HC participants. We also predicted that the HIV group would display larger, hyperactive amygdalae and that these factors would correlate with reduced social function. Our hypothesis regarding the HIV group was not supported by the results. In HIV patients, greater amygdalae volumes and activation in response to highly potent social stimuli were associated with a higher degree of social interaction. These data provide preliminary evidence that individuals with HIV demonstrate a relationship between social functions and amygdalae structure and function, consistent with previous findings in HC samples. This suggests that enlarged amygdalae volumes do not negatively impact HIV patients' social functioning and this in itself can be a message of hope to this clinical population. The results suggest that HIV patients' abilities to form relationships and maintain social networks are not necessarily adversely impacted by the disease. Our findings also suggest that amygdalae enlargement and increased activation may potentially be associated with positive neuropsychiatric outcomes (i.e., complex social networks).

The results of the study also indicate that the HIV participants were similar to HC participants on the various measures that were given to assess mood and perceived stress. In the present study, the HIV participants did not display neuropsychiatric difficulties. Our findings conflict with previous research that suggests there is a strong link between HIV infection and neuropsychiatric difficulties. The disease is associated with higher rates of multiple psychiatric disorders when compared to the general population rates (Hinkin, Castellon, Atkinson, & Goodkin, 2001). A study conducted by Bing et al. (2001) involving 2864 individuals with HIV reported that nearly 50% of the participants screened positive for at least one of the following psychiatric disorders - major depression, dysthymia, generalized anxiety disorders, and panic attacks. More than a third of the participants screened positive for major depression (Bing et al., 2001). We expected the HIV participants to display neuropsychiatric difficulties given the body of literature that indicates there is a relationship between the infection and psychiatric dysfunction. One reason the HIV participants in the present study did not display neuropsychiatric difficulties may be due to our small sample size. The HIV group had higher means than the HC groups on all of the mood and perceived stress measures; however, these differences did not reach significance. We believe that adding more participants to the study would have resolved this issue, and the two groups would show significant differences on these measures.

The HIV group and the HC group differed only on number of years of education, but we do not feel as though this impacted our results, as the fMRI task that we administered was not a cognitively demanding or complex task. The participants viewed angry and fearful faces and were asked to make a judgment about which emotion was being displayed. The conclusion that participants' levels of education had no influence on the results is supported by Kirouac and Dore's (1985) finding that there is no significant link between participants' levels of education and emotion recognition.

There are several issues with the present study that warrant further consideration. One of the limitations of this study is its small sample size, which reduced the chances of observing significant group differences between the HIV and HC groups in terms of the neuropsychiatric and volumetric analyses. The independence of the participant samples presents another limitation of the present study. HC participants were recruited from the surrounding community, but they were also acquaintances of the HIV participants. The recruitment strategies suggest that these participants could share some common or overlapping social networks. A possible confounding variable is that numerous studies have suggested that social networking may play a protective role in both physical and mental health in individuals with HIV and healthy individuals (Bassuk, Glass, & Berkman, 1999; Pinquart & Duberstein, 2010; Robbins et al., 2003).

Future studies utilizing larger samples are needed to further investigate these preliminary findings. These studies might also want to consider including stress as a covariate in the analyses since it has been shown to be a factor in increased amygdalae size and hyperactivity in HIV patients as well as otherwise healthy individuals (Clark et al., 2012, Tottenham et al., 2010).

The present study was conducted to investigate the relationship between amygdalae volume and activation and social network size in individuals with HIV. The HIV and HC groups did not significantly differ on measures of social functions, amygdalae volumes, or amygdalae activation. In both participant groups, trend level correlations were observed between increased left amygdala volume and social network size. A significant correlation between right amygdala activation and social network complexity was observed in the HIV group; however, these correlations were not significant in the HC group. Taken together, these findings indicate that in HIV patients, greater amygdalae volumes and activation were associated with a higher degree of social interaction. These data have high clinical significance in that they provide preliminary evidence that individuals with HIV demonstrate a similar relation between social functions and amygdalae structure/function, as has been previously shown in HC samples. Studies with larger samples are needed in order to investigate these preliminary findings further.

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