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History of Alcohol Consumption and HIV Status Relate to Functional Connectivity Differences in the Brain During Working Memory Performance

Vaughn Bryant, Ph.D., Sc.M.^{a,b}, Joseph Gullett, Ph.D.^b, Eric Porges, Ph.D.^b, Adam J. Woods^b, Robert L. Cook, MD, MPH^a, John Williamson, Ph.D.^b, Nicole Ennis, Ph.D.^c, Kendall Bryant, Ph.D.^d, Ronald A. Cohen, Ph.D.^b

^aDepartment of Epidemiology, University of Florida, Gainesville, USA

^bDepartment of Clinical and Health Psychology, University of Florida, Gainesville, USA

^cDepartment of Behavioral Sciences and Social Medicine, Florida State University, Tallahassee, USA

^dNational Institute of Alcohol Abuse and Alcoholism, Bethesda, USA

Abstract

Background: Poorer working memory function has previously been associated with alcohol misuse, Human Immunodeficiency Virus (HIV) positive status, and risky behavior. Poorer working memory performance relates to alterations in specific brain networks.

Objective: The current study examined if there was a relationship between networks involved in working memory and reported level of alcohol consumption during an individual's period of heaviest use. Furthermore, we examined whether HIV status and the interaction between HIV and alcohol consumption was associated with differences in these brain networks.

Method: Fifty adults, 26 of whom were HIV positive, engaged in an n-back working memory task (0-back and 2-back trials) administered in a magnetic resonance imaging (MRI) scanner. The Kreek-McHugh-Schluger-Kellogg (KMSK) scale of alcohol consumption was used to characterize an individual's period of heaviest use and correlates well with their risk for alcohol dependence. Connectivity analyses were conducted using data collected during n-back task.

Results: Functional connectivity differences associated with greater alcohol consumption included negative connectivity, primarily from parietal attention networks to frontal networks. Greater alcohol consumption was also associated with positive connectivity from working memory nodes to the precuneus and paracingulate. HIV positive status was associated with more nodes of negative functional connectivity relative to alcohol consumption history alone, particularly in the fronto-parietal networks. The HIV positive individuals with heavier drinking history related to negative fronto-parietal connectivity, along with positive connectivity from working memory nodes to mesolimbic regions.

⁶.CONFLICT OF INTEREST

There are no conflicts of interest to report.

Conclusion: Findings allow for a better understanding of brain networks affected by HIV and alcohol and may provide avenues for interventions.

Graphical Abstract

b Brain connectivity analyses examining HIV x alcohol interaction when seeding in the left inferior parietal lobule. Darker shades of red = stronger connectivity. Darker shades of blue = weaker connectivity.

1. INTRODUCTION

1.1 Alcohol and HIV

Use of alcohol among people living with HIV (PLWH) is a significant public health concern. Across large U.S. samples of people living with HIV, rates of hazardous drinking have ranged from 5 to 33% [1–3]. Alcohol use among PLWH has previously been associated with poor retention in care [4, 5], reduced adherence to antiretroviral therapy (ART) [6], increased sexual risk behaviors [7] and reduced immunological and virological response to antiretroviral therapy [8, 9]. However, this morbidity and mortality can be stemmed with effective alcohol interventions. One study, which used a computer simulation model of an alcohol intervention, demonstrated that a 45% reduction in unhealthy alcohol consumption could prevent nearly half of new infections over 20 years in a nation with high rates of HIV, such as Kenya [10]. Given that the decision to use alcohol, along with the decision to engage in other risk behaviors relates to cognitive networks, it is important to understand these cognitive networks to develop effective interventions.

1.2 Working Memory and Decision Making

Poorer working memory function has previously been associated with alcohol misuse, HIV and the decision to engage in risk behavior [11–14]. There may be mechanistic linkages between brain systems affected by HIV, alcohol use and risky behavior. Understanding these mechanisms may improve our ability to adequately address risky behavior in this population. The basic role of working memory has been defined as a form of memory that supports the temporary storage and maintenance of internal representations and mediates the controlled manipulation of these representations [15, 16]. Furthermore, there are executive processes involved in operating based upon retrieving the information from storage [11, 17]. Working memory differs from short term memory in that working memory function incorporates storage and manipulation of the information, whereas short-term memory focuses on the simple temporary storage of information [18, 19].

1.2 Working Memory and Substance Use

Working memory impairments are related to an increased likelihood of future drinking habits [14, 20–22]. Poorer working memory is a predictor of problematic substance use, including alcohol dependence [23], relapse in smokers [24], and crack-cocaine and methamphetamine dependence [11]. One previous study, of a community sample of adolescents, suggests that weakness in working memory (at baseline) predicted both alcohol use quantity during that time period and increased frequency of use each subsequent year, over the four year study period [14]. Working memory has been cited as a critical factor in future drinking behavior among alcohol dependent individuals [21, 22]. Working memory decline may also be a consequence of alcohol use, both acutely [25, 26] and as a result of heavier drinking over the previous 60 days [27].

1.3 Working Memory, Substance Use and Functional Connectivity

Functional connectivity from functional MRI (fMRI) may serve as a systems-level biomarker to identify individual differences related to: disease expression, cognitive functioning abilities and disorder classification [28, 29]. Previous research on the topic of prefrontal response and fronto-striatal connectivity suggests that differences in connectivity strength are related to differences to behavior patterns in addiction [30]. One study examined default mode connectivity during a spatial working memory task, comparing alcohol dependent individuals and non-dependent individuals [31]. Alcohol dependent individuals performed similarly to controls, but demonstrated more robust connectivity between left posterior cingulate and left cerebellar regions, which the authors suggest, related to compensatory systems operating through an alternative network. Mayhugh and colleagues demonstrated that moderate and heavy drinkers tended to exhibit decreased central executive network connectivity during 1-back working memory task. The authors used a metric called scaled inclusivity, which considers overlap and disjunction between all modules in a whole-brain analysis [32]. However, no studies among HIV positive individuals have examined verbal working memory task-based connectivity differences comparing individuals with a history of alcohol dependence compared to those without a history of alcohol dependence.

1.4 HIV and Altered Functional Connectivity

Reviews of HIV and fMRI suggest that fronto-striatal regions are particularly impacted [33, 34]. One study of HIV and resting state functional connectivity suggests reduced internetwork connectivity among HIV positive individuals relative to HIV negative individuals, specifically between the default mode and dorsal attention network. [35]. Another study examining HIV and resting state functional connectivity suggests reduced connectivity between the striatum and ventral attention cortical areas. [36].

1.5 Brain Regions Impacted by Both Alcohol and HIV

According to [37], the primary brain regions impacted by both alcohol and HIV include the cortex (frontal and parietal), numerous white matter pathways (periventricular and supraventricular), basal ganglia and thalamus. Possible other regions influenced by alcohol and HIV include the temporal lobe, cerebellum, brain stem and subcortical white matter. Given that we are studying working memory networks, in this study we would expect frontal, parietal, subcortical (primarily striatal) networks to be affected during engagement in a working memory task.

1.6 Objectives and Hypotheses

Our objectives were to examine if there was a relationship between networks involved in working memory and reported level of alcohol consumption during an individual's period of heaviest use. Furthermore, we aimed to examine whether HIV status and the interaction between HIV and alcohol consumption was associated with differences in these brain networks. We hypothesized that individuals with higher levels of alcohol consumption during their period of heaviest use would demonstrate significantly negative functional connectivity from dlPFC to parietal regions, along with positive connectivity from dlPFC to mesolimbic regions relative to individuals with lighter drinking histories. Additionally, we hypothesized that individuals with higher levels of alcohol consumption during their period of heaviest use would demonstrate significantly negative functional connectivity from IPL to frontal regions relative to individuals with lighter drinking histories and positive connectivity with mesolimbic regions. Finally, HIV + individuals with higher levels of alcohol consumption during their period of heaviest use would demonstrate more clusters of negative connectivity relative to other comparison groups due to the negative effects of HIV and alcohol on attention and working memory networks.

2. MATERIALS AND METHOD

2.1 Ethics Approval and Consent to Participate

fMRI data participants were recruited via the R01 (MH074368) Age Effects on HIV-Associated Brain Dysfunction) grant. Prior to collection of MRI data, the project was submitted for approval to the Brown University Ethics Committee [Institutional Review Board (IRB)]. The study protocol was approved by the local IRB and informed written consent from each subject was obtained prior to study inclusion. This study was conducted according to the Declaration of Helsinki principles. Demographic data are noted in Table 1.

2.2 Imaging Data

A sub-set of individuals from the HIV and Aging study were asked to participate in n-back scanner task and functional imaging. Nineteen subjects were removed from analyses (16 due to motion exceeding outlier parameters, one due to exceedingly low hit rate, 1 due to exceedingly high false positive rates, one due to inconsistent reporting of alcohol use). Fifty subjects were included in the final imaging analyses. Six participants had missing data related to performance (reaction time, accuracy) and were thus excluded from performance analyses, leaving 44 individuals for inclusion in the performance analyses. The majority of performance data for these six individuals fell within expected times and hit rates. Thus, rather than sacrificing power, we included them in the imaging analyses. Demographic and substance use information is displayed in Table 1.

2.3 Inclusion criteria

1) Age: 30–70 yrs.; 2) English speaking; 3) Physically Mobile; 4) Current CD4 < 350 (HIV patients); 5) CD4 Nadir < 200. 6) Duration of ART therapy > 2 years 7) Time since HIV diagnosis > 2 years & <10 years

2.4 Exclusion criteria

1) History of significant pre-existing neurological brain disease, including Alzheimer's disease, Stroke, Seizure Disorder, & > than mild Traumatic Brain Injury; 2) Chronic psychiatric illness involving psychosis (e.g., Schizophrenia) according to DSM-IV criteria using the CIDI; 3) End-stage disease (life expectancy < 12 months) to optimize likelihood that patients enrolled will complete the study; 4) A positive pregnancy test; 5) Evidence of opportunistic CNS infections (toxoplasmosis, progressive MLS, neoplasm); 6) History of ascites, encephalopathy, esophageal variceal bleeding, hepatorenal syndrome or evidence of severe liver disease. The inclusion/exclusion criteria for the seronegative controls are identical to that for seropositive patients, except for criteria pertaining to HIV disease status.

2.5 Neuroimaging methods

Neuroimaging was conducted on a Siemens Magnetom TrimTrio syngo MR B17 located at the Miriam Hospital in Providence Rhode Island. The scanning sequence took about 75 min. fMRI was conducted using echoplanar BOLD imaging, with data acquired using a Siemens TrimTrio 3.0 tesla high resolution scanner at the Miriam facility. Scanning parameters for BOLD scanning included: 42 interleaved axial 3mm slices, TR 2500 ms, volumes = 147, TE 28 ms, Flip Angle = 90°, FOV = 192×192 mm, matrix = 64×64.

2.6 Stimulus Presentation

The N-back was presented using E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA) with the video signal back-projected onto a screen at the participant's feet. The screen was viewed through a double-mirror attached to the head coil. An MR-compatible piano-key response box attached to the stimulus presentation computer collected performance data. We applied a cushioned-pillow head stabilizer to minimize head movement during the scanning procedure.

2.7 2-Back Paradigm

Verbal working memory has been assessed using the same methods in previous studies [38, 39]. Participants determined if each stimulus was the same or different from previously stimuli, responding by binary button press (yes vs. no). Executive control, phonemic buffering, and sub-vocal phonemic rehearsal are required. Each letter was presented for 500ms with a 2500ms inter-stimulus interval. Uppercase and lowercase letters were randomly presented. 0-back and 2-back conditions were used in this experiment. See Figure 1. Data were acquired in two separate task runs. Each run consisted of alternating blocks of 3 36s 0-back trials, 3 45s 2-back trials, and 3 30s resting block during which a stationary cross was presented; including instruction time, total task length was approximately 12 minutes.

2.8 ROIs

Primary tests of hypotheses were conducted using *a priori* ROIs, previously noted in the Owen [40] meta-analysis of 24 studies demonstrating regions of activation during the n-back. *A priori* ROIs were created using the MarsBaR toolbox for SPM 12 and analyses were conducted in a MATLAB environment (Math-works, Natick, MA). Spherical ROIs were designed based on the Owen meta-analysis. ROIs were created using the WFU Pick Atlas and analyzed using the MarsBaR toolbox for SPM12 along with MATLAB. Three primary ROI's of interest were used, which included, left dlPFC (−36, 44, 20, radius = 6.2mm), left dlPFC (−44, 18, 22, radius 14.3mm), left IPL (−36, −50, 50, radius = 10mm). Two dlPFC seeds were used because of the critical role of the dlPFC in working memory, along with the findings in the Owen et al. meta-analysis of two robust regions of activation in the left hemisphere during the n-back task.

2.9 fMRI Analyses

fMRI preprocessing was conducted using the CONN (NITRC) toolbox for SPM12. Other analyses were performed using SPM12, the CONN toolbox for SPM12, and IBM SPSS Statistics 22. Regarding preprocessing, within each subject, the functional images were slice-time corrected and realigned using 6-parameter rigid body transformation. The T1 anatomical scan was segmented and normalized into Montreal Neurological Institute (MNI) space. This transformation was then applied to the functional images. Movement outliers (z-score > 2.5 SD from the mean power or > 1mm of movement) were identified using the ARTifact detection Tools software package (ART). Runs with greater than 44 outlier TRs (15% of the run) were excluded from further analysis. Sixteen participants were excluded from analysis due to excessive movement. Functional runs were then smoothed with an 8mm full-width half-maximum Gaussian kernel. Next the functional runs were denoised, such that potentially confounding temporal covariates and physiological noise were removed from the time series using the anatomical CompCor approach. Notably, the main effect of each condition was entered into the model as a potential confound, such that areas that were co-activated during task would not be mistaken as functionally connected. We acknowledge that some of the activation occurring during a particular block may be related to shifts between conditions. This problem was mitigated by removing the first three seconds at the beginning and end of each block to remove this transition effect. Additionally, a high bandpass filter

of .008 Hz was applied and linear detrending was conducted. Finally, the generalized psychophysiological interaction (gPPI) analysis was performed for whole-brain seed-to-voxel analyses. Bivariate-correlations for the relationship between the mean BOLD time series for each seed and the mean BOLD time series for all other voxels were computed for 2-back > 0-back contrasts. A Fisher Z transformation was applied to convert our bivariate correlations to a normal distribution. These individual maps were entered into the second-level analysis, where group level differences in network activation was explored. Voxel-wise analyses utilized multiple comparison correction for analyses of BOLD response using false discovery rate (FDR) correction $p < .05$.

2.10 Alcohol Measure

Considerable deliberation went into how alcohol use was measured. The Kreek McHugh Kellogg (KMSK) scale for alcohol dependence [41] was used to assess for alcohol dependence categorization. Previous ROC analyses suggest that a sum score of 11 is the optimal cut-off for sensitivity and specificity for determining alcohol dependence. The sum score is calculated by adding three measures together (quantity, frequency, duration).

2.11 Statistical Analysis of Behavioral Performance and Second Level

Statistical analyses were performed using SPSS Statistics Version 24, and CONN. Spearman correlations were conducted to examine the relationship between alcohol consumption, HIV status, and performance (accuracy, reaction time), due to skewness in the distributions. Mann-Whitney U tests were conducted to examine the relationship between HIV status and performance. This statistical approach has been used previously to examine n-back performance [42]. Regarding connectivity analyses, in the first model, the KMSK sum score was the covariate of interest. It was examined relative to 2>0 back in the left dlPFC, and left IPL. HIV was also examined using the same strategy and seeds in the second model. Finally, in the third model, the interaction term for KMSK sum score and HIV was examined as the covariate of interest.

3. Results

3.1 Reaction Time

The 0-back reaction time variable was negatively skewed [skewness = 1.062, SE = .357; kurtosis = 1.286, SE = .702] and thus, non-parametric tests were used to examine this variable. Alcohol consumption during period of heaviest use was associated with slower reaction time 0-back [Spearman $\rho = .298$, $p = .048$]. Mann-Whitney U Test of Independence was conducted to examine the relationship between HIV status and 0-back reaction time for correct targets. HIV positive status was associated with slower reaction time [$U = 155$, $p = .045$]. HIV positive status was also associated with slower 2-back reaction time [$t(42) = -2.362$, $p = .023$].

3.2 Accuracy

Alcohol consumption during period of heaviest use was not significantly associated with performance on the 0-back or 2-back. However, being HIV positive was associated with

weaker performance accuracy on the 0-back [$U = 152$, $p = .033$] and the 2-back [$U = 133.5$, $p = .012$].

3.2 DLPFC Connectivity Related to Alcohol Use

Two seeds located in the dlPFC were utilized ($-44, 18, 22$ and $-36, 44, 20$). Significant relationships will be subsequently discussed. The first dlPFC seed demonstrated negative connectivity with the superior frontal gyrus. Additionally, there was negative connectivity between the dlPFC and a portion of the left inferior frontal gyrus and left frontal pole. The first dlPFC seed demonstrated positive connectivity with the precuneus area. The second dlPFC seed demonstrated positive connectivity with the paracingulate region. Cluster sizes, t-values and p-values after FDR correction are noted in tables 2–4.

3.3 IPL Connectivity Related to Alcohol Use

Seeding in the inferior parietal lobule indicated that individuals who were heavier users of alcohol during their period of heaviest use demonstrated negative connectivity with occipital, frontal, and other parietal regions. However, these individuals demonstrated positive connectivity with the caudate and the precuneus.

3.4 DLPFC Connectivity Related to HIV

Seeding in the dlPFC was associated with negative connectivity to a number of frontal regions (superior frontal gyrus, left and right frontal poles, left inferior frontal gyrus) and temporal (middle temporal gyrus, temporal pole) regions, along with more posterior regions (posterior cingulate, precuneus, lateral occipital lobe cortex, angular gyrus). However, similarly to alcohol use, the dlPFC was associated with positive connectivity with the precuneus, and paracingulate areas.

3.5 IPL Connectivity Related to HIV

Seeding in the IPL was related to negative connectivity in mostly frontal regions including the left and right frontal poles, and anterior cingulate, along with more posterior regions including the superior parietal, angular gyrus and, posterior cingulate. The IPL was also associated with positive connectivity to the caudate.

3.6 DLPFC Connectivity Related to HIV x Alcohol

Being HIV positive with a history of alcohol dependence was associated with positive connectivity to a couple of regions when seeding in the dlPFC, which include the precuneus and paracingulate. It was also associated with positive connectivity to a number of regions including multiple frontal regions (superior frontal gyrus, orbitofrontal cortex, medial temporal gyrus), angular gyrus, and cerebellum.

3.7 IPL Connectivity Related to HIV x Alcohol

Seeding in the IPL was related to negative connectivity to the caudate, along with negative connectivity to the frontal pole, anterior cingulate, and angular gyrus. Figure 2 shows ROI to ROI maps depicting the connectivity strengths (p uncorrected) between IPL seed and other networks in the HIV x Alc interaction.

4. DISCUSSION

4.1 Behavioral Performance

Contrary to our hypotheses there was no effect of previous alcohol use on accuracy. However, heavier alcohol use was associated with slower reaction time on the 0-back, but not on the 2-back. HIV was associated with slower reaction time on both the 0-back and 2-back. Consistent with previous literature, HIV was significantly associated with slower reaction time on the n-back [13] and weaker performance on both the 0-back and 2-back (Cohen et al., 2017).

4.2 Alcohol

Consistent with our hypotheses, fronto-parietal network dysfunction was demonstrated among individuals who consumed greater amounts of alcohol during their period of heaviest use. Seeding in the IPL was associated with negative connectivity to the frontal pole and medial frontal gyrus among heavier alcohol consumers. However, seeding in the dlPFC was not associated with negative connectivity to parietal regions. Seeding in the dlPFC did demonstrate negative connectivity with other frontal regions such as the superior and inferior frontal gyri suggesting poor communication within frontal networks as well as between parietal and frontal networks. Consistent with our second hypothesis, there was positive connectivity between certain working memory regions of interest and mesolimbic areas. The IPL was significantly associated with positive connectivity to the caudate. However, the dlPFC was not significantly associated with positive connectivity to any mesolimbic systems. Both the dlPFC and IPL seeds demonstrated positive functional connectivity to the precuneus. Furthermore, both dlPFC seeds demonstrated positive connectivity to the paracingulate.

4.3 HIV

HIV was also associated with negative connectivity between IPL and multiple frontal regions including frontal pole and SFG. Additionally, the IPL was associated with positive connectivity to the caudate. This aligns with other fMRI research, particularly one meta-analysis, which suggests that the primary regions more generally affected are the inferior frontal gyrus and left caudate. [34] Additionally, there is previous evidence of greater bilateral precuneus and basal ganglia activation when comparing 2 > 0 back [42]. Thus, dynamic range activation aligns with functional connectivity results. The dlPFC seed was associated with negative connectivity to multiple frontal, temporal and parietal regions. The dlPFC seed was also associated with positive connectivity to the paracingulate. Thus, similar to individuals with heavier alcohol use histories, HIV positive individuals tended to demonstrate negative connectivity between frontal regions, along with positive connectivity between attention/working memory networks and striatal circuits critical to addiction.

4.4 HIV x Alcohol Interaction

HIV positive individuals with a history of alcohol dependence also demonstrated positive connectivity between the dlPFC and precuneus, along with the dlPFC and paracingulate. Additionally, this group demonstrated negative connectivity between the dlPFC and other

frontal regions. Furthermore, this group also demonstrated positive connectivity between IPL and caudate, along with negative connectivity between IPL and multiple frontal, cingulate and occipital regions. Finally, these individuals demonstrated positive connectivity between ACG and a number of frontal, parietal and occipital regions, as well as the amygdala. Thus, as noted above, HIV positive individuals with a history of alcohol dependence demonstrated even more focal attentional resources directed at areas important for reward processing, and self-monitoring, rather than having more diffusely distributed resources across working memory networks.

4.5 Precuneus and Alcohol Related Behaviors

Previous research has focused on the critical role of “exteroception” in addiction [43]. Exteroception is defined as the processes related to the perception of environmental stimuli, which allow an individual to adapt. Exteroception has been implicated in addiction with the theory that an individual becomes more likely to misuse substances due to the heightened relevance of external cues [44]. The precuneus is critical to exteroception and addiction [45, 46]. The precuneus has been associated with cue-reactivity [47], along with self-centered mental imagery [48], with the idea that the precuneus may be involved in “self-referential” processes or “self-projection” in terms of higher-order decision making because of its evaluation of self-related to future scenarios.

4.6 Paracingulate and Alcohol Related Behaviors

Paracingulate and cingulate circuits are important in addiction and relate to craving and subjective experiences of “rush” and “high”, along with drug reinforcement [49, 50]. Thus, heavier alcohol consumption during period of heaviest use related to fronto-parietal network dysfunction, along with positive connectivity between critical working memory nodes and pathways critical for addiction and exteroception. Perhaps dysregulation of exteroception and self-referential processes is the nexus of dysfunctional behavioral patterns relating the executive control network and addiction pathways.

4.7 Caudate and Alcohol Related Behaviors

Furthermore, the positive connectivity between IPL and caudate was notable and among the strongest effects when seeding in the IPL. The caudate is a component of the striatum, which acts as the major input station for the basal ganglia. The striatum receives a number of dopaminergic inputs from the ventral midbrain. Thus, the striatum is critical to regulation of a number of brain functions such as learning, performance, cognition and emotion. Alcohol influences these processes through alcohol seeking, intoxication, dependence and withdrawal [51]. Given the role of the inferior parietal lobule in the interpretation of sensory information and emotional processing, along with the caudate’s role in motivation, craving, drug seeking and addiction, it is likely that individuals with a history of heavier alcohol consumption may attend more to alcohol related cues, and thoughts. The fact that this connectivity relationship occurred within the context of performance of a high load working memory task suggests that attentional resources may be misallocated toward more reward-based processing, rather than distributed more diffusely across working memory nodes.

4.8 Limitations

While the current study demonstrated robust effects of heavier past alcohol use on working memory network dysfunction there are a number of limitations. Firstly, while the sample size of 50 was reasonable to detect a moderate effect, a larger sample would have provided more power to detect an effect and greater confidence in the findings. Furthermore, while the KMSK provides a unique measure of past drinking history and likelihood of alcohol use disorder, there are limitations to self-reported measures of drinking. Future studies should incorporate a biological measure of drinking either as confirmation of self-report or a more accurate measure of drinking history. Additionally, while the KMSK correlates with alcohol use disorder, a clinical assessment would help to differentiate between groups demonstrating behavioral consequences of alcohol use and may grant insight into potential differences between groups. Additionally, while most of the HIV positive participants had well controlled viremia, there were variations in lifetime HIV course (duration, CD4nadir, adherence) Thus, future studies with larger samples may be able to parse some of the effects of these factors.

5. CONCLUSION

Connectivity enhancements between working memory nodes and the precuneus, paracingulate and caudate, along with negative fronto-parietal connectivity, may relate to differences in processing self-referential information and how an individual interacts with the external environment. This is important as it may relate to an increased focus on the saliency of alcohol related cues and misallocation of attentional resources toward drug seeking. Furthermore, these deficits may contribute to reduced intervention effectiveness through reduced information retained in session, along with a reduced ability to utilize intervention information in the presence of alcohol. Finally, while rates of HIV dementia have declined, persisting neurocognitive deficits are still a prevalent concern [52]. Alcohol use is one potential contributing factor to these deficits. Thus, finding appropriate interventions to reduce HIV associated neurocognitive disorders is paramount.

Future research should examine the role of different co-factors (hepatitis C, tobacco use, aging) in modulating the effects of alcohol and HIV on working memory networks. Furthermore, future research should examine how alcohol reduction interventions, along with working memory interventions might influence working memory networks and drinking behavior. Future studies should examine longitudinal models of alcohol consumption, particularly among individuals without premorbid working memory deficits to see what effects consumption may have on working memory networks. Alternatively, it is important to examine how working memory deficits might affect future substance use trajectory. Thus, longitudinal studies examining individuals with working memory deficits and tracking their alcohol consumption over time would be an important contribution to research. Furthermore, future studies could incorporate more sophisticated motion assessment techniques that would take into account pixel-level displacements. This approach has previously been used by [53]. Thirdly, there are a number of viable interventions for both reducing alcohol use and improving working memory function. Given the consequences of previous heavy drinking to working memory, along with the role of

working-memory in decision making, future research should examine the relationship between changes in working memory and alcohol consumption, particularly when alcohol consumption is reduced or working memory is enhanced. As noted previously, neuromodulation is an exciting area of research that could potentially enhance working memory function [54, 55] and may contribute to reduced alcohol use [56, 57]. Future research should examine the effects of using different montages to improve working memory, as well as to reduce alcohol use. These factors should be considered in different populations as well, such as elderly individuals and individuals with a history of alcohol use disorder.

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Example of a 2-Back Working Memory Task

ISI = Interstimulus Interval

Figure 1.

sequence for the 2-back working memory task. The participant is presented the stimuli one by one and would begin responding at stimulus “S” if it was the same as the stimulus presented two letters back. The first correct target is stimulus “L.” Stimulus “S” and stimulus “E” are distractors (not the same as the letter that was presented two letters back).

Figure 2.

Map of whole brain ROI to ROI connectivity analyses examining the HIV x alcohol interaction when seeding in the left IPL (p-uncorrected). Note. Darker shades SubCalc = subcallosal cortex, MedFC = medial frontal cortex, SMG = supramarginal gyrus, PostCG = postcentral gyrus, MTG = medial temporal gyrus, PreCG = precentral gyrus, MidFG = middle frontal gyrus, FP = frontal pole, IPL = inferior parietal lobule, Ver = vermis, Cereb = cerebellum, OP = occipital pole, PT = planum temporale, PO = parietal operculum, CO = central operculum, OFusG = occipital fusiform gyrus, TOFusC = temporal occipital fusiform cortex, Caud = caudate, Thal = thalamus, Accumb = nucleus accumbens, SensMot = sensory motor, Lat = lateral, FEF = frontal eye field, l = left, r = right

Table 1.

Imaging study demographics

Variable	HIV+ (n = 26)	HIV – (n = 24)	Total (N = 50)
Demographics			
Male	16(61.5)	12(50.0)	28(56.0)
Age(Years)	46.42(10.49)	44.71(11.48)	45.6(10.9)
<i>Race</i>			
Caucasian	18(69.2)	16(66.7)	34(68)
African American	2(7.7)	5(20.8)	7(14)
Latino	3(11.15)	0(0)	3(6)
Asian	0(0)	1(4.2)	1(2)
Other	3(11.5)	2(8.3)	5(10)
Education(years)	14.15(2.36)	13.29(3.34)	13.74(2.88)
HIV +			24(48)
KMSK Score	9.58(3.68)	8.75(3.85)	9.18(3.75)
Alcohol Dependent(>10)	13(50)	9(37.5)	22(44)

Note. N or Mean(% or SD); None of the means or frequencies were significantly different by HIV status.

Table 2.

Significant clusters of connectivity by history of alcohol use

seed	label	clusters	region	size	T	size p-FDR
-44, 18, 22	dlPFC	-08 -56 50	precuneus	530	6.76	.000000
		-42 44 -06	inferior frontal gyrus	219	-5.36	.000320
		-08 36 48	superior frontal gyrus	152	-5.25	.002010
-36, 44, 20	dlPFC	-06, 56 08	paracingulate	1224	7.67	.000010
-36, -50, 40	IPL	-16, -60, 52	precuneus	181	5.19	.001133
		42, -64, 56	lateral occipital cortex	169	-5.69	.001133
		36, 62, 04	frontal pole	147	-5.64	.001883
		-44, 54, 04	frontal pole	120	-5.32	.003650
		-34, -62, 62	lateral occipital cortex	119	-6.00	.003650
		46, 54, 12	frontal pole	115	-6.01	.004870
		-10, 04, -02	caudate	113	5.46	.004870
		12, -52, 58	precuneus	89	5.12	.012370
		-04, -08, 32	anterior cingulate gyrus	76	-5.16	.020530
		-44, 26, 44	middle frontal gyrus	60	-5.13	.040620
		52, 38, 22	frontal pole	59	-5.42	.040620
		52, 40, -12	frontal pole	54	-5.07	.049150

Table 3.

Significant clusters of connectivity relative to HIV status

seed	label	clusters	region	size	T	size p-FDR
-44, 18, 22	dlPFC	-02, 40, 50	superior frontal gyrus	612	-6.66	.000000
		-38, 42, -16	frontal pole	549	-6.49	.000000
		-58, -48, 18	angular gyrus	547	-6.77	.000000
		48, 38, -10	frontal pole	428	-5.47	.000000
		-64, -46, -12	middle temporal gyrus	207	-5.22	.000300
		-48, 10, -22	temporal pole	206	-6.13	.000300
		64, -48, 36	superior middle gyrus	180	-5.18	.000610
		-08, -66, 34	precuneus	162	-4.85	.001000
		-08, -88, -04	inferior frontal gyrus	137	-4.63	.002200
		02, -14, 38	posterior cingulate cortex	133	-6.48	.002300
-36, 44, 20	dlPFC	-08, 32, -18	paracingulate	612	-5.65	.000020
-36, -50, 40	IPL	-10, 04, -04	caudate	481	5.47	.000000
		42, -62, 56	lateral occipital cortex	233	-5.15	.000094
		-04, -10, 34	anterior cingulate cortex	152	-4.67	.001487
		34, 54, -04	frontal pole	137	-5.19	.002122
		00, -36, 24	posterior cingulate cortex	101	-3.56	.008844
		-34, -62, 62	superior parietal lobule	77	-5.87	.002590
		-44, 56, 04	frontal pole	73	-5.15	.030230
		46, 54, 14	frontal pole	70	-5.99	.030810

Table 4.

Significant clusters of connectivity relative to Alc x HIV status.

seed	label	clusters	region	size	T	size p-FDR
-44, 18, 22	dlPFC	-08, -56, 50	precuneus	416	7.19	.000010
		-08, 36, 48	frontal pole	230	-5.47	.000260
		-38, 40, -16	orbitofrontal	180	-4.66	.000880
		38, 44, -18	orbitofrontal	134	-4.36	.003570
		-64, -44, -12	medial temporal gyrus	85	-3.90	.002290
-36, 44, 20	dlPFC	-06, 42, 04	paracingulate	1466	7.68	.000010
		-28, -52, 12	lateral occipital cortex	96	-5.06	.028060
		32, 52, -18	frontal pole	89	-4.66	.028060
		-28, -40, -26	cerebellum	85	-5.23	.028060
		-24, -74, -22	cerebellum	71	-4.11	.044100
-36, -50, 40	IPL	-10, 06, -02	caudate	535	5.50	.000001
		42, -62, 56	angular gyrus	255	-5.47	.000129
		34, 62, 06	frontal pole	176	-5.24	.001091
		34, 54, -04	frontal pole	137	-5.95	.002122
		-32, -60, 64	angular gyrus	155	-5.84	.001751
		-04, -10, 32	anterior cingulate	107	-4.76	.021498
		46, 54, 14	frontal pole	73	-5.24	.021705