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Neuropsychological Consequences of HIV and Substance Abuse: A Literature Review and Implications for Treatment and Future Research

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Abstract

Neuropsychological dysfunction, ranging from mild cognitive symptoms to dementia has been a consistent part of the clinical picture of HIV/AIDS. However, advances in clinical management, particularly antiretroviral (ARV) treatment, have mitigated the neuropsychological effects of HIV and revised the pattern and nature of cognitive deficits, which are observed in HIV-infected individuals. The attendant improvements in mortality and morbidity have led to a need for programs and interventions that sustain healthy behavior and prevent a resurgence of HIV transmission risk. Psychiatric risk factors, particularly substance use, which often contribute to initial acquisition of HIV, still require attention. These risk factors may also exacerbate neuropsychological dysfunction and compromise adherence to prevention recommendations and treatment. Specifically, a more complete understanding of the effects of substance abuse on the progression of HIV related cognitive decline can inform evaluation and management of HIV seropositives with concurrent substance use disorders. This review provides an overview of the neuropsychology of HIV and substance abuse and the extant research that has examined the effects of both HIV disease and substance use on neuropsychological functioning and implications for treatment and future research.

Keywords

Neuropsychology; substance abuse; HIV; treatment; future research

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INTRODUCTION

HIV/AIDS continues to be a global problem, with more than 40 million people worldwide living with the disease [1]. In view of the fact that antiretroviral (ARV) regimens have extended the life expectancy of most HIV-infected individuals, it is critical to focus on the physical and mental health of these patients. Many people with HIV are living longer, healthier lives thanks to ARV treatment. However, the neurocognitive effects of substance abuse, and the need for ongoing studies of HIV related neuropsychological dysfunction, particularly in substance abusers is still needed.

Additionally, an improved understanding of the neuro-psychological sequelae of HIV disease, particularly in relation to substance abuse, is important to the evaluation and management of persons living with HIV (PLWH) with co-morbid substance abuse disorders. The co-occurrence of HIV and substance abuse may compound medical and psychiatric problems, difficulties with HIV medication compliance, and poorer treatment outcomes (beyond those associated with HIV disease alone).

The bio-medical consequences of psychiatric disorders, particularly substance abuse in the HIV-infected population are a serious public health problem. Comorbid populations are more likely to participate in risky behaviors, enhancing the spread of the infectious disease [2, 3]. There is less likelihood of adhering to antiretroviral treatments, thereby worsening prognosis and increasing the probability of drug-resistant strains. Comorbid disease progression has been defined as an altered or presumptively accelerated disease progression due to the physiological interactions of HIV infection and substances of abuse [4]. HIV and substance abuse comorbidity presumably hasten disease progression *via* direct mechanisms by acting on common biological substrates in the brain, as well as by indirect actions mediated through alterations in central and peripheral immune and nervous systems.

Characteristically, an HIV infection can progress for more than a decade before the clinical syndrome (AIDS) occurs. This long latency period has contributed too many problems relating to diagnosis and control. Multiple factors, including genetics and behavioral factors (i.e., substance abuse), determine the speed of disease progression in a given individual. Comprehensive neuropsychological assessments that consider both HIV disease and substance abuse may allow for the early detection of complications before irreversible neuronal damage occurs, which may facilitate the development and implementation of appropriate and targeted therapies and treatment.

However, to develop and implement appropriate and effective therapies and treatments for People Living with HIV (PLHW) with comorbid substance abuse disorder, it is beneficial to review research conducted with this population. Areas that will be examined include the neuropsychology of HIV and substance abuse, and the potential interaction of HIV disease and substance abuse. In addition, implications for future research and treatments are discussed.

Pathophysiology

Shortly after seroconversion, HIV crosses the blood brain barrier *via* infected monocytes and CD4+ cells [5]. These infected monocytes differentiate into macrophages, and ultimately infecting microglia with HIV. At times, monocytes and microglia will fuse, and form multinucleated giant cells. These cells are distinct pathological hallmarks of HIV encephalopathy. Collectively, macrophages, microglia, and multinucleated giant cells serve as pools from which HIV is replicated and expressed in the brain.

Although this explanation of central nervous system infection is generally accepted, the mechanism by which neurologic dysfunction develops is less than certain. Despite the presence of HIV within the brain, there is little evidence of direct effects of the virus on the brain. In particular, HIV is tropic for glial cells, macrophages, and endothelial cells within the brain rather than neurons, and little HIV is typically detected in neurons [5]. Furthermore, the amount of neurologic damage is disproportionate to the presence of HIV in the brain [6], and cell loss may occur without overt neuronal infection.

Most evidence indicates that the neuropathogenesis of HIV occurs indirectly [7]. HIV is presumed to trigger the release of cytokines, tumor necrosis factor, and granulocytemonocyte colony-stimulating factors. These inflammatory proteins and cytokines in turn are likely toxic to neuronal activity and neurotransmitter function, and they probably increase secondary inflammation (e.g., encephalitis), cause leukoencephalopathy, or catalyze cell death through apoptosis [7–9].

Gross Cerebral Changes

There is ample evidence that HIV infection may be associated with diffuse cerebral atrophy, multinucleated giant cells, leukoencephalopathy (myelin pallor), gliosis, axonal damage, and microglial nodules. Subcortical gray matter in the limbic and striatal systems is also diminished. These abnormalities occur more often as the disease progresses, and they appear most often in people with AIDS [10–12].

Remarkably, this diffuse cerebral pathology does not seem to correspond with neuropsychological impairment. Indeed, most studies have not found a relationship between global cortical atrophy and neuropsychological impairment [13]. Additionally, global measures of cerebral activation (e.g., evoked potential response, functional magnetic resonance imaging) are often abnormal in HIV infection, but typically are unrelated to neuropsychological impairment [14–16].

Although global brain abnormalities fail to correspond with neuropsychological deficits, structural and functional abnormalities involving the basal ganglia, hippocampus, and frontal lobes appear to correspond with cognitive impairment in HIV. In an extensive literature review, Paul *et al.* (2002) found that caudate atrophy was the brain region most consistently associated with neuropsychological dysfunction in HIV [12]. More recently, Ances *et al.* (2006) found that cognitively impaired HIV patients had smaller caudate volumes and less caudate blood flow than a control group [17].

Additionally, reduced volumes in the putamen and hippocampus correlate with poor performance in HIV infection [18]. Other investigations have found that neuropsychological impairment correlates with diminished gray matter volume in the tissue bordering the basal ganglia and lateral ventricles as well as and gray and white matter in the frontal lobes [19–21].

NEUROPSYCHOLOGY OF HIV AND AIDS

Neuropsychology can be defined as applied neuroscience and is broadly focused on understanding brain-behavior relationships that may be impacted by brain injury or disease, such as cognitive, sensorimotor, emotional, and general adaptive capacities of the individual [22, 23]. The discipline encompasses both neurocognitive and neurobehavioral processes. Neurocognitive processes include perceptual abilities, abstraction and conceptualization, executive functions, perceptual motor integration, learning, remembering, and attention. Neurocognitive functioning can also be described in terms of speed, efficiency, and flexibility. Neurobehavioral processes are broader in scope, including neurocognitive processes and functioning as well as other brain-mediated behaviors, such as mood and affect, personality, coping, and temperament. It is theorized that significant changes in the neurocognitive functioning are the most explicit measures of underlying pathologic changes in the brain, while neurobehavioral changes can occur for many non-neuropathological reasons (e.g., change in mood brought on by unhappy news) [24].

Because of HIV's focus upon frontal-striatal circuits, certain neurobehavioral deficits may be expected. In particular, these cerebral circuits appear to be neural substrates of initiative, motivation, impulse control, concept-formation, and problem-solving [25]. Consistent with this expectation, people with HIV often display deficits in conceptual reasoning, working memory and attention, memory, speed of information processing, and psycho-motor speed, and may appear apathetic, anhedonic, and amotivated [26]. Neurological examinations may also demonstrate abnormalities involving rapid limb movements and hyper-reflexia.

It should be noted that the frequency and severity of neurobehavioral deficits increases as the disease progresses [27]. Studies of asymptomatic individuals indicate mild abnormalities in a small proportion of individuals [28–31]. The frequency and severity of impairment increases with the disease progression. For instance, cognitive impairment is seen in as many as 10–30% of asymptomatic patients, 44 % of symptomatic patients, and 55–86% of AIDS patients [26, 32, 33].

Two meta-analyses of HIV-related neurobehavioral dys-function have been conducted during the past decade [33–34], and both studies reached similar conclusions. Overall, asymptomatic people display small deviations from normal on neuropsychological tests, whereas symptomatic individuals demonstrate moderate deviations from normal. In the asymptomatic group, language dysfunction was the most commonly observed deficit, whereas symptomatic patients showed weaknesses most commonly on measures of verbal fluency, working memory, speed of information processing, verbal learning, visual spatial perception, and coordination. In people who had progressed to AIDS, moderate to large deficits occurred across all cognitive domains. The most common areas of deficit included

executive function, working memory, speed of information processing, new-learning, and coordination. Notably, the memory difficulties in HIV seem to involve retrieval of memory more so than acquisition or retention [33]. This pattern of performance is consistent with other subcortical disorders. Indeed, in a discriminant function analysis, Robinow *et al.* 1988 found that people with HIV manifest a pattern of dysfunction most similar to people with Huntington's disease [35].

It is worth noting that studies examining neuropsychological performance in asymptomatic HIV seropositives prior to the advent of highly active antiretroviral treatments revealed inconsistent findings [36]. Significant variability in sample sizes, composition of test batteries, definitions of impairment, and treatment of test scores was quite variable. Fifty-seven studies were reviewed and it was found that 32% differences between asymptomatic seropositives and sero-negative controls exist while 47% did not [36]. Among studies showing differences, more comprehensive test batteries tended to be employed. In addition, many of the studies using larger batteries failed to adjust for Type I error. Relatively few investigations examining cognitive deficits in asymptomatic HIV seropositives employed longitudinal designs. Among those available, some found few differences between asymptomatic seropositives and seronegative controls [37], whereas others described significant differences [38]. Taken together, research suggests that neuropsychological dysfunction is present in a small number of sero-positive individuals, and is mild when present.

To depict the patterns of HIV-associated neuropsychological deficit in a comprehensive manner, a nosology was proposed by the American Academy of Neurology (AAN: [39]), and it is gaining acceptance. In this classification system, there are three stages of cognitive impairment in HIV infection. Individuals with mild impairment in two domains of function are described as having HIV-associated asymptomatic neurocognitive impairment. If mild impairment is accompanied by impairment in activities of daily living, this presenting syndrome is described as HIV-associated mild neurocognitive disorder. Severe impairment in two or more neuropsychological domains occurring with deficits in activities of daily living is classified as HIV-associated dementia.

It should be noted that the American Psychiatric Association included dementia due to HIV in the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders [40]. Unfortunately, the DSM-IV criteria for this syndrome are modeled after the criteria for Alzheimer's disease, and as such place a heavy emphasis on cortical abnormalities such as apraxia and aphasia, symptomatology that is typically not consistent with the characteristic neuropsychological sequelae of HIV infection. However, cognitively impaired HIV seropositive patients often meet DSM-IV diagnostic criteria by virtue of criteria A1 (memory impairment) and A2d (executive dysfunction). Accordingly, many clinicians and researchers who work with HIV infected patients prefer the recently published nosology of the AAN which better captures the clinical realities of varying severity of HIV associated cognitive impairment and the subsequent subdivisions of clinical conditions. In addition, the AAN criteria more adequately describes the subcortical nature of the disorder through inclusion of key diagnostic criteria (e.g., attentional impairment and cognitive slowing) not reflected in the DSMIV criteria.

Impairment is not entirely static. Many individuals who present with mild cognitive impairments never develop progress to a demented state. Some recover fully while others have a relapsing-remitting course. Clinically significant neuropsychological declines in the asymptomatic phase of HIV are rare. However, if risk factors that negatively impact cognitive reserve (e.g., low education, substance use, and pre-morbid CNS factors such as history of head injury) are present, the threshold for the onset of clinically significant NP declines is decreased, even in asymptomatic persons [41, 42].

Since the advent of highly active antiretroviral treatments (HAART), for instance, some studies have demonstrated considerable benefit of HAART, with cognitively-impaired individuals displaying significant improvement in function [43, 44]. Since the introduction of HAART, the incidence of HIV dementia has decreased by approximately 50% [45]. While the incidence of dementia has decreased significantly, and patients are living longer as a result of HAART, prevalence of less serious HIV-associated neurological impairments may be increasing and can occur even during potent antiretroviral treatment [46].

Substance Misuse and HIV

Because the nature and severity of dysfunction varies with stage of illness, and among individuals at the same level of disease, it appears that cognitive dysfunction in HIV is moderated by individual differences. Accordingly, recent investigations have attempted to identify risk factors for neurobehavioral dysfunction in HIV infection. For instance factors such as immune status [47], viral burden [19, 48–50], disease duration [51], symptomatic infection [52], adherence to highly active anti-retroviral treatment [53], hepatitis C co-infection [54–57], depressive symptomatology [58], and increasing age [59, 60] have been shown to moderate the impact of HIV on neuropsychological dysfunction. Another factor that may contribute to HIV-associated cognitive impairment is substance misuse.

Many seropositive individuals are past or current abusers of drugs [61]. Ominously, abuse of certain drugs corresponds with cognitive dysfunction. Furthermore, some drugs of abuse may compromise immune function, which in turn may increase the likelihood of further neurobehavioral dysfunction through secondary infection (e.g., toxoplasmosis, CMV, etc.). Accordingly, many infected people with histories of substance misuse may manifest neuropsychological impairment more than their non-drug abusing counterparts. Yet, despite this possibility, there is relatively little research concerning the effect of co-morbid substance abuse and HIV infection. In the review that follows, we will survey the literature concerning the neurobehavioral and immunological effects of drugs that are popularly abused by individuals infected with HIV. Specifically, we will focus upon cocaine, opiates, alcohol, marijuana, and amphetamines. In doing so, we hope to suggest mechanisms by which abuse of these substances may exacerbate or contribute to neurobehavioral dysfunction in HIV infection.

Cocaine

Cerebral Morphology and Function.—Although cocaine has a diffuse effect upon neurotransmitter systems, it affects the dopaminergic system especially. Cocaine is a dopaminergic agonist, and it stimulates dopamine production and inhibits its reuptake. After

sustained use, this yields diminished dopamine availability on the presynaptic terminal and post-synaptic receptor supersensitivity. Resulting changes in dopaminergic response are thought to be most prominent in the basal ganglia, orbitofrontal cortex, and cingulate gyrus [62].

Cocaine abuse induces vasoconstriction, and increases the risk of a cerebrovascular accident [63]. These vascular changes correspond with decreased frontal lobe and basal ganglia activation [64] which may persist with abstinence [65–68]. Consequently, sustained cocaine misuse may yield durable changes in brain function. Additionally, chronic cocaine use may also alter brain structure. Pascual-Leone *et al.* (1991b) compared cerebral volumes in groups of cocaine users and drug-naïve subjects [69]. Long-term use corresponded with cerebral atrophy, and there are indications that such atrophy may be especially pronounced in the frontal lobes [63].

Neuropsychological Function.—Chronic cocaine misuse corresponds with poor executive functioning, new-learning and speed of information processing [63, 70–72]. Deficits in memory, visuospatial perception, and attention remain present despite several weeks of abstinence [70,72], but some improvement occurs over longer periods of abstinence [73]. There are some indications that cocaine-induced brain atrophy correlates with neuropsychological deficits [74]. Severity of neuropsychological deficits has also been related to lifetime amount of cocaine used [75].

Immune Function.—Cocaine abuse suppresses T-cell response and various other immune cell interactions [76, 77], and the degree of immunosuppression may also be related to the amount of cocaine used [78]. Moreover, there are indications that cocaine abuse exacerbates HIV replication [79]. In addition, cocaine increases the susceptibility of the brain to infection by increasing permeability of the blood brain barrier to viral strains including HIV [80, 81].

HIV and Cocaine Use.—Overall, this literature implies that cocaine abuse exacerbates neuropsychological impairment in people with HIV. Cocaine is toxic to brain tissue, and manifests as abnormal cerebral function and structure. Cocaine abuse may also lead to infections of brain tissue, thereby impairing neuropsychological function. Consistent with this implication, Durvasula *et al.* (2000) administered a battery of neuropsychological tests to nearly 240 African-American men, 172 of which were HIV seropositive [82]. Most were either current or past cocaine users. Regardless of HIV status, moderate to heavy users of cocaine demonstrated psychomotor slowing. Worsening HIV status also corresponded with psychomotor slowing. Yet, there was no interaction of HIV status and cocaine misuse. Cocaine use did not seem to increase neuropsychological impairment in people with HIV. More recently, Levine *et al.* (2006) examined vigilance performance in people with HIV, approximately half of whom were abusers of cocaine and methamphetamine [83]. Drug use corresponded with impaired vigilance, but there was no evidence that it exacerbated impairment in seropositive individuals.

Opiates

Cerebral Morphology and Function.—The literature concerning opiate abuse on brain structure is inconsistent, with some studies showing abnormal volumes [84, 85], and others finding no anomalies [86]. Among the few studies involving functional imaging, Rose *et al.* (1996) and Danos *et al.* (1998) found hypoperfusion over the frontal and temporal lobes, and this abnormal function remitted with abstinence [86, 87].

Neuropsychological Function.—The research concerning effects of opiate abuse on neuropsychological function are also not entirely clear. In an early study of heroin addicts, Fields and Fullerton (1975) found no deficits [88]. Yet, studies of opiate misuse among polysubstance users suggests that neuropsychological deficits are present. Specifically, opiates induce impairments in the areas of attention, information processing, problem solving, coordination, working memory, and psychomotor speed and performance [89–94]. Further, research indicates that opiate users in methadone maintenance may have significantly more neuropsychological impairment than those in treatment, suggesting that methadone exacerbates cognitive dysfunction in opiate users [95].

Immune Function.—Accumulating data indicate that opiate abuse is immunosuppressive. For example, morphine and heroin reduce CD4 T lymphocyte counts and other indices of immune system integrity (for reviews, see [96, 97]) immune response can persist despite abstinence for several months [98].

Opiates and HIV Infection.—The synergistic and immunosuppressive effects of opiates may be particularly significant in HIV infection. Morphine stimulates the replication of the HIV virus [99], and may accelerate progression to AIDS [100]. Opiate misuse also seems to increase rates of symptomatic illness in people with HIV [101]. Given that HIV related illness and increasing viral burden corresponds with worsening neuropsychological function [19,102–105], opiate use may ultimately exacerbate neuropsychological dysfunction.

In this vein, some studies have examined the effects of opiate misuse among seropositive individuals. Remarkably, most early studies found no morbidity associated with opiate misuse [106–109]. Yet, the investigators only examined the main effects of substance abuse and infection, and the interaction of drug use and HIV status went unexamined. More recent investigations have found that combined opiate and cocaine dependence corresponds with worsening neuropsychological function in people with HIV [103]. However, this research did not include seronegative individuals, thereby making it impossible to determine whether opiate misuse exacerbated cognitive deficits in HIV.

In research that included seronegative opiate misusers, the results are similarly inconclusive. In a study by Vazquez-Justo *et al.* (2003), seropositive and seronegative intravenous drug users were compared to seronegative non-drug users [110]. Those drug users with HIV were impaired across multiple cognitive domains, and the seronegative drug users showed only mild neurobehavioral abnormalities. However, because no non-drug using seropositive individuals participated, the combined effect of opiate misuse and HIV status could not be examined. Rodriguez *et al.* (2006) conducted a similar study, and found that intravenous drug use corresponded with cognitive impairment [111]. Compared to the seronegative

opiate misusers, only some of the seropositive drug users had higher rates of cognitive impairment. Yet, these individuals were maintained on methadone treatment, and they had lower education and greater immunocompromise. Consequently, the data imply that opiate misuse corresponds with cognitive deficits, but it remains uncertain whether opiate use exacerbate cognitive dysfunction in people with HIV.

Taken together, these findings fail to provide a consensus regarding the effects of opiate abuse on neuropsychological function in people with HIV. Research involving brain imaging and neuropsychological assessment has yielded equivocal and conflicting results. Nevertheless, there is a growing consensus that opiate abuse diminishes immune response, and may actually contribute to a more severe disease stage such as AIDS. This assertion is tenuous, and remains untested.

Alcohol

Lifetime prevalence of alcohol abuse and dependence is high in people with HIV, with prevalence estimates ranging 29–60% [112]. Thus, alcohol misuse disorders are among the most common co-morbid disorders among people infected with HIV.

Cerebral Morphology and Function.—Alcohol misuse exerts broad damage to multiple neurotransmitter systems including acetylcholine, norepinephrine, glutamate, and GABA [62]. Additionally, cortical atrophy over the frontal temporal, and parietal lobes [113], reduced subcortical volumes, and white matter abnormalities [114] have been reported. Furthermore, hypometabolism occurs in the frontal and parietal lobes [68, 115, 116] and remains despite abstinence [68,117].

Neuropsychological Function.—Prevalence of cognitive deficits is heightened in chronic alcohol misusers, and non-verbal intelligence, abstract reasoning, concept formation, memory, speed of information processing, attention, and visual-spatial perception are commonly impaired [118–122]. Similar to morphological changes, cognitive difficulties may remain after several years of abstinence [123].

Immune Function.—Chronic alcohol misuse corresponds with immunosuppression [124–129], and this is manifested by suppressed monocytes, macrophages, and lymphocytes, including T-cell responses [127, 130]. Additionally, infection rates are higher in alcoholics [131]. Among seropositive individuals, alcohol misuse is associated with faster HIV replication, accelerated progression from asymptomatic to symptomatic illness, and greater permeability of the blood brain barrier to infectious agents [132, 133]. Hence, alcohol misuse in people with HIV may interact to exacerbate neuro-psychological impairment beyond what might be expected of each factor independently.

HIV and Alcohol Misuse.—The existing literature reveals that alcohol abuse impairs brain structure and function, neuropsychological performance, and immune response in sero-negative individuals. Accordingly, alcohol abuse in HIV may exacerbate risk of neuropsychological deficit. Despite this suggestion, many imaging studies have shown no effect of alcohol abuse and HIV status [134, 135]. Unfortunately, owing to design

limitations, these studies examined only the main effects of alcohol use and HIV status rather than their interaction (e.g., comparing alcoholic and non-alcoholic seropositives).

Among studies that have examined the simultaneous effect of HIV status and alcohol use history, there are indications of an interaction. One study examined the effects of HIV infection and chronic alcohol consumption on cerebral phosphorus metabolites in order to determine whether chronic alcohol abuse is a risk factor for the progression of neurological effects of HIV infection [135]. Ninety six individuals were categorized into four groups: 15 HIV-seronegative alcoholics, eight HIV-seronegative light/non-drinkers, 32 HIV-seropositive alcoholics, and 41 HIV-seropositive light/non-drinkers. Magnetic resonance spectroscopy was used after magnetic resonance imaging to examine two brain volumes in the super white and subcortical gray matter. Chronic alcohol consumption and AIDS were associated with reduced white matter concentrations of phosphodiester (PDE) and phosphocreatine (PCr), compared with both HIV seronegative and clinically asymptomatic HIV seropositive subjects. A successive decrease of white matter PDE and PCr concentrations in the order of HIV seronegative light/non-drinkers, HIV-seronegative alcoholics, HIV-seropositive light/non-drinkers, and HIV-seropositive alcoholics was found, providing evidence that adverse metabolic effects of HIV on the brain are exacerbated by chronic alcohol abuse.

Regarding neuropsychological function, several large investigations have concluded that neurobehavioral abnormalities in HIV are not attributable to alcohol abuse [26,106,136]. Yet, because of design limitations, these investigations could only examine main effects of HIV status and alcohol misuse history; the interaction of these variables was not addressed. More recent studies have overcome this limitation. Green *et al.* (2004) compared four groups of homosexual men on a battery of neuropsychological tests [137]. The men varied according to HIV status and history of alcohol misuse. History of alcohol misuse corresponded with diminished verbal intelligence, concept formation, auditory working memory, and reaction time. Compared to seronegative individuals, the seropositive participants performed worse on measures of verbal learning and motor speed. Notably, HIV status interacted with alcohol misuse history; HIV-seropositive participants with a history of alcohol abuse demonstrated poorer performance on measures of verbal intelligence, concept formation, and visual reaction time relative to other groups. Additionally, in the HIV negative group, history of alcohol abuse had no significant effect.

Other studies have reported similar outcomes. For example, Rothlind *et al.* (2005) grouped 268 adults according to HIV status and level of alcohol use (light/non-drinkers vs chronic drinkers) [50]. Light/non-drinkers (LD) were operationally defined as participants with lifetime average consumption of fewer than or equal to 45 (35 for women) standard alcoholic drinks per month without past or current alcohol dependence or significant periods of drinking more than 45 drinks per month. Classification as a heavy drinker was based on self-report of an average consumption of at least 100 (80 for women) standard alcoholic drinks per month for the prior three years and active drinking at the time of study (HD). Multivariate analysis of covariance revealed no significant alcohol and HIV interactions. However, the HD group was stratified into two groups: currently heavy drinkers (CHD - reporting an average of fewer than six drinks per occasion of drinking during the past week), and currently very heavy drinkers (CVHD - reporting an average of more than six drinks per

occasion during the past week). Using the trichotomous variable for alcohol status (LD, CHD, and CVHD), significant HIV-alcohol interactions were revealed. HIV-seropositive persons who were very heavy drinkers had lower processing speed compared to uninfected persons. Also, very heavy current drinking and HIV showed synergistic adverse effects on aspects of motor and visuomotor functioning.

A study of 497 community resident African American men with varying levels of alcohol consumption and HIV status (310 HIV-, 187 HIV+), among HIV-negative, ninety-six were non drinkers, 112 were light drinkers (< seven drinks/week); 53 were moderate drinkers (seven 21 drinks per week), and 49 were heavy drinkers (>21 drinks per week) examined neurocognitive functioning. Among HIV-positive, the numbers were 48, 81, 27, and 31, respectively. Neuropsychological assessment was conducted using the UCLA/WHO Neuropsychology Battery, a comprehensive battery comprised of measures included in the WHO's cross-cultural multicenter study of HIV-associated neuropsychiatric disorders. This was supplemented by traditional clinical neuropsychological tests widely used in the U.S. After controlling for age, education, substance use, recent drug exposure, and a history of head injury/loss of consciousness, MANCOVA analyses revealed a significant interaction effect between alcohol consumption and HIV status, with HIV+ heavy drinkers showing significant impairment in the neuropsychological areas of psychomotor speed, reaction time, and motor speed. These findings reinforce the view that HIV infection and heavy alcohol use interact to exacerbate neurocognitive dysfunction [139].

A study of 191 men and women: 55 alcohol dependent HIV+; 44 alcohol dependent HIV-; 43 HIV+ without history of alcohol abuse; and 49 controls (HIV-, no history of alcohol abuse) examined neurocognitive functioning. Neuropsychological tests included the digit symbol subtests of the Wechsler Adult Intelligence Scale, fine finger movement, Rey-Osterrieth Complex Figure and Color Trails. Also, participants completed the revised Beck Depression Inventory and the Peabody Picture Vocabulary Test. Results indicated that ALC+HIV group scored below the control group, ALC, and HIV groups on the number of boxes completed in ninety seconds. The same group was significantly slower than the other three groups in time to complete the entire grid. Associative learning was examined by tracking performance in fifteen-second epochs. A repeated measures ANOVA revealed significant effects for group, time epoch, and their interaction. ALC+HIV were impaired relative to the other three groups. Repeated measures analyses of subsequent epochs revealed that HIV performed significantly faster over time, ALC performed at a relatively constant pace, and ALC-HIV declined over time. The degree of recentness of drinking was not a significant factor and did not interact with time epoch in repeated measures ANOVA. Alcoholism combined with HIV infection resulted in deficits in visuospatial psychomotor function, as assessed by the DS test, although deficits were not observed in either disease condition alone. Combined cognitive and motor adverse effects of alcoholism and HIV infection were manifest in psychomotor speed, sustained attention and associative learning of visuospatial material [140].

Collectively, these investigations suggest that heavy sustained alcohol use may interact with HIV status to exacerbate some aspects of neurobehavioral function. There are indications [50, 138, 140, 141] that such abuse may interact in a manner that increases the risk for

demonstrating neuropsychological impairment. This occurs over and above the main effects of either alcohol or HIV alone, and it seems to affect speed of information processing and psychomotor speed primarily. At present, this literature provides only tentative implications and few conclusive assertions, and additional research will be necessary to clarify matters.

Marijuana

Cerebral Morphology and Function.—The principal psychoactive ingredient of marijuana (delta-9 tetrahydrocannabinol: THC) has receptors throughout the brain, most prominently in the cerebellum and in the hippocampus [142]. There are indications that THC has an especially adverse effect upon hippocampal nuclei and medial pre-frontal cortex [62,143]. In studies involving functional imaging methods, marijuana use seems to correspond with cerebral hypoactivation [144, 145]. There is little evidence of structural abnormalities associated with marijuana use.

Neuropsychological Function.—Acute marijuana intoxication corresponds with deficits involving memory, attention, speed of information processing, cognitive flexibility, motor coordination, and visual spatial perception [62], and these effects linger for several hours after drug administration [146]. More controversial, however, are the effects of chronic marijuana abuse, and whether residual cognitive deficits develop. Pope and colleagues have examined the effects of marijuana abuse after brief periods of abstinence, and found deficits involving memory, attention, concept formation, and psychomotor speed. These abnormalities were unlikely associated with premorbid cognitive ability or co-morbid psychiatric illness or substance abuse [147–149]. However, as acknowledged by Pope *et al.*, it is uncertain whether such deficits remain after longer periods of abstinence.

Immune Function.—Klein and colleagues have shown that marijuana misuse modulates T and B lymphocytes and cytokine response, decreases natural killer cell activity [150, 151], and diminishes immunity to infection [152, 153]. Thus, the likelihood that an HIV seropositive individual will become symptomatic or convert to AIDS will increase.

HIV and Marijuana Misuse.—There is at least one investigation of co-morbid marijuana abuse and HIV infection upon neuropsychological function. Cristiani *et al.* (2004) found that symptomatic seropositive individuals performed worse than a control group on measures of intellect, executive function, working memory, new-learning, speed of information processing, and motor speed [154]. Individuals with a history of marijuana misuse had impaired new-learning and auditory working memory. Furthermore, HIV status interacted with marijuana use on a global index of impaired neuropsychological test scores. Specifically, among those who used marijuana, the seropositive-symptomatic group performed significantly worse than the asymptomatic or seronegative groups. Among those who did not use marijuana, worsening disease status did not exacerbate neuropsychological impairment. Thus, marijuana use increased the likelihood that HIV infection exacerbated neurobehavioral dysfunction. These results should be viewed with caution, because it is a single study, and it awaits replication.

Amphetamine

Cerebral Morphology and Function.—Amphetamines and methamphetamines act as agonists upon the norepinephrine and dopamine systems [155], and chronic abuse can deplete the amount of norepinephrine and dopamine in the brain. Despite abstinence of three years, amphetamine abusers continue to show abnormally depleted amounts of dopamine in the caudate and putamen [156]. With functional imaging methods, amphetamine and methamphetamine abusers display abnormal patterns of activation in the frontal and temporal lobes, cerebellum, cingulate, and thalamus [157–161], and such anomalous activation may remain after long periods of abstinence [160]. Furthermore, amphetamine use results in vasoconstriction, thereby increasing the risk of vascular inflammation, hypertension, and stroke [62]. However, apart from strokes, there is little evidence that chronic amphetamine abuse yields structural abnormalities.

Neuropsychological Function.—Regarding neuropsychological effects of amphetamine intoxication or abuse, little is known. McKetin and Mattick (1997; 1998) found that individuals with long or severe histories of abuse have compromised memory and attention performance [162, 163].

Immune Function.—Research concerning the effects of amphetamine abuse upon immune response is scant. The available literature derives from animal and human studies, and shows that amphetamine use decreases T-lymphocyte response and increases flu virus replication [164–166]. Chronic amphetamine abuse also corresponds with changes in hormonal and lymphocytic activity that reflects immuno-suppression [167, 168].

HIV and Amphetamine Misuse.—A number of studies have examined the interaction of HIV and methamphetamine use on cerebral structures and metabolites in the brain. In a study involving 103 individuals varying in their history of methamphetamine use and serostatus, significant correlations were observed between diminished hippocampal volume and increasing neurocognitive impairments, but only in the HIV+/METH+ group [169]. In contrast, in a study of 119 individuals likewise varying according to history of methamphetamine use and serostatus, lower levels of metabolites, specifically N-acetylaspartate (NAA) were found in the frontal white matter of HIV-seropositive subjects, regardless of their drug status, suggesting no exacerbated drug effect [170]. NAA is a putative marker of neuronal integrity and can be related to neuropsychological functioning. Thus, there is inconsistent evidence of exacerbated cerebral dysfunction in amphetamine using seropositive individuals.

Recent evidence suggests that drug use can accelerate disease progression in HIV [171]. Methamphetamine abusers with greater immunosuppression had the greatest rates of NP impairment which supports the possibility of an additive relationship between HIV, drug use, and disease progression on NP performance [172].

The data suggest that at least among stimulant abusers, there is some likelihood of an additive or interactive effect of drug use and HIV in NP functioning. Several mechanisms have been suggested to underlie this effect. In animal models, potentiation of HIV Tat protein mediated neurotoxicity by methamphetamine has been demonstrated, which can

result in striatal proinflammatory cytokine stimulation and activation of redox-regulated transcription factors [173]. Other mechanisms which have been suggested include mitochondrial dysfunction and subsequent oxidative stress. Dopaminergic, serotonergic, and glutamatergic systems are impacted by stimulant use and HIV, and dual vectors impacting these systems could result in additive neuropsychological effects [174, 175].

Regarding cognitive performance, Rippeth *et al.* (2004) examined the coincident effects of methamphetamine misuse and HIV status on neuropsychological function [176]. Among the patients who were HIV seropositive and meth-amphetamine dependent, nearly 60% were impaired, whereas only 20% of the control group (HIV seronegative and non-methamphetamine dependent) were impaired. Among individuals who were HIV seropositive/nonmethamphetamine dependent and those who were HIV sero-negative/methamphetamine dependent, approximately 40% were impaired. As such, there seems to be an interactive influence of HIV seropositivity and methamphetamine use on neuropsychological function. Likewise, Cherner *et al.* (2005) examined the effects of HIV and methamphetamine dependence [54]. These risk factors both yielded significant main effects upon cognitive impairment, but their combined effects exacerbated the severity of impairment. Similarly, Carey *et al.* (2006) examined the effects of methamphetamine dependence and CD4 suppression on neuropsychological function [172]. The combined effects of drug use and immunocompromise exacerbated impairment over the independent effects of either variable alone. Thus, the combined effects of methamphetamine dependence and HIV have greater neurobehavioral consequences than methamphetamine dependence or HIV infection alone.

Several other studies have examined the interaction between HIV serostatus and polysubstance misuse, including amphetamine and cocaine. In one study, individuals who were dependent on methamphetamine, cocaine, or both (STIM+) were classified according to HIV status. Comprehensive neuropsychological testing revealed that stimulant misuse and HIV status increased neuropsychological dysfunction, and those who were seropositive and currently misusing stimulants had the worst level of impairment. Presence of stimulant metabolites in the urine was also associated with a heightened rate of impairment [177]. A recent study of 40 HIV-seropositive individuals (12 non-drug users and 17 stimulant users, which included cocaine and/or meth-amphetamine) examined sustained attention by comparing groups on overall performance, as well as patterns of performance across time. Compared to the non-drug users, stimulant users showed a gradual increase in reaction time variability and omission errors, suggesting that recent stimulant use among HIV-infected persons adversely affects sustained attention [178]. In another recent study of 104 HIV seropositive individuals, looking specifically at sustained attention among HIV+ individuals, stimulant users were found to have a greater number of omission errors and variability in reaction time than had non-drug-users, indicative of impaired sustained attention. No difference was found on a general global neuropsychological ability rating or, importantly, on other tests comprising the attention domain between the groups. That finding underscores the importance of a multifaceted assessment of attention [179].

Other Drugs

Other studies have examined the effects of polysubstance misuse on cognitive functioning. These studies controlled for HIV status and non-specific drug use, categorizing individuals who use various drugs as drug users. One study of 102 persons examined cognitive functioning in three groups (56 HIV-seropositive drug users, 19 HIV-seronegative drug users, 27 HIV-seronegative non-drug users). Subjects underwent neuropsychological tests designed to explore cortical and subcortical function. HIV-seropositive drug users showed significantly lower performance scores than the HIV-seronegative groups. There were no differences between the two groups of HIV-seronegative persons. Among persons with HIV, progression of the disease (prior to AIDS) did not determine a decrease in intellectual performance. Instead, cognitive function was affected by the chronic and current use of illicit substances, with the subsequent decline in cognitive function among the HIV-seropositive group being attributed to a chronic use of illicit substances rather than HIV infection [180].

A study of 42 African American women with a history of poly-drug use examined neuropsychological functioning among four sub-groups based on HIV status (seronegative, asymptomatic seropositive, symptomatic seropositive, full-blown AIDS). Results revealed no evidence of HIV-related cognitive impairment in patients in the early stages of HIV; however, significant deficits in psychomotor processing and verbal recall emerged as the disease progressed. The cognitive deficits in AIDS patients, however, were not related to the recentness of drug use [181].

METHODOLOGICAL PITFALLS IN THE NEUROPSYCHOLOGICAL (NP) ASSESSMENT OF HIV AND SUBSTANCE USE

Many methodological and measurement issues confound the accurate assessment of NP functioning in PLWH with concurrent substance often making it difficult to interpret findings. Further, the accurate assessment of drug and alcohol use is often complicated by poor recall, intentional mis-reporting, and inconsistent patterns of drug/alcohol use (frequency, type, quantity) over time. Polysubstance use is typically the norm, and over time, multiple drugs may be used simultaneously, or drug preference may change. Periods of abstinence can punctuate periods of heavy use and “current” labels of drug use may not capture the variable history, which preceded the person’s current status.

The use of diagnostic categories (e.g., abuse/dependence) to capture drug and alcohol use can result in slightly greater reliability as certain uniform requirements (e.g., minimum period of use, impairments in social/occupational functioning, tolerance, withdrawal) imply a minimum level of use. However, categorizing participants solely based on diagnosis can miss those with a recent history of heavy use or of abstinent. In addition, diagnostic interviews may yield less than valid findings due to dissimulation and poor recall. While drug toxicological assessment may provide more accurate finding of recent drug use, they typically cannot provide valid data of drug use beyond 72 hours. Because of these limitations, interpretation of extant literature on the NP sequelae of HIV and substance use may be equivocal.

DISCUSSION

A review of the research indicates a plethora of studies documenting neuropsychological complications that are associated both with HIV disease and various substances of abuse. However, the research focusing on the interaction or exacerbating effects of various substances of abuse on neuropsychological impairment among PLWH is more limited with most studies focused on methamphetamine and alcohol use. Research examining the possible interaction effects of other substances was scarce. Among the available research, the study findings revealed mixed results with only some studies showing an effect of substance use on neuropsychological complications among HIV-infected persons. Such discrepancies may derive from several sources including type of drug used, measurement of substance use *vs* abuse, polysubstance use, pre *vs* post ARV, types of NP measures employed, and socio-demographic variables, such as socioeconomic status, age, and gender, which may play a role in cognitive functioning [182]. However, these findings, along with the neurological implications associated with HIV disease and substance abuse, suggest several future directions. While the separate effects of HIV disease and substance use on brain structure and functioning have been well-documented, research needs to focus more on the effect of substance use on the severity and progression of HIV-associated psychoneurological complications. Currently, there is limited information to indicate whether a history of substance use either accounts for, or interacts with, HIV serostatus to facilitate the progression of neuropsychological impairment [4]. Expanding inquiry in this area appears critical, considering the implications that comorbid substance abuse and HIV infection may have for treatment management, cognitive functioning, and ultimate morbidity. Evidence indicates that neuropsychological impairment and substance abuse are associated with an increased difficulty in adhering to medication for HIV-infected persons; as such, there is a critical need for expanded research in this area [183].

A more complex and comprehensive approach to the study of different substances of abuse may be needed that examines not only the type of substance abused, but also such factors as the frequency and quantity of substance abuse since these are most important in the magnitude of the NP compromise [184]. Age, gender, race, ethnicity, and a variety of geo-population differences are may also be other pivotal factors to examine.

Future research efforts might be best focused on poly-drug abuse because this is becoming increasingly common; there is, at present, very little information on combined abuse. This may serve as a confounder that can complicate attribution of adverse drug effects to any single substance. Co-factors that frequently accompany drug use include lower socioeconomic status, nutritional abnormalities, lower education levels, histories of head injury or other neurological compromise, and relatively higher rates of psychiatric disorder, all of which can complicate interpretation of the effects of drug use [184]. Longitudinal studies may allow a more precise evaluation of the neuropsychological effects of substance use and HIV disease. Such studies may help to elucidate whether comprehensive substance abuse treatment can reduce the neuropsychological complications associated with HIV disease, which may facilitate a “cognitive safety net”, both for individuals with a history of substance abuse and for current substance abusers who are living with HIV.

Finally, study design might profit by considering whether substance disorders are idiopathic or primary in nature and predate HIV infection, versus being syndromic. Such designs may discriminate between shared and independent contributors to comorbid disease progression. Ultimately, the primary goal of comorbidity research is improve treatment outcome (e.g., quality of life) for individuals suffering from multiple problems. The identification of the genetic, molecular, and cellular mechanisms that contribute to such problems appears vital in guiding therapeutic interventions. The rational design of novel adjunctive therapies demonstrating both immunomodulatory and neuroprotective actions appears important. In this pursuit, interdisciplinary research directed to viral and emotional stress response systems and that utilize innovative approaches and study designs will be critical to advancing the field and overcoming the inherent limitations associated with patient and disease heterogeneity [4].

IMPLICATIONS FOR BEHAVIORAL AND PREVENTION SCIENCES

The implications of cognitive functioning and HIV-preventive behavior are of particular interest. Table 1 summarizes the association between cognitive functioning and HIV-preventive behavior among PLWH [185].

There is a noted association between cognitive functioning and treatment outcome of which may be important in developing treatment interventions for substance-using PLWH. Traditional cognitive-behavioral treatment for substance users focus on the acquisition of skills needed to prevent relapse, including identifying high risk situations; understanding the antecedents and consequences of events; learning alternative coping strategies; correcting maladaptive thinking patterns; improving decision-making and problem-solving abilities; and planning for and coping with “slips”. [185, 186]. Learning, retaining, and generalizing these skills to daily life requires a wide array of cognitive capabilities that may be compromised in chronic drug users infected with HIV. To address the potential for cognitive dysfunction in HIV+ substance abusers, a number of cognitive remediation strategies may be helpful. The use of a multimodal presentation of material stimulates interests and facilitates learning. The use of verbal, visual, and experiential modalities can be beneficial to achieving learning goals. Also, the frequent review of material facilitates learning and retention. In addition, fatigue, distractibility, and poor concentration impede learning and may be particularly problematic for cognitively impaired clients who are attempting to learn new skills. Providing breaks during treatment sessions, using a multimodal presentation of materials, and holding groups in a quiet room with minimal distractions can improve concentration. Providing consistency may be crucial to the successful treatment of cognitively impaired individuals (e.g., meeting at the same time and place each week and following the same structured format). The assessment of knowledge and skill acquisition provides cognitively-impaired individuals with the opportunity to evaluate the effectiveness of various learning strategies and to receive feedback. Assessment also provides the opportunity for additional review of important material. Treatment groups can end with a post-session quiz to assess the acquisition of basic concepts covered in the groups, and counselors can provide immediate feedback to group members on their performance on the quiz. In addition, a comprehensive post-program quiz can be administered to assess longer-term skill acquisition. Also, knowledge and skills acquired in treatment need to generalize to

the cognitively impaired individual's daily life. Counselors can provide real-world examples when group material is presented experientially, and clients can be encouraged to complete at-home exercises. In addition, counselors can seek the cooperation of clients' other health care providers and family and friends to provide an integrated team approach to improving clients' functioning in daily life.

A client workshop can be based on a memory book system, which is designed to improve not only memory for group material, but also for organizing and remembering activities related to healthy living. Another strategy that may be helpful with cognitively impaired HIV+ drug users is that of learning by doing. Games provide a non-threatening context in which cognitively impaired individuals can practice skills. Immediate feedback during game playing can reinforce appropriate behavior and increase self-esteem and self-confidence. Lastly, management of stress may be essential for improving cognitive functioning because stress can impair concentration, and increase cognitive dysfunction, and the potential for relapse.

Group treatment may be the preferred modality with neuropsychologically impaired individuals because it permits generalizable prosocial behaviors to be practiced and strengthened. Group treatments can also reduce the isolation often experienced by individuals with HIV and can provide interpersonal support from individuals with similar problems and life circumstances. Group treatment can be cost-effective and readily incorporated into community-based drug treatment. In addition, participation of the client's significant other or a close friend/family member who is supportive of the client's recovery is recommended. Because rehabilitated peers can provide appropriate modeling of desired behaviors, it is also recommended that counseling groups include "peer guides" whenever possible. It may be helpful for peer guides to be HIV-positive individuals who are in recovery from addiction and have a recent history of drug abstinence [186] as well as being willing to demonstrate their knowledge and support of harm reduction strategies and share their knowledge with others. Peer guides can deliver announcements at group meeting (e.g., NA meetings) and community activities and can assist counselors by initiating games and experimental segments.

There are common clinical problems that may exist this population, including continued high risk behavior, medical deterioration, psychiatric deterioration, and changes in cognitive functioning. Because changes in cognitive functioning during treatment is possible (e.g., due to continued drug use, abstinence, or HIV progression), clients should be monitored closely and treatment strategies modified to match clients' needs and cognitive abilities. Furthermore, with treatment issues such as poor compliance or missed appointments, the client's cognitive status should be considered carefully and treatment plans made accordingly.

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Learning Objectives

- To inform health care professionals and interested researchers about the possible neuropsychological consequences of HIV and substance abuse.
- To discuss implications of this co-morbidity for treatment.
- To provide areas for future research in this area.

Future Research Questions:

- Does HAART protect the brain by restraining progresses of the initial infection, or whether by controlling replication in the periphery and keeping circulating virus at a minimum?
- Is the older brain more susceptible to neurocognitive disorders than the younger HIV-infected brain, especially among drug users?
- Damage to dopaminergic systems caused by drug abuse has been attributed to the fact that dopaminergic neurons are a key target for illicit drugs. Is this really the case-is atrophy of the CNS, particularly in the temporal lobe, to be the cause of the damage or are their other factors into play?
- Why is it pertinent to separate the direct effects of drugs on the brain from those of co-morbid factors such as hepatitis B and C infection?
- Since drugs of abuse can induce changes in the brain which resemble those seen more dramatically as a result of HIV infection, the question arises as to whether the effects of drugs could be additive or synergistic to those induced by HIV, thereby leading to a greater degree of clinical deterioration, with possible accelerated progress and a greater degree of underlying neuropathological abnormality?
- In order to assess pathologically the degree of drug associated damage in the context of HIV infection, it is essential to study a number of different groups such as HIV-drug users, presymptomatic HIV positive drug users, drug users progressing to AIDS without HIV encephalitis (HIVE) or CNS infections, non-drug users in AIDS with no evidence of CNS pathology, drug users in AIDS with evidence of CNS pathology, non-drug users in AIDS with HIV and HIVE, and no CNS pathology, HAART-treated HIV positive drug users, and controls, which include non-drug using HIV negative persons. What is the best way to study these groups? Which methodology would be best used to achieve valid and reliable results?
- How does knowing this information inform the development of harm-reduction for drug users and therapy for those who are already cognitively impaired?

Table 1.**Association Between Cognitive Functioning and HIV-Preventive Behavior**

Capacities Required for HIV Preventive Behavior	
Acquire, retain, and use HIV preventive information and behavioral skills	
Motivation to engage in HIV preventive behavior	
Understand the antecedents and consequences of behavior	
Identify high-risk situations	
Self-regulation of psychological and physiological states	
Problem solving and decision making	
Negotiation with partners	
Know how to reduce harm in the event of a “slip”	
Cognitive Deficits that may Impede HIV Preventive Behavior	
Memory Deficits:	
Difficulty learning, retaining, and retrieving new information and skills	
Difficulty recalling details of high-risk situations	
Difficulty remembering treatment recommendations	
Attention/Concentration Deficits	
Distractibility during information and skill acquisition	
Poor listening and communication skills	
Decreased ability to shift attention	
Attention limited to possibly tangential aspects of the situation	
Deficits in Executive Functions	
Difficulty initiating action	
Difficulty self-correcting, self-regulating	
Concreteness and Mental Inflexibility	
Decreased ability to appropriately generalize across experiences	
Decreased empathy	
Difficulty identifying alternative solutions to problems	
Deficits in Insight, Reasoning, and Judgment	
Poor judgment in high risk situations	
Decreased ability to predict consequences of actions	
Decreased decision making ability	
Decreased ability for sequential concept formation and “logical” reasoning	