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NEUROPSYCHOPATHOLOGY IN THE SIV/MACAQUE MODEL OF AIDS

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1. ABSTRACT

Of the 40 million people living with HIV/AIDS worldwide in 2003, only 7% received highly active antiretroviral treatment (HAART). Without treatment, approximately half of AIDS patients will suffer from NeuroAIDS including neurological dysfunction, peripheral neuropathies, motor impairment, cognitive difficulties and frank dementia. HAART has reduced mortality from AIDS in the developed world, but CNS/neurological complications continue to be a leading cause of death or disability in AIDS patients on HAART. Despite years of use in developed countries, it is still not clear what the long-term impact of HAART will be on NeuroAIDS. The mechanisms of AIDS-related CNS pathology, in the presence or absence of HAART, are not completely understood. Infection with simian immunodeficiency virus (SIV) in macaques provides an excellent research model of AIDS, including AIDS-related CNS pathology and cognitive/behavioral impairments. A major goal of research with the SIV/macaque model has been to characterize behavioral and cognitive impairments in NeuroAIDS and elucidate the CNS pathology behind these impairments. Review of the studies assessing cognitive impairment in SIV infected macaques demonstrates the high concordance between neuropsychological impairment in human and simian AIDS. Consistent with results in human AIDS patients, SIV-infected monkeys tend to be impaired most often on tasks dependent upon intact frontal cortical and/or subcortical functioning. Building on the strengths of the SIV/macaque model of AIDS, directions for future research are discussed including further mechanistic studies of the neuropathology leading to cognitive impairment as well as assessment of the impact of antiretroviral therapy or drugs of abuse on NeuroAIDS.

2. INTRODUCTION

Neuropsychopathology, or central nervous system (CNS) dysfunction that leads to behavioral changes, is an important aspect of the acquired immunodeficiency syndrome (AIDS) pandemic (1). Early in the course of infection, human immunodeficiency virus (HIV) enters the CNS, and HIV is detectable in the CNS throughout the course of infection. However, HIV does not infect neurons, but rather it infects cells of the monocytic lineage in the brain, namely macrophages and microglia (2-5). The neurotoxicity resulting from HIV infection therefore results from an indirect mechanism, possibly involving toxic viral proteins or inflammatory mediators produced by activated macrophages and microglia (6-10). Taken together the neurological, motor and cognitive impairments in AIDS have been termed NeuroAIDS.

Of the 40 million people infected with HIV worldwide in 2003, only 7% will receive antiretroviral treatment (11, 12). Without treatment, approximately half of AIDS patients will have neurological dysfunction, including peripheral neuropathies and Minor Cognitive/Motor Disorder (MCMD) seen in roughly 5-10% of early stage HIV patients and 25-30% of late stage patients (6, 13-18). MCMD significantly worsens quality of life for AIDS patients, increasing self-reports of 'pain/discomfort', 'mobility', 'self-care', and inability to engage in 'usual activities' (19). Cognitive impairment and impairment of psychomotor speed were both highly correlated with reductions in quality of life (20, 21), suggesting that impairment of motor function or speed predicts reductions in the quality of life for AIDS patients (20). MCMD is also associated with an increased risk of employment loss above and beyond illness from immunosuppression (15, 20, 22). The reduction of the quality of life of NeuroAIDS patients and their families is therefore a significant, but often overlooked, aspect of AIDS. In addition to MCMD, 5-15% of symptomatic AIDS patients develop the disabling HIV associated dementia (HAD), making HAD one of the leading causes of dementia in the non-elderly (6, 13-18).

In developed nations, highly active antiretroviral therapy (HAART) has led to a decline in mortality and in the incidence of CNS effects of AIDS, including nearly a 50% reduction in the incidence of HAD (23, 24); however, the overall prevalence of HAD has been increasing with prolonged survival times of AIDS patients on HAART (25-28), and CNS/neurological complications continue to be a leading cause of death or disability in AIDS patients on HAART (28-30). Therefore, while fewer HIV positive patients progress to AIDS with HAART, those that do have the same or increased incidence of NeuroAIDS.

HAART has been reported to be beneficial in some (25, 31-35), but not all cases of MCMD and HAD (21, 36). As many as 40% of HAD patients may not improve with HAART treatment (37) suggesting that not all pathology may be reversed by reducing viral load (29, 38). Treatment failure has become a significant concern with HAART, whether due to non-compliance, development of resistant viral strains, intolerable side-effects or other causes (39--41). Despite recent initiatives increasing treatment availability, the cost of HAART treatments makes them unavailable for most of the 35 million HIV-infected individuals in developing countries (11). Additionally, most HIV therapeutics do not readily penetrate the blood-brain barrier, and the long-term effects of reducing peripheral viral loads while sparing virus in the CNS are not well understood (42, 43). For these reasons, understanding the mechanisms of neuropsychopathology induced by HIV remains an important research goal.

Simian immunodeficiency virus (SIV) infection of macaques has proven to be a useful research model of HIV infection in humans. The SIV/macaque model produces simian AIDS with the advantage of a much shorter disease progression than HIV/AIDS. The neuropathology induced by SIV recapitulates most aspects of HIV-induced neuropathology (44-46), including the characteristic multifocal and perivascular aggregates of brain macrophages and multinucleated giant cells that serve as the major host cells for productive replication of virus (44, 47-51).

The precise mechanism by which HIV and SIV produce their neuropathology remains unknown. Since most studies do not find that HIV or SIV directly infect CNS neurons, current hypotheses are centered largely on indirect mechanisms: a) factors related to the host's immunologic response (e.g. release of neurotoxic cytokines); b) degradation of the blood-brain barrier; and c) increases in neurotoxic molecules such quinolinic acid (Quin), or neurotoxic viral proteins (45, 46, 52). The compressed time course of disease progression of SIV in macaques (measured in months) compared with HIV in humans (measured in years) is being exploited by AIDS researchers in many disciplines, including those investigating neuropathology and behavioral/cognitive impairment produced by AIDS.

Despite the similarity of AIDS in monkeys and man, or perhaps because of it, characterizing the behavioral effects of SIV in monkeys has proven to be challenging. A major difficulty is that frank AIDS dementia occurs in a relatively small percentage of AIDS cases; therefore, to study full-blown SIV dementia would require a very large number of subjects. Accordingly, some laboratories have been developing behavioral tests more sensitive to psychomotor functions that are affected in a majority of SIV-infected animals. As reported below, cognitive and behavioral tests have been developed that are sensitive to simian equivalents of both AIDS dementia and MCMD. This review includes studies to date that involve assessment of behavioral/cognitive functions in the SIV/macaque model of AIDS.

3. STUDIES OF COGNITIVE AND BEHAVIORAL EFFECTS OF SIV INFECTION

The studies reviewed below use a variety of SIV viruses. There are many SIV strains, clones and swarms that are in use in the study of SIV/AIDS, each with their own characteristics. Burundi and Fox, (2001) have recently reviewed the characteristics and derivation of the majority of SIV viruses used in the SIV/macaque model (53).

3.1. Observational Studies of Behavior Following SIV Infection

Several studies of SIV-infected monkeys, including two described below, have assessed behavior using relatively informal measures. Details of these neurological examinations were confined to the monkeys being "monitored clinically" or "examined daily by trained laboratory personnel and/or the authors".

The unavailability of verbal instructions when working with non-human primates greatly limits the extent of neurological examinations compared with those possible for people. Detailed neurological examinations are routine in a veterinary context, the animals are usually companion animal species such as cats and dogs that are habituated to manipulation by humans. Macaques do not readily habituate to procedures such as direct manipulation of limbs and percussive testing of reflexes; therefore observational techniques are typically used.

Examination by observation alone will reveal only such clinically obvious alterations to neurologic function as extreme tremor or favoring of limbs. As signs like these are generally associated with advanced disease, this method is of limited sensitivity as an indicator of disease progress. Despite the disadvantages, studies involving neurological examinations provide information as to what percentages of animals display gross behavioral changes, and the timing of such changes.

1. Heyes, (1992) measured atrophy in discrete brain areas using magnetic resonance imaging in rhesus monkeys infected with a sooty mangabey isolate of SIV (SIVsm) (58). They also measured levels of cerebrospinal fluid (CSF) Quin and symptoms of neurological disorder in the progression of SIV disease. Neurologic signs included mild to severe lethargy, clonus, and loss of balance. Six of 11 SIV-infected monkeys presented neurologic signs. In four of these, Quin levels and brain atrophy were raised and

survival times greatly decreased (survival times less than 12 weeks) relative to monkeys without neurologic signs (survival times greater than 37 weeks).

2. Sopper, (1998) reported ataxia, apathy, seizure, and opisthotonus (large spasm in back muscles) in 6 of 12 rhesus monkeys rapidly progressing to AIDS, but in only 1 of 7 monkeys slowly progressing to AIDS. Rapid progressors displayed AIDS symptoms within 7 months of infection with SIVmac251, and had a mean survival time of 4.5 months. Slow progressors had a mean survival time of 14.5 months. Three of 12 rapid progressors also displayed neurologic signs as the first and only clinical signs of AIDS (54). In humans approximately 5-10% have been reported to have the initial symptoms of AIDS to be related to NeuroAIDS (55-57). Sopper, (1998) also confirmed the previou report of Heyes, (1992) that rapid progressors failed to produce virus-specific immune responses in either the periphery or CNS (58). Importantly, there was an apparent increase in neurologic/CNS effects of SIV in rapid progressors compared to animals with slower disease progression.

3.2. Environmental Variables and Individual Differences on SIV Disease Progression

Observational techniques can be formalized to allow for more quantifiable data than the neurological examination. Capitanio, (1991, 1998, 1999) used a more rigorous approach to investigate sources of variation in the speed of SIV disease progression, comparing variables in the monkey's history to markers of AIDS progression in rhesus macaques used in several studies of SIV infection (59-61). Two different classes of factors were investigated: environmental impacts on the host and individual differences in the host's behavioral histories.

Capitanio and Lerche (1998, 1999) used archival methods, gathering data from four Regional Primate Research Centers in the U.S.A. on environmental variables including demographic, viral, clinical, and housing histories for a total of 260 rhesus macaques productively infected with several strains of SIV (59, 60). Results of their statistical modeling linked housing changes between 90 days pre-infection and 30 days post-inoculation with an increased death rate after controlling for SIV inoculum and medical variables (60). Additionally, separations from familiar companions within 90 days prior to SIV inoculation was associated with reduced latencies to leukopenia and lymphopenia and increased risk of weight loss greater than 10% of initial body weight (59). These authors postulate that stress-response systems such as increased corticosteroid secretion may have affected either the host immune response or viral replication. Human AIDS patients often experience adverse environmental or psychosocial stressors, such as problems with social support, employment, health care and housing (60). Understanding the mechanisms by which environmental or psychosocial variables affect AIDS progression may significantly lessen the negative impact on quality of life.

Individual animals have unique behavioral repertoires providing unique mixes of the various behaviors characteristic of their species. In humans, these can be scored with adjective-based rating scales resulting in an assessment of the construct of "personality." Such scales can be rated by the subject, or by others familiar with the subject. Capitanio, (1999) investigated the effects of "personality dimensions" on markers of AIDS progression in monkeys employing the latter approach to score rhesus macaques with a 25 adjective list, including, for example, "aggressive," "confident," "motherly," and "fearful" (61). The 25 questions cluster into 4 "personality dimensions" including the factors of: "Equable," "Sociable," "Confident," "Excitable." Scores from this list have been shown to be predictive of social behavior in male rhesus monkeys over a 4.5 year time span (61). Several personality dimensions were found to correlate to physiologic and disease factors in SIV. For instance, Sociability, comprising scores of the adjectives "sociable," "playful," and "curious," was found to be significantly correlated with plasma cortisol (inversely), anti-RhCMV IgG (positively), and viral load (positively correlated early in infection then inversely correlated later in infection). The effect of personality on physiology was in the "small to medium" range and statistically reliable (61). These results suggest that personality dimensions may interact with immune function to affect the course of SIV disease progression.

3.3. Studies Using Operant Behavioral Techniques with SIV Infection

As opposed to observational techniques, operant behavioral techniques entail organisms interacting with (or operating on) their environment. Operant procedures typically use more objective measures and collect readily quantifiable data compared with observational studies or neurological examinations. There is a large body of literature describing the effects of CNS dysfunction on different cognitive/behavioral tasks in macaques. CNS dysfunction can be induced by many mechanisms including ablative lesions and selective neurotoxins, and the behavioral effects of these lesions help characterize the neural substrates of particular behavioral/cognitive tasks. Using tasks with identified neural substrates allows for assessment of function in different brain regions. Furthermore, because many behavioral tasks are impaired by CNS dysfunction prior to onset of clinical signs, the use of such tasks allows for the identification of changes in neuropsychological function not obvious clinically. A drawback of this approach can be the need for specialized equipment and months to years of training prior to infection with SIV.

Studies using operant behavioral tests following SIV infection have drawn upon human neuropsychological studies as guideposts for tests that may be sensitive to SIV-induced neuropathology. Neuropsychological assessments of AIDS-related cognitive and motor disruptions, including both AIDS dementia and MCMD associated with AIDS, have resulted in the working hypothesis that dysfunction in frontal cortical and subcortical systems plays a large role in the cognitive / motor effects resulting from HIV infection (62, 63). Neuropsychological tests sensitive to frontal cortical function have been disrupted in both AIDS patients

and HIV+ asymptomatic individuals (64, 65). For example, impairments in executive function (e.g. planning complex behaviors) have been reported in HIV/AIDS (65, 66) as has impairment in other cognitive domains mediated by frontal-cortical areas or frontal-striatal circuitry, such as working memory in both HIV/AIDS and SIV/AIDS, (e.g. spatial working memory) (66-71). There are numerous reports of slowing of reaction time (RT) in AIDS patients (72-76), and subcortical (striatal) dopaminergic systems have been shown to be important to normal RT functioning (77-81). Arendt (1989, 1992, 1994) explored the effects of HIV on motor control by measuring voluntary finger movements, postural tremor, and isometric force production (82-84); they demonstrated that finger movement and force production measures not only differed between HIV+ and control groups, but were also predictors of speed of disease progression (84). Such studies with AIDS patients provided the framework for future behavioral studies using the SIV/macaque model of AIDS.

1. In the first published study to report cognitive and motor impairment following infection of rhesus macaques with SIV, Murray, (1992) trained 15 monkeys on a battery of food reinforced behavioral tests and observed them for changes in spontaneous behavior in their home cages (92). The behavioral battery, described in table 1, employed tests to measure 1) visual memory with a delayed matching to sample paradigm using novel stimuli each trial, 2) recency memory with a delayed matching to sample paradigm using the same two stimuli repeated each trial, 3) visual discrimination learning and retention, 4) fine motor control with the removal of rewards from a rotating turntable, and 5) unconditioned behavior in the home cage. The advantages of this selection of tasks were twofold: a) learning, memory and fine motor control had been shown to be affected in some HIV positive individuals and b) the neural substrates of some of these tasks have been previously investigated in macaques. Therefore, changes in performance of these tasks may provide both an indication of functional impairment of the CNS following infection with the Delta B670 strain of SIV as well as clues to the locations of the affected brain areas.

Eight of the 15 monkeys inoculated with SIV became productively infected and displayed some impairment on at least one test prior to either their death (2 monkeys) or scheduled euthanasia after 11 months (6 monkeys). For 5 infected monkeys performance on the motor control task was the only impairment demonstrated. The other 3 productively infected monkeys had impaired performance on the visual discrimination task, both learning and retention, and one of these 3 monkeys was also impaired on the delayed match to samples (DMS) recency memory test (two repeated stimuli). None of the monkeys showed changes in the home cage behaviors observed.

2. Using data from the same monkeys, Rausch and colleagues (1994) reported that in 7 of the 8 monkeys with motor impairment the onset of motor impairment was associated with elevated Quin in the CSF (85). However, the onset of cognitive impairment was not associated with elevated Quin. Reactive astrogliosis was coincident with or preceded the onset of motor impairment. The association of Quin and motor impairment is consistent with the results of Heyes, (1992) where Quin levels were elevated in 4 of 6 monkeys with neurologic symptoms (58). CSF Quin increases have also been related to neuropsychological deficits in both adult and juvenile HIV patients (86, 87). Indeed, Quin injected intrastriatally is one model of the degenerative brain disease Huntington's Disease (88, 89). The concentrations of Quin following HIV and SIV infection are similar to, or higher than, concentrations shown to be neurotoxic experimentally (58). Thus Quin levels appear to be a marker for CNS dysfunction resulting in motor impairment. The fact that Quin is also a potential neurotoxin makes it a very interesting marker; however, Quin-mediated neurotoxicity in AIDS has yet to be definitively established.

3. The same battery of tests from Murray, (1992) was used in later studies on the effects of zidovudine (AZT) on survival and CNS effects of perinatal SIV infection (90, 91). Neonatal rhesus monkeys were divided into uninfected untreated controls (CON; N=5), SIV infected untreated controls (SIV+AZT-; N=5), SIV infected treated with AZT (SIV+AZT+; N=8). AZT was administered under 2 regimens but as the dosing strategy did not affect the outcome, these groups have been collapsed. SIV inoculations (or vehicle injections) and AZT treatments were administered within 48 h of birth. AZT administration continued for 6 months.

At approximately 10 weeks of age, the monkeys began fine motor control testing with the rotating turntable task. Two of the 4 surviving SIV+AZT- monkeys had impaired motor control at this time; however, none of the SIV+AZT+ monkeys displayed impaired motor control. CSF Quin levels were lower in the AZT+ than the AZT- monkeys. At 6 months of age, AZT administration was terminated in the treated groups, and testing began for recognition memory and discrimination learning. At the beginning of DMS and discrimination learning testing only 3 of 5 SIV+AZT- monkeys survived while all 8 SIV+AZT+ monkeys survived to begin training. Behavioral training continued for all surviving monkeys for an additional 6 months. During this period, 3 of 8 SIV+AZT+ and 1 of 3 surviving SIV+AZT- monkeys had transiently impaired motor performance. Additionally, 2 of 8 SIV+AZT+ showed impaired performance of discrimination learning but performance was not affected in any of the 3 SIV+AZT- for as long as they survived. The results of this study demonstrated that AZT treatment prolonged survival times and delayed the onset of cognitive/motor impairment following infection with SIV. Once AZT treatment was discontinued, the AZT treatment did not appear to provide lengthy protective effects as all SIV+/AZT+ monkeys developed disease following the end of the AZT treatment period.

The AZT studies provided further evidence of a relationship between elevated Quin and impairments in motor behavior. The relationship between Quin and motor impairment is even more intriguing when coupled with the

Table 1. Summary of Behavioral Methods

Behavioral Paradigm	Description	Reference
Delayed matching to sample	Three sample stimuli appear in succession separated by 2.5 s intervals on a touch-sensitive computer monitor. Trial proceeds only after each sample touched. After an 8 s delay, sample stimuli are repeated in reverse order paired with novel stimuli. Touching the sample stimulus is rewarded with food and counted as a correct response. Touching the novel stimuli was not rewarded and counted as incorrect. Delays used were 8, 13, and 18 s.	Murray (92)
Recency memory test	One sample stimulus appears followed by a 5 sec delay after which there were two choice stimuli. The same two stimuli are used repeatedly. Trial by trial, each stimulus is randomly assigned as either sample stimulus or incorrect stimulus.	Murray (92)
Visual discrimination task	Twenty pairs of stimuli are presented in the same order each test day. One of the two stimuli was arbitrarily determined to be "correct" and touching this stimulus produced a food reward and blanked the screen, while touching the "incorrect" stimulus only blanked the screen.	Murray (92)
Rotating turntable test	A rotating turntable contains wells baited with food. The speed of rotation was titrated until the speed at which the monkey retrieved food on 50% of the trials was determined	Murray (92) Marcario (94)
Unconditioned home cage behavior	Several 5 min observation periods sampled per month of behavioral testing for duration and frequency of locomotion, interaction with an enrichment ring in the cage, environmental exploration, social interaction, self grooming and stereotyped behavior.	Murray (92)
Simple reaction time	Performed by both the left and right hands separately, with the alternate hand restrained. Monkeys pressed on a switch plate until a target stimulus was displayed on a touch-sensitive computer monitor. Touching the target within 1.25 sec was rewarded with food pellets.	Marcario (93)
Choice reaction time	Both hands were required to press switch plates. Different colored stimuli indicate whether the right or left hand was to be released from the switch plate and used to touch the target on the touch-sensitive computer monitor. The alternate hand was required to remain pressing the switch plate to receive reinforcement.	Marcario (93)
Self-ordered spatial search	2-5 colored boxes were displayed in different positions on a touch-sensitive computer monitor. Monkeys were required to touch each box only once within a trial. Each correct touch was rewarded with a food pellet, and followed by a 2 s delay. Trials ended when all boxes were touched, or when one box was touched twice (error).	Weed (67)
Intra / extra-dimensional shift	A computerized analog of the Wisconsin card sort task used to test category abstraction in humans.	Weed (110)
Delayed non-matching to sample task	Monkeys performed an observing response on the computer monitor to one visually abstract, multi-colored stimulus; following a delay, the initial stimulus was presented alongside a novel stimulus. Touching the novel stimulus resulted in a food reward. The delays ranged from simultaneous, 0, 16, 32 and 64 s.	Weed (67)
Bimanual motor skills (BMS) task	Monkeys coordinated both hands to retrieve fifteen raisins from a hole board while the procedure is timed.	Weed (67)
CANTAB choice RT task	Five circles appeared on the touch-sensitive computer monitor. Holding a lever (1-5 sec) produced a stimulus flash in one circle. Touching that circle was reinforced with food pellets.	Weed (67)
Progressive-ratio (PR) schedule	The number of lever presses required for food reinforcement progressively increased within a session.	Weed (67)
Repeated Acquisition	5-step sequence of 3 key choices (i.e. left, center, right, right, center) with one new sequence learned each day (learning) and one sequence that was the same each day (performance). Every fourth correct sequence was reinforced with food pellets.	Winsauer (132)

lack of relation between elevated Quin and cognitive impairment. In their 1994 review, Rausch and colleagues discussed similar findings with glial fibrillary acidic protein (GFAP; the marker for astrocytosis/astrogliosis mentioned above) and somatostatin (85). For each marker there was a strong association with motor impairment but not with cognitive impairment. This dissociation is consistent with at least two hypotheses regarding the mechanisms of motor and cognitive impairments in NeuroAIDS: 1) that there are different mechanisms for the cognitive and motor impairments or, 2) that the cognitive and motor impairments result from the same mechanism with the cognitive impairments representing a more advanced stage of the same process. At this time the mechanisms of cognitive or motor impairments remain unclear.

4. Marcario, (1999) described an extensive analysis of reaction time (RT) performance of rhesus monkeys infected with SIVmac –R71/17E (93). Two RT paradigms were employed in chair-restrained monkeys:

simple and choice. Both required release, on cue, of one hand from a switch plate to touch a target. The choice RT task, however, was complicated by the subject having to hold two switch plates, releasing either right or left hand depending on the color of the target. In the simple RT, one hand was restrained. Primary data collected for both RT tasks consisted of reaction time (time from target presentation to release of switch plate) and movement time (time from release of switch plate to touch of the target).

In 8 of the 9 monkeys tested, RT performance was impaired on at least one measure for the mean of the last 10 RT sessions prior to euthanasia relative to 10 pre-infection baseline sessions. Reaction times in the simple RT paradigm were slowed in more monkeys (5 of 9) than in the choice RT paradigm (3 of 9). In addition, movement times were slowed in more monkeys in the choice RT paradigm (6 of 9) than in the simple RT paradigm (4 of 9). Impairments in simple or choice RT performance varied somewhat independently, with not all monkeys impaired on simple RT also being impaired on choice RT, and vice versa.

Despite the similarity of the two RT paradigms, the overall motor requirements to respond to the screen did differ (i.e., in the choice RT paradigm the opposite hand had to continue to press on the switch plate while the monkey touched the screen), and this slight difference may be related to the different sensitivities of the two paradigms. This last point illustrates how very subtle differences in behavioral paradigms (opposite hand restrained in the simple RT paradigm versus opposite hand maintaining a press in the choice RT paradigm) may lead to differences in sensitivity of the tests, even within the same animals. Alternately, the increasing cognitive load (i.e. processing which stimulus signaled release of which hand in the choice RT task) may have affected sensitivity of the performance to SIV infection.

5. Marcario, (1999) provided a supplement to the analysis of fine motor control using the rotating turntable test (92) in the same cohort of monkeys from the previous paper (93, 94). Overall, 6 of 9 SIV infected monkeys showed impaired motor performance on this task, and for 5 of the 6 impaired monkeys the motor impairment preceded onset of clinical neurological signs. Interestingly, the 5 monkeys where motor impairment came before clinical neurological impairment all had a rapid course of disease progression (i.e., within 4 months following infection).

An observational study of home cage behaviors was also used in this cohort. Eighteen behaviors were scored from 1 hr per week videotaping sessions. Behaviors scored included lying down, sitting, walking around the cage, and scratching. Two of the 9 SIV infected monkeys showed statistically significant changes in home cage behaviors; however, these changes typically occurred weeks after the changes in RT or motor control. The contribution of general malaise, lack of interest in food or other “sickness behaviors” to behavioral changes seen following SIV infection is an important consideration in these studies. The observational analysis complemented the behavioral performance measures by providing evidence that the monkeys were not overtly sick during the time of RT or turntable performance changes. Overall, these results highlight the difference in sensitivity between operant and observational techniques (93).

6. Based on the fact that HIV and SIV are thought to induce neuropathology by indirect means including the release of toxic products from microglia within the CNS, Berman, (1999) attempted to correlate markers of microglial activation with clinical, behavioral and neurophysiological markers indicating the progression of simian AIDS (95). They found that the expression of class two major histocompatibility antigens (MHCII) on microglial cell surfaces to be associated with the progression of neurobehavioral impairment, increased latency of evoked potentials and the development of clinical signs of simian AIDS (95, 96).

7. Studies conducted at The Scripps Research Institute (TSRI) took the behavioral approach of Murray, (1992) a step further using additional behavioral tasks with well-studied neural substrates (92). A computerized behavioral battery based upon human neuropsychological tests was developed to assess cognitive behaviors of non-human primates (97, 98).

Neuropsychological tests have traditionally relied on human-specific responses, usually employing paper and pencil. Tests have been developed that use minimal verbal instruction and record responses with touch-sensitive computer monitors. The CANTAB battery (CAmbridge Neuropsychological Test Automated Batteries or CANTAB; Lafayette Instruments, Lafayette, IN) is a group of computerized tests developed utilizing advances in understanding of the neural substrates of cognitive functions gained from animal psychology, such as delayed matching to sample tests, and tests of spatial memory. Other battery tests are computerized analogs of standard human neuropsychological tests. Over the past decade, numerous human populations have been evaluated with this battery including healthy controls, children, elderly, neurosurgical patients, and populations with diseases such as Alzheimer's, Huntington's, Parkinson's, multiple systems atrophy and AIDS. Brain imaging studies have contributed to the identification of brain areas involved in the performance of specific tasks, and pharmacological studies have investigated the neurotransmitter systems influencing performance.

The non-verbal nature of the CANTAB tests has facilitated their use in non-human primates. Individual tests from the battery have been used to study the behavioral effects of brain lesions and toxin administration in marmosets (99-102). Pharmacological investigations using rhesus monkeys have documented how several neurotransmitter systems differentially affect performance on the CANTAB battery (81, 103-106).

The goal of using the CANTAB battery in rhesus monkeys is the same goal sought by Murray, (1992) and the same goal as using CANTAB in human populations: to

use performance profiles from the battery to infer functional impairment of brain regions (92). As a monkey's performance on a given task can decline for a number of reasons (107), the use of a number of tasks increases the validity of both the neuropsychological evaluation of a given subject and of the comparative neuropsychology between species.

The test battery used to study the effects of SIV on cognitive behaviors in rhesus monkeys included six tests for 1) memory, using the self-ordered spatial search and 2) the delayed non-matching to sample task; 3) attention and learning, using the intra-dimensional / extra-dimensional shift task (ID/ED); 4) fine motor performance with the bimanual motor task; 5) reaction time; and 6) the reinforcing efficacy of food reward using a progressive-ratio schedule. Methods for most of these tasks are described in detail in Weed, (1999) (98). ID/ED methods are described in Weed and Gold, (2001) (110). Data summarized here includes data published in several papers (67, 108-110).

The self-ordered spatial search (SOSS) task is an analog of the radial arm maze used to assess spatial working memory in rodents. Performance of other spatial working memory tests has been impaired by lesions or dysfunction of the frontal cortex (111-113) as has performance on similar SOSS tasks (97) in both marmosets (99) or man (114, 115). Additionally, both asymptomatic and symptomatic HIV seropositive patients exhibited increased errors in the SOSS task relative to HIV seronegative controls (65).

The intra-dimensional / extra-dimensional shift task is a computerized analog of the Wisconsin card sort task used to test category abstraction in humans (97, 116). Lesions or dysfunction of the frontal cortex have been shown to impair performance on this attentional set-shifting task in both marmosets (117) and man (118). Both asymptomatic and symptomatic HIV seropositive patients have demonstrated increased errors on the ID/ED task relative to HIV seronegative controls (65).

DMS, (delayed matching to sample), or delayed non-matching to sample (DNMS) tasks have been used extensively in the study of memory, and studies of neuroanatomical lesions in monkeys strongly implicate temporal cortical involvement of this task (119). In human patients, temporal excisions, but not frontal excisions, produce impairments on DMS (120). However, lesions in some areas within the frontal cortex can impair performance of delayed matching or non-matching tasks (121-124). Combined with tasks more selectively sensitive to frontal cortical dysfunction, such as the SOSS or ID/ED tasks, DNMS performance can serve as an indicator of temporal cortical function.

The bimanual motor skills (BMS) task involved a modification of the tasks used by Brinkman (1981) and Mark and Sperry (1968), in which monkeys must coordinate both hands to retrieve raisins from a holeboard (125-6). Another test of motor control was the choice reaction time (RT) task. In the CANTAB choice RT task, 5 circles appear on the computer monitor. Depressing a lever and holding it down produces a stimulus flash in one circle. Pressing that circle is reinforced and ends the trial. This RT paradigm has been shown to be sensitive to the effects of dopamine receptor antagonists in rhesus monkeys (81).

A progressive-ratio (PR) schedule of reinforcement, wherein response requirements are progressively increased within a session, was included in the rhesus test battery. PR schedules have been used to measure the reinforcing effects of a variety of reinforcers including food, drugs, and electrical brain stimulation (127-129). Performance under the PR schedule provided a control for changes in motivation such as changes in reinforcer efficacy of the food reinforcer, and in the ability to perform the operant required for most battery tasks (i.e., touching the monitor). A monkey's performance was determined to be impaired when it was outside the 95% confidence limits of the performance from the month prior to infection for that monkey.

Weed, (2004) summarized the majority of the behavioral data obtained in SIV studies using the CANTAB battery (67). Rhesus monkeys were infected with SIVmac230 or SIVmac182 (derived from SIVmac251). Both types of SIV proved to be equally neurovirulent and caused similar behavioral impairments; therefore, behavioral data was pooled for analysis. Following infection, cognitive and behavioral impairment was consistently demonstrated for tests of spatial working memory (measured by SOSS), psychomotor speed (measured by RT), motivation (measured by PR), and fine motor control (measured by BMS). For SOSS, seven of nine monkeys showed impairment on speed of response while five of nine showed a reduction in accuracy. On the RT task, release latency was impaired for two of six monkeys and movement time increased for four. Six of ten monkeys trained on the PR task showed a decline in the number of reinforcers acquired at some time during the course of their infection. BMS performance declined significantly in seven of ten monkeys. Impairment on set-shifting tasks (ID/ED) and recognition memory (DNMS) was less consistent. Three of seven monkeys exhibited increased errors on the ID/ED shift (110). Three of six monkeys showed a decline in accuracy with DNMS while one showed increased response latency.

In general, results using the CANTAB battery demonstrated that SIV-infected rhesus monkeys were impaired in a fashion consistent with impairments demonstrated by humans infected with HIV performing similar tests. As with other studies of SIV-infected macaques, a high percentage of the monkeys were impaired on tests thought to be dependent on function in the frontal cortical and striatal systems. Performance was affected in at least 70% of the animals on tests of spatial working memory, psychomotor speed, and fine motor control.

8. Weed, (2003) analyzed the behavioral component of the effects of an accelerated model of SIV (138). Dual inoculation with both a molecularly cloned,

neurovirulent virus, SIV/17E-Fr and an immunosuppressive virus swarm, SIV/DeltaB670, achieves a greatly compressed time to the development of CNS pathology with over ninety percent of pigtail macaques developing SIV encephalitis within three months (130, 131). The aim of this study was to correlate cellular and viral measures with behavioral impairment following SIV infection. Two measures of motor control, simple reaction time (SRT) and BMS were chosen along with assessment of general motor activity because of the above-mentioned investigations that have identified motor function as the earliest and predominant sign of neurobehavioral dysfunction in SIV infection.

Twelve pigtail macaques were divided into two cohorts. Scheduling one for euthanasia two months post-innoculation (PI) and one three months PI permitted examination of the infected animals at different stages of disease progression. General motor activity was recorded with a collar attached to the neck of each monkey and movement was recorded on a minute by minute basis. All monkeys were trained on the SRT task. Briefly, for SRT, monkeys pressed and held a lever prior to presentation of a visual release signal. Quickly releasing the lever resulted in the delivery of a food pellet. Data collected included percent correct lever releases (accuracy), median reaction time, percent false alarms and total trials completed per session. Finally, monkeys comprising the cohort scheduled for euthanasia three months PI were also trained on the BMS task (see table 1).

Following inoculation with the SIV/17E-Fr and SIV/DeltaB670 mixture, general activity decreased in all animals. In accord with other studies, BMS performance was impaired in five of six monkeys. SRT performance was also impaired as group mean response latency increased following infection; however omissions and number of trials completed showed no significant change. Individually, half of the monkeys in each cohort showed impaired RT performance. These results parallel other SIV models and confirm the validity of the accelerated SIV model.

Markers of axonal damage (accumulation of ß-amyloid precursor protein in the corpus callosum) and increased microglial activation and macrophage infiltration (levels of CD68 and Ham56 immunostaining) were significantly correlated with impaired fine motor control on the BMS task. These results suggest a relationship between behavioral impairment and axonal damage following infection with SIV. The immediate cause of the axonal damage was not apparent, but given the correlation with immune activation, the damage may have resulted from neuroimmune responses including microglial and macrophage activation. However, it was not clear why the markers of axonal damage were associated with only one of the three motor behaviors measured in this study. Axonal damage may be a morphologic manifestation of neuronal dysfunction underlying development of behavioral impairment in NeuroAIDS.

9. An elevated level of alcohol abuse among the HIV-infected population compared with the general population is of great concern to health authorities. Alcohol abuse is associated with neuronal damage and a decline in learning ability that may interact with the MCMD and HAD that are frequent consequences of HIV infection. As both agents induce neuropathology, the potential for aggravated CNS damage when they are combined has serious public health significance.

Winsauer, (2002) paired chronic ethanol exposure and SIV infection (132). Male rhesus monkeys were divided into four groups for SIV inoculation and ethanol administration, namely, SIV-/EtOH-, SIV+/EtOH-, SIV-/EtOH+ and SIV+/EtOH+. Effects on learning ability were monitored by training the monkeys in a repeated acquisition task that required the establishment of a new sequence of responses in each session. Because a decline in psychomotor function could affect performance in this task, a second task that required monkeys to perform an established response sequence followed each acquisition task session. This way, separate effects on learning ability and psychomotor function could be distinguished. Training continued until each monkey's behavior stabilized, then data comprising response and error rates were collected from testing under baseline conditions followed by testing under the ethanol administration regime and ultimately after introducing SIV. To separate the effects of acute ethanol intoxication from chronic damage, ethanol administration was carried out weekly from Thursday to Sunday and behavioral testing took place on the other three days of the week.

Overall, chronic alcohol administration had no main effect on the response rate or accuracy outside days when ethanol was administered, however there was an unequivocal effect on learning ability in SIV-infected monkeys vs. non-infected monkeys when they performed the task after ethanol administration. The authors proposed that ethanol exposure compounded CNS dysfunction following SIV infection, but in a fashion that was not evident during routine performance. This suggests that under routine performance of the repeated acquisition task the monkeys could compensate for the increased CNS dysfunction caused by ethanol in addition to SIV infection. However, the dysfunction was revealed in the SIV+/EtOH+ monkeys by their increased sensitivity to ethanol, relative to SIV+/EtOH- monkeys. Therefore combined SIV and ethanol exposure produced impairments not under routine conditions, but did produce impairments when SIV+/EtOH+ monkeys were further taxed by ethanol exposure.

Subclinical CNS impairments have been reported with other drugs that produce CNS changes . These subclinical impairments are typically only revealed when the CNS is challenged pharmacologically. One example is the dopamine or serotonin neurotoxicity produced by drugs of abuse such as methamphetamine (133, 134) and MDMA ('ecstasy') (135, 136). Often, the functional effects of such lesions are only revealed when dose-response determinations of challenge drugs reveal increased sensitivity to performance decrements. The Winsauer study supports the utility of pharmacological probes

targeted at specific neural substrates to increase the sensitivity of behavioral techniques to CNS dysfunction (132). Further pharmacological study of CNS impairments following SIV infection may be useful to elucidate impairments within specific neurotransmitter systems in AIDS.

3.4. Ancillary Behavioral/Physiologic Techniques

1. In addition to the operant techniques reported above the TSRI group have incorporated a number of techniques for studying SIV-infected macaques, including radio-telemetry measurements of gross motor activity, body temperature and EEG readings, as well as complex behavioral analyses (137). Following infection with SIV mac182, gross motor activity decreased relative to the pre-infection baseline in the second and third months PI, to approximately 80% and 40% of baseline, respectively (137). This finding has been replicated in SIV-infected pig-tailed macaques wearing collar activity monitors (138). The decrease in spontaneous motor activity following SIV infection appears to be an early and reliable indicator of SIV disease progression when continuously measured. Locomotor activity measured by observational methods was not reported to differ following SIV infection (92). Although gross motor activity is a reliable marker of disease progression, the neuroanatomic substrates of gross motor activity are not as well defined as those of the instrumental behaviors described above. Gross motor activity is modulated by various systems within and outside the CNS and is thus a useful, albeit global, behavioral measure that complements the more discretely-regulated behavioral measures in the behavioral batteries.

2. Fox, (2000) infected rhesus monkeys with SIVmac182 and monitored brainstem evoked potentials, gross motor activity and body temperature (108). Throughout the third month PI, at a time of productive infection but prior to onset of clinical AIDS symptoms, an antiviral drug (9-(2-phosphonylmethoxypropyl)-adenine (PMPA; a reverse transcriptase inhibitor)) was administered. PMPA treatment lowered viral load, normalized evoked potentials and body temperature, but failed to alter the progressive decline in motor activity. In the fourth month PI the PMPA treatment was discontinued and viral load, body temperature and evoked potentials returned to previous levels, suggesting a return to the typical SIV disease progression. It is not clear why the gross motor activity did not respond to the PMPA treatment when nearly all other measures showed a robust positive effect.

3.5. Internal Checks and Balances, a Central Component of Study Design

Although there is now considerable information on the relationship between functional lesions and their neural substrates, it must be remembered that each behavioral task entails the concerted action of multiple neural systems. For example, all tasks incorporate a motor component which, in turn, relies on not one, but many complementary central and peripheral neural mechanisms for completion. Hence motor dysfunction becomes a potential confounding variable in assessing changes in other CNS capabilities. Clearly, identifying the site of neuropathology is not a simple matter of matching a decline in individual task performance with a specific region of the CNS.

Murray, (1992) responded to the challenge by selecting three tasks with overlapping demands (92). The DMS and recency memory tasks (table 1) are good examples for illustrative purposes. They have essentially indistinguishable motor components but different cognitive loads. While both require a monkey to distinguish between visual stimuli, for the recency memory task the same stimuli are used repeatedly with each stimulus arbitrarily being assigned as “correct”. This process engenders a greater degree of cognitive difficulty because of “interference” from earlier trials.

The CANTAB battery offers a comprehensive array of internal controls built into the tests to aid in the interpretation of performance decrements. A monkey’s performance on a given task can decline for a number of reasons, including neuronal dysfunction, loss of stimulus control, or rule comprehension. CANTAB tasks include trials with lesser memory loads that control for changes in stimulus control or rule comprehension. Failure on such “easy” trials indicates the animal may have forgotten the “rules” of the task. For instance, on the SOSS task of spatial working memory, SIV induced selective impairments in the “harder” trials involving 4 or 5 boxes per trial, while sparing easy trials involving 2 boxes. Because the accuracy on the 2-box trials didn’t change it is clear that the monkeys are physically capable of performing the task and have not forgotten the procedure. These controls allow a clear determination of impairment in spatial working memory following SIV infection. Controls such as these help ensure that any behavioral deficits are more likely due to CNS compromise than nonspecific factors such as “sickness behavior” or non-CNS clinical symptoms of AIDS.

3.6. "Sickness Behavior" a Potential Confound of Disease Studies

A potential confound in the study of viral effects on behavior is the contribution of general malaise or "sickness behavior" to measured behavioral performance. For example, 7-14 days following infection with HIV or SIV an initial viremia produces "flu-like" symptoms. Additionally, opportunistic infections in immuno-compromised animals may adversely affect behavioral performance through a non-SIV mechanism. Both of these conditions can be easily controlled for. In the former case, SIV viremia is transient, and data collected during the initial 2-3 weeks post infection is typically analyzed separately from that collected as SIV disease progresses. In the latter case, veterinary diagnosis of an opportunistic infection may exclude that animal's data from analysis. SIV studies normally include daily veterinary monitoring of the animals. Subjects with opportunistic infections or gross neurologic dysfunction are excluded from analysis, eliminating potential confounds. Additionally, Murray, (1992) and Marcario, (1999) videotaped home cage behavior as a measure to control for sickness behavior. If

home cage behavior changed in a manner indicating "sickness behavior", these observational data are considered along with performance changes (92-94). In fact, significant sickness behavior was seen mostly in very late stages of disease and usually after changes in task performance had already occurred. Interestingly, spontaneous activity can decrease to very low levels (e.g. 20-30% of baseline) while performance in behavioral tasks remains largely unchanged (109, 138).

Measures of motivation to work for food are often affected during the initial viremic period of SIV infection. For example, Weed, (2003) reported a transient reduction in both the number of RT trials completed and in gross motor activity two weeks PI (during the initial viremia), but there were no changes in RT release latency during the acute viremia (138). Release latency was impaired only in the later stages of the disease progression (138). Testing batteries with larger cognitive loads, such as the CANTAB, typically confirm motivational changes in the initial viremia (e.g. reduced number of trials performed without systematic decline in accuracy measures on spatial working memory tasks; Weed, unpublished results). Therefore there are qualitative differences between behavioral changes resulting from sickness behavior and the specific neuropathological effects of the SIV. These differences are an important control to help distinguish general sickness behavior from specific cognitive impairments in NeuroAIDS.

4. DISCUSSION

The studies described above clearly demonstrate that SIV infection in macaques produces cognitive and motor impairments similar to HIV infection in humans. SIV disease in macaques, like HIV disease in humans, can cause dysfunction in both cognitive and motor behaviors, with behaviors mediated by subcortical and frontal cortical areas at higher risk of impairment. In light of the percentage of human AIDS patients that develop minor cognitive/motor disorder or ADC (up to half have some complaint), the behavioral tests employed to date in the SIV model have proven quite successful in that the SIV/macaque model identifies impaired cognitive or motor function in the vast majority of SIV-infected macaques. These studies represent the first stages of research in this area and have resulted in production of efficient models and characterization of the cognitive impairment produced by simian AIDS.

The exquisite sensitivity of behavioral function to CNS insults, makes behavioral assessment a vital part of NeuroAIDS research. Animals that appear normal upon observation may have latent cognitive or motor impairments that are only apparent when the monkeys execute challenging cognitive tasks or motor tasks requiring unusual speed and dexterity. Operant behavioral techniques permit precise adjustment of motor and cognitive load to expose impairment otherwise concealed from observation. Behavioral analysis can be tailored to the needs of different study objectives to include simple but efficient indicators of disease progression such as gross motor activity or complex assessments of cognitive function.

The addition of pharmacological manipulations to behavioral assessments is a relatively unexplored but potentially rewarding avenue in the study of NeuroAIDS. Studies from CNS lesions resulting from neurotoxins or drugs of abuse have repeatedly demonstrated that CNS lesions do not have to produce overt changes to compromise the organism (133-136). Subclinical lesions that do not cause behavioral changes during routine performance can be revealed by challenge with pharmacological agents. For instance, dopamine depletions caused by methamphetamine exposure did not impair baseline motor control. However, subsequent pharmacological probes revealed changes in sensitivity to dopaminergic drugs (134). Winsauer, (2002) applied this technique to reveal differences in sensitivity to ethanol between SIV infected and SIV infected/ethanol exposed monkeys (132). The results show that despite no change in baseline performance, monkeys exposed to ethanol and SIV were more sensitive to ethanol than ethanol naïve monkeys. The Winsauer study is the only published report of pharmacological challenge of behavioral performance using the SIV/macaque model thus far (132).

Behavioral assessments of humans and monkeys with NeuroAIDS have contributed to the understanding of the mechanisms leading to cognitive and motor impairment. HIV does not productively infect neurons, and yet AIDS produces several different types of CNS pathology: including focal lesions in diverse brain regions (i.e. perivascular cuffs of mononuclear cells, mulitifocal glial nodules, multinucleated giant cells, etc. (139, 140)) and damage within specific brain regions (i.e. changes in frontal cortical dendritic morphology (141, 142), and degeneration of dopaminergic neurons in the substantia nigra (143-146)). The characterization of an overall pattern to NeuroAIDS, that of subcortical and fronto-striatal dysfunction, is an important contribution because it limits which CNS changes are likely to be the ones involved in functional impairment. For instance, random focal lesions are less likely to explain the frontal-striatal pattern of dysfunction because such lesions occur widely across the brain and would impair performance on a wide variety of neuropsychological tests. However, the degeneration of dopaminergic neurons would be expected to have consequences for functioning in both the frontal cortex and striatum.

Dopamine neurotoxicity is a compelling mechanism because of dopamine’s involvement in both movement and memory (147-150). Dopamine cell bodies that are located in the substantia nigra project to striatal and frontal cortical areas and contribute importantly to the frontal-striatal circuitry. Patients with HAD have been reported to have decreased dopamine transporters in the striatum, suggesting loss of presynaptic dopamine neurons (151). Similarly, decreases in striatal dopamine and components of dopaminergic signal transduction mechanism occur in SIV-infected monkeys (152). Reports of dopamine deficits in the postmortem striatum of AIDS

patients (145) and declines in cerebrospinal fluid dopamine levels or metabolite levels in AIDS patients and SIV-infected monkeys (153, 154) also suggest that both HIV and SIV infection lead to impaired CNS dopaminergic function.

Functional dopaminergic damage is also suggested by the increased sensitivity to motor effects of dopamine receptor antagonists reported in AIDS patients (155-157). Striatal dopaminergic systems have been shown to be important to RT performance (77-81), and RT performance is typically impaired in NeuroAIDS. Dopaminergic involvement in NeuroAIDS is further supported by the ability of levodopa or methylphenidate treatment to ameliorate symptoms of MCMD (158, 159). The results of these studies are consistent with CNS dopaminergic dysfunction contributing to many of the cognitive and motor effects of AIDS.

At this stage in the study of NeuroAIDS, several research areas are apparent. Foremost may be the identification of CNS injuries responsible for AIDS's cognitive impairments. Small steps in this direction have already been taken with correlations between behavioral impairment and levels of Quin or markers of neuronal damage (85, 91, 138). One limitation of this area is the use of ex vivo measures of pathology that require euthanasia prior to evaluation. Developing techniques that allowed for longitudinal evaluation of CNS pathology and behavior changes would greatly facilitate this quest. For instance, the measurement of cerebrospinal fluid allowed for demonstration of increases in Quin immediately prior to performance decrements (91). Similar studies correlating markers for dopamine function with behavioral changes could address the proposed role of dopamine dysfunction in motor impairment more directly. Brain imaging studies in SIV-infected macaques have demonstrated alterations in metabolism in the frontal cortex and basal ganglia, areas with significant dopaminergic innervation. Similar imaging studies with behaviorally trained monkeys would be of particular interest to identify the brain changes driving cognitive impairment. Additionally, development of behavioral tests that are sensitive to impairment earlier in the disease progression would be helpful. Current behavioral tests are typically impaired late in the disease progression when the CNS is often compromised by multiple pathologies. Behavioral tests affected earlier in the disease progression would allow ex vivo researchers to focus on how the CNS of impaired animals differed when there are fewer kinds of pathology.

To date there has been very little direct testing of mechanistic hypotheses in this area. For instance, the involvement of dopaminergic dysfunction in NeuroAIDS is a directly testable hypothesis in the SIV/macaque model. If dopaminergic dysfunction is responsible for cognitive and motor impairment in NeuroAIDS then agents that decrease dopamine (DA) tone (e.g. DA antagonists or DA depleting-treatments) should further impair performance. There are anecdotal reports of several of these in AIDS patients (e.g. amelioration of MCMD with methylphenidate (158) or increased sensitivity to neuroleptics in psychotic AIDS patients (155-157)) but there have been no tests of dopaminergic manipulations on behavioral assays in the SIV/macaque model.

The SIV/macaque model could be utilized for pharmacological studies; however there are risks due to unexpected actions on either the host immunology or viral activity. For instance, the hypothesis of dopaminergic dysfunction suggests that drugs which increase dopaminergic tone (e.g. direct or indirect DA agonists, DA precursors) should ameliorate cognitive/motor impairment in AIDS. This approach was recently tried with the administration of the DA precurser l-DOPA and a monoamine oxidase inhibitor selegiline. Both compounds enhance dopamine availability in CNS, but both compounds increased CNS viral replication and CNS pathology (160, 161). This surprising finding underscores the complexity of the SIV/macaque model and the difficulty in controlling for multiple consequences of experimental treatments. The neuropharmacology of l-DOPA and selegiline are well known and would not cause these effects in uninfected monkeys; however, the immunological effects of these drugs has not been well studied. The mechanism behind the increased replication or pathology is currently not clear.

Another area for future study lies in the response behavioral/cognitive impairment to anti-retroviral treatment. Few studies of anti-retroviral treatments in the SIV/macaque model have included behavioral assessments. One of these reported normalization of several indices of disease progression (e.g. reduced viral load, normalized evoked potentials) but not the most general and reliable behavioral index of disease progression – general motor activity (108). Which behavioral impairments are responsive to antiretroviral treatment is of interest because antiretroviral therapy is ineffective in a significant percentage of HAD patients (37). Manipulations of dose and duration of antiretroviral treatment would help elucidate the responsiveness of certain behaviors to treatment and help elucidate the CNS mechanisms involved. These studies would only be possible using the SIV/macaque model of AIDS.

Finally, the SIV/macaque model is ideal for the study of the interaction between drugs of abuse and AIDS. In the U.S. roughly one third of new HIV infections are related to injection drug use (12, 162, 163). In Russia and the Ukraine that number is closer to 80% (12, 162). At least two studies have shown a higher HIV seroprevalence in cocaine addicts over those using other drugs (164, 165). Additionally, as many as 41% of AIDS patients meet criteria for alcoholism (166). Furthermore, alcohol abuse can be a major risk factor for contracting HIV/AIDS (167-170). The active ingredient in marijuana, THC, has been proposed to increase appetite in AIDS patients (171, 172). The SIV/macaque model allows for control of drug exposure, medical care, nutritional status, viral inoculum and other factors that simply cannot be controlled in human studies. Because of the large number of people exposed to both drug abuse and HIV, understanding the impact of drugs abuse on the progression of HIV/AIDS, is an important focus for researchers in this field.

In summary, the SIV/macaque model of AIDS has proven to be a valuable research tool for understanding the etiology and pathogenesis of AIDS, including mechanisms of CNS pathology. The similarity of cognitive and motor impairments following SIV infection to neuropsychological impairments in HIV/AIDS confirms the validity of the SIV/macaque model and suggests that pathogenic mechanisms elucidated from the SIV/macaque model will be important to HIV/AIDS as well. Having established the nature of cognitive/motor impairments following SIV infection in macaques, researchers in this area will be able to expand research into mechanisms causing the impairments and the impact of other risks, such as drugs of abuse, on progression of NeuroAIDS.

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