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Review

Behavioral and neurophysiological hallmarks of simian immunodeficiency virus infection in macaque monkeys

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Macaque monkeys infected with various neurovirulent forms of simian immunodeficiency virus (SIV) represent highly effective models, not only of systemic acquired immunodeficiency virus (AIDS), but also neuroAIDS. Behavioral studies with this model have clearly established that SIV-infected monkeys show both cognitive and motor impairments resembling those that have been reported in human immunodeficiency virus (HIV)-infected humans. This paper combines data from a number of behavioral studies in SIV-infected macaque monkeys to obtain an overall estimate of the frequency of impairments in various motor and cognitive domains. The results were then compared to similar data from studies of HIV-infected humans. Whereas cognitive functions are most commonly impaired in HIV-infected humans, motor function is the domain most commonly impaired in SIV-infected monkeys. Electrophysiological studies in SIV-infected macaques have revealed deficits in motor-, somatosensory-, visual-, and auditory-evoked potentials that also resemble abnormalities in human HIV infection. Abnormalities in motor-evoked potentials were among the most common evoked potential deficits observed. Although differences in behavioral profiles of human HIV disease and SIV disease in monkeys exist, the results, nevertheless, provide strong validation for the use of macaque models for translational studies of the virology, immunology, pathophysiology, and treatment of neuroAIDS. *Journal of NeuroVirology* (2008) **14,** 301–308.

Keywords: AIDS; behavior; evoked potential; macaque; SIV

Introduction

It is essential in developing animal models of human disease to determine the extent to which the model replicates the disease's primary features. The basic virological and immunological aspects of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) in humans have been extensively studied for many years and are now well known (Fauci *et al,* 1996; Gonzalez-Scarano and Martin-Garcia, 2005). The neurobehavioral aspects of human HIV infection were slower to be recognized but are now also well documented (Grant *et al*, 1995), although progress continues in understanding the full spectrum of HIV-related neurobehavioral impairments in humans and how these conditions should be classified for clinical purposes (Grant, 2008). At the same time that a major effort has been devoted to understanding the virological and immunological basis of human HIV disease, a parallel effort has been underway to develop appropriate animal models of the disease. One of the leaders in this effort was Opendra (Bill) Narayan, whose studies on the pathogenesis of lentiviral infections and the development of new viral models in primates have contributed enormously to progress in this field. One particular area of emphasis was the development of a macaque

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model that would replicate the neurological aspects of human AIDS. This effort succeeded with certain strains of macrophage-tropic virus (SIVmacR71/E17), derived from passaged SIVmac239, and with properties similar to SIVmac251. Narayan and colleagues (Narayan *et al*, 1997, 1998) showed that this viral "swarm," when given as a bone marrow injection or intravenously, produced a relatively rapid onset of acute symptoms and within 2 weeks of inoculation, productive virus replication was underway in the brain. Encephalitis develops in most of these animals along with the classic hallmarks of HIV-related neuropathology, namely, microglia nodules and multinucleate giant cells.

Although this work represented a critical step in establishing an animal model of neuroAIDS, an important question remained. Do animals with brain infection demonstrate actual neural dysfunction evident in the form of neurobehavioral impairments and/or neurophysiological abnormalities? Of course, we now know the answer is yes. But reports showing that AIDS-related neuropathology does not always correlate with neurobehavioral impairments further emphasized the need for actual behavioral testing in the macaque model (Masliah *et al*, 1992). Although much effort has been devoted to understanding the virological and immunological aspects of SIV disease, behavioral and neurophysiological studies have been relatively limited despite their importance. In part, this is due to the difficulty in undertaking such studies, particularly behavior, on relatively large groups of animals. Nevertheless, a compelling literature on behavioral impairments in SIV disease now exists, and the goal of this review will be to summarize this work in relation to the impairments observed in HIV-infected humans. An alternative approach to testing the functional integrity of brain systems is multimodal evoked potentials. A brief review of these studies will also be provided.

Domains of behavioral impairment in HIV-infected humans

Given that one of the goals in developing an animal model of neuroAIDS is to replicate the behavioral impairments of HIV disease in humans, it is first necessary to understand the nature and extent of these impairments. HIV-related neurobehavioral impairments in humans have been extensively studied (Ances and Ellis, 2007; Antinori *et al*, 2007; Arendt *et al*, 1990, 1994; Bottiggi *et al*, 2007; Dunlop *et al*, 1992, 1993; Grant *et al*, 1995; Grant, 2008; Hardy and Hinkin, 2002; Heaton *et al*, 1995; Karlesen *et al*, 1992; Koralnik *et al*, 1990; Perdices and Cooper, 1989; Sacktor *et al*, 2007). The American Academy of Neurology Working Group in 1991 identified two syndromes of neurobehavioral impairment associated with HIV on the basis of the severity of symptoms and impact on ability for independent living. The more serious condition, AIDS-related dementia complex, consisted of severe cognitive, motor, and/or emotional and personality disturbances, whereas HIV-associated cognitive-motor disturbance involved milder impairments, with less impact on ability for independent living. A recent revision of this classification has been proposed (Antinori *et al*, 2007), which would create three syndromes, all of which are characterized by the presence of HIV-associated neurocognitive disturbance (HAND). These conditions include (1) asymptomatic neurocognitive impairment (ANI), (2) mild neurocognitive disorder (MND), and (3) HIV-associated dementia (HAD). Diagnosis relies heavily on neuropsychological testing but disruption of activities of daily living also constitutes an important criterion. In ANI there is no disruption of activities of daily living; MND is associated with mild disruption, whereas in HAD there is severe disruption of activities of daily living requiring some form of assistance. The incidence of HAD is generally estimated to be 20% to 30%. It is important to note that milder conditions do not typically progress to HAD (Heaton *et al*, 1995).

Grant (2008) recently reviewed the neurobehavioral deficits associated with HIV disease. Figure 1 summarizes the domains of impairment and their prevalence from a series of over 100 cases of HAND. First, it is noteworthy that the deficits are not confined to a particular domain but include a broad range of abilities. Specific subjects typically show only a subset of these impairments. The most common disturbances are in tests of attention, learning, verbal ability, memory, and motor abilities. The fewest disturbances occur in sensory domains and abstraction. HIV-associated dementia is considered a subcortical dementia where white matter and subcortical grey matter are preferentially damaged. Other diseases in this category include Huntington's disease, Parkinson's disease, and multiple sclerosis. In contrast, the so-called cortical dementias, such as Alzheimer's disease, are characterized by pathology focused in the cortical gray matter. The ease with which recent versus more distant events can be recalled is a defining characteristic of cortical versus subcortical dementias. A temporal gradient related to the recall of remote events exists in cortical dementias where the more distant the event, the greater the difficulty in recalling the event (Salmon and Filoteo, 2007). This gradient does not exist in subcortical dementias.

Characteristics of the SIV-infected macaque model of neuroAIDS

For practical reasons, efforts to develop a viable monkey model of neuroAIDS have focused on development of viruses that produce progression to end-stage disease rather quickly compared to the normal time

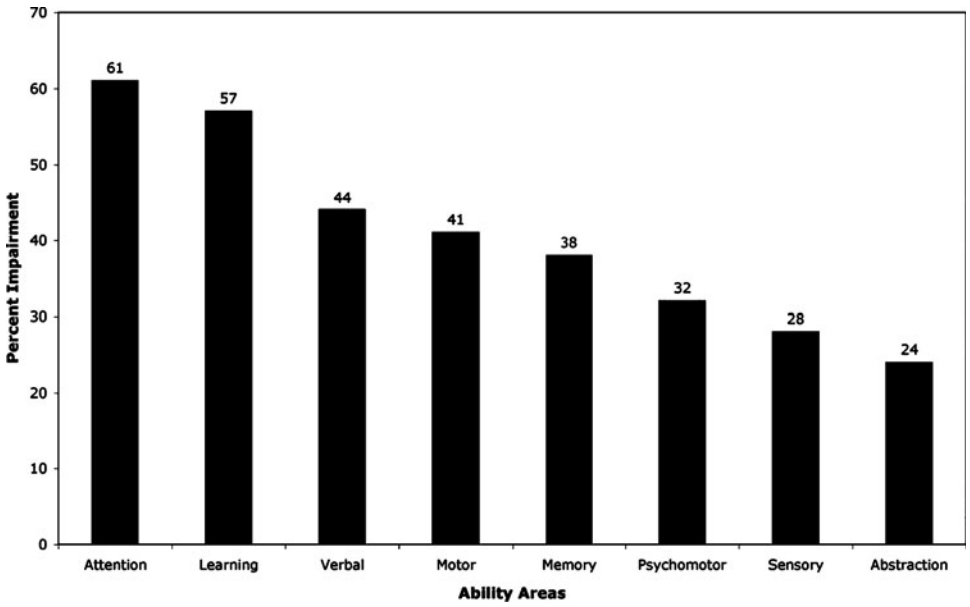

Figure 1 Prevalence of deficits in various motor and cognitive ability domains from a series of over 100 HIV-positive human subjects rated as being neuropsychologically impaired. Number above each column is the percent impaired (from Grant, 2008).

course of HIV disease in humans. Accordingly, the time from infection to end-stage in macaque models of AIDS is generally 3 months to 2 years (Narayan *et al*, 1997). As in human HIV disease, about 20% to 30% of SIV-infected macaques will develop neurological symptoms, although this is certainly viral strain dependent and requires macrophage-tropic viruses. Within 2 weeks of inoculation, SIV can be recovered from the central nervous system (CNS) (Narayan *et al*, 1997). The temporal course of viral proliferation is similar to that of HIV in humans but on a much-accelerated scale. An acute transient period of viral proliferation occurs over the first 2 to 3 week following inoculation followed by a sharp reduction as the monkey's immune system gains control over the virus. Over the next several months, viral levels in plasma and cerebrospinal fluid (CSF) tend to rise continuously culminating in simian AIDS and end-stage disease. Our work with SIVmac17E/R71 has shown that SIV-infected macaques progress to end-stage along two time courses—rapid and slow (Marcario *et al*, 1999a, 1999b; Raymond *et al*, 1998, 1999, 2000). Rapid progressors have high viral loads in the plasma and CNS, develop severe systemic and neurological disease, and reach end-stage disease within 3 to 5 months of inoculation. Slow progressors have relatively low plasma CNS viral loads and develop few if any neurological symptoms. However, most of the slow progressors do eventually progress to end-stage disease over a time course of 12 to 18 months, but the disease is dominated by systemic symptoms and opportunistic infections. Westmoreland *et al* (1998) also reported a high incidence of SIV encephalitis in monkeys with rapidly progressing disease (end stage within 200 days) compared with those with slowly progressing disease.

Although of practical benefit, rapid rates of progression limit the time frame available for study of a stable asymptomatic phase. However, recently Roberts *et al* (2006) reported on a cohort of four macaques infected with SIVmac182 and six control animals followed for a period of 92 to 114 weeks post inoculation. This period was prolonged and simulated the latent, asymptomatic phase of HIV infection in humans. These monkeys all had stable plasma viral loads and viral RNA was present in the brains of all four. Behavioral and evoked potential testing in the 6 months before termination revealed clear deficits in all four animals.

Domains of behavioral impairment in SIV-infected macaques

To what extent do the behavioral impairments in SIV-infected macaques match the domains of impairment observed in HIV disease in humans? In humans, three forms of HIV-associated neurocognitive disturbance can be distinguished as described above. The specific criteria obviously cannot be the same for monkeys, but is it possible to identify a condition of mild cognitive-motor impairment as well as more severe condition resembling frank dementia? Several studies have identified behavioral impairments in SIV-infected monkeys in advance of AIDS-related clinical signs (Table 1). The study of Roberts *et al* (2006) is particularly relevant in this respect because the authors were able to take advantage of a relatively long asymptomatic period (2 years) in four

Table 1 Summary of behavioral impairments in SIV-infected macaques derived from operantly conditioned motor and cognitive tasks

Study	Virus type	Behavioral task	Functional domain	No. of monkeys impaired	% Impaired
Murray *et al*, 1992	SIV/Delta B670	Delayed matching to sample	Visual recognition/recency memory[b]	1/8	13%
		Visual discrimination and learning	Learning	3/8	38%
		Rotating turn table	Fine motor control	7/8	88%
Marcario *et al*, 1999a, 1999b	SIVmac R71/17E[c]	Simple RT	Psychomotor speed	6/9	67%
		Choice RT	Psychomotor speed + decision making	3/9	33%
		Movement time[a]	Movement speed	7/9	78%
		Motor skill	Fine motor control	6/9	67%
		Self-ordered spatial search[g]	Working memory	6/9	67%
		Progressive ratio task	Motivation	6/9	67%
Weed *et al*, 2004[f]	SIVmac230[d], $n = 4$	Self-ordered spatial search	Working memory	5/9	56%
	SIVmac182[d], $n = 6$	Delayed nonmatching to sample	Visual recognition memory[b]	3/6	50%
		Intra/extradimensional task	Attention shifting	3/7	43%
		Choice reaction time	Choice reaction time	2/6	33%
		Movement time[a]	Movement speed	4/6	67%
		Bimanual motor skill	Fine motor control	7/10	70%
Weed *et al*, 2003[e]	SIV/17E-Fr + SIV/Delta 670	Simple RT	Psychomotor speed	6/12	50%
Gray *et al*, 2006[e]		Bimanual motor skill	Fine motor control	5/6	83%
		Object retrieval-detour test	Executive function	3/6	50%
Roberts *et al*, 2006	SIVmac182	Self-ordered spatial search	Working memory	2/4	50%
		Delayed nonmatching to sample	Visual recognition memory[b]	0/4	0%
		Reaction time[h]	Psychomotor speed	1/3	33%
		Movement time[a]	Movement speed	0/3	0%
		Bimanual motor skill	Fine motor control	4/4	100%

[a]From reaction time (RT) tasks; [b]"Other memory" in Figure 2; [c]Results from seven rapid and two slow progressors combined; [d]Derived from SIVmac251; [e]Same cohort of monkeys; [f]Includes monkeys from Table II of Weed and Gold, 2001; [g]From unpublished data; [h]Type of RT task not specified so omitted from Figure 2.

monkeys to show that behavioral deficits were also present in all four SIV-infected macaques during the final 6 months of this period. However, the latent period in SIV-infected macaques is often brief with precipitous progression to end-stage disease. It is possible that treatment with antiretroviral drugs could produce a higher incidence of more slowly developing CNS disease in monkeys, with characteristics more closely resembling mild neurocognitive disturbance in HIV disease. Nevertheless, we can conclude that two forms of CNS disease can be distinguished in macaques, one comparable to the asymptomatic phase of human disease, in which specific behavioral deficits can be demonstrated in the absence of clinical symptoms, and the second, more comparable to HIV dementia, in which multiple clinical symptoms are present, often including frank neurological conditions (e.g., tremor, ataxia) as the animal approaches end-stage disease.

What are the specific domains of impairment in the SIV monkey model and how do they compare with those observed in humans? Table 1 summarizes the results of existing studies where specific aspects of behavioral function in SIV-infected macaques were tested using motor and cognitive operant tasks. In Figure 2, the results from different studies in Table 1 were combined and the overall percent of impaired animals was calculated for different behavioral domains and plotted as a bar graph for direct comparison with impairments observed in humans (Figure 1). It is clear from Figure 2 that measures of motor function are the ones most commonly impaired in association with SIV infection. Seventy-eight percent of monkeys tested showed impairment on tests of fine motor control. A large percentage of animals (61%) also showed slowing in reaction time tasks (movement speed) and this may correlate with SIV-associated damage to the basal ganglia (Marcario *et al*, 2004). Of the cognitive tasks, working memory revealed deficits in the greatest number of monkeys (59%). Surprisingly, other tasks that rely on memory processing were least affected. Also, somewhat surprising was the fact that performance on choice reaction time tasks revealed deficits in fewer monkeys than the simple reaction time version of the same task. However, this may be attributable to the fact that the cognitive component of the task results in longer and more variable reaction times that may "hide" underlying changes in simple reaction time.

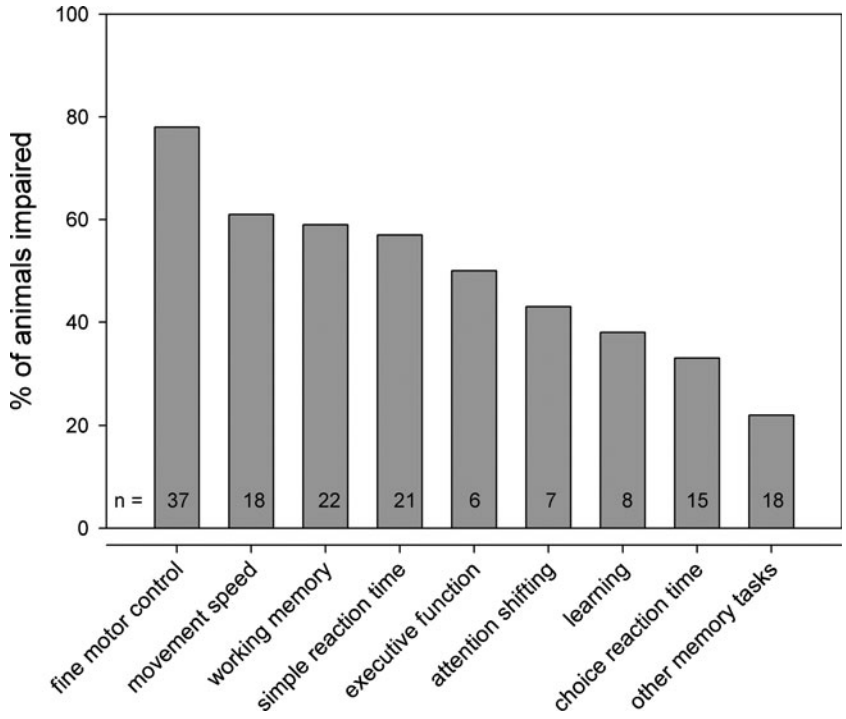

Figure 2 Prevalence of deficits in various motor and cognitive ability domains in SIV-infected macaque monkeys. Number at the bottom of each bar is the number of subjects studied. Data were derived by combining the results of numerous studies listed in Table 1.

Some additional points deserve mention. First, the onset of behavioral impairment preceded the onset of clinical disease by an average of 2.6 weeks in the studies by Marcario *et al* (1999a, 1999b). The onset of clinical disease was based on scoring of home cage behavior from lengthy periods of videotaping each week and also from the appearance of clinical signs, including weakness, tremor, ataxia, cyanosis, diarrhea, appetite loss, skin lesions, dermatitis, oral lesions, edema, ecchymosis, dyspahgia, gingivitis, epistaxis, tumors, and jaundice. Because the onset of behavioral impairments preceded the onset of clinical signs, it is highly unlikely that the behavioral deficits observed were a reflection of sickness behavior. The fact that monkeys showed deficits on some tasks but not others also supports this argument. Rarely do monkeys show impairment on all tasks. Typically, one or two tasks will be impaired initially, and as the disease progresses, the level of impairment will increase and other measures may become abnormal.

How closely do the impairments observed in SIV-infected monkeys match those observed in HIV-infected humans? Clearly, as in humans, both motor and cognitive functions are impaired, but a clear disparity exists in the domains of function that are most affected, with motor function most affected in the monkey model and cognitive functions most affected in humans. In the human data, attention, learning, and language were impaired most frequently. Of course, language, other than some relatively simple vocalizations, does not exist in monkeys. Attention is a component of all tasks, so specific measures are needed to dissociate attention from other behavioral functions. The one study that used such a task (intra-extradimensional shift) reported that three of seven SIV-infected monkeys were impaired on the task (Weed and Gold, 2001). This suggests a weaker effect of infection on attention measures in monkeys than in humans. Similarly, specific learning tasks have been tested in SIV-infected monkeys and the incidence of impairment was also clearly in the low end of the range, rather than the high end as observed in humans. The percentage of HIV-infected human subjects with motor function impairment is 32-41% (Figure 1). This is substantially lower than the frequency of impairment on pure motor function tasks observed in SIV-infected macaques (57% to 78%). The reason for this difference is unclear. The possibility that it may be related to the robustness with which specific motor and cognitive functions can be assessed in monkeys compared to humans must be considered, but this seems unlikely. For example, in Table 1 and Figure 2, the "other" memory tasks and the learning and executive function tasks contain very specific designs that should have provided conditions equally robust as the working memory and fine motor control tasks.

Evoked potential abnormalities in SIV-infected macaques

Multimodal evoked potential analysis provides an alternative to behavioral studies as a means of

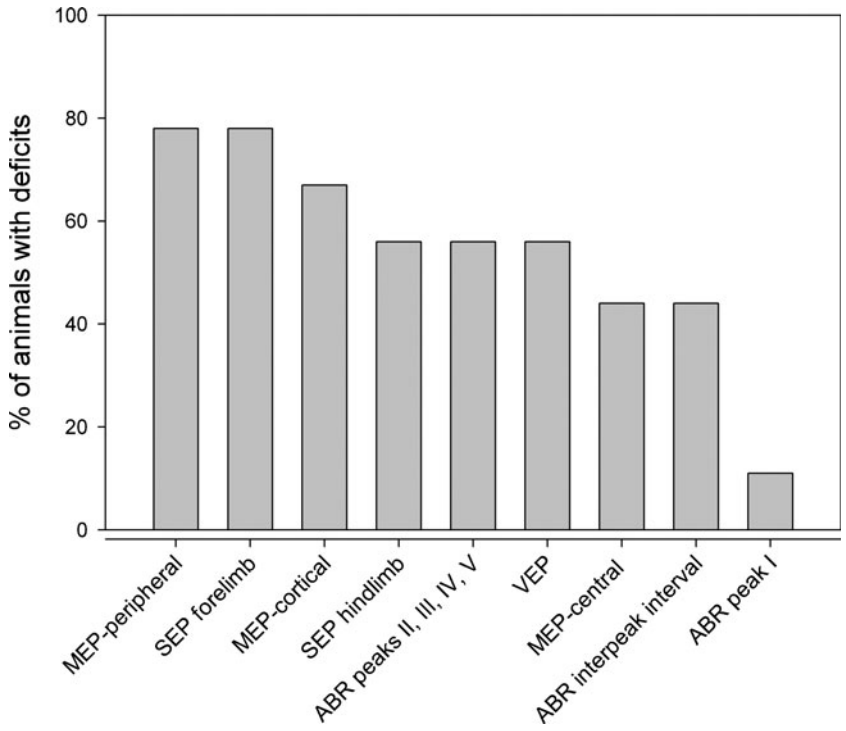

Figure 3 Prevalence of deficits in various sensory- and motor-evoked potential parameters from a study of SIV-infected macaque monkeys (Raymond *et al,* 1998, 1999, 2000). MEP-peripheral, peripheral motor-evoked potential latency from stimulating the spinal cord; MEP-central, central conduction time from subtracting peripheral conduction time from total cortical MEP conduction time; SEP, somatosensory-evoked potential; ABR, auditory brainstem response; VEP, visual-evoked potential.

evaluating the functional integrity of specific brain systems. Evoked potential abnormalities are typically evident as delays in the onset or peaks of electrophysiological waveforms. Figure 3 has the same format as Figure 2 and summarizes the frequency of deficits in sensory- and motor-evoked potentials from a cohort of SIV-infected rhesus macaques (Raymond *et al*, 1998, 1999, 2000). Abnormalities were observed in all modalities of evoked potentials studied, although not all animals were abnormal for all evoked potential types. As with the behavioral studies (Figure 2), the motor system was a frequent target of virus-induced dysfunction based on evoked potential analyses. Both cortical and spinal cord (peripheral) motor-evoked potentials (MEPs) were frequently delayed in SIV-infected animals. The origin of this increased latency was both central (MEP-central), involving conduction over the corticospinal tract, and peripheral, involving conduction along motor axons. The most significant changes in latency were associated with end-stage disease. Peripheral neuropathy and peripheral conduction slowing along motor and sensory axons is also present in HIV-infected humans (Parry *et al*, 1997; Jakobsen *et al*, 1989; although see Connolly *et al*, 1993). Increases in cortical MEPs have also been reported in asymptomatic, HIV-infected humans (Arendt *et al*, 1992). The increase in latency in this study was due primarily to peripheral conduction slowing; central conduction time was normal. These deficits might contribute to movement slowing observed in SIV disease and HIV disease, although basal ganglia pathophysiology is probably a more likely explanation (Arendt *et al*, 1990).

Sensory-evoked potentials, including auditory brainstem-evoked responses (ABRs), visual-evoked potentials (VEPs), and somatosensory-evoked potentials (SEPs), also showed clear abnormalities. In some cases, the abnormalities were severe, involving complete loss of a detectable evoked potential waveform (Raymond *et al*, 2000). ABR abnormalities were greatest for the later peaks. Peak I was rarely abnormal (Figure 3). The ABR is a robust measure of the transmission of a sound-evoked volley of neural activity through the peripheral and central auditory pathways. Because of its highly reproducible nature and the exact timing of peaks in the ABR, it has the potential to be a sensitive marker of early neuronal damage and pathophysiology related to viral infection.

Abnormalities in auditory- and visual-evoked potentials in SIV-infected macaques have also been reported by other groups (Prospero-Garcia *et al*, 1996; Gold *et al*, 1998; Horn *et al*, 1998; Fox *et al*, 2000; Roberts *et al*, 2006). Numerous studies have also demonstrated similar abnormalities in HIV-infected humans (Baldeweg *et al*, 1993; Castello *et al*, 1998; Farnarier and Somma-Mauvais, 1990; Jabbari *et al*, 1993; Malessa *et al*, 1995; Ronchi *et al*, 1992; Smith *et al*, 1988; Zandrini *et al*, 1990).

Conclusion

Macaque monkeys infected with various neurovirulent forms of SIV represent highly effective models, not only of systemic AIDS, but also neuroAIDS. Behavioral studies with this model have clearly established that SIV-infected monkeys show both cognitive and motor impairments resembling those that have been reported in HIV-infected humans. However, whereas cognitive functions are more commonly impaired in HIV-infected humans, motor function is most commonly impaired in SIV-infected monkeys. Electrophysiological studies in SIV-infected macaques have revealed deficits in motor-, somatosensory-, visual-, and auditory-evoked potentials that also resemble abnormalities in human HIV infection. The fact that in the macaque model these changes occur over a shortened time frame of months to a few years makes this model highly useful for translational studies of the virology, immunology, pathophysiology, and treatment of neuroAIDS.

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