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The Impact of Neuropsychological Functioning on Adherence to HAART in HIV-Infected Substance Abuse Patients

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Abstract

This study assessed the frequency of neuropsychological impairment and its relationship to adherence in a sample of HIV-infected injection drug users (IDUs) in treatment. One hundred eight participants recruited between September 2006 and October 2008 completed psychodiagnostic and neuropsychological assessments and monitored HAART adherence over a 2-week period via the use of Medication Event Monitoring System (MEMS) electronic pill caps and self-report. Assessment of concurrent functioning included clinician-rated scales of depression and substance use severity, and a battery of neuropsychological tests. Findings from individual neuropsychological tests were converted to *Z* scores relative to standard norms and averaged to form a composite score (NPZ). NPZ was generally poor (mean = −1.505, standard deviation = 1.120), with 76.9% of the sample being classified as highly impaired. Self-reported adherence was significantly higher than MEMS cap adherence. In contrast with previous studies, overall neuropsychological functioning was not a significant predictor of electronically monitored or self-reported adherence. However, examiner-rated current global severity of substance use and delayed word list recall emerged as significant predictors of self-reported adherence. Additionally, estimated premorbid verbal intelligence emerged as a significant predictor of the discrepancy between electronically monitored and self-reported adherence. Given the extent of neuropsychological impairment in this sample, future studies should examine the degree to which the impact of neuropsychological impairment may moderate interventions for this population, and the extent to which skills to cope with neuropsychological problems may boost the potential efficacy of such interventions.

Introduction

Before the introduction of highly active antiretroviral therapy (HAART), over half of adults infected with HIV developed neuropsychological complications, from subtle cognitive-motor deficits to severe dementia.[1–3] The frequency and severity of neuropsychological complications decreased significantly with the introduction of HAART in 1996.[4–8] However, less severe deficits in memory, concentration and attention abilities remain common,[9–11] with some estimates as high as almost 40%.[6] Substance use, also common in this population, is a major risk factor thought to exacerbate neuropsychological dysfunction,[12] and the risk of neuropsychological impairment may be particularly high in opiate users[13,14] and methadone maintenance patients,[15–19] regardless of HIV status. However, at least one study[20] suggests that engagement in methadone maintenance therapy improves neuropsychological performance.

The introduction of HAART has been met by an increased focus on factors that impact HIV management, including neuropsychological functioning. Neuropsychological impairment in HIV-infected adults has been shown to negatively impact adherence to HAART.[21–26] Studies indicate that poor overall neuropsychological functioning—as well as deficits in individual domains of functioning, including psychomotor speed, memory, and executive functioning—is associated with poor adherence.[24,25] This clinical picture is further complicated by substance abuse, which increases HIV-infected adults' risk

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for poor adherence.[27–29] Indeed, many studies indicate an inverse association between adherence and drug use in general,[30–33] and injection drug use in particular.[34–38]

Adherence to antiretroviral medications is commonly assessed using self-report measures or electronic pill caps (i.e., Medication Event Monitoring System [MEMS] caps). Studies of both methodologies in HIV-infected adults present self-report estimates that are significantly higher than those indicated by MEMS caps,[39–41] suggesting that self-report may yield overestimation of medication adherence, may be prone to social desirability and recall bias,[23] and hence may be less diagnostically accurate than electronically monitored adherence.[42] Similarly, there is evidence that patient report of psychological distress may be less valid than clinician ratings of such distress.[43,44]

Taken together, the literature referenced above[21,40,41] indicates that neuropsychological impairment negatively impacts both electronically monitored and self-reported adherence. This literature also suggests that neuropsychological impairment may affect the discrepancy between the two, in that those with such impairment may be less accurate in recalling and reporting their level of adherence. The purpose of the present study was to examine the frequency and severity of neuropsychological impairment, to examine the variability of electronically monitored and self-reported adherence, and to examine the degree to which overall and individual domains of neuropsychological functioning impacts adherence to HAART in a sample of HIV-infected injection drug users (IDUs) in substance abuse treatment.

Method

Participants

Participants were 108 HIV-infected adults (63 men and 45 women) who completed enrollment and screening visits for a randomized controlled trial of cognitive behavioral therapy for adherence and depression in HIV. Participants completed a baseline diagnostic assessment, 2 weeks of monitoring medications with an electronic pill cap (MEMS), and a clinician-administered assessment battery including a set of neuropsychological tests and a rating of depression. Inclusion criteria for completion of this screening included: being HIV-seropositive and taking HIV antiretroviral medication; having a history of injection drug abuse/dependence; current enrollment in methadone maintenance or other substance abuse treatment program; and age 18 to 65.

Demographic characteristics are presented in Table 1. Seventy-three (68.2%) participants were enrolled in a methadone maintenance program, two (1.9%) were taking Suboxone (buprenorphine HCl/naloxone HCl; Reckitt Benckiser Pharmaceutical, Inc., Richmond, VA), and 32 (29.9%) were actively enrolled in nonmedication therapeutic or support activities such as individual or group counseling, Narcotics Anonymous, or Alcoholics Anonymous.

Table 1. Sociodemographic Characteristics of Respondents (by Gender, Valid Percents)

Variable	n	%
Gender		
Male	63	58.3
Female	45	41.7
Substance abuse treatment		
Methadone	73	68.2
Suboxone	2	1.9
Other	32	29.9
Race/ethnicity		
Not Hispanic/Latino	67	71.3
Hispanic or Latino	27	28.7
Sexual Orientation		
Exclusively heterosexual	73	79.3
Bisexual	5	5.4
Exclusively homosexual	3	3.3
Other	27	12.0
Religion		
Catholic	51	53.1
Protestant	13	13.5
Jewish	1	1.0
Islamic	4	4.2
Other	17	17.7
Relationship status		
Single	44	45.4
Married/living with someone as if married	32	33.0
Other	32	21.6
Education Level		
Eighth grade or lower	12	12.2
Partial high school	28	28.6
High school graduate/GED	26	26.5
Partial college	23	23.5
College graduate	7	7.1
Partial graduate school	1	1.0
Graduate school degree	1	1.0
Employment		
Full-time work	2	2.1
Part-time work	7	7.3
On disability	66	68.8
Other	5	5.2
	M	*SD*
Age	46.68	7.24
Years of Education	11.28	3.00

SD, standard deviation.

Recruitment

Participants were recruited by clinicians and through advertisements at methadone treatment clinics, other drug abuse treatment centers, HIV clinics, and through newspaper advertisement in Massachusetts and Rhode Island. If a clinic staff member invited an individual to participate and he or she agreed, the participant completed a contact information card.

Materials

Clinician-administered psychological assessments. *Diagnostic evaluation.* The Mini-International Neuropsychiatric Interview (M.I.N.I)[45] is a short structured diagnostic interview that has reliability and validity comparable to the *Structured Clinical Interview for DSM-IV* (*SCID-IV*). The M.I.N.I. was used to assess current and lifetime alcohol use, anxiety disorders, mood disorders, and psychosis. This information was used in conjunction with the ASI-Lite to create the CGI for substance abuse score (see below for details).

Rating of depression. The Montgomery-Asberg Depression Rating Scale (MADRS)[46] is an assessment of 10 commonly occurring symptoms of depressive illness over the past week and is a widely used and valid instrument. Scores on the MADRS range from 0 to 60, with scores between 0 and 6 indicating no depression; scores between 7 and 19 indicating mild depression; scores between 20 and 34 indicating moderate depression; and scores between 35 and 60 indicating severe depression.

Global severity and impairment. The Clinical Global Impression (CGI; National Institutes of Mental Health) [47] for severity of symptoms of depression and substance use (1 = not ill, to 7 = extremely ill) and the Global Assessment of Functioning (GAF; American Psychological Association),[48] are the measures of global severity and impairment. The CGI is a widely used scale and is disorder specific, and the GAF is the *DSM-IV* Axis V rating, ranging from 1 to 100 (e.g., 71+ = no symptoms, 70−61 = mild symptoms, 60−51 = moderate symptoms, 50−41 = serious symptoms) and assesses general functioning across disorders taken together.

Rating of drug and alcohol use. The Addiction Severity Index Lite (ASI-Lite)[49] measures the severity of problems in seven areas of functioning that are frequently affected in patients with substance use disorders. For this protocol, the number of different substances used and the total number of days of use (of all substances) over the past month were used as indicators of substance abuse.

Measurement of adherence. *Electronic pill caps.* MEMS caps were one of two methods used to assess adherence over a 2-week period. The MEMS caps were used to monitor the medication that patients took the most frequently or found to be the most difficult to remember. Doses were counted as "taken" if the bottle was opened within 2 hours of the prescribed time. The percent of doses taken as prescribed was calculated by dividing the number of times the bottle was opened by the number of times it should have been opened as per the prescription. Participants were instructed to keep a log of any doses not recorded by the MEMS caps that were "pocketed" or taken without opening the pill cap. Pocketed doses, as well as doses that remained in the bottle at the end of the 2-week monitoring period, were recorded by study therapists and used to create a "therapist-corrected" MEMS rating.

Self-report questionnaire. Adherence was also assessed using the AIDS Clinical Trials Group (ACTG) Adherence Questionnaire, which asks patients about the number of doses prescribed and the number of doses missed each day for each prescription over specified time periods.[23] For the present study, we asked participants about their adherence "yesterday," "the day before yesterday," "the past week," and "the past 2 weeks" for all of the HIV medications that they were currently taking. A separate variable that indicated self-reported adherence for the medications monitored via MEMS caps was created and used in the present analyses.

Neuropsychological assessments. Participants completed a battery of neuropsychological tasks designed to assess estimated verbal intelligence, processing speed, organization and planning, working memory, episodic (verbal) learning and memory and visuospatial constructional ability.

Wechsler Test of Adult Reading (WTAR).[50,51] The WTAR was used to estimate premorbid verbal intelligence and has a large national normative sample and excellent clinical validity. The WTAR required participants to pronounce out loud a list of 50 words with atypical grapheme to phoneme translations. The target variable was the number of words pronounced accurately.

Hopkins Verbal Learning Test—Revised (HVLT-R).[52] This test measures episodic and strategic memory. The HVLT-R is a valid screening test for dementia, has high test-retest reliability, a large normative sample, and excellent construct, concurrent, and discriminant validity. The HVLT-R has also demonstrated high degrees of diagnostic reliability and validity in HIV-infected adults.[53,54] Participants were asked to encode a supraspan (i.e., 12 items) word list across three trials. Delayed recall and delayed recognition memory were also assessed. The target variables were immediate recall (the total number correct over the three learning trials) and total delayed recall.

Trail Making Test.[55] The Trail Making Test is sensitive to a variety of disorders, including HIV infection[56] and substance use,[57,58] as well as engagement in methadone maintenance therapy.[59] Trails A is an assessment of motor speed, visual scanning and visual-motor integration, and required participants to connect a series of 25 numbered circles in numeric order as quickly and as accurately as possible. Trails B is an assessment of executive functioning, including cognitive flexibility, attention and planning, visual scanning and motor speed. The targets for Trails B contain both letters and numbers and respondents were asked to connect the circles in alternating sequence (i.e., 1-A-2-B-3-C, etc.) as quickly and accurately as possible. The target variables were time to completion on Trails A and Trails B.

Symbol Digit Modalities Test (SDMT).[60] This measure of divided attention, visual scanning, tracking, and motor speed is sensitive to a number of psychological and neurologic conditions, including HIV.[61,62] The SDMT involved having participants pair specific numbers with specific symbols, using a reference key. Participants made as many pairings as possible in 90 seconds. The target variable was the number of correct pairings.

Controlled Oral Word Association Test (COWAT).[63] This measure has two components. The F-A-S task assesses executive functioning and required participants to verbally report exemplars beginning with specific phonemes (i.e., words starting with the letters F, A, and S) over a 60-second period. The target variable for the F-A-S task was the total number of words reported across the three phonemic categories. The category fluency task, an assessment of semantic fluency, required participants to report exemplars of semantic categories (i.e., animals) over a 60-second period. The target variable for the category test was the total number of words reported. The COWAT has been found to be a reliable and valid test of executive cognitive functions and expressive language.[55,64]

Table 2. Descriptive Statistics for Neuropsychological Tests (Z Scores)

Variable	*Mean*	*Median*	*Mode*	*SD*	*Range*
WTAR	−0.89	−1.00	−1.67	1.07	−3.33–1.67
Trails A	−0.80	−0.41	−0.15	1.92	−11.59–1.84
Trails B	−2.67	−1.82	0.58	3.24	−17.62–1.81
SDMT	−1.56	−1.56	−2.93	1.18	−4.17–1.14
HVLT total	−2.29	−2.31	−2.50	1.43	−5.79–0.82
HVLT delayed	−2.50	−2.48	−2.48	1.70	−5.82–1.12
COWAT FAS	−1.34	−1.31	−2.21	0.93	−2.85–1.46
COWAT category	−0.46	−0.91	−1.09	2.49	−4.71–8.76
Rey total	−2.76	−2.31	−0.87	2.76	−11.7–1.32
NPZ	−1.51	−1.50	−5.25	1.20	−5.25–2.33

Rey Complex Figure Test (RCFT, Copy Trial).[65] This measure of executive functioning, including working memory and visuospatial constructional ability, involved having participants copy a target figure that was presented in a standardized manner. Accuracy and organization of reproduction comprised the scoring of 18 distinct figural elements. The number of elements drawn correctly and accurately placed was the target variable. The RCFT has published norms and excellent clinical validity.[66]

Psychosocial self-report assessment battery. *Demographics.* This included information about race, ethnicity, age, gender, sexual orientation, as well as educational and employment status.

Procedure

At the first study visit, participants discussed the study procedures and signed a detailed consent form. The study staff then conducted a diagnostic assessment using the M.I.N.I. and instructed participants on the use of the MEMS caps. At the second study visit, participants completed the self-report psychosocial assessment battery, and the study staff assessed depression and substance use, and administered the neuropsychological battery.

The study was reviewed and approved by the Institutional Review Boards for Massachusetts General Hospital and Rhode Island Hospital, respectively.

Calculation of the NPZ score

Neuropsychological functioning was assessed using the HVLT-R (immediate and delayed trials), Trails A and B, SDMT, COWAT (FAS and category tests) and the RCFT. The results of each neuropsychological test were converted to *Z* scores using published norms; these *Z* scores were then averaged to form an overall neuropsychological *Z* score (NPZ), or estimate of neuropsychological functioning, for each participant. This method of using NPZ scores as an indicator of overall neuropsychological functioning has been used before with HIV-infected samples.[67–69]

Results

Paired samples *t* tests were conducted to assess for differences between self-reported and electronically monitored adherence. There was a significant difference between electronically monitored and self-reported adherence, $t(100) = -10.15$, $p < 0.001$, with participants reporting higher rates over the 2 weeks than were indicated by their MEMS cap counts (mean for MEMS over the 2 weeks was 68.21%, mean for self-reported adherence was 93.82%). Hence, analyses were carried out separately for self-reported and MEMs adherence.

Overall neuropsychological performance, as indicated by the NPZ score, was poor among the entire sample. Compared to general population norms, across tests participants performed well below expected levels (mean = −1.51, standard deviation = 1.20). Moreover, their performance was lowest on tests of executive functioning (i.e., the Trails B, Rey Complex Figure, Copy) and highest on tests of semantic fluency and visual attention (i.e., COWAT, Trails A). For example, participants performed significantly higher on Trails A than on Trails B ($t(106) = 7.22$, $p < 0.001$) and significantly higher on the COWAT (category) than on the Rey Complex Figure Copy trial ($t(108) = 6.81$, $p < 0.001$). Table 2 presents descriptive statistics for the neuropsychological tests.

For descriptive purposes, neuropsychological functioning was further assessed by dividing the sample into three categories: high impairment (performance at or below $Z = -2$ on two or more domains of functioning); moderate impairment (performance at or below $Z = -2$ on one domain of functioning); and low impairment (performance above a $Z = -2$ on all domains). This method has been used in previous studies examining neuropsychological functioning in HIV-infected adults.[70,71] According to this division, 76.9% of the sample was classified as highly impaired, 16.7% as moderately impaired, and 6.5% as having low levels of impairment.

Multiple regression analyses were conducted to assess the extent to which NPZ and individual domains of functioning accounted for variance in self-reported and electronically monitored adherence. The proxy for premorbid verbal intelligence (WTAR) was entered in the first block, and the NPZ and the *Z* scores for each of the eight individual tests were entered into the second block, with MEMS-based and self-reported adherence as the outcome variable in separate analyses. The results indicated that neither the NPZ score nor the individual tests were significant predictors of MEMS-based or self-reported adherence. However, the WTAR showed a trend toward significance in predicting MEMS-based adherence, $F(1, 99) = 3.47$, $p = 0.065$, $R^2 = 0.067$. The WTAR was not a significant predictor of self-reported adherence.

These hierarchical regression analyses were re-run with additional covariates which have been shown to impact adherence to HAART. Age, depression (according to the MADRS), gender, and years of education were each entered independently into the first block, the WTAR in the second, and the remaining neuropsychological test variables in the third. The addition of these covariates did not alter the results. However, as presented in Table 3, when the severity of current substance use (as indicated by the CGI for substance use) was added as a covariate, it emerged as a significant predictor, both on its own ($F(1, 97) = 10.25$, $p < 0.05$) and over and above variance due to the individual neuropsychological tests or overall NPZ score ($F(10, 88) = 2.039$, $p < 0.05$). Higher CGI scores were predictive of higher rates of self-reported adherence, and on its own, substance use severity accounted for 9.6% of the variance in self-reported adherence. Moreover, in this model, the HVLT delayed score emerged as a significant

Table 3. The Contribution of Severity of Substance Abuse and Neuropsychological Impairment to Self-Reported Adherence

Regression variable	R^2	F	p *value*	*β*
Block 1	0.096	10.251	0.002	
CGI-SA				−0.309[a]
Block 2	0.097	5.147	0.008	
CGI-SA				−0.318[a]
WTAR				0.036
Block 3	0.188	2.039	0.038	
CGI-SA				−0.332[a]
WTAR				−0.053
Trails A				0.147
Trails B				−0.169
HVLT Total				.277
HVLT Delayed				−0.276[a]
COWAT FAS				0.041
COWAT Category				0.015
SDMT				0.067
Rey				0.017

[a]Significant at the $p < 0.05$ level.

predictor of self-reported adherence ($t(98) = -2.20$, $p < 0.05$); poorer scores were indicative of higher rates of self-reported adherence, a relationship contrary to the direction that was originally expected. The correlate model with MEMS adherence as the outcome variable is presented in Table 4. In this model, substance use was not an independent significant predictor of adherence, although when combined with the WTAR it accounted for 7.6% in the variance in adherence, $F(2, 96) = 3.96$, $p < 0.05$.

Finally, we created an adherence discrepancy score by examining the difference between MEMS and self-reported adherence for each participant, and re-ran all regression analyses to examine the extent to which NPZ and individual neuropsychological test domains accounted for discrepancy scores. The WTAR was the only significant predictor of discrepancy, $F(1, 96) = 5.045$, $p < 0.05$, and accounted for 11.4% of the variance in discrepancy scores. The addition of age, gender, depression, years of education, and severity of substance use as covariates in these analyses did not significantly alter these findings.

Discussion

In this study, neuropsychological impairment among HIV-infected individuals in substance abuse treatment was exceptionally high; over three-quarters of the sample was considered "highly impaired." This rate of impairment is considerably higher than found in prior studies with similar samples.[16,72] Additionally, neuropsychological impairment was not associated with adherence and was not associated with a discrepancy between self-reported and a more objective (MEMS) measure of adherence. However, the WTAR—used here as a proxy for premorbid verbal intelligence—was a significant predictor of the discrepancy between electronically monitored and self-reported adherence. Participants with higher WTAR scores had smaller discrepancies in their adherence scores than participants with lower WTAR scores; they were not only more adherent than participants with lower WTAR scores, but they were more accurate reporters of their adherence.

The mean adherence over 2 weeks according to MEMS and self-reported adherence measures was 68.21% and 93.82%, respectively. While this self-reported rate is close to the ideal of 95%,[73] electronically monitored adherence was far below this standard. However, the difference between electronically monitored and self-reported adherence was not surprising, and was similar to those described in prior studies of adherence.[40,74] It was nonetheless unexpected that only one measure of neuropsychological functioning was a significant predictor of adherence in the present study. Previous studies [22,24,41] have found that overall assessments of neuropsychological functioning, as well as measures of executive functioning and working memory, were significant predictors of adherence. Here, only the HVLT delayed recall subtest was a significant predictor of self-reported adherence. Poorer performance on the HVLT recall subtest was a significant predictor of higher self-reported adherence, which is interesting given that performance on a delayed recall test has face validity with regard to the ability to remember to take medications. Given our initial hypotheses regarding the impact of neuropsychological functioning on adherence, we expected that the inverse relationship—higher performance on the HVLT recall subtest would be a significant predictor of higher self-reported adherence—would have presented itself. As such, this finding challenges the accuracy of the self-reported adherence, particularly for participants with poor performance on the HVLT delayed subtest. Moreover, the wide range of scores on the battery of neuropsychological tests did not account for these results, as the same findings emerged when the analyses were re-run using truncated *Z* score values (i.e., a range of *Z* scores from −3 to 3) for the NPZ and the individual neuropsychological tests.

It is therefore possible that the high levels of impairment evidenced by this sample may account for the absence of a

Table 4. The Contribution of Severity of Substance Abuse and Neuropsychological Impairment to MEMs Adherence

Regression variable	R^2	F	p *value*	*β*
Block 1	0.024	2.406	0.124	
CGI-SA				−0.156
Block 2	0.076	3.962	0.022	
CGI-SA				−0.210[a]
WTAR				0.235[a]
Block 3	0.106	1.044	0.414	
CGI-SA				−0.211
WTAR				0.242
Trails A				0.043
Trails B				−0.044
HVLT Total				0.072
HVLT Delayed				−0.062
COWAT FAS				−0.050
COWAT Category				−0.178
SDMT				0.016
Rey				−0.065

[a]Significant at the $p < 0.05$ level.
MEMS, Medication Event Monitoring System.

relationship between the battery of neuropsychological tests and the measures of adherence. These levels of impairment may have resulted—in part—from engagement in methadone maintenance therapy and testing post-methadone dosing (72% of participants were active in methadone programs at the time of testing), as well as from comorbid substance abuse. Indeed, comorbid abuse of an array of psychoactive substances was common among study participants, despite their enrollment in methadone or other treatment programs, and therefore the high levels of impairment may be a reflection of active substance use in which the participants were engaged. Furthermore, substance use was the only variable that emerged as a significant predictor of adherence. Participants with more severe substance use reported higher levels of adherence, although their electronically monitored adherence was not higher than participants with lower CGI scores. It seems, therefore, that substance use impaired participants' ability to accurately report their adherence. This finding may help to clarify the relationship between the HVLT delayed score and self-reported adherence.

The present study did not consider the impact of the timing of methadone dosing on neuropsychological functioning. As 72% of the sample was actively engaged in methadone maintenance therapy, it is possible that there may have been an effect of the timing of the assessment (i.e., before or after dosing), as well as an effect of the length of time that participants had been in methadone therapy. The present study also did not consider the number and types of substances that participants were currently abusing. This information may have helped to elucidate the relationship between neuropsychological functioning and adherence. Additionally, the present sample was generally quite impaired, and hence did not have a wide range of neuropsychological functioning. Finally, there may have been an effect of the two-week monitoring period. Other studies that have found that neuropsychological impairment is a significant predictor of adherence have assessed adherence for a longer (e.g., 1 month) period.[22,23,25,26] It is therefore possible that asking participants to monitor their adherence may itself have resulted in a temporary increase in adherence, and that if participants had monitored adherence for a longer period of time, a relationship between neuropsychological impairment and adherence may have emerged (i.e., participants with neuropsychological impairment would not have been able to sustain such high levels of adherence over a longer period of time).

Although not predictive of adherence, the high level of neuropsychological impairment evidenced by this sample underscores the necessity for interventions that target adherence or other functional outcomes in similar samples to consider the impact of neuropsychological functioning on an individual's ability to benefit from such intervention. Neuropsychological impairment may reduce the capacity to benefit from adherence counseling and hence, providers should bear neuropsychological functioning in mind when designing and implementing interventions. As this sample was part of a larger randomized controlled trial of cognitive behavioral therapy for adherence and depression, it will be interesting to examine the role that neuropsychological impairment plays in participants' ability to benefit initially from the intervention and maintain therapeutic gains over time.

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Author Disclosure Statement

No competing financial interests exist.

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