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Speech in noise perception as a marker of cognitive impairment in HIV infection

Yi Zhan¹, Abigail M. Fellows², Tangkai Qi¹, Odile H. Clavier³, Sigfrid D. Soli⁴, Xiudong Shi¹, Jiang Gui², Yuxin Shi¹, and Jay C. Buckey²

¹Shanghai Public Health Clinical Center, Fudan University, Shanghai, China

²Geisel School of Medicine at Dartmouth, Lebanon, NH, USA

³Creare, LLC, Hanover, NH, USA

⁴University of British Columbia, Vancouver, Canada

Abstract

Objective—HIV+ individuals report hearing difficulties, but standard audiological tests show no, or small, changes in peripheral hearing ability. The hearing complaints may reflect central nervous system (CNS) auditory processing deficits, rather than middle or inner ear problems, and may result from CNS damage due to HIV infection or treatment. If central auditory task performance and cognitive deficits in HIV+ individuals are shown to be related, then central auditory tests might serve as a “window” into CNS function in these patients.

Design—We measured cognitive performance (Mandarin Montreal Cognitive Assessment (MoCA)) and speech-in-noise perception (Mandarin hearing-in-noise test (HINT)) in 166, normal-hearing HIV+ individuals (158 men, 8 women, average age 36) at the Shanghai Public Health Clinical Center in Shanghai, China.

Methods—Data collection included audiometry, tympanometry, and the Amsterdam Inventory of Auditory Handicap (AIAH), which assesses the subjective ability to understand speech and localize sound.

Results—Subjects had no middle ear disease and met criteria for normal hearing sensitivity (all thresholds 20 dB HL or less). A significant negative relationship between speech reception thresholds (SRT) and MoCA scores ($r^2=0.15$, $F=28.2$, $p<0.001$) existed. Stepwise linear regression showed that when the factors of age, MoCA scores, hearing thresholds, and education level were considered, only age and MoCA scores contributed independently to the SRT results (overall model $r^2=0.30$, $F=38.8$, $p<0.001$). Subjective hearing complaints from the AIAH supported the

Address correspondence to Jay C. Buckey, M.D., One Medical Center Drive, Lebanon, NH 03755, Ph. 603-650-6012, jay.buckey@dartmouth.edu.

Declaration: Y.Z. was primarily responsible for running the study, enrolling patients, and supervising data collection. She assisted with study design, data analysis, and data interpretation. A.F. was primarily responsible for training, and assisted with study design, data collection, data analysis and data interpretation. T.Q. assisted with study design and with enrolling patients. O.C. assisted with study design, test development, and data analysis. S.S. assisted with data analysis and interpretation. Y.S. assisted with study design and was primarily responsible for study oversight in Shanghai. J.G. helped with statistical analysis. J.B. was the principal investigator, and was involved in study design, training, data analysis, and data interpretation. All authors assisted with revising the final work, and approved the final version to be published. All authors agree to be accountable for all aspects of the work and ensuring that questions about the accuracy or integrity of any part of the work are appropriately investigated and resolved.

HINT results. AIAH and MoCA scores were also related ($r^2=0.05$, $F=8.5$, $p=0.004$), with those with worse MoCA scores having more problems on the AIAH. When the cohort was divided into those with normal and abnormal performance on the MoCA, those with abnormal performance on the MoCA had significantly higher average SRTs ($p<0.001$).

Conclusions—Understanding speech in noise measured both objectively with the HINT and subjectively with the AIHA was inversely related to cognitive abilities, despite a normal ability to hear soft sounds determined by audiometry. Although age was also an important independent factor affecting speech perception, the age relationship within the speech findings in this study may represent more than just age-related declines in speech in noise understanding. Although reliable data on disease duration are not available, the older members of this cohort likely had HIV longer, and probably had more severe symptoms at presentation than the younger members since early detection and treatment of HIV in Shanghai has improved over time. Therefore, the age relationship may also include elements of disease duration and severity. Speech perception, especially in challenging listening conditions, involves cortical and subcortical centers and is a demanding neurological task. The problems interpreting speech in noise HIV+ individuals have may reflect HIV-related, or HIV-treatment-related, central nervous damage, suggesting that central nervous system complications in HIV+ individuals could potentially be diagnosed and monitored using central auditory tests.

Keywords

HIV; Central auditory pathway disorders; Neurocognitive disorders

Introduction

Neurocognitive disorders are a devastating consequence of HIV infection, which occur despite active antiretroviral treatment (Heaton et al. 2010). The central nervous system (CNS) can serve as an anatomic reservoir for HIV, and continued immune activation of macrophages and microglia in the brain can lead to central neurological signs and symptoms (Gray et al. 1996). Reliable biomarkers of central nervous effects in HIV infection are essential to diagnose and track this debilitating consequence of HIV infection. Traditionally, neurocognitive/neuropsychological test batteries are used, which can be time-consuming, labor-intensive, and sometimes stressful for the patient. They can be insensitive to early or subclinical changes. When these tests are applied to monitoring concussions in athletes, for example, the tests often miss subtle changes and can take hours to administer (Randolph et al. 2005). An alternate way to assess central nervous system function in HIV infection may be through the central auditory system.

We have shown that although HIV+ individuals seem to have relatively normal peripheral hearing, they have signs of central auditory processing deficits (Maro et al. 2014). HIV+ adults in Tanzania on anti-retroviral therapy (ART) had higher gap detection thresholds and reported more subjective difficulty understanding speech-in-noise than HIV+ adults not on ART, even though measures of peripheral hearing (audiometry) were not different (Maro et al. 2014). These findings likely reflected central nervous system damage in these patients, since detecting gaps in noise, processing sound, and interpreting speech in noise are demanding central nervous tasks involving multiple brain areas. The central nervous system

damage could result from various factors, such as neurotoxicity from antiretroviral therapy (Ma et al. 2016; Underwood et al. 2015), lack of adherence to drug therapy, inadequate penetration of antiretroviral therapy into the CNS (Letendre 2011), ongoing inflammation, or continued HIV replication in the central nervous system despite therapy.

Although the central auditory system has centers with special functions (e.g. recognizing pitch and timing), the overall task of extracting meaning from sound is distributed throughout the central nervous system (Kraus et al. 2016; Kraus et al. 2015). This suggests that processes producing diffuse damage to the central nervous system, such as HIV infection, could affect central auditory processing in multiple ways (Zhan et al. 2017). Studies in patients with concussions, show that this generalized brain injury is reflected in performance on central auditory tasks (Gallun et al. 2012; Kraus et al. 2016). Similarly, there are suggestions that speech perception in noise is correlated with cognitive performance in general (Ellis et al. 2016; Pichora-Fuller et al. 2016).

The data from our previous studies, and the growing body of data showing a link between cognitive performance and central auditory performance, raise the possibility that central nervous system effects of HIV infection or treatment could be screened using central auditory test batteries that may be shorter than neurocognitive testing or MR imaging. These tests may be sensitive to central nervous system changes because processing speech--particularly in a demanding listening environment--is a very computationally demanding task that involves microsecond-level resolution of timing cues (Kraus et al. 2016). Speech-in-noise testing, for example, engages auditory, linguistic, memory, and binaural processes, and engages the subject in challenging testing (Erb et al. 2013; Kraus et al. 2016; Rudner et al. 2014). Central auditory effects might appear earlier or independently from other neurological findings, so detecting these changes could enhance current testing methods. Central auditory tests may be a complementary way to assess CNS function in people with HIV that may have benefits in certain testing circumstances and may have broader acceptability than current testing methods.

For central auditory effects to be used as a biomarker, however, the central auditory findings seen in HIV infection need to be confirmed and related to cognitive performance as well as shown to be reliable, reproducible, and associated with changes in the pathophysiological substrate (e.g., predictive of disease development or treatment). One weakness in our previous study was that the evidence for difficulty in understanding speech in noise was from self-report, rather than from direct measurements. Also, the study did not include any measures of neurocognitive performance, so it was not possible to say if the findings were related to cognitive symptoms. To determine whether neurocognitive symptoms and performance on central auditory tasks are related, direct measurements of central auditory performance (such as the ability to understand speech in noise) are needed from a cohort of HIV+ individuals with a concurrent neurocognitive assessment.

HIV+ individuals followed at the Shanghai Public Health Clinical Center in Shanghai, China performed a comprehensive set of peripheral and central auditory tests. They also had their neurocognitive status assessed using the Mandarin version of the Montreal Cognitive Assessment (MoCA) (Hu et al. 2013). We hypothesized that individuals with lower scores

on the MoCA would have more difficulty understanding speech in background noise. Since the ability to understand speech in noise can be affected by damage to the inner and middle ear, all the subjects were screened to have normal middle ear function and normal hearing sensitivity in both ears. The object of the study was to show whether central auditory tests could be used as a “window” for central nervous HIV effects, which would offer a new and potentially improved way to assess the central neurological co-morbidities of HIV infection.

Material and Methods

Study Participants

Participants were HIV+ adults who received their HIV care at the Shanghai Public Health Clinical Center (SPHCC) in Shanghai, China. The SPHCC is the Chinese national infectious disease specialist training center, the AIDS clinical continuing education base of China's Center for Disease Control (CDC), and the clinical center of Shanghai's CDC. Patients were eligible to participate if they had a confirmed diagnosis of HIV, and had not been exposed to factors that could temporarily affect their hearing on the testing day (i.e. they were excluded if they had been noise-exposed within the day prior to testing, or if they had taken high doses of aspirin (more than six 325mg tablets in the last 24 hours), which can damage hearing (Cazals 2000)). Currently, monitoring of high-risk groups in Shanghai has increased, but previously, individuals would often present for care after they had developed signs and symptoms of AIDS.

Study Procedures

Institutional review board approval was obtained at both Dartmouth and the Shanghai Public Health Clinical Center. All subjects provided informed consent. All subjects had an otoscopic examination and cerumen was removed as needed. Subjects responded to a computer-based questionnaire that asked about hearing ability and exposure to noise, solvents and ototoxic drugs (gentamicin, tobramycin, amikacin, streptomycin chemotherapy, furosemide, quinine, chloroquine, diclofenac, and ibuprofen). The questionnaire included a Chinese translation of the Amsterdam Inventory of Auditory Handicap (AIAH), which assesses self-reported difficulties with central auditory related tasks (speech detection, sound localization, sound recognition) (Kramer et al. 1995). The questions in the AIAH were translated into Mandarin and then back translated into English to verify the translation. The AIAH included 30 questions that assessed an individual's self-reported ability to understand speech both in noise and in quiet. It also asked about localizing and recognizing sounds. The questionnaire provided a total score as well as six subscales (Speech Intelligibility in Noise, Speech Intelligibility in Quiet, Auditory Localization, Recognizing and Identifying Sounds, the Detection of Sounds in General, and the Perception of Music). In case there were participants who could not read, the questions were asked both verbally through a video/ audio recording and in text. All the participants in this study, however, could read.

Tympanometry was performed on both ears using an Interacoustics Titan Tympanometer. In measuring compliance, admittance < 0.3 and > 1.70 mmho were considered abnormal. Negative pressures exceeding 150 daPa were considered abnormal. Shape was determined by measuring the width of the tympanogram tracing at 50% of its static compliance. Widths

>114 daPa or <51 daPa were considered abnormal (Margolis et al. 1987) and ear volumes of > 2.5 mmhos were considered abnormal. Subjects with abnormal tests were referred to the ENT clinic for treatment.

All other hearing tests were conducted using a Creare Hearing Assessment (CHA) instrument system (Creare LLC, Hanover, NH). The CHA consisted of a handheld device connected to an external headset, and connected to a computer via a USB interface for data exchange. The handheld device housed electronics designed to control the sound stimuli and the logic of each hearing test. Software housed on the computer provided a user interface to interact with the CHA, select test parameters, view the progress and results of each test, and store measurements in a database. This software also provided an interface for all questionnaires, as well as for the external tympanometer.

The importance of speech information in different frequency regions for English, as defined in the ANSI standard for the Speech Intelligibility Index, indicates that only 5-10% of this information is found at frequencies above 4 kHz (American National Standards Institute 1997). The spectrum levels above 4 kHz for Mandarin are several dB lower than for English, as determined from unpublished spectral analyses of the Mandarin (Wong et al. 2008) and English (Vermiglio 2008) masking noises, which are spectrally matched to the average long term spectrum of the HINT sentences for each language. Thus, both the importance and audibility of Mandarin speech information above 4 kHz is limited. To keep the overall protocol length within a reasonable amount of time, audiometric thresholds up to 4000 Hz were measured. Air conduction pure tone audiometric thresholds were measured in a sound booth at frequencies of 500, 1000, 2000, and 4000 Hz using a Békésy-like tracking procedure described previously (Maro et al. 2014). Stimuli were pulsed tones with a duration of 250 msec, a rise and fall time of 20 msec and an interstimulus interval of 500 msec. When the subject first pressed the button, the tone levels decreased in 4-dB steps until the subject released the button (the first reversal). Subsequently, the tone levels decreased or increased in 2-dB steps when the subject pressed or released the button respectively. When the subject released the button the tones increased in 2-dB steps. A total of 6 reversals were counted and averaged. The total time for testing was less than 5 min/ear. Normal hearing was defined as a threshold of 20 dB HL or less at all frequencies in both ears.

Speech-in-noise testing was done in a sound booth using the Mandarin language version of the Hearing In Noise Test (HINT) (Nilsson et al. 1994; Soli et al. 2008; Vermiglio 2008; Wong et al. 2008). The HINT test was chosen because to the authors' knowledge it is the only Mandarin speech test that has been normed and published in international scientific journals. Also, because the HINT is intended to measure the same parameters in different languages (and has been shown empirically to do so) the results in Mandarin can be generalized and replicated in other languages throughout the world, since the HINT currently exists in over 20 languages. During a HINT test, the left and right ear signals are processed to simulate different spatial locations of the speech and noise sources (Soli and Wong 2008)—Noise Front, Noise Right and Noise Left. The test was administered in these three conditions using Sennheiser HDA 300 headphones provided with the instrument. In each test, a different list of 20 sentences was presented in random order in the presence of the reference HINT noise. The presentation level of the noise remained fixed at 65 dBA and

the test instrument adjusted the level of each sentence adaptively depending on whether the test administrator indicated that the previous sentence was repeated correctly. The presentation level of the sentence was reduced if the previous sentence was repeated correctly, and increased if the previous sentence was repeated incorrectly. This adaptive procedure was used to determine the presentation level of each sentence in the list. The average presentation level of all sentences after the first four sentences defined the speech reception threshold (SRT) for the test condition, which was expressed as a signal-to-noise ratio (SNR). The test instrument automatically selected a different sentence list each time a test was performed. The test instrument automatically displayed the SNRs for each test condition as well as the composite SNR, and stored the results in a database. The composite SNR represented the combination of scores from all conditions (noise front, noise left, noise right). The negative values for the SNRs meant that the individual could hear sounds presented at levels softer than the noise (which is typical for normal hearing adults).

Cognitive testing was done using the Montreal Cognitive Assessment (MoCA) available at www.mocatest.org. The specific items in the MoCA have been described by Nasreddine et al. (Nasreddine et al. 2005). It includes items on short-term and long-term memory recall, visuospatial abilities, executive functioning, attention, concentration, and working memory. Short-term memory recall is evaluated with two trials of learning five nouns and recalling them after approximately five minutes (five points). A clock-drawing task is used to assess visuospatial abilities (three points) along with a task that involves copying a three-dimensional cube (one point). Executive functions are evaluated with a Trail Making task (one point), a phonemic fluency task (one point), and a two-item verbal abstraction task (two points). A sustained attention task (target detection using tapping; one point), a serial subtraction task (three points), and a repeating digits forward and backward task (one point each) are used to assess attention, concentration, and working memory. A three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros; three points), a repetition of two syntactically complex sentences task (two points), and the aforementioned fluency task are used to assess language. Finally, orientation to time and place is evaluated (six points) (Nasreddine et al. 2005). The MoCA is a one-page 30-point test administered in 10 minutes. The Chinese version was used in this study (Hu et al. 2013). Although we will refer to the results of the MoCA as reflecting cognitive function or cognitive performance, the MoCA is only a brief screening measure for cognitive function and is not an indepth test of cognitive abilities.

Statistical Analysis

To reduce the possibility that middle ear or cochlear problems in either ear might affect the SRT results, only subjects who had normal audiometry in both ears were evaluated. Composite SNR scores and AIAH scores were correlated with MoCA scores using linear regression analysis. Since several factors can affect the SNR in addition to cognitive performance (e.g. age, hearing thresholds, educational level) stepwise linear regression was used to assess the relationship between the composite SNR and MoCA. With stepwise linear regression, an initial model is created, and then other factors are added and removed from the model to assess their influence on the main response variable. In this case, we started with a model with composite SNR as the response variable, and age as the predictor variable

(since age can have an effect on SNR composite results). Then the factors of MoCA scores, hearing thresholds at 4 kHz, and educational levels were each considered to determine their influence on the final model.

Additionally, subjects were divided into abnormal and normal cognitive status groups based on their MoCA scores. Those with MoCA scores greater than 26 were considered not to have a cognitive deficit, based on data from Brouillette et al., who had evaluated the MoCA in HIV+ individuals (Brouillette et al. 2015). Subjects were also divided into normal or abnormal SRT groups based on whether their composite SNR was louder than the Mandarin HINT norm (a composite SNR of -5.7 dB (Soli and Wong 2008)) by two standard deviations. SRT scores and AIAH scores were compared between the abnormal and normal cognitive status groups using the Kruskal-Wallis test.

Results

One hundred and sixty six HIV+ individuals were enrolled (158 men, 8 women, average age 36 years) who all had normal tympanometry and audiometry. Table 1 summarizes the subject characteristics for the overall cohort, and also summarizes the subject characteristics when the subjects are divided by cognitive status and HINT scores. Figure 1 shows the main results from the study. The slope of the regression line between the composite SNR and the MoCA was significantly different from zero indicating a significant negative relationship between cognitive ability and the ability to understand speech in noise ($r^2=0.15$, $F=28.2$, $p < 0.001$). When the SNR values were compared between the normal and abnormal cognitive status groups using the Kruskal-Wallis test (Figure 2), the SNR levels were significantly higher (worse) in the abnormal cognitive status group (-5.5 ± 1.3 dB abnormal vs. -6.6 ± 1.1 dB normal, Chi square 19.5, $p < 0.001$).

The questionnaire data supported the SNR results. The slopes of the regression lines for the AIAH total score, and for the scores on the six AIAH subscales, compared to MoCA scores were all negative, indicating worse scores on the subscales with lower MoCA scores. The relationships were significant for the AIAH total score ($r^2=0.05$, $F=8.5$, $p=0.004$), and for the speech in noise ($r^2=0.03$, $F=5.2$, $p=0.02$), speech in quiet ($r^2=0.03$, $F=5.0$, $p=0.03$), sound detection ($r^2=0.04$, $F=6.8$, $p=0.01$), and music perception subscales ($r^2=0.07$, $F=12.3$, $p=0.001$). When the data were analyzed by comparing scores between the normal and abnormal cognitive status groups using the Kruskal-Wallis test, the AIAH total score (Chi square 3.9, $p=0.05$) approached significance, and the music perception score (Chi square 4.4, $p=0.04$) was significantly different between groups.

Another important finding, however, was that age was also significantly related to the composite SNRs ($r^2=0.22$, $F=46.9$, $p < 0.001$, Figure 3). Also, the composite SNRs were related to the audiometry results at 4 kHz and to pure tone averages (PTAs), with those with worse hearing at 4 kHz and worse PTAs having worse SNRs. The relationship between thresholds at 4 kHz and composite SNRs was stronger than the relationship between PTAs and composite SNRs indicating that most of the variability was accounted for by just by the differences at 4 kHz. Also, there were small, but significant relationships between years of education and SNRs and between education and MOCA scores. To assess the relative

contribution of these factors (age, audiometric thresholds, education level), the data were analyzed using multiple linear regression with the SRT composite score as the outcome variable and age, MoCA score, years of education, and thresholds at 4 kHz on the right and left as predictor variables. The results from this analysis is shown in Table 2. The two largest contributors to the SNR results were age and MoCA scores.

This was confirmed using stepwise linear regression, using a starting model with SNR composite score as the response variable and age as the predictor variable. In the regression model we added the additional possible predictors of MoCA score, education level, and audiometric thresholds at 4 kHz for the right and left ear. Terms were added and subtracted to optimize the sum of squares error. When this was done, the only two parameters retained in the model were age and MoCA score. The % of variability accounted for in the model increased from 22.2% with age alone to 32.2% with the addition of the MoCA score.

To assess the possibility that some of the results may be due to the effects of age on the MoCA scores, a stepwise linear regression was done using a starting model with MoCA score as the response variable, and age as the predictor variable. The additional predictors of years of education and SNR composite score were then also considered in the model. Only years of education and SRT composite were in the final model indicating that age was not a strong predictor of MoCA scores. The % of variability accounted for in the model increased from 9.9% with years of education alone to 19.6% with the addition of the SNR composite score.

Discussion

These findings confirm and expand our previous research (Maro et al. 2014) which showed the HIV+ individuals had higher gap detection thresholds and also reported difficulty understanding speech in noise—findings which were consistent with a central auditory processing deficit. In the study from Tanzania, however, the evidence for difficulty in understanding speech in noise was from self-report, rather than from direct measurements. The present study confirms objectively that many HIV+ individuals with normal hearing (thresholds 20 dB HL at 500, 1000 thresholds 20 dB HL at 500, 2000, 4000 Hz) have difficulty understanding speech in noise. Additionally, this study shows that speech in noise performance is related to performance to cognitive measures. These data suggest that poor performance on speech-in-noise testing may reflect damage to the central nervous system.

Several lines of evidence suggest that some HIV+ individuals have signs of central auditory processing deficits (Bankaitis et al. 1995; Maro et al. 2014; Matas et al. 2010; Pagano et al. 1992). These deficits could reflect HIV-related central nervous system damage because even with active antiretroviral therapy, HIV+ individuals continue to develop neurocognitive deficits (Heaton et al. 2010). To date, however, there has been no evidence relating performance on a central auditory focused task (like understanding speech in noise) to cognitive deficits in HIV+ individuals. This study is the first to show that HIV+ individuals with cognitive deficits (as measured by the MoCA) have worse speech in noise perception than those without them. Since this is occurring despite otherwise normal hearing sensitivity up to 4000 Hz, the changes might be explained by deficits in central auditory processing. It

could, however, also be related to damage to hair cells not reflected in the audiogram or to damage to the synapses between hair cells and the cochlear nerve. Recent data suggest that a synaptopathy in the synapses between the hair cells and cochlear nerve can lead to difficulties with speech in noise perception despite normal audiometry (Kujawa et al. 2009; Liberman et al. 2016). If the changes reflect deficits in central auditory processing, then this suggests the auditory system could potentially offer a “window” into the central neurological changes taking place with HIV infection.

Other studies have shown a relationship between the ability to understand speech in noise and central nervous system damage. Gallun et al. examined a group of blast-exposed veterans with a battery of central auditory processing tests. They found that 12/31 of their blast-exposed population showed abnormalities in understanding speech in noise using both ears, despite normal ability to recognize words. Only 1/29 control subjects had abnormal performance ($p < 0.01$) (Gallun et al. 2012). A growing body of evidence shows that speech perception in noise is correlated with cognitive performance in general. Ellis et al. studied 1509 individuals using internet-delivered cognitive and speech-in-noise testing, and found a strong negative relationship between scores on the trail-making test and the ability to understand speech in noise (Ellis et al. 2016). Pichora-Fuller et al. reviewed the link between diminished central nervous system performance and the ability to understand speech in challenging environments and provided a theoretical framework for understanding this link (Pichora-Fuller et al. 2016). The results from the present study demonstrate an association between cognitive function and speech-in-noise perception in HIV infected individuals as well.

In addition to the relationship to cognitive performance, performance on the HINT was also independently related to age. The ability to understand speech in background noise is known to be age-related, and declines with age, particularly after age 60 (Dubno et al. 1984). This decline, however, is not necessarily a linear function of age. Kim et al. evaluated the effect of age on the speech intelligibility in normal hearing adults using the HINT test (Kim et al. 2006). They divided their subjects into young (10-37 years), middle-aged (38-57 years), and old (>58 years) groups. The young and middle-aged groups did not differ significantly in their performance on the HINT test (although there was a tendency for the speech recognition thresholds to be worse in the middle aged group compared to the young group). The decline in HINT performance due to age was predominantly due to worse performance in those over 58 years old. In our study, only three subjects were greater than 58 years old. The age findings from this study may represent more than just age-related declines in speech in noise understanding. These age findings may also be related to the duration or severity of HIV. Although screening of high-risk groups in Shanghai has improved recently, in the past it was common for individuals to present with HIV once they had already developed the signs and symptoms of AIDS. This “late diagnosis” effect is a well-recognized problem in China (Jin et al. 2016). The older members of this cohort likely have had HIV longer and have had more severe AIDS symptoms, than the younger members. Reliable data on HIV duration in the cohort, however, are not available.

An additional area for further study is that HIV may have effects on central auditory processing that are independent of its effects on cognition or that develop prior detectable

prior to detectable cognitive deficits. For example, there were several people in this cohort who had poor speech-in-noise performance, but had normal MoCA scores. It is possible that in addition to reflecting differences in cognitive status, the HINT scores may also be markers of HIV severity and duration. This aspect of the study, however, requires further study.

Limitations

The focus of this study was on the results from the HINT, which is a test of functional hearing ability and not a pure test of central auditory processing abilities. The HINT can be affected by damage to the peripheral hearing system. Although the subjects studied here all had normal audiometry up to 4 kHz, it's possible that there could be subtle effects on the cochlea from HIV infection that influence the ability to detect speech. For example, in our previous studies we showed that otoacoustic emissions were slightly, but significantly, smaller in HIV+ individuals compared to HIV-controls (Maro et al. 2016; Maro et al. 2014). In HIV infection, the virus can be found in many locations (it has been demonstrated in the cochlea (Pappas et al. 1994), and it's possible that one potential location affected either by the virus or by HIV treatment is between the cochlear and the auditory nerve (Kujawa and Liberman 2009; Liberman et al. 2016).

We also did not measure the HINT in the quiet condition. It's possible that those with significant cognitive challenges would show abnormalities on the HINT in both the quiet and noise conditions. But, other studies have shown only minor changes in speech and word recognition in patients with HIV (Luque et al. 2014; Torre et al. 2016). Similarly, in a study on veterans with mild traumatic brain injury, there were only minor differences in word recognition scores in quiet, while speech in noise scores were significantly affected (Gallun et al. 2012).

Age also had an effect on speech in noise perception in this group, so it's possible that the findings are related to age rather than HIV-related central nervous system damage. The multiple regression and stepwise regression analyses, however, showed that both age and MoCA score contribute significantly to the model and support the previous findings of elevated gap detection thresholds. Taken together, these findings support the conclusion of a primary effect of cognitive performance on speech performance, rather than an indirect effect due to age.

Conclusion

This study suggests that the effects of HIV on the central nervous system could be tracked with central auditory tests, which might offer reliable, quantitative, time efficient, and repeatable ways to assess central nervous system function. Central nervous system damage can be a devastating consequence of HIV infection, with a major impact on quality of life. MR imaging and pathological studies show evidence of glial activation and inflammation in treated HIV patients even without documented cognitive deficits (Chen et al. 2009; Gray et al. 1996; Sailasuta et al. 2016). The ability to detect HIV-associated central nervous system effects early, and to follow their progress reliably, is important for studying, assessing, and treating this disabling HIV co-morbidity. This study shows that performance on the HINT is related to cognitive status. If performance on central auditory tests can be shown to be an

early marker of central nervous damage in HIV infection, detecting these early changes in clinical practice could lead to changes in treatment (e.g. changing drug regimens to include drugs with better central nervous system penetration). Affected individuals could also receive auditory rehabilitation and training.

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Figure 1.

A significant negative relationship exists between scores on the MoCA and the composite SNR for the HINT test.

Figure 2.
SRT composite scores were significantly higher in the abnormal cognitive status group (n=31) compared to the normal cognitive status group (n=150).

Figure 3. Scatter plot of the regression model. Both age and MoCA scores are significantly related to the composite SNR scores. The surface shows the range of SRT results for different MoCA scores and ages.

Table 1

Overall cohort characteristics as well as values when the cohort is divided by cognitive status (Normal=MoCA > 26), and by HINT result (Normal -5.7). PTA=pure tone average. All individuals were HIV +

	Normal Cognition Normal HINT N=110	Abnormal Cognition Normal HINT N=13	Normal Cognition Abnormal HINT N=25	Abnormal Cognition Abnormal HINT N=18	Total Cohort 158 M 8 F
MoCA Score	28.5±0.9 (27-30)	24.4±1.6 (20-26)	28.4±0.9 (27-30)	23.4±2.9 (15-26)	27.6±2.2 (15-30)
SRT Composite	-7.0±0.7 (-9.2-5.7)	-6.6±0.5 (-7.5-5.9)	-5.0±0.7 (-5.7-3.3)	-4.7±1.0 (-5.6-2.0)	-6.4±1.2 (-9.2-1.9)
Age	33.6±7.3 (21-54)	33.0±6.8 (20-45)	41.7±10.2 (25-60)	42.2±10.8 (23-58)	35.7±8.9 (20-60)
PTA Left	6.9±4.0 (-4.3-16.3)	8.7±4.8 (0.6-16.3)	7.7±3.1 (2.8-15.6)	7.3±3.9 (0.7-14.5)	6.7±3.9 (-4.3-16.3)
PTA Right	8.3±3.8 (-9.9-16.3)	9.5±3.7 (4.3-15)	8.7±2.9 (4.3-16.4)	8.1±2.5 (2.6-12.1)	8.2±3.7 (-9.9-16.3)
Years of education	14.9±2.3 (9-21)	15.4±4.5 (9-24)	14.8±3.2 (9-22)	11.8±3.8 (5-16)	14.6±3.0 (5-24)

Table 2

Results from multiple linear regression. SE=standard error, tStat=t statistic. Stepwise linear regression also showed that of the parameters listed only age and MoCA score are significant contributors to the model of the SRT results.

Factor	Estimate	SE	tStat	pValue
(Intercept)	-3.49	1.06	-3.30	0.0012
MOCA Score	-0.15	0.04	-4.18	4.72e-05
Age	0.05	0.01	5.6	9.02e-08
Threshold at 4 kHz (left)	-0.002	0.01	-0.12	0.90
Threshold at 4 kHz (right)	0.01	0.02	0.58	0.55
Years of education	-0.05	0.03	-1.68	0.09