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Auditory neurophysiology reveals central nervous system dysfunction in HIV-infected individuals

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HIGHLIGHTS

- Auditory-neurophysiological responses were disrupted in HIV+ patients despite normal hearing thresholds.
- Objective evidence of central nervous system (CNS) dysfunction associated with HIV.
- Neurophysiology may provide viable approach to study CNS health in HIV.

ABSTRACT

Objective: To test the hypothesis that human immunodeficiency virus (HIV) affects auditory-neurophysiological functions.
Methods: A convenience sample of 68 HIV+ and 59 HIV- normal-hearing adults was selected from a study set in Dar es Salaam, Tanzania. The speech-evoked frequency-following response (FFR), an objective measure of auditory function, was collected. Outcome measures were FFRs to the fundamental frequency (F0) and to harmonics corresponding to the first formant (F1), two behaviorally relevant cues for understanding speech.
Results: The HIV+ group had weaker responses to the F1 than the HIV- group; this effect generalized across multiple stimuli (d = 0.59). Responses to the F0 were similar between groups.
Conclusions: Auditory-neurophysiological responses differ between HIV+ and HIV- adults despite normal hearing thresholds.
Significance: The FFR may reflect HIV-associated central nervous system dysfunction that manifests as disrupted auditory processing of speech harmonics corresponding to the first formant.

1. Introduction

Central nervous system (CNS) dysfunction is associated with HIV infection even with effective anti-retroviral therapy (ART). Several hypotheses account for this dysfunction, including chronic inflammation, lingering damage from the acute infection, poor passage of ARTs through the blood–brain barrier, neurotoxic effects of ARTs, and oxidative stress from a cascade of immune system activation (Ellis et al., 2007; Saylor et al., 2016; Thakur et al., 2019). While the prevalence and severity has declined with the adoption of combination ART, by some estimates up to 45% of HIV patients still develop HIV-associated neurocognitive disorders (HAND) (Heaton et al., 2011).

Neuroimaging tests have shown structural, functional, and metabolic group differences between HIV+ and HIV- individuals, some of which are associated with cognitive function (Chang et al., 2001; Roc et al., 2007; Stout et al., 1998). For example, Sanford et al. (2018) compared 48 HIV+ adults to 29 HIV- adults and reported lower cortical thickness and subcortical brain volumes in the HIV+ group that were stable for approximately 2 years. Areas related to auditory processing are likely involved (Zhan et al., 2017a). Similarly, some studies have shown group differences in

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electrophysiological and magnetoencephalographic measures between HIV+ and HIV- individuals (reviewed by Fernández-Cruz and Fellows, 2017). These approaches can produce inconsistent results and are difficult to scale.

Measures of auditory function may offer a wider "window" into CNS health. Successful auditory processing relies on accurate and precise neural coding of fine-grained spectrotemporal cues, such as the features of speech that clue listeners into a sound's location and identity. Many populations with neurological declines or dysfunction exhibit difficulties with auditory tasks, including children with learning disabilities (White-Schwoch et al., 2015; Wright et al., 1997) and individuals with a concussion (Kraus et al., 2016; Thompson et al., 2018). Additionally, older adults with normal hearing thresholds, but typical age-related difficulties hearing in noise, exhibit diminished neural processing of speech (Anderson et al., 2012) and performance on behavioral tests of central auditory processing augur risk of Alzheimer's disease (Gates et al., 2011).

While there are mixed reports of sensorineural hearing loss in HIV+ individuals (Kohan et al., 1988; Chao et al., 2012; Torre et al., 2015), converging evidence suggests the auditory periphery is relatively healthy (Buckey et al., 2019; Maro et al., 2016, 2014). Yet, a study of 449 HIV+ individuals compared to 303 HIV- individuals showed those with HIV were more likely to complain on questionnaires of difficulties understanding speech in background noise (Maro et al., 2014). There is some evidence that HIV+ individuals have difficulty making fine-grained temporal judgments (detecting gaps in noise; Maro et al., 2014). It has been suggested that cognitive dysfunction underlies these effects, and that auditory tests such as sentence-in-noise perception could offer simple and fast proxies to cognitive abilities (Zhan et al., 2017b).

The extent to which these auditory processing difficulties can be attributed to (*i*) HIV itself, (*ii*) treatment for HIV, and/or (*iii*) immune activation in the CNS remains debated. Regardless, auditory processing difficulties appear to be part of the HIV phenotype, supporting the idea that measures of auditory function could serve as proxies of CNS health in this population. The concept of auditory system dysfunction, even while receiving ART, fits with evidence of sensorimotor dysfunctions documented in otherwise-healthy HIV + individuals (Fernández-Cruz and Fellows, 2017; Robinson-Papp et al., 2008; Wilson et al., 2013).

Our working hypothesis is that these auditory processing difficulties are grounded in the central nervous system. The speech-evoked frequency-following response (FFR) is an objective, non-invasive electrophysiological measure of auditory processing. In this test, syllables such "ba", "ga", or "da" are played into the ear and electrophysiological responses are measured with surface electrodes (similar to an electroencephalogram; see Krizman and Kraus, 2019 for review). This electrophysiological response reflects the central nervous system's ability to process sound. The response is generated predominantly by the inferior colliculus of the auditory midbrain, which is a site of convergence for ascending and descending input (Chandrasekaran and Kraus, 2010).

Here we used the FFR to measure CNS function in HIV+ individuals compared to HIV- controls. We tested the specific hypothesis that the auditory system exhibits CNS dysfunction associated with HIV status. The primary outcome measures were FFRs to the first formant and fundamental frequency of speech. These are two behaviorally relevant acoustic features of speech that identify a phoneme's and talker's identities, respectively. FFRs were elicited to consonant–vowel syllables, which are spectrotemporally complex stimuli known to challenge populations with listening difficulties (Anderson et al., 2012; Kraus et al., 2016; White-Schwoch et al., 2015). We tested our hypothesis in a sample of HIV+ and HIV- adults in Dar es Salaam, Tanzania. We predicted that the HIV+ group would exhibit diminished FFRs to these speech features.

2. Materials and Methods

Data collection took place in Dar es Salaam, Tanzania. Study procedures were approved by the Committee for the Protection of Human Subjects at Dartmouth, and by the Research Ethics Committee at the Muhimbili University of Health and Allied Sciences. Subjects provided informed consent to participate. Data presented here are a subset of a larger, longitudinal study of auditory and cognitive outcomes associated with HIV in Tanzania (Maro et al., 2014).

2.1. Subjects & groups

Subjects were recruited from the greater Dar es Salaam area and were $\geq$ 18 years of age. HIV+ subjects had to have two positive results for enzyme-linked immunosorbent assay antibody (ELISA) tests for HIV. All HIV+ subjects were on ART. HIV- subjects were recruited by word of mouth. All tested negative on an ELISA test.

The study database has approximately 400 adults, ages 18–72, approximately 75% of whom are HIV+ and 66% of whom are female. Because age (Anderson et al., 2012), sex (Krizman et al., 2012), and hearing thresholds (Anderson et al., 2013a) affect the FFR, we wanted two groups of approximately equal size matched on these parameters. We screened the database for HIV- individuals between ages 18–55 with normal hearing thresholds (pure-tone averages $\leq$ 25 dB hearing level) and replicable FFRs (i.e., the two runs of 3,000 subaverages were similar, see below). We then screened the database of HIV+ individuals within approximately 10-year age bins corresponding to the HIV- group and randomly selected matches by sex from the database. For example, if in the HIV- group there were 7 females and 4 males between the ages of 18–30, we randomly selected about that many HIV+ females and males from the database. We erred on the side of inclusivity, and ended up with groups matched sex and hearing thresholds with slightly more HIV+ (N = 68) than HIV- (N = 59) subjects.

2.2. Electrophysiology

Speech-evoked frequency-following responses (FFRs) were collected in a SmartEP system (Intelligent Hearing Systems, Miami, FL). The stimuli were the speech sounds /da/, /ba/, and /ga/. Each began with a consonant-to-vowel transition region, during which formants—high-frequency acoustic cues that convey phonetic identity—changed. The /da/ consisted of a 40 ms consonant-to-vowel transition region only; thus it was phonetically a /d/ but still perceived as "da." The /ba/ and /ga/ began with a 50 ms transition region and then had a 120 ms acoustically stable vowel portion.

Stimuli were presented to the right ear through electrically shielded insert earphones at 80 dB SPL in alternating polarities at rates of 10.9 Hz (/da/) and 4.35 Hz (/ba/ and /ga/). Responses were recorded with three Ag-AgCl electrodes at Fpz (active), A2 (reference), and Fz (ground). Responses were digitized at 40 kHz (/da/) or 13.333 kHz (/ba/ and /ga/), filtered online from 0.05–3 kHz (with a 50 Hz notch filter), and epoched from –20–55 ms re stimulus onset (/da/) and –40–190 ms re stimulus onset (/ba/ and /ga/). Any trial exceeding ± 35 μV was rejected as artifact. Two runs of 3,000 artifact-free responses to each stimulus were collected. After collection responses were filtered either from 0.1–1.5 kHz (/da/) or 0.7–2 kHz (/ba/ and /ga/). The two runs were averaged to generate final FFRs comprising 6,000 artifact-free trials.

2.3. Outcome measures

Of primary interest were FFRs to the fundamental frequency (F0) and speech harmonics, in particular the harmonics corresponding to the first formant of speech (F1). The F0 and F1 are independent components of speech that convey the pitch of a talker's voice and the phonemic identity of a sound (i.e. /a/ vs. /e/), respectively. Because the FFR mimics the acoustic properties of a waveform, we can map these components of the stimuli directly onto FFR properties.

For the F1, responses to alternating polarities were subtracted and were (Hanning) windowed 10 ms on either side. Spectra were then computed using the fast Fourier transform (FFT). For response to the /da/, FFTs were run over 19.5–44.2 ms re stimulus onset. Two FFTs each were run for responses to /ba/ and /ga/, one corresponding to the response to the consonant-to-vowel transition (20–60 ms re stimulus onset) and the other to the steady-state vowel (60–170 ms). Spectral bins of interest were broader for the /da/, because its pitch was dynamic. For responses to /da/, the mean amplitude from 175-750 Hz was calculated. For response to /ba/ and /ga/, the mean amplitude at 700 Hz (20 Hz bin) was calculated (Anderson et al., 2013a; Skoe and Kraus, 2010).

Procedures for quantifying the response to the F0 were identical except that FFTs were performed on the sum of responses to the alternating polarities. For responses to /da/, the mean amplitude from 75-175 Hz was calculated whereas for responses to /ba/ and /ga/ the mean amplitude at 100 Hz (20 Hz bin) was calculated.

Finally, to gauge the level of noise in each response, the root-mean-squared amplitude of the prestimulus region was calculated. This corresponds to the response to the silent gap between each presentation of the speech stimulus and provides an indicator of broadband noise in the FFR recording

2.4. Experimental design and statistical analyses

The HIV+ and HIV- groups' responses to the F0 and F1 for each stimulus and time region were compared with repeated-measures analyses of variance (2 × 2 × 3 RMANOVA), covarying for each individual's age. Stimulus was the within-subjects factor and group was the between-subjects factor. Where group means are reported they are accompanied by 95% confidence intervals (bootstrapped with 10,000 iterations). Significance level was set to 0.05 and all tests were two-tailed. Our study design provided power to detect effect sizes as small as $d \approx 0.3$. Power analyses were conducted in G*Power 3.1 (Faul et al., 2007) and statistical analyses in SPSS Version 25 (IBM, Armonk, NY).

3. Results

This study reports on a sample of 68 HIV+ and 59 HIV- subjects. The mean age was 35.2 yr (SD, 10.6 yr; range: 18.1–52.9 yr). The HIV+ and HIV- groups had a similar distribution of males and females ($\chi^2 = 1.82$, p = .176). The HIV+ group was about 6 years older than the HIV- group (t(125) = 3.24, p = .002) and so all analyses co-varied for age. The groups had similar pure-tone-average hearing thresholds in the right and left ears (both controlling for age, main effect: F(1,124) = 0.42, p = .515, and not controlling for age, main effect: F(1,125) = 1.49, p = .23). Details on demographics and hearing thresholds are presented in Table 1. Middle-ear health were further evaluated by tympanograms, on which the groups did not differ ($\chi^2 = 4.09$, p = .252).

We quantified FFRs to the fundamental frequency (F0) and speech harmonics corresponding to the first formant (F1) of each speech sound—chief acoustic cues that convey the sound's pitch and phonetic identity, respectively (see Fig. 1 for each groups' average FFR for each stimulus and Table 2 for mean amplitudes for each stimulus, time region, and acoustic cue). The stimuli could be divided into two time regions: (*i*) the "transition" region, which reflects the initial onset of the speech sound and the dynamic spectrotemporal shift from the consonant to the vowel, and (*ii*) the vowel region, which is spectrotemporally static. There was an acoustic cue (F0 vs. F1) × group (HIV- vs. HIV+) interaction for the transition region (F(1,120) = 4.864, p = .029, $\eta^2 = 0.039$; Fig. 2A) but not the vowel region (F(1,124) = 2.158, p = .144, $\eta^2 = 0.017$; Fig. 2B).

Table 1
Descriptive statistics for each group. Reported are the number of males and females in each group, the mean age, and the pure-tone-averaged (PTA) hearing thresholds in the right and left ears. Also reported are 95% confidence intervals.

	HIV+	HIV-
Males : Females	37 : 31	34 : 25
Age (yr)	38.6 [36.1, 41.1]	32.7 [30.2, 35.1]
PTA-Right	7.84 [6.56, 9.20]	6.97 [4.21, 10.04]
PTA-Left	6.72 [5.17, 8.27]	4.38 [2.16, 6.62]

In both the transition (consonant to vowel) and vowel regions of the FFR there are F0 and F1 responses. For the F0 and F1 in the transition region, F1 responses were smaller in the HIV+ group over the transition region of all stimuli (/da/, /ba/, and /ga/; main effect of group, F(1,120) = 13.642, p < .001, d = 0.67). Averaged across all stimuli, the HIV+ group had responses 2.99 nV smaller than the HIV- group (95% CI: [1.80, 4.17]). The magnitude of the difference was similar across all stimuli (no group × stimuli interaction, F(2,119) = 0.75, p = .48). For F0 responses, there was neither a group main effect (F(1,120) = 1.96, p = .16) nor a group × stimulus interaction (F(2,119) = 1.01, p = .37).

The HIV+ group's F1 responses were also smaller over the vowel regions for the two stimuli with a static vowel (/ba/ and /ga/; main effect of group, F(1,124) = 10.81, p = .001, d = 0.59). Averaged across both stimuli, the HIV+ group had responses 6.10 nV smaller than the HIV- group (95% CI: [3.34, 8.85]. The magnitude of this difference was also similar across stimuli (no group × stimuli interaction, F(1,124) = 0.67, p = .41). For F0 responses, there was neither a group main effect (F(1,124) = 0.05, p = .82) nor a group × stimulus interaction (F(1,124) = 0.25, p = .62).

Importantly, these group F1 differences could not be attributed to the noise levels of the FFRs. We quantified noise by calculating the magnitude of the prestimulus period of each response. The HIV+ and HIV- groups were matched with respect to noise levels for all stimuli (/da/, /ba/, and /ga/: no main effect of group F(1,120) = 0.45, p = .50; no group × stimuli interaction, F(2,119) = 1.46, p = .238).

Previous work has shown a small, but reliable, difference in DPOAEs between HIV+ and HIV- individuals (Maro et al., 2014). Here, as a summary statistic, we calculated the mean DPOAE SNR from 1500-8000 Hz measured at L1/L2 values of 65/55 dB SPL and 70/70 dB SPL bilaterally. The mean DPOAE amplitudes in the HIV+ group was slightly lower than in the HIV- group (HIV+ mean = 19.93, SD = 4.23; HIV- mean = 21.43, SD = 4.53) although the group difference was only trending towards statistical significance (t(121) = 1.883, p = .062, d = 0.341). Still, we reran analyses on FFR data controlling for DPOAE amplitudes. When controlling for mean DPOAE SNR, all results held. There remained an acoustic cue (F0 vs. F1) × group (HIV- vs. HIV+) interaction for the transition region (F(1,120) = 4.903, p = .029, $\eta^2 = 0.041$) but not the vowel region (F(1,124) = 2.522, p = .113, $\eta^2 = 0.021$). This analysis suggests the group differences we document in the FFR can be attributed to differences in CNS function and not peripheral auditory function.

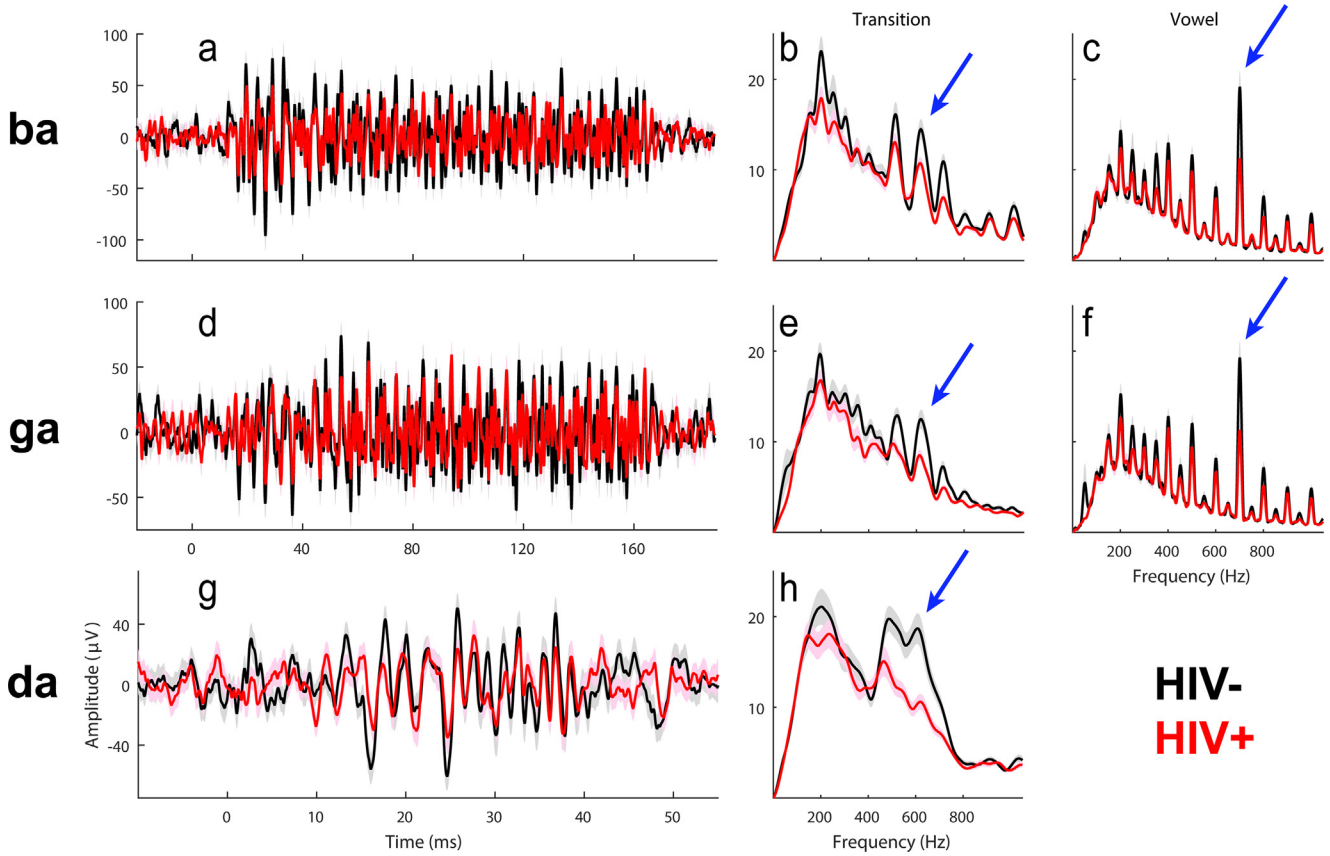

Fig. 1. Frequency-following responses for HIV+ (red) and HIV- (black) groups. Illustrated are averaged responses to ba (top row), ga (middle row), and da (bottom row). Responses are shown in the time domain (a, d, g) and frequency domain. Spectra were calculated over the consonant region (b, e, g) and vowel region (c and f; the da stimulus only contains the consonant region). Arrows point to the response harmonics corresponding to the first formant (F1) component of each stimulus. Shaded regions indicate ± 1 SEM. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Frequency-following response amplitudes for each group (nV). Data presented are mean with 95% confidence intervals. Reported are amplitudes for responses to speech harmonics corresponding to the first formant (F1, for which the groups differ; top panel), fundamental frequency amplitudes (F0, groups are matched; middle panel), and the prestimulus amplitudes, an indicator of broadband noise in the FFR recording (groups are matched; bottom panel). Also reported are 95% confidence intervals. Groups differ on the F1 measures, indicated in bold.

			HIV+	HIV-
F1	**Transition**	**da**	**12.47 [11.17, 13.77]**	**15.76 [14.4, 17.12]**
		ba	**6.14 [5.36, 6.91]**	**9.02 [7.76, 10.28]**
		ga	**4.41 [3.77, 5.06]**	**6.24 [5.23, 7.26]**
	Vowel	**ba**	**8.77 [7.64, 9.89]**	**14.21 [11.54, 16.88]**
		ga	**8.81 [7.66, 9.96]**	**14.28 [11.67, 16.9]**
F0	Transition	da	36.51 [31.51, 41.51]	37.54 [33.93, 41.16]
		ba	38.62 [34.53, 42.72]	34.81 [30.17, 39.45]
		ga	36.99 [31.57, 42.41]	34.04 [30.25, 37.84]
	Vowel	ba	22.3 [18.65, 25.94]	25.95 [21.85, 30.05]
		ga	21.19 [17.5, 24.87]	24.86 [20.92, 28.79]
Prestimulus		da	64.74 [57.9, 71.57]	63.15 [55.77, 70.53]
		ba	61.61 [55.86, 67.37]	56.2 [51.53, 60.88]
		ga	57.81 [51.05, 64.57]	59.0 [53.05, 64.94]

4. Discussion

This paper is our first test of the specific hypothesis that auditory CNS dysfunction associated with HIV status is reflected in the FFR. We measured speech-evoked FFRs to compare auditory-neurophysiological functions in HIV+ and HIV- patients. We specifically tested for differences in the coding of two behaviorally relevant speech cues, the fundamental frequency (F0) and speech harmonics corresponding to the first formant (F1). Contrary to our predictions, only the F1 component of the FFR was diminished in the HIV+ group, whereas the groups were matched on the F0 components. Thus, subcortical auditory processing, as measured by the FFR, is only partially disrupted in individuals with HIV.

In contrast to the F0, the neural coding of harmonics corresponding to the F1 hinges on extremely fine temporal precision: it is the aggregate of subcortical auditory neural ensembles synchronizing their output at 700 Hz (or 1.42 ms). This suggests the CNS dysfunction we document in HIV+ individuals is due to subtle changes in fine-grained neural coding (White-Schwoch et al., 2017). Even subtle variations in neural timing, such as those due

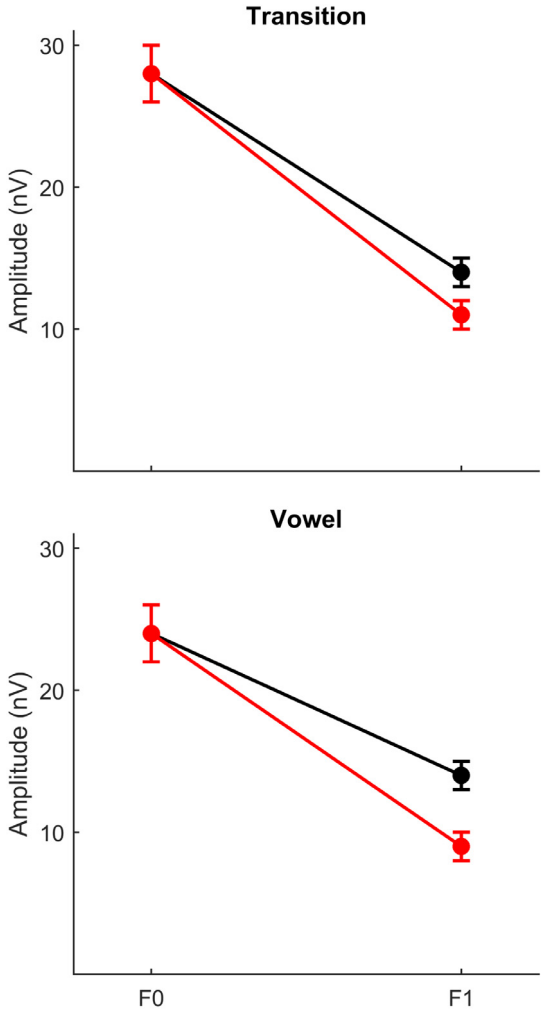

Fig. 2. Mean amplitudes for fundamental frequency (F0) and harmonics corresponding to the first formant formant (F1) for the consonant (top) and vowel (bottom) regions. Groups have matched responses to the F0, whereas the HIV- group has diminished responses to the F1. HIV- black, HIV+ red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to synaptic damage (Roux et al., 2006) or misbalances between inhibition and excitation (Caspary et al., 2008; Wehr and Zador, 2003), could lead to this deficit in temporal precision. While our results cannot distinguish between different hypotheses for the mechanisms underlying neural injury in HIV, many, including synaptic injury and chronic inflammation, could conceivably induce this subtle dyssynchrony in auditory processing.

Older adults with normal hearing also have diminished neural coding of these high-frequency speech features, which is associated with difficulties understanding speech in noise. But, those declines tend to emerge 10 + yr later than we document here. Although there was a wide age range in our HIV+ group, we explicitly controlled for patients' ages in our statistical models. The observation that these declines mirror those observed in sexagenarians suggest that HIV-associated CNS dysfunction may be akin to early aging, which suggests early emergence of aging-related neurocognitive deficits in HIV+ individuals.

Unlike behavioral tests, the FFR is recorded passively: subjects may sleep or watch a movie. Thus, it is not affected by an individual's compliance, understanding, or ability to complete the test. This makes it a candidate for further research into CNS health and, potentially, cognitive function in HIV+ individuals. Auditory processing—including the aspects measured by the FFR—correlates with performance on cognitive tasks in HIV- individuals (Anderson et al., 2013b). A second important feature of the FFR is its speed and portability. While previous neuroimaging and electrophysiological studies have shown differences between HIV+ and HIV- individuals, these approaches are difficult to transport to resource-limited settings such as sub-Saharan Africa, where > 70% of the world's HIV+ population lives and where there is some evidence that neurocognitive symptoms are more severe (Sacktor et al., 2007; Saylor et al., 2016). Thus, the FFR holds promise as a research tool to further study CNS health, particularly in resource-limited settings.

Several hypotheses account for the mechanisms of CNS dysfunction in HIV (Ellis et al., 2007; Saylor et al., 2016; Thakur et al., 2019). One of the difficulties in arbitrating among them is the disconnect between information available in animal models and that accessible in humans. The FFR is robust and replicable in multiple species: identical FFR protocols as reported here have been used in primate (Ayala et al., 2017) and small rodent models (White-Schwoch et al., 2017). The FFR might be a viable cross-species measure of CNS function in HIV, using animal models to understand the underlying mechanisms of CNS disease and humans to understand their clinical sequelae.

All HIV+ patients in this study received ART. As in many complex diseases, it is difficult to dissociate effects of the disease from its treatment. ART is the standard of care for HIV and so our patients are representative of the broader population in this regard. A limitation of our study is the moderate sample size and single observation. While the effects we show replicated across stimuli, it will be important to (*i*) replicate these effects in a larger sample, (*ii*) follow cohorts longitudinally, particularly in early stages of infection, and (*iii*) test for the generality of these effects in other populations, especially in light of evidence of interactions between genetics and susceptibility to the neurological sequelae of HIV (Sacktor et al., 2007). Our HIV+ population was also slightly older, on average, than our HIV- population. Although we covaried for age it will be important to replicate these effects in more closely matched cohorts.

Moreover, it will be important to pursue additional research to disentangle peripheral and central consequences of HIV infection. This will help resolve conflicting reports in the field. There do seem to be subtle, but reliable, differences in DPOAEs between HIV+ and HIV- patients (Buckey et al., 2019; Maro et al., 2014). In the current study there was a slight, trending difference in DPOAEs between our groups, but controlling for this difference did not affect FFR results. Although DPOAEs are not sufficient to generate FFRs (White-Schwoch et al., 2019), there is evidence that DPOAE amplitudes correlate mildly with FFR amplitudes (Dhar et al., 2009). Large, longitudinal studies can disentangle the peripheral and central effects of HIV infection on auditory processing, and potential interactions between the two sources of dysfunction.

5. Conclusions

In summary, we document a deficit in auditory processing associated with HIV. Specifically, we show that the FFR, an objective auditory-neurophysiological measure, indicates reduced neural coding of harmonics corresponding to the first formant of speech. Neural coding of the fundamental frequency does not appear to be associated with HIV. Poor coding of this behaviorally salient speech cue may underlie certain perceptual and cognitive deficits associated with HIV. We envision the FFR as a viable approach to further understand the mechanisms of HIV-associated CNS dysfunction.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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