



OPEN Altered auditory brainstem responses are post-acute sequela of SARS-CoV-2 (PASC)

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The Post-acute Sequela of SARS-CoV-2 (PASC) syndrome, also known as Long-COVID, often presents with subjective symptoms such as brain fog and cognitive fatigue. Increased tinnitus, and decreased hearing in noise ability also occur with PASC, yet whether auditory manifestations of PASC are linked with the cognitive symptoms is not known. Electrophysiology, specifically the Auditory Brainstem Response (ABR), provides objective measures of auditory processing. We hypothesized that ABR findings would be linked to PASC and with subjective feelings of cognitive fatigue. Eighty-two individuals, 37 with PASC (mean age: 47.5, Female: 83%) and 45 healthy controls (mean age: 38.5, Female: 76%), were studied with an auditory test battery that included audiometry and ABR measures. Peripheral hearing thresholds did not differ between groups. The PASC group had a higher prevalence of tinnitus, anxiety, depression, and hearing handicap in addition to increased subjective cognitive fatigue. ABR latency findings showed a significantly greater increase in the wave V latency for PASC subjects when a fast (61.1 clicks/sec) compared to a slow click (21.1 clicks/sec) was used. The increase in latency correlated with cognitive fatigue scores and predicted PASC status. The ABR V/I amplitude ratio was examined as a measure of central gain. Although these ratios were not significantly elevated in the full PASC group, to minimize the confounding effect of age, the cohort was median split on age. Elevated V/I amplitude ratios were significant predictors of both predicted PASC group classification and cognitive fatigue scores in the younger PASC subjects compared to age-matched controls providing evidence of elevated central gain in younger individuals with PASC. More frequent tinnitus also significantly predicted higher subjective cognitive fatigue scores. Our findings suggest that PASC may alter the central auditory pathway and lead to slower conduction and elevated auditory neurophysiology responses at the midbrain, a pattern associated with the typical aging process. This study marks a significant stride toward establishing an objective measure of subjective cognitive fatigue through assessment of the central auditory system.

Some individuals with SARS-CoV-2 infection develop a poorly understood post-viral syndrome (Post-Acute Sequelae of SARS-CoV-2 Infection - PASC) that persists for weeks, months, or even years^{1–4}. Even those with no neurological signs during acute infection can develop “brain fog” often characterized by cognitive fatigue, difficulty concentrating, and problems with memory. These symptoms suggest that PASC may result from central nervous system (CNS) dysfunction from the virus^{5–8}. Cognitive fatigue is the most common and persistent CNS concern in PASC^{1,5,9,10}, but cognitive fatigue is subjective, difficult to quantify, and not specific to PASC.

CNS dysfunction may be detectable using the auditory system. Behavioral auditory symptoms such as difficulty with auditory discrimination, speech perception in background noise, presence of vertigo, and increases in tinnitus and hyperacusis (heightened sensitivity to sound) are often overlooked manifestations of PASC^{11–15}. Using auditory brainstem responses (ABRs), an electrophysiologic technique, al, Gedik et al.¹⁶, found increased III-V interpeak latencies in those with history of COVID-19 infection (not PASC). Ozturk et al.¹⁷ found delays in the individual wave I, III and V peaks, among those with a history of COVID-19 but no significant difference in interpeak latencies. Dorobisz et al.¹⁸ found delayed latency (i.e., slower conduction time) of ABR waves

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III and V in those with PASC, as well as delayed I–III and I–V interpeak intervals. These articles focused on damage to the cochlea or peripheral hearing system as measured by the audiogram, OAEs, and the ABR (Wave I). Changes in ABR latencies and amplitudes, however, may also reflect damage to the central hearing system (i.e., the brainstem). Rather than examining only the latencies of individual peaks, effects on nerve function might be revealed better by using differences in Wave V latencies between slow and fast ABR click rates^{19–21}. Latencies of ABR waves increase with faster click rates. Diseases that affect nerve transmission, such as multiple sclerosis^{22,23} will lead to greater increases in latency with faster click rates compared to controls. Evidence shows that coronaviruses can be both neuroinvasive and neurovirulent. This could affect nerve conduction, which might be manifest in the differences in wave V latencies between slow and fast click rates.

Also, the ABR peaks, specifically the V/I amplitude ratio, may be useful for looking at changes in central gain^{24,25}. Decreases in the primary inhibitory neurotransmitter, GABA, have been reported in those with PASC^{26–28}. Given the link between GABA and central auditory gain, this sets up the possibility of heightened central gain in PASC and associated disruptions to auditory perception. Studies suggest tinnitus, the sensation of sound absent an external stimulus, can arise through abnormal neural gain mechanisms in the central auditory pathway²⁹. Tinnitus, a frequently reported PASC symptom, is arguably one of the most prevalent, yet also one of the most complex, auditory conditions, often with an undetermined etiology or multifactorial cause^{30,31}. Studies suggest it can arise from changes to the auditory nerve (e.g., microvascular compression or degeneration), and/or CNS dysfunction^{29,32,33}. Gain escalation may emerge at multiple levels of the CNS in response to auditory trauma, hearing loss, or advanced age, leading to an over-application of sound-evoked neural activity in midbrain and cortex as well as disordered auditory percepts^{25,28,29}. Auditory central gain can be quantified objectively and non-invasively using auditory brainstem responses (ABRs), by comparing electrical activity produced by the cochlear nerve (ABR wave I amplitude) to activity in midbrain (ABR wave V amplitude)^{34,35}. Central gain models may explain other auditory disorders, including hyperacusis (i.e., loudness intolerance), which has also been reported with PASC^{29,36}. The ABR profile of tinnitus has been extensively studied³⁷. Several studies have demonstrated that individuals with tinnitus, despite having normal hearing sensitivity, exhibit significantly reduced amplitudes of ABR wave I and often display elevated or at least normal wave V amplitudes compared to control subjects, leading to abnormal V/I ratios indicative of increased central gain^{33,38–40}. Central gain models are potentially wide reaching in their explanatory power. They may explain the spectrum of loudness and background noise tolerance observed in healthy young participants⁴¹ and age-related sound-evoked changes in midbrain and cortex from decreased central inhibition²⁵.

To explore the link between PASC cognitive symptoms and both latencies and amplitudes on the ABR, we recorded ABRs on participants recruited from a PASC clinic. The focus was on using the increased stimulus repetition rate effects slow-fast wave V latency difference as a measure of diminished nerve function and the wave V/I ratio as a measure of central gain. Demographic information was collected, and hearing questionnaires and peripheral and central auditory tests were performed. The PASC group was compared to controls, who self-reported never having tested positive for COVID-19 or having what they believed to be COVID-19 symptoms. The goal was to examine the ABR for indications of delayed slow-fast latencies and elevated auditory central gain to determine whether the ABR could predict subjective cognitive symptoms in those with PASC.

Materials and methods

Participants

Eighty-two individuals participated in this cross-sectional study, including 37 with PASC (mean age: 47.5, Female: 83%) and 45 healthy controls (mean age: 38.5, Female: 76%) (See Table 1). The age range for all subjects was

	Controls	PASC	P value
N-size	45	37	N/A
Females (%)	34 (76%)	31 (83%)	0.171
Age (SD)	38.5 (15.4)	47.5 (13.0)	0.003
Pure Tone Average – Right Ear (SD)	2.01 (5.25)	4.76 (8.02)	0.079
Pure Tone Average – Left Ear (SD)	3.26 (5.04)	5.22 (7.02)	0.160
Education (SD)	17.5 (2.06)	16.8 (2.81)	0.295
Amsterdam Inventory of Auditory Handicap (SD)	6.58 (7.39)	12.8 (11.4)	0.011
Beck Anxiety Inventory (SD)	3.60 (3.81)	11.7 (10.5)	< 0.001
Beck Depression Inventory (SD)	5.70 (7.60)	14.5 (8.51)	< 0.001
Chalder Fatigue Score (SD)	3.77 (0.84)	9.54 (1.89)	< 0.001
Tinnitus Prevalence (%) (more than once a week)	4 (9%)	14 (38%)	0.019

Table 1. Demographics. This table shows similar sex, hearing ability, and education between the two experimental groups. Age, reported auditory handicap, anxiety, depression, cognitive fatigue, and tinnitus were significantly different between groups. Pure tone average was the average hearing thresholds at 0.5, 1.0, 2.0, 4.0, 6.0, and 8.0 khz. All *p*-values were derived from a T-test for independent groups, except for sex and tinnitus differences which was derived using a Chi-Square test.

18–69 years. All subjects were required to have a documented COVID-19 vaccination before beginning testing. PASC subjects were recruited from local communities in New Hampshire and Vermont, and the dedicated PASC Clinic at Dartmouth-Hitchcock Medical Center. Control subjects were recruited from communities in New Hampshire, Vermont, and Connecticut. Participants recruited from Connecticut were tested at the University of Connecticut, while all other participants were tested at Dartmouth-Hitchcock Medical Center.

Control group eligibility criteria included no history or diagnosis of COVID-19. The PASC group was defined by persistent cognitive fatigue, as determined by a score of >5.7 on the cognitive fatigue subscale from the Chalder Fatigue Scale, completed at least 2 months after a confirmed COVID-19 diagnosis via PCR (polymerase chain reaction). Exclusionary criteria for both groups were abnormal otoscopy or tympanograms (Type B or C), or a history of significant ear pathology, concussion, significant noise exposure, neurological disease, severe mental illness, or ototoxic antibiotics. The research protocol was approved by the Committee for the Protection of Human Subjects of Dartmouth-Hitchcock Medical Center, Dartmouth College, and the Institutional Review Board of the University of Connecticut and performed in accordance with the Declaration of Helsinki. All research was performed in accordance with relevant guidelines/regulations, and written informed consent was obtained from all participants.

Questionnaires

Subjects completed questionnaires on self-reported hearing ability and general health. Two questions about tinnitus from the National Health and Nutrition Examination Survey (NHANES) were included in the hearing ability questionnaire⁴². The first asked, “In the past 12 months have you been bothered by ringing, roaring, or buzzing in your ears or head that lasts for 5 minutes or more?” If they answered yes, they were asked how often the symptoms occurred. Self-reported auditory handicap was measured using the Amsterdam Inventory of Auditory Handicap (AIAH)⁴³. Depression and anxiety were measured with the Beck Depression Inventory (BDI-II) and the Beck Anxiety Inventory (BAI), respectively^{44–46}. Fatigue was measured using the Chalder Fatigue Scale (CFQ)⁴⁷. This scale includes separate sub-scales for physical and mental/cognitive fatigue^{47,48}. The CFQ includes items asking about symptoms suggestive of CNS dysfunction such as difficulty concentrating, trouble finding words, and problems with memory. The CFQ asked individuals to compare how they felt now to have they felt prior to contracting COVID-19, with responses measured on a Likert scale and summed. PASC group membership required CFQ scores one standard deviation or more above the mean on the cognitive fatigue subscale (i.e., >5.7)⁴⁹. The Neurobehavioral Symptom Inventory (NSI) was also given to assess PASC symptom severity⁵⁰. In this study we specifically examined the NSI somatosensory (NSI-ss), cognitive (NSI-cog), and affective (NSI-a) factors based on the three-factor, 22-item NSI model described by Caplan, Ivins, Poole, Vanderploeg, Jaffee and Schwab⁵¹. For the subscales, somatosensory scores can range from 0 to 40, cognitive scores from 0 to 16, and affective scores from 0 to 28.

Peripheral auditory assessment

Otoscopy and tympanometry were performed on all subjects. Pure tone audiometry was completed with Creare LLC's hearing test system with Sennheiser HD-200 headphones controlled through a laptop while in a sound booth. Air conduction thresholds were measured with a Békésy-like tracking procedure at octaves from 0.5 to 8 kHz plus the 6-kHz inter-octave. A pure tone average was calculated from 0.5 to 8.0 kHz for each ear.

Auditory brainstem response testing

The ABR was measured using the SmartEP system (Intelligent Hearing Systems). The ABR was collected using a 1-channel electrode array, with an electrode attached to the right earlobe as reference, a ground electrode at F_{pz} , and an electrode at the high forehead (F_z) as the noninverting electrode. The stimuli were 100-ms rarefaction clicks presented through insert earphones (ER-3As). As the ABR is sensitive to the effect of stimulus rate on neural synchrony, two rates, 21.1/s (slow) or 61.1/s (fast) at 80 dB SPL to the right ear were used to assess the increase in latency that occurs with a higher click rate. A grand mean waveform was also calculated by averaging the two click rates together. Two repetitions of each click rate were recorded and then averaged together (total, 4000 sweeps, 2000 sweeps per rate). Responses were online filtered from 0.1 to 1.5 kHz (second-order Butterworth). Online recordings were epoched with a -5–12 ms window and averaged. The absolute latencies and amplitudes of waves I, III, and V were measured on the average waveform from the zero-microvolt line as well as from peak to subsequent trough. Rate differences on latency measures were also calculated. Central gain was assessed by measuring the amplitude ratio of wave V to wave I. Peaks to stabilize the V/I ratio were identified by two independent selectors blinded to group membership. A third highly experienced selector adjudicated any discrepancies between selectors.

While the V/I ratio is a common measurement approach in the ABR literature, there are statistical challenges to using ratios that are not often considered in the literature. When Wave I is significantly reduced (close to zero), this produces exceeding high ratios. To address this limitation and stabilize the ratio, a constant was added to the Wave I and Wave V amplitudes before calculating the ratio. Specifically, we added the cohort average amplitude for each peak (wave I – 0.183 mV and wave V – 0.311 mV).

Experimental design and statistical analysis

Efforts to match groups based on age, sex, and hearing ability during targeted recruitment were not fully successful. Consequently, two analysis approaches were used. First, group analysis using all subjects was employed. Second, participants were median divided into two age groups: a younger group aged 18–45 years, and an older group aged 45–69 years (See Table 2). In the younger age range, problems with auditory processing are rare and so any findings in this age group could be particularly noteworthy. A four-group cross-sectional design was used to assess differences in ABR measures between younger and older PASC subjects and their

	Young controls	Young PASC	P value	Older controls	Older PASC	P value
N-size	27	15	N/A	18	22	N/A
Females (%)	20 (74%)	13 (87%)	0.030	15 (83%)	18 (80%)	0.900
Age (SD)	27.5 (3.81)	34.8 (5.85)	0.001	55.1 (6.54)	57.3 (6.97)	0.319
Pure Tone Average – Right Ear (SD)	-0.45 (3.81)	0.51 (4.27)	0.472	5.72 (5.01)	7.66 (8.74)	0.385
Pure Tone Average – Left Ear (SD)	0.83 (3.63)	2.07 (5.35)	0.429	6.91 (4.71)	7.36 (7.32)	0.815
Education (SD)	16.9 (2.23)	16.8 (2.44)	0.956	18.1 (1.79)	16.7 (3.07)	0.139
Amsterdam Inventory of Auditory Handicap (SD)	8.37 (8.37)	12.6 (9.54)	0.155	4.16 (4.14)	12.4 (13.2)	0.011
Beck Anxiety Inventory (SD)	4.00 (3.77)	13.9 (13.3)	0.022	2.72 (4.00)	10.3 (8.36)	0.001
Beck Depression Inventory (SD)	6.70 (8.35)	16.8 (10.6)	0.018	3.63 (4.73)	13.0 (6.70)	<0.001
Chalder Fatigue Score (SD)	3.59 (0.74)	9.66 (1.95)	<0.001	4.05 (0.93)	9.45 (1.89)	<0.001
Tinnitus Prevalence (%) (more than once a week)	1 (4%)	4 (27%)	0.027	3 (17%)	10 (45%)	0.153

Table 2. Demographics of age subsets. Pure tone average was the average hearing thresholds at 0.5, 1.0, 2.0, 4.0, 6.0, and 8.0 khz. All p-values were derived from a T-test for independent groups, except for sex and tinnitus differences which was derived using a Chi-Square test.

respective control groups. Demographic characteristics of the experimental groups were compared with t-tests for independent groups and a chi-square distribution test for sex and tinnitus prevalence. Primary analyses focused on the difference between ABR variables between PASC and control subjects and within age groups. Logistic and linear mixed effect models explored the relationship between ABR measures and PASC diagnosis as well as subjective cognitive fatigue scores on the Chalder and Neurobehavioral Symptom Inventory using MATLAB 2023b (MathWorks). Mixed-effects models were chosen for two reasons: (1) they can model correlated data, such as repeated measurements of the ABR, which leads to more accurate estimates of model parameters. (2) mixed effect models also require fewer assumptions about the underlying data distribution compared to ANOVA or traditional regression models. Due to the exploratory nature of this study and limited sample size, correction for multiple comparisons was not implemented. Implementing such corrections could potentially increase the risk of Type II errors, where true effects may be falsely dismissed as non-significant. Therefore, to maintain sensitivity and avoid excessive conservatism in our analysis, we have opted to interpret our results without correction for multiple comparisons, with the understanding this may increase the likelihood of Type I errors.

Results

Demographic, hearing thresholds and questionnaire results

Overall, PASC and controls were matched on sex, education, and peripheral hearing ability (pure tone averages from 0.5 to 8.0 kHz), but showed a clear age difference (Table 1). PASC subjects had higher perceived hearing handicap, as well as higher anxiety, depression, and cognitive fatigue. The PASC subjects were significantly more likely to report tinnitus more than once a week or more frequently. The younger and older groups showed similar education and peripheral hearing ability within groups (Table 2). The older group showed similar sex distribution and age between PASC and controls, however, the younger PASC group showed slightly higher female percentage and older age compared to the younger controls. Compared to controls, younger PASC subjects were significantly more likely to report frequent tinnitus. While we did not directly ask about the difference in tinnitus symptoms before and after COVID-19 infection, multiple subjects spontaneously reported their tinnitus was more noticeable after diagnosis or the subjective perception began since diagnosis (14/37 all PASC subjects). No control subject reported constant tinnitus perception (i.e., “Always”), while 30% of the PASC subjects reported constant tinnitus (Supplemental Fig. 1). Within the age subgroups, the older PASC group had the largest percentage of constant tinnitus (Supplemental Fig. 2).

On mood measures, the PASC group had significantly higher levels of depression, anxiety, and negative affect compared to controls (all $p < .001$). Supplemental Figs. 3 and 4 shows box plots of questionnaire results for the entire cohort and subgroup analysis respectively. Somatosensory complaints (NSI-ss) were also higher in the PASC group ($p < .001$). Subjective cognitive fatigue (CFQ) and subjective cognitive functioning (NSI-cog) was also significantly higher in the PASC group compared to controls (all $p < .001$). In the subgroup analysis, all PASC groups showed higher levels of depression, anxiety, and negative affect compared to controls (all $p < .002$). While the CFQ was expected to be higher in those with PASC (i.e., part of inclusion criteria), the NSI further supported the presence of subjective cognitive concerns such as poor concentration, slowed thinking, forgetfulness, and difficulty with decision making. Notably, the PASC group also reported higher subjective hearing handicap (AIAH) as compared to controls in the overall cohort ($p = .011$) and the older subgroup analysis ($p = .011$), but not the younger group ($p = .155$).

ABR results—entire cohort

Grand mean waveforms and the fast and slow click rates for the overall cohort are plotted in Fig. 1. Two main findings revealed differences in wave I amplitude and wave V latency between PASC and controls. Although the data showed a trend toward amplitude differences between groups on multiple peaks, the PASC and controls groups differed only on wave I amplitude in the grand mean ($p = .011$) and using the fast click rate ($p = .006$) with controls having larger amplitudes (Supplementary Table 1). The V/I amplitude ratio was not different between PASC and controls ($p = .144$). While wave I amplitude differences were likely due to the age disparity between groups, a larger wave V latency difference between slow and fast click rate was observed for PASC subjects ($p = .042$).

Figure 2 shows a plot of ABR V/I ratio across age collapsed across click rate. The controls show a gradual increase in V/I ratio with age; a second order polynomial using the least absolute residuals was determined as best fit for the control group. This best fit line was used as the basis for analyzing the PASC group. For the PASC subjects, we calculated how many subjects in each group were above and below the line of best fit. Although PASC subjects were more likely to be above the line (60%), Fisher's Exact test showed no difference in V/I ratio across the age range ($p = .144$).

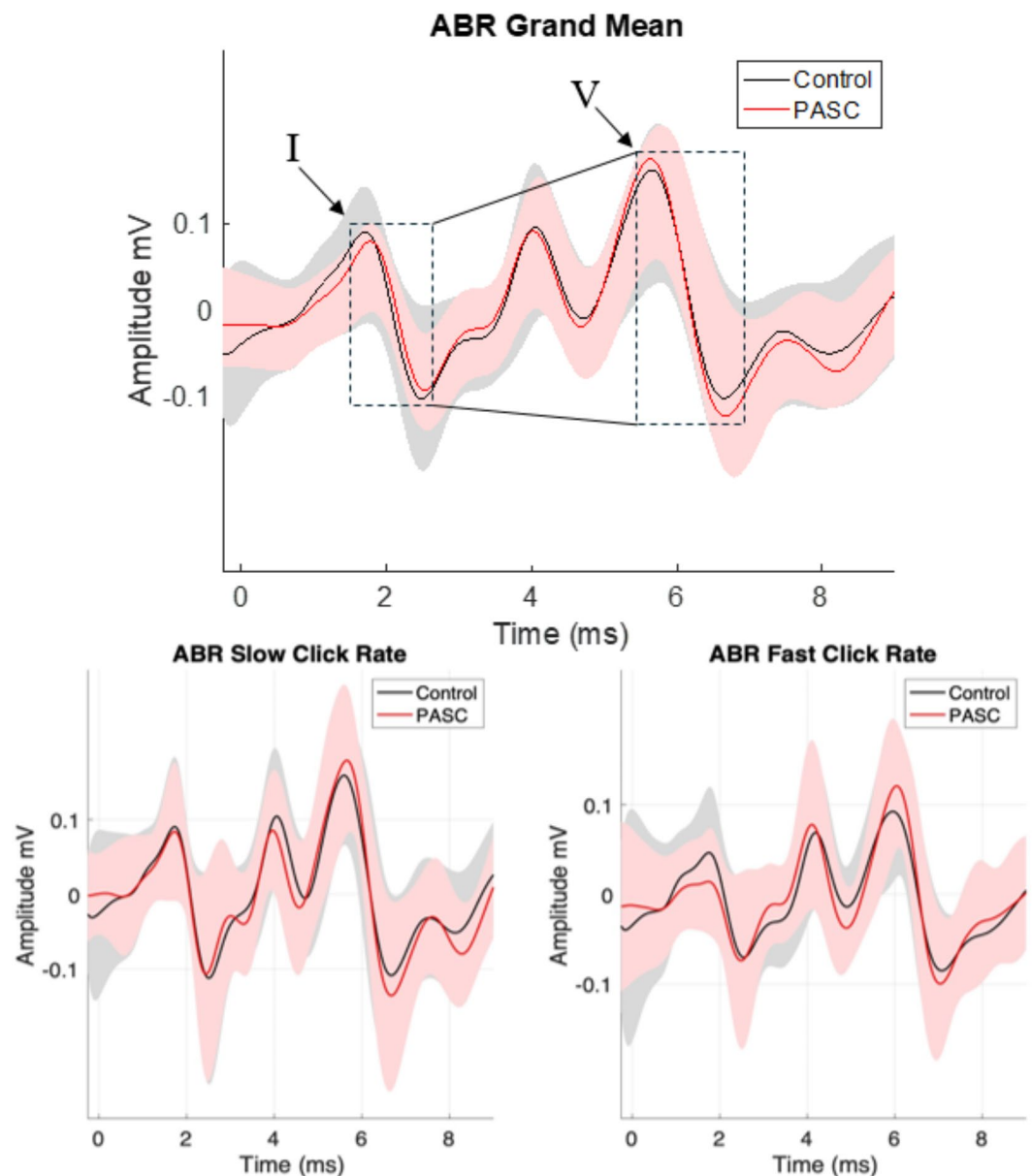


Fig. 1. ABR Grand Mean Waveforms for PASC and Control Subjects – The top panel shows the averaged grand mean waveforms for both PASC and control subjects. Control subjects are plotted with a black line while PASC patients are plotted in red. The bottom two panels show the slow click rate (right – 21.1 per second) and fast click rate (left – 61.1 per second). Shading represents +1 standard deviation. Waves I and V are outlined with dashed rectangles.

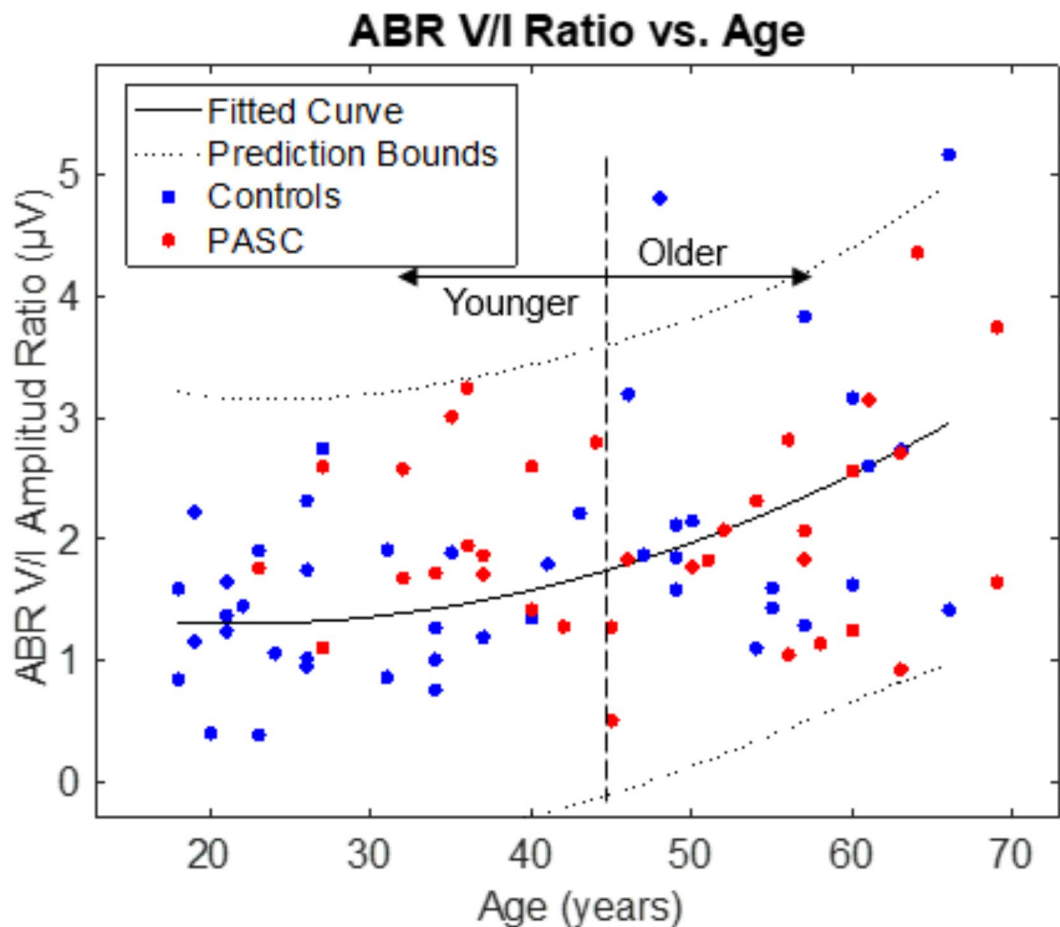


Fig. 2. Age vs. ABR V/I Ratio. The solid black line is a second order polynomial fit using least absolute residuals to control subjects (blue dots). Dotted lines above and below the line of best fit represent the upper and lower bounds of the polynomial fit. PASC subjects (red dots) were then overlaid.

ABR results—age subgroup analysis

In the subgroup analysis, both cohorts showed clear morphology, but the younger adults displayed larger amplitude peaks (Fig. 3). Wave I amplitude and the V/I amplitude ratio were significantly larger in the grand mean waveforms in younger controls than younger PASC ($p = .001$ and $p = .003$, respectively - Supplementary Table 2). Wave III and I-V interpeak latencies were also significantly different, but the younger PASC group had earlier latencies compared to controls ($p = .048$ and 0.034 , respectively - Supplementary Table 2). The older PASC and controls did not differ on any peak measure.

Figure 3, when divided by age subgroup, shows 80% (12/15) of the younger PASC group had V/I amplitude ratios above the fitted line compared to 48% (13/27) of the younger controls. However, using Fisher's Exact test, we found that younger PASC subjects were not significantly ($p = .056$) more likely to have a larger V/I ratio (i.e., above the line) compared to young controls. While older PASC and control subjects had higher V/I ratios compared to younger subjects, there were no differences between V/I amplitude ratios between groups.

ABR relationship to group and cognitive fatigue

To assess how ABR measures related to group membership and reported cognitive fatigue on the CFQ and NSI, mixed effect models focused on using wave V latency difference in the entire cohort and V/I amplitude ratio in the subgroup analysis (Table 3). In the entire cohort wave V latency difference predicted PASC group membership ($p = .036$), CFQ ($p = .004$), and NSI ($p = .004$) cognitive fatigue. Tinnitus perception also predicted CFQ ($p = .012$), and NSI ($p = .015$), but not PASC group membership ($p = .054$).

In the age subgroups, higher ABR wave V/I amplitude significantly predicted PASC group membership ($p = .018$), and CFQ ($p = .029$), but its association with NSI scores ($p = .132$) was not significant for the young subgroup (Table 3). For the older group no association between cognitive fatigue or PASC group membership and V/I ratio was observed (all $p > .364$). Tinnitus perception was also a significant predictor of CFQ and NSI scores ($p = .004$ and $p = .005$, respectively) in the young subgroup. That is, frequent tinnitus perception predicted higher cognitive fatigue scores on two independent questionnaires in the entire cohort and the younger subgroup.

To understand which ABR components were driving the V/I amplitude ratio effects, wave I and V amplitude were plotted separately across age (Fig. 4). Using a linear fit to the data, wave I showed similar decreasing

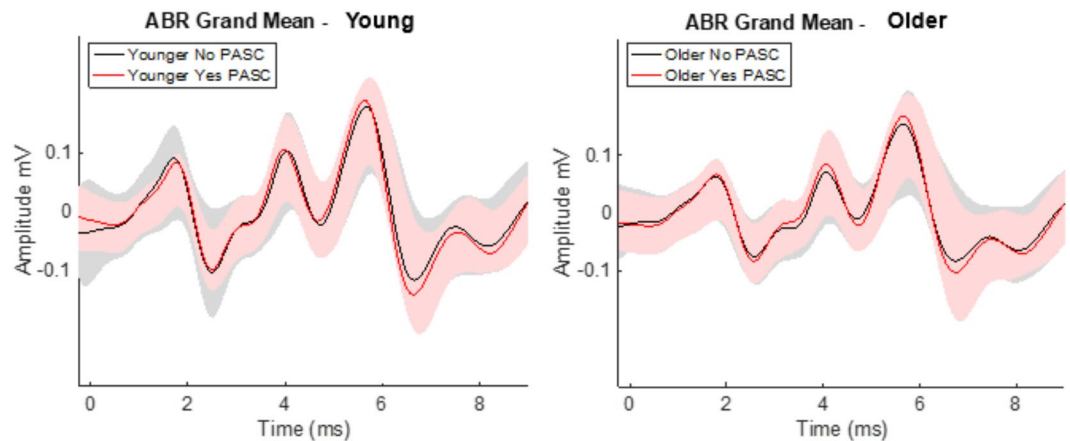


Fig. 3. ABR Grand Mean Waveforms for Younger and Older Subgroups—The left panel shows the averaged grand mean waveforms (averaged across click rate) for younger PASC and control subjects and the left panel shows the older subjects. Control subjects are plotted with a black line while PASC patients are plotted in red. Shading represents +1 standard deviation. Waves I and V are outlined with dashed rectangles.

trajectory of amplitude with increased age for both PASC and controls in the entire cohort. The wave V fit, however, shows a greater slope for the PASC group with higher wave V amplitudes for younger ages. This finding was contrary to results of the individual peak measures that showed significant differences in wave I and no differences between wave V in the overall cohort and in the younger subgroup. Therefore, an analysis was conducted to assess the difference between PASC and controls on waves I and V in the two subgroups. While the older subgroup showed complex trajectories, the younger subgroup displayed lower wave I and higher wave V amplitudes. Interestingly, the younger PASC subjects who experienced tinnitus most frequently were observed to have the lower wave I amplitudes. Linear mixed effect models were then conducted to assess the effect of age, tinnitus, and PASC group membership on waves I and V amplitude. The overall model showed that the PASC group had higher wave V amplitudes, and age reduced wave I in all subjects, but the interaction between age and PASC group showed no significant effect even on wave V ($p = .051$). Individual subgroup analysis showed younger PASC subjects had smaller wave I amplitude ($p = .044$) and those with higher perceived tinnitus had smaller wave V amplitude ($p = .008$). In the older subgroup, age was a strong predictor of wave I amplitude ($p = .009$), but no other significant effects were found for wave V. Taken together, this is consistent with smaller wave I amplitude in younger PASC and an undefined effect of PASC and tinnitus on wave V.

Discussion

This study investigated the link between PASC cognitive symptoms and objective auditory electrophysiology in patients with and without PASC. Compared to controls, PASC subjects showed an increased prevalence of tinnitus and more perceived hearing handicaps despite matched peripheral hearing ability, in addition to increased cognitive fatigue, anxiety, and depression. ABR wave V latency differences between the slow and fast click rate revealed larger differences in the PASC group, similar to previous work in MS²³. Increased stimulus repetition rate effects on wave V latency also predicted PASC membership and subjective cognitive fatigue on both the CFQ and NSI. When divided into younger and older ages, tinnitus prevalence was increased in younger PASC subjects, while older PASC subjects had more perceived hearing handicap compared to age-matched controls. ABR showed reduced wave I amplitude and heightened ABR wave V/I ratios in younger PASC subjects. While older adults showed an overall increase in the V/I amplitude ratio due to age, no differences were found between PASC and controls. Moreover, tinnitus perception and V/I amplitude ratio, a measure of central gain, predicted younger PASC group membership, degree of subjective cognitive fatigue on the CFQ, with greater gain associated with greater fatigue.

To date, biological indices of subjective fatigue have been elusive. Interesting findings to emerge from this study were that ABR slow-fast latency rate differences predicted subjective cognitive fatigue and younger PASC subjects show signs of elevated central gain, similar to what was observed in older adults. The reduction of wave I amplitude in the younger group could potentially suggest a subclinical dysfunction to the cochlea or auditory nerve. Together, young adults may be more susceptible than older adults to adverse effects of COVID-19 on central auditory processing, or that the changes may be more difficult to detect with aging⁵².

This study and others suggest that COVID-19 may have long-lasting effects on the CNS. Our study aligns with others showing significant effects on wave latencies compared to controls, indicating potential brainstem dysfunction^{16,17,53}. This supports the hypothesis that persistent brainstem dysfunction may contribute to PASC, given the brainstem's vulnerability to SARS-CoV-2 infection and its role in regulating various physiological processes⁵⁴. Subtle delays in neural transmission within the brainstem could have severe downstream consequences. Some COVID-19 cases exhibit demyelinating features, with symptoms resembling acute disseminated encephalomyelitis⁵⁵. As neurons do not readily regenerate, neural transmission dysfunction in the brainstem dysfunction may be long-lasting and has been implicated in other similar disorders, such as

Outcome	Predictor	Estimate	t Stat	p Value
<i>Entire cohort</i>				
PASC Group (Logistic Mixed Effect Model)	Tinnitus Perception	1.221	1.953	0.054
	Age	0.037	2.114	0.037
	Wave V Latency Difference	3.570	2.171	0.036
Chalder Fatigue Scale (Linear Mixed Effect Model)	Tinnitus Perception	2.033	2.566	0.012
	Age	0.037	1.703	0.092
	Wave V Latency Difference	6.132	2.959	0.004
Neurobehavioral Symptom Inventory Cognition Scale (Linear Mixed Effect Model)	Tinnitus Perception	0.727	2.504	0.015
	Age	-0.007	-0.821	0.415
	Wave V Latency Difference	2.345	2.978	0.004
<i>Young adults</i>				
PASC Group (Logistic Mixed Effect Model)	Tinnitus Perception	2.530	1.728	0.092
	Age	0.101	1.636	0.110
	ABR V/I Ratio	3.747	2.462	0.018
Chalder Fatigue Scale (Linear Mixed Effect Model)	Tinnitus Perception	3.737	2.994	0.004
	Age	0.099	1.790	0.081
	ABR V/I Ratio	2.539	2.262	0.029
Neurobehavioral Symptom Inventory Cognition Scale (Linear Mixed Effect Model)	Tinnitus Perception	1.515	3.128	0.005
	Age	-0.012	-0.503	0.620
	ABR V/I Ratio	0.903	1.574	0.132
<i>Older adults</i>				
PASC Group (Logistic Mixed Effect Model)	Tinnitus Perception	0.064	0.839	0.406
	Age	0.587	1.220	0.230
	ABR V/I Ratio	0.689	0.919	0.364
Chalder Fatigue Scale (Linear Mixed Effect Model)	Tinnitus Perception	0.609	0.601	0.551
	Age	-0.004	-0.056	0.954
	ABR V/I Ratio	0.494	0.452	0.653
Neurobehavioral Symptom Inventory Cognition Scale (Linear Mixed Effect Model)	Tinnitus Perception	0.245	0.664	0.524
	Age	-0.011	-0.374	0.710
	ABR V/I Ratio	0.018	0.045	0.964

Table 3. Logistic and linear mixed effect models for the entire cohort as well as younger and older subgroups. Wave V latency difference (between slow and fast click rate) was a significant predictor of PASC group inclusion and both cognitive fatigue scores in the entire cohort. ABR V/I amplitude was a significant predictor of PASC group inclusion and continuous Chalder fatigue scores in only the younger subgroup. Yet, ABR V/I amplitude was not a significant predictor of neurobehavioral symptom inventory for the younger subgroup. No significant predictors are noted for the older subgroup.

chronic pain, migraine and chronic fatigue syndrome^{56,57}. Our latency results also match rate-based effects seen in those with MS, another population that is affected by cognitive fatigue^{58,59}. Robinson and Rudge⁶⁰ were the first to report ABR wave V latency and amplitude changes in MS with increasing click rate. Since then, studies have found that increasing ABR stimulus rates can improve the detection of abnormalities in MS patients²³. Interestingly, the results of our study were not evident in the faster rate (61.1), but in the difference between the rates, indicating earlier slow rate latencies and delayed faster rate latencies. This effect was independent of age, which is consistent with the literature showing remarkably similar rate effects in young and older adults when peripheral hearing ability is normal in both age groups¹⁹. Importantly, this latency result predicted cognitive fatigue on two independent measures in PASC patients. While the exact mechanisms of PASC neurotropism and neuropathogenesis are still under investigation, the potential for both acute and long-term neurological consequences is a growing concern. Objective auditory electrophysiological evidence of CNS dysfunction linked to cognitive fatigue could serve as a valuable marker for PASC and other populations experiencing cognitive fatigue though further research is needed to confirm and expand on these findings.

Previous work has also shown that gain enhancement may emerge concurrently at multiple levels of the CNS in response to auditory dysfunction or trauma, leading to increased sound-evoked neural activity in midbrain and cortex and disordered auditory perceptions, such as tinnitus²⁹. In studies of patients with tinnitus, elevated amplitudes, specifically the wave V/I ratio, have been thought to reflect overactivity in the central pathway extending from ventral cochlear nucleus to inferior colliculus³⁸, this overactivity being associated with cochlear neural degeneration in many, but not all, reports⁶¹. In the case of our PASC subjects, heightened central gain may be a consequence of disruptions to the cochlea or cochlear nerve, as wave I amplitude was significantly smaller in PASC subjects, particularly those younger than 45 years. Also, wave V could be contributing to larger V/I ratios in PASC, suggesting increased sound-evoked activity in inferior colliculus. Nonetheless, wave V amplitude

Outcome	Predictor	Estimate	t Stat	p Value	
<i>Entire cohort</i>					
Wave I Amplitude (Linear Mixed Effect Model)	Age	-0.004	-5.920	< .001	
	PASC Group	-0.054	-1.072	0.287	
	Tinnitus	-0.019	-1.074	0.286	
	Age * PASC Group Interaction	0.001	0.932	0.354	
Wave V Amplitude (Linear Mixed Effect Model)	Age	-0.001	-0.608	0.544	
	PASC Group	0.179	2.132	0.036	
	Tinnitus	-0.053	-1.722	0.089	
	Age * PASC Group Interaction	-0.003	-1.980	0.051	
Subgroup	Outcome	Predictor	Estimate	t Stat	p Value
Younger adults	Wave I Amplitude (Linear Mixed Effect Model)	Age	-0.001	-0.995	0.325
		PASC Group	-0.055	-2.082	0.044
		Tinnitus	-0.016	-0.451	0.654
	Wave V Amplitude (Linear Mixed Effect Model)	Age	0.001	0.552	0.583
		PASC Group	0.060	1.707	0.095
		Tinnitus	-0.134	-2.782	0.008
Older adults	Wave I Amplitude (Linear Mixed Effect Model)	Age	-0.003	-2.750	0.009
		PASC Group	0.022	1.250	0.219
		Tinnitus	-0.019	-1.019	0.314
	Wave V Amplitude (Linear Mixed Effect Model)	Age	-0.001	-0.093	0.926
		PASC Group	-0.022	-0.563	0.576
		Tinnitus	-0.017	-0.440	0.661

Table 4. Linear mixed effect models for waves I and V. This table shows outcomes of linear mixed effect models for wave I and V amplitude for the entire cohort (top) and age subgroups (bottom). Unsurprisingly, age was a significant predictor of wave I amplitude in the entire cohort and in the older subgroup. The age * PASC interaction was included in the overall cohort due to the expected age differences, but not in the subgroup analysis. PASC group was a significant predictor of higher wave V in the overall cohort and lower wave I in the younger cohort, consistent with younger PASC subjects having smaller wave I amplitude. Higher perceived tinnitus was also a significant predictor of smaller wave V amplitude in the younger PASC subgroup.

independently predicted group membership in the overall cohort, while wave I amplitude was predictive in the younger PASC subgroup. However, neither wave amplitude was predictive of PASC in the older subgroup. Notably, the younger and older groups did not differ on other dimensions of the ABR, including peak and inter-peak latencies, suggesting that heightened gain is not comorbid with deficient synaptic transmission.

What might then be the mechanistic underpinning of heightened central gain in younger PASC patients? Although not directly measured in the current study, decreased GABA could be a driving force behind the wave V/I ratio results. GABA, the primary inhibitory neurotransmitter in the central auditory system, maintains the balance of neural excitation and inhibition⁶². Relevant to the COVID-19 virus, GABA also plays a role in modulating inflammatory autoimmune responses⁶³. Decreased GABA has been associated with a panoply of physiological and pathophysiological neurological conditions and has been reported in PASC^{64,65}. Insufficient inhibition due to lower GABA concentrations, altered GABA distribution within the auditory system, or altered receptor density or GABA affinity could explain, and potentially link, the tinnitus and ABR findings in this population⁶⁶. Altered GABA is not necessarily specific to the auditory system in PASC; altered GABA could be more systemic and even potentially underlie depressive and anxiety symptoms⁶⁷, which were also elevated in the PASC group.

In this study, results from the ABR, an obligatory electrophysiological measure that does not require attention to the stimulus, were related to subjective cognitive fatigue on the Chalder Fatigue Scale. These results suggest central auditory involvement in PASC and highlight that ABRs could offer an objective correlate of cognitive fatigue. This symptom currently can only be assessed using subjective measures. Auditory tests are particularly relevant in assessing cognitive fatigue because sound engages cognitive processes related to perception, attention, and memory^{68,69}. Studies of patients with chronic fatigue syndrome^{70,71} have shown increased neural resource allocation when processing complex auditory information compared to demographically similar healthy adults⁷². The same may be true in PASC. Delayed neural conduction time and increased central gain in the midbrain could give rise to functional cortical processing disparities in PASC. Therefore, ABRs could serve as an objective indicator of upstream cortical dysfunction^{73–75}. Future research should study later auditory evoked potentials and fMRI, and simulate real-world communication environments, to further clarify these findings within this population.

While latency results were found in the entire cohort, a wide age range (18–69) prompted additional analysis on age subgroups. ABR V/I amplitude ratio clearly showed an increasing trend with advanced age. Age-related changes in the auditory midbrain and cortex from decreased central inhibition are well-described literature^{25,76}

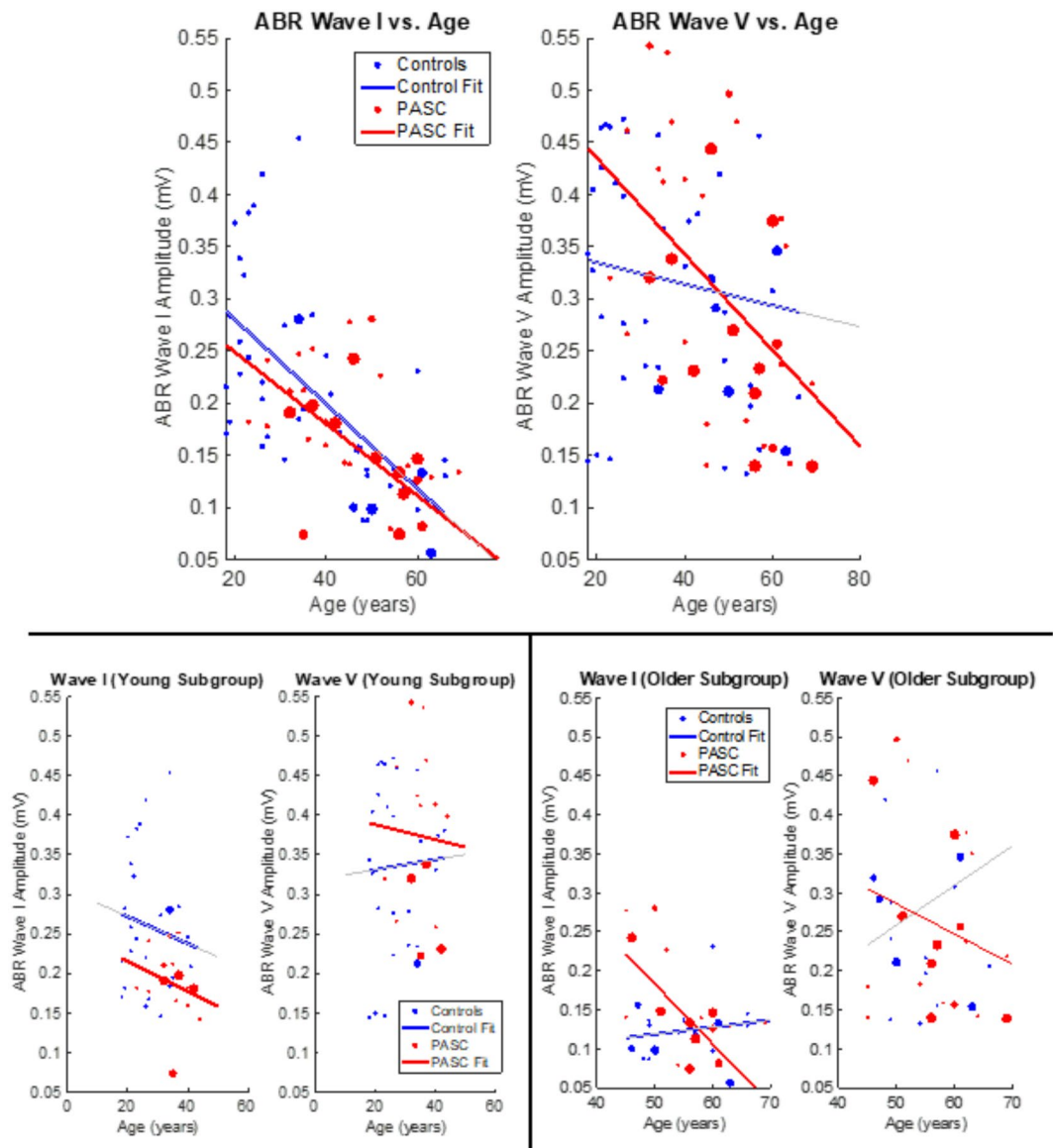


Fig. 4. Amplitude of Waves I and V for Entire Cohort and Age Subgroups. The top panel shows amplitude of wave I (top left panel) and wave V (top right panel) for PASC (red) and Controls (blue). A linear fit is also plot for both groups. The size of the individual datapoints represents the perceived tinnitus of the subject. Larger dots equate to more frequently perceived tinnitus. The bottom four panels show waves I and V for the younger and older group respectively.

and are evident in our dataset as well, where we see a decrease in wave I with age and corresponding trend for increasing V/I amplitude with age (regardless of group). Thus, with the aging process, there is a natural deterioration of cochlear output with age (i.e., presbycusis) that leads to a hypothesized increase in central gain^{25,28}. The observed increased latency of wave V due to a rapid click rate is likely not attributable to an age-related effect¹⁹, opening a new avenue for further investigation. Nonetheless, the V/I ratio increase in the PASC groups, particularly the younger subjects, potentially exceeds central changes that are expected to occur with natural aging. Indeed, in the PASC group, the younger subjects patterned similarly to the older subjects for wave V/I ratio and in wave I reduction. In alignment with this, the relationship between the V/I ratio and Chalder score was reduced with increasing age. This could suggest a form of accelerated central auditory aging in COVID-19^{77,78}; future longitudinal studies need to assess the progression of central gain with biological aging in patients who develop PASC at younger vs. older ages.

Interestingly, frequent tinnitus significantly predicted CFQ scores, and tinnitus also independently predicted cognitive scores from a subset of the NSI in the entire cohort. However, the younger PASC group seemed to drive this effect (i.e., no tinnitus result in the older subgroup) with more frequent tinnitus related to heightened central gain but simultaneously related to smaller ABR wave V amplitude. This supports the hypothesized link between central gain and tinnitus, although in this cross-sectional study it is not possible to know how the wave V/I ratio

might have changed with COVID in a given individual and whether this change was related to tinnitus severity or development. An intuitive explanation for the causation of tinnitus is that a reduction in auditory input, typically due to hearing loss or cochlear damage, leads to increased gain in the central auditory pathways^{79–81}. In other words, auditory neurons that receive reduced input at lower levels compensate by amplifying their response to maintain their baseline activity level at higher level. Like our younger subgroup, several studies have demonstrated that subjects with tinnitus and normal hearing sensitivity show significantly reduced ABR wave I amplitudes and elevated or at least normal wave V amplitudes compared with control subjects, suggesting increased central auditory gain^{38,40}. Indeed, studies have shown possible cochlear neural degeneration in normal-hearing individuals with tinnitus with reduced wave I amplitudes and smaller action potential amplitudes using electrocochleography^{33,40,82}. Vasilkov et al. showed tinnitus status was a significant predictor of ABR wave I, even after controlling for factors such as sex, auditory thresholds, and concussion history. But there are mixed findings in the literature on ABRs and the V/I ratio in those with tinnitus^{24,25,79–81,83}. Tinnitus symptoms are also known to vary as a function of mental health⁸⁴ and environmental conditions^{85,86}. Thus, it could be that increased fatigue leads to increased social isolation, greater time in quiet environments, and an unmasking of tinnitus symptoms previously unobserved by the person. The degree to which some of the reported group differences predate PASC is unknown as data on tinnitus, depression, anxiety, hearing handicap, and hearing thresholds prior to contracting PASC in our sample were not available. Additionally, the tinnitus questionnaire used in this study lacked the depth and specificity of other validated measures, such as the Tinnitus Handicap Inventory (THI)⁸⁷. As a result, the subjective perceptions reported in this study may not fully capture or accurately reflect a true tinnitus percept or how tinnitus impacts someone's social emotional well-being. Another limitation is the lack of extended high-frequency thresholds. Studies have clearly demonstrated that extended high-frequency hearing loss is prevalent among individuals with tinnitus^{88,89} and could be contributing to PASC group results. The small sample size and not adjusting for multiple comparisons also hinder generalizability and increases the likelihood of falsely identifying significant effects. Another limitation is that our healthy controls were also defined from self-report of cognitive fatigue and absent symptoms of COVID-19 infection. Controls could have had asymptomatic infections; also, as subjects were required to be vaccinated to participate in the study, it was not possible to use PCR to confirm that controls had never had COVID-19. Increased tinnitus perception following the SARS-CoV-2 vaccine⁹⁰ cannot be ruled out. Data collection took place in 2021–2022 at a point in the pandemic when it became increasingly difficult to find individuals who had never had COVID-19; thus, we cannot rule out that the individuals in the control group have other characteristics that differentiate them from those who contracted the illness.

Conclusions

Compared to controls, PASC subjects showed an increased prevalence of tinnitus, more perceived hearing handicap, and increased slow-fast wave V latency difference for the two stimulus rates. When separated into younger and older age ranges, increased ABR wave V/I ratios were found in only the younger PASC subjects. Increased stimulus repetition rate effects on wave V latency and wave V/I amplitude ratio predicted PASC group membership and subjective cognitive fatigue on the Chalder Fatigue Scale. These findings indicate abnormal central auditory processing in individuals with PASC, particularly notable in those under 45 years old, where such effects are typically unexpected. These results also suggest central auditory involvement determined using auditory electrophysiology in PASC could offer an objective correlate of subjective cognitive fatigue, but additional testing is needed to confirm the use of this methodology.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

C.N. - Study design lead; funding; enrollment; data collection, analysis, and interpretation; manuscript preparation. E.S. - Study design; funding; data analysis and interpretation; manuscript preparation. S.L. - Enrollment, data analysis and interpretation; manuscript preparation. L. Z. - Enrollment; data collection; manuscript preparation. M. D. - Enrollment; data collection; manuscript preparation. A. K. - Enrollment; data collection; manuscript preparation. S. S. - Enrollment; data collection; manuscript preparation. J. P. - Enrollment; data collection, analysis, and interpretation; manuscript preparation. C. M. - Enrollment; data collection, analysis, and interpretation; manuscript preparation. C. E. - Enrollment; data collection, manuscript preparation. O. C. - Study design; data collection; manuscript preparation. J. G. - Statistical analysis, and interpretation; manuscript preparation. A. W. - Enrollment; data analysis, and interpretation. R. R. - Study design; enrollment; data collection, interpreta-

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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