EBioMedicine 61 (2020) 103065

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

The age-related trajectory of visual attention neural function is altered in adults living with HIV: A cross-sectional MEG study

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ARTICLE INFO

Article History:
Received 10 July 2020
Revised 25 September 2020
Accepted 28 September 2020
Available online xxx

Keywords:
HIV
Attentional reorientation
Magnetoencephalography
Validity effect
Ageing

ABSTRACT

Background: Despite living a normal lifespan, at least 35% of persons with HIV (PWH) in resource-rich countries develop HIV-associated neurocognitive disorder (HAND). This high prevalence of cognitive decline may reflect accelerated ageing in PWH, but the evidence supporting an altered ageing phenotype in PWH has been mixed.

Methods: We examined the impact of ageing on the orienting of visual attention in PWH using dynamic functional mapping with magnetoencephalography (MEG) in 173 participants age 22–72 years-old (94 uninfected controls, 51 cognitively-unimpaired PWH, and 28 with HAND). All MEG data were imaged using a state-of-the-art beamforming approach and neural oscillatory responses during attentional orienting were examined for ageing, HIV, and cognitive status effects.

Findings: All participants responded slower during trials that required attentional reorienting. Our functional mapping results revealed HIV-by-age interactions in left prefrontal theta activity, alpha oscillations in the left parietal, right cuneus, and right frontal eye-fields, and left dorsolateral prefrontal beta activity ($p<.005$). Critically, within PWH, we observed a cognitive status-by-age interaction, which revealed that ageing impacted the oscillatory gamma activity serving attentional reorienting differently in cognitively-normal PWH relative to those with HAND in the left temporoparietal, inferior frontal gyrus, and right prefrontal cortices ($p<.005$).

Interpretation: This study provides key evidence supporting altered ageing trajectories across vital attention circuitry in PWH, and further suggests that those with HAND exhibit unique age-related changes in the oscillatory dynamics serving attention function. Additionally, our neural findings suggest that age-related changes in PWH may serve a compensatory function.

Funding: National Institutes of Health, USA.

1. Introduction

Combination antiretroviral therapy (cART) has dramatically increased the life expectancy of persons with HIV (PWH), which now approximates that of uninfected individuals [1,2], and markedly reduced the incidence of HIV-associated dementia (HAD) [3,4,5]. Nevertheless, 35–70% of PWH continue to experience milder forms of HIV-associated neurocognitive disorder (HAND) [4,6-10]. Such cognitive impairments impinge on activities of daily living and sharply lower the quality of life in PWH [11-15]. In addition, at least some PWH exhibit so-called accelerated or pathological ageing relative to their uninfected peers [16-20], which can lead to increased age-related comorbidities affecting both the CNS and peripheral organ systems [21-24].

Many previous neuroHIV studies have suggested that attention processing and executive functions are critically affected, with altered neural responses mainly in the fronto-parietal regions [25,26]. While these and other fMRI and structural MRI studies have

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https://doi.org/10.1016/j.ebiom.2020.103065

Research in context:

Evidence before this study:

Attention related cognitive deficits are common in persons with HIV (PWH) and appear to become more severe with increasing age, a phenomenon that has been attributed to accelerated ageing. Though molecular studies have supported the idea of accelerated ageing in PWH, the literature more broadly remains inconclusive and this is especially true for neuroimaging evidence.

The use of advanced neuroimaging methods, including dynamic functional mapping with magnetoencephalography, may be sensitive to previously undetected interaction effects among HIV and ageing within critical aspects of the visual attention circuitry.

Added value of this study:

This study quantifies the neural dynamics within active visual attention networks, and identifies the precise regions where ageing differential modulates the oscillatory dynamics serving attentional orienting in PWH and controls. The study further shows unique age-related gamma changes, primarily in the nodes of the ventral attention network that differ in PWH based on their cognitive status. This study is one of the largest functional neuroimaging studies of neuroHIV to date and, to our knowledge, the first study to probe the multi-spectral oscillatory dynamics serving attentional orienting in ageing PWH.

Implications of all the available evidence:

This study provides key evidence for altered ageing phenotypes in PWH that may further differ based on the cognitive outcome of the individual patient. Together with the molecular and other data available on ageing phenotypes in neuroHIV, the evidence supports the notion that PWH experience altered ageing, although future studies remain warranted.

identified the brain regions and networks most susceptible to the effects of the disease [27-30], more recently, the neural dynamics have become an increasing area of focus. In fact, both resting-state and task-based magnetoencephalography (MEG) studies have substantially enhanced our understanding of the pathophysiology, as they enable direct quantification of neurophysiology with excellent temporal resolution and good spatial precision, as opposed to other neuroimaging modalities that measure brain activity indirectly [31-33].

For example, an early resting-state MEG study found abnormally reduced activity in PWH in multiple brain regions, including the posterior cingulate and superior parietal, and such activity was significantly correlated with memory performance and measures of executive function [34]. Additionally, in a later study of working memory and executive function, older PWH exhibited altered neural dynamics across prefrontal, temporal, and hippocampal areas during the memory maintenance phase of the task [35]. MEG work has also shown that PWH exhibit decreased neural activity in the right dorsolateral prefrontal cortex and frontal eye fields relative to demographically-matched controls during a visual processing task [36]. Perhaps most relevant to the current study, Wiesman and colleagues found that some occipital neural responses during a visual processing task distinguished PWH based on their impairment status and were significantly correlated with behavioral performance [37]. A more recent study using a similar visual processing task extended these findings by showing that such neural dynamics were differentially affected by age in PWH and controls [38]. Finally, a multimodal neuroimaging (MEG and MRI) study suggested that at least some aberrant oscillatory neural responses in PWH may be associated with reductions in local grey matter volume [39]. Though these recent studies have mainly focused on relatively healthy cohorts of PWH (i.e., virally-suppressed and with low depressive symptoms), they are clinically relevant, as the majority of PWH in the developed world are being treated with cART and have low to undetectable viremia. In sum, these MEG studies have strongly contributed to our current understanding of HIV-related alterations in the neural dynamics serving cognition, but the degree to which these changes reflect pathological ageing remains poorly understood.

Some have suggested that these alterations in attention networks and neural dynamics may reflect accelerated ageing in PWH [29]. Briefly, an influential DNA methylation study recently provided strong evidence of accelerated ageing in PWH [16], which has helped ground more than a decade of circumstantial evidence [40-43]. For example, several structural MRI studies have demonstrated accentuated ageing-related brain atrophy in PWH [44,45] and suggested that premature ageing may be the underlying factor. Moreover, a recent study using diffusion tensor imaging revealed evidence of an augmented ageing process in white matter microstructure [46], which they suggest reflects premature brain ageing in PWH. Though a large body of literature has supported this framework by reporting either additive or synergistic effects of ageing with HIV [22,47-49], other studies have found the two parameters to be independent. One often cited example is a study from Ances and colleagues showing that HIV and age negatively, but independently affect both cerebral blood flow and the fMRI signal in occipital cortex [50]. In fact, this study suggested that functional brain responses in PWH were similar to those observed in controls who were 15−20 years older, but that the two factors did not interact [50]. Similar conclusions have been reached in neuropsychological studies where no interactions between age and HIV were observed [12,51]. Thus, currently there are clear discrepancies in the literature surrounding the concept of accelerated ageing in HIV, and the degree to which HIV and ageing effects interact in the CNS. Molecular studies have provided strong evidence in favor, whereas neuroimaging studies have been mixed with many finding the effects of HIV and ageing to be independent. Herein, we address this discrepancy by directly quantifying cortical neurophysiology and behavioral performance in a large sample of PWH and uninfected controls who were 22−72 years-old at enrollment. All participants underwent neuropsychological evaluation to ascertain their cognitive status, and underwent MEG during a cued attention task based on the classic Posner paradigm, which enabled the oscillatory dynamics serving attentional reorientation to be directly probed in PWH and uninfected controls as a function of ageing.

Attentional reorienting is a key component of day-to-day cognitive function and involves concurrent activations in both the dorsal and ventral attention networks [52-63]. The Posner attention cuing task is a well-established paradigm that has been widely used to study such attentional reorienting [64], including normative MEG work examining the multispectral oscillatory dynamics [53]. Importantly, other cognitive domains rely heavily on intact attention function. For example, aspects of executive function, including cognitive control and behavioral flexibility, rely on intact attention circuitry and fronto-parietal cortices for optimal performance [65]. Both flexible allocation of neural resources and attentional shifting are pertinent to working memory [66], which itself supports many different cognitive processes. Previous literature shows compensatory recruitment of brain regions in these networks during such cognitive processing in older adults [67,68], as well as evidence for deficits in discrete components of executive function and working memory in adults with HIV [35,69]. In the current study, we examined possible interactions between HIV, cognitive status (i.e., with or without HAND), and ageing on the neural dynamics serving attentional reorienting. We focused on the neural oscillations serving visual attention reallocation because, as discussed above, many neuroHIV studies

have shown that attention is critically affected [25,26,31,37,70], but the role of ageing in such deficits is largely unknown. Broadly speaking, frontal theta activity has been associated with cognitive control [71] and executive function more broadly, while decreases in the alpha and beta ranges are thought to reflect disinhibition in local brain regions and has been shown to be modulated by ageing [72]. Moreover, gamma activity has been repeatedly linked to the active engagement of a cortical region of interest [73]. Our primary hypotheses were that age would differentially modulate the spectrally-specific signatures of attentional reallocation in uninfected controls and PWH, and that cognitive status in PWH would have a unique impact on these neural interactions with ageing.

2. Methods

2.1. Participants

We enroled 254 adults (age range: 22–72 years) in this study. Exclusionary criteria included any medical illness affecting CNS function (other than HIV-infection/HAND), any neurological or psychiatric disorder, pregnancy, history of head trauma, illicit drug use in the past three months, moderate to severe depressive symptoms according to the Beck Depression Inventory (i.e., > 19) [74], missing or artifactual MEG task data, and the MEG laboratory's standard exclusion criteria (e.g., ferromagnetic implants). At the time of the visit, all PWH were receiving effective cART and had complete viral suppression (< 50 copies/mL, except one person with 54 copies/mL). Uninfected controls were recruited to match PWH at the group level based on their race/ethnicity, age, and sex. The groups were also matched on the alcohol use disorders identification test (AUDIT-C; Table 1) [75]. In addition, an equal representation across ages in both groups was targeted during enrolment. Following all exclusions, 173 participants remained (Fig. 1), including 51 unimpaired PWH (mean age = 47.82, 20 females), 28 impaired PWH (i.e., HAND; mean age = 47.04, 10 females), and 94 unimpaired HIV-negative controls (mean age = 45.60, 42 females). Based on previous relevant studies from our laboratory and others [31,33,35,37,76,77], we had a reasonable sample size per group for both behavioral and neural comparisons. Participants completed a neuropsychological battery assessing multiple functional domains, including attention [WAIS-III Symbol Search [78] and Stroop Word [79]], speed of processing [Trail Making Part A[15], WAIS-III Digit Symbol, and Stroop color], executive functioning [Trail Making Part B, Stroop interference, phonemic verbal fluency and semantic verbal fluency[80]], fine motor [grooved pegboard [80,81]], verbal learning and memory [Hopkins Verbal Learning Test–Revised [82]] and language [Wide Range Achievement Test-4th edition [83], Word Reading subtest]. Along with an assessment of activities of daily living, these scores were used to diagnose HAND according to the Frascati guidelines (84). The study was approved by the Institutional Review Board of the University of Nebraska Medical center (IRB # 225-14-EP) and all participants gave written informed consent.

Table 1
Demographics, HIV metrics and Neuropsychology.

	Controls	Unimpaired PWH	HAND
Demographics	(*n* = 94)	(*n* = 51)	(*n* = 28)
Mean age in years (SD)	45.60 (15.69)	47.82 (12.26)	47.04 (13.37)
Sex,% Females	42 (44.7%)	21 (41.2%)	10 (35.7%)
Race (frequency,%)			
White	68 (72.3%)	35 (68.63%)	14 (50%)
Non-White	26 (27.66%)	16 (31.37%)	14 (50%)
Ethnicity,% Non-Hispanic	88 (93.6%)	49 (96.1%)	24 (85.7%)
% Right-handed	80 (85.1%)	46 (90.2%)	27 (96.4%)
Mean years of Education (SD)	18.06 (3.17)	15.54 (2.44)	14.32 (2.31)
Mean BDI score (SD)	3.14 (3.16)	7.04 (5.56)	5.46 (5.20)
Alcohol use			
AUDIT-C (SD)	2.38 (1.72)	2.37 (2.04)	2.00 (1.98)
Disease-related Factors			
Mean years since HIV diagnosis (SD)	NA	11.65 (7.34)	13 (7.41)
Mean years on ART (SD)	NA	9.31 (6.15)	11.43 (7.15)
Mean CD4 nadir (cells/μl, SD)	NA	232.28 (158.0)	219.79 (146.2)
Mean current CD4 count (cells/μl, SD)	NA	773.75(420.8)	679.25 (383.4)
*Neuropsychology**			
Executive function			
Verbal fluency	−0.223 (1.06)	−0.206 (0.91)	−0.907 (0.86)
Semantic fluency	0.193 (1.13)	0.278 (0.97)	−0.429 (0.99)
Stroop interference	0.228 (1.0)	−0.171 (0.93)	−1.386 (1.30)
Trail Making Part B	0.107 (0.82)	0.377 (0.84)	−0.575 (0.83)
Attention			
Symbol search	0.688 (0.75)	0.503 (0.73)	−0.631 (0.76)
Stroop word	0.001 (1.01)	−0.461 (0.81)	−1.505 (1.32)
Speed of processing			
Digit symbol	0.833 (0.74)	0.608 (0.97)	−0.428 (0.63)
Stroop colour	0.187 (0.79)	−0.005 (0.79)	−1.166 (1.24)
Trail Making Part A	−0.120 (0.95)	0.439 (1.18)	−0.550 (0.96)
Wide Range Achievement Test			
Word Reading subtest	0.639 (0.96)	0.614 (1.17)	−0.498 (0.83)
Hopkins Verbal Learning Test	−0.342 (1.14)	−0.228 (1.05)	−1.450 (1.10)

*All neuropsychology scores are z scores, standardized using published normative data (see methods: neuropsychological testing).
PWH = People with HIV, HAND =HIV-associated neurocognitive disorder, SD = standard deviation, BDI = Beck depression inventory, ART = Antiretroviral therapy, μl = microliters.

2.2. Experimental paradigm

The cognitive experiment used in this study was a cued attention paradigm based on the classic Posner task (Fig 2A) [64]. During this task, the participants were seated in a magnetically shielded room and told to fixate on a crosshair presented centrally for 1500 ms (+/− 50 ms). Following that, a green bar (the cue) was presented either to the left or right of the crosshair for 100 ms. The cue appeared on a given side 50% of all trials and could either be valid (presented on the same side as the upcoming target) or invalid (presented on the opposite side relative to the target). At 300 ms (200 ms after cue offset), a target was presented on either the left or the right side of the crosshair for 2500 ms, and this was comprised of a box with an opening on either its top (50% of trials) or bottom. Participants were instructed to respond as to whether the opening was on the top (right middle finger) or the bottom (right index finger) of the box. Each target variant appeared an equal number of times and each trial lasted 4300 ms (+/− 50 ms). A total of 200 trials were collected (100 valid, 100 invalid) per participant, leading to a total run-time of approximately 14.5 min. Trials were pseudo-randomly organized so that no more than three of the same target responses or target/cue laterality combinations occurred in succession.

2.3. MEG data acquisition

All recordings were conducted in a one-layer magnetically shielded room with active shielding engaged for environmental noise compensation. With an acquisition bandwidth of 0.1–330 Hz, neuromagnetic responses were sampled continuously at 1 kHz using an Elekta/MEGIN MEG system (Helsinki, Finland) with 306 sensors, including 204 planar gradiometers and 102 magnetometers. During data acquisition, participants were monitored via real-time audio-visual feeds from inside the shielded room. Each MEG dataset was individually corrected for head motion and subjected to noise reduction using the signal space separation method with a temporal

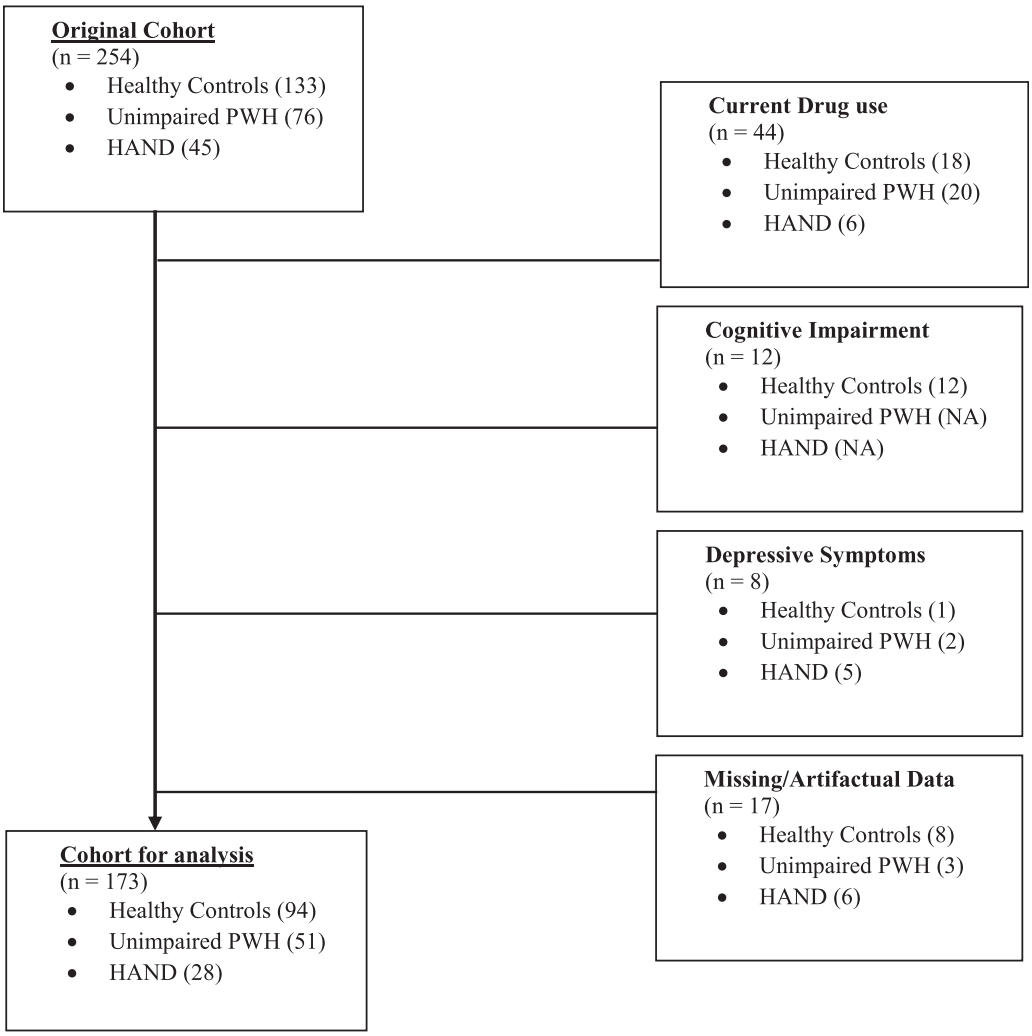

Fig. 1. Flow Diagram: A total of 133 controls and 121 PWH were enroled, including 76 unimpaired PWH and 45 with HAND. Exclusions were made for current drug use, cognitive impairment (in controls), moderate to severe depressive symptoms, and missing or artifactual data. The final sample included 94 unimpaired controls, 51 unimpaired PWH and 28 participants with HAND.

extension [85]. Only data from the gradiometers were used for further analysis.

2.4. Structural MRI processing and MEG co-registration

Prior to MEG measurement, four coils were attached to the subject's head and localized, together with the three fiducial points and scalp surface, with a 3-D digitizer (FASTRAK 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). Once the subjects were positioned for MEG recording, an electric current with a unique frequency label (e.g., 322 Hz) was fed to each of the coils. This induced a measurable magnetic field and allowed each coil to be localized in reference to the sensors throughout the recording session. As coil locations were also known with respect to head coordinates, all MEG measurements could be transformed into a common coordinate system. With this coordinate system, each participant's MEG data were co-registered with their structural T1-weighted MRI prior to source space analysis using BESA MRI (Version 2.0). Structural MRI data were aligned parallel to the anterior and posterior commissures and transformed into standardized space. Following source analysis (i.e., beamforming), each subject's functional MEG images were also transformed into standardized space using the transform that was previously applied to the structural MRI volume and spatially resampled.

2.5. MEG preprocessing and time-frequency transformation

Eye blinks and cardiac artifacts were removed from the data using signal space projection (SSP), which was accounted for during source reconstruction [86]. The continuous magnetic time series was divided into epochs of 3500 ms duration, with 0 ms defined as the onset of the cue and the baseline being the −600 to 0 ms window before cue onset. Given our task and epoch design, the target onset occurred at 300 ms. Epochs containing artifacts were removed based on a fixed threshold method, supplemented with visual inspection. In brief, for each individual, the distribution of amplitude and gradient values across all trials were computed, and those trials containing the highest amplitude and/or gradient values relative to the full distribution were rejected by selecting a threshold that excluded extreme values. Importantly, these thresholds were set individually for each participant, as inter-individual differences in variables such as head size and proximity to the sensors strongly affects MEG signal amplitude. An average of 86.00 (SD = 9.45) trials per condition and participant were used for further analysis. To ensure there were no systematic differences in the number of trials, a statistical analysis was conducted which revealed no main effect of condition ($F(1168)$ 0.392, p = .532), age ($F(1168) = 662$, p = .417), condition by age ($F(1168) = 0.080$, p = .777), condition by group ($F(2168) = 1.198$, p = .304), group by age ($F(2168) = 1.671$, p = .191), or condition by

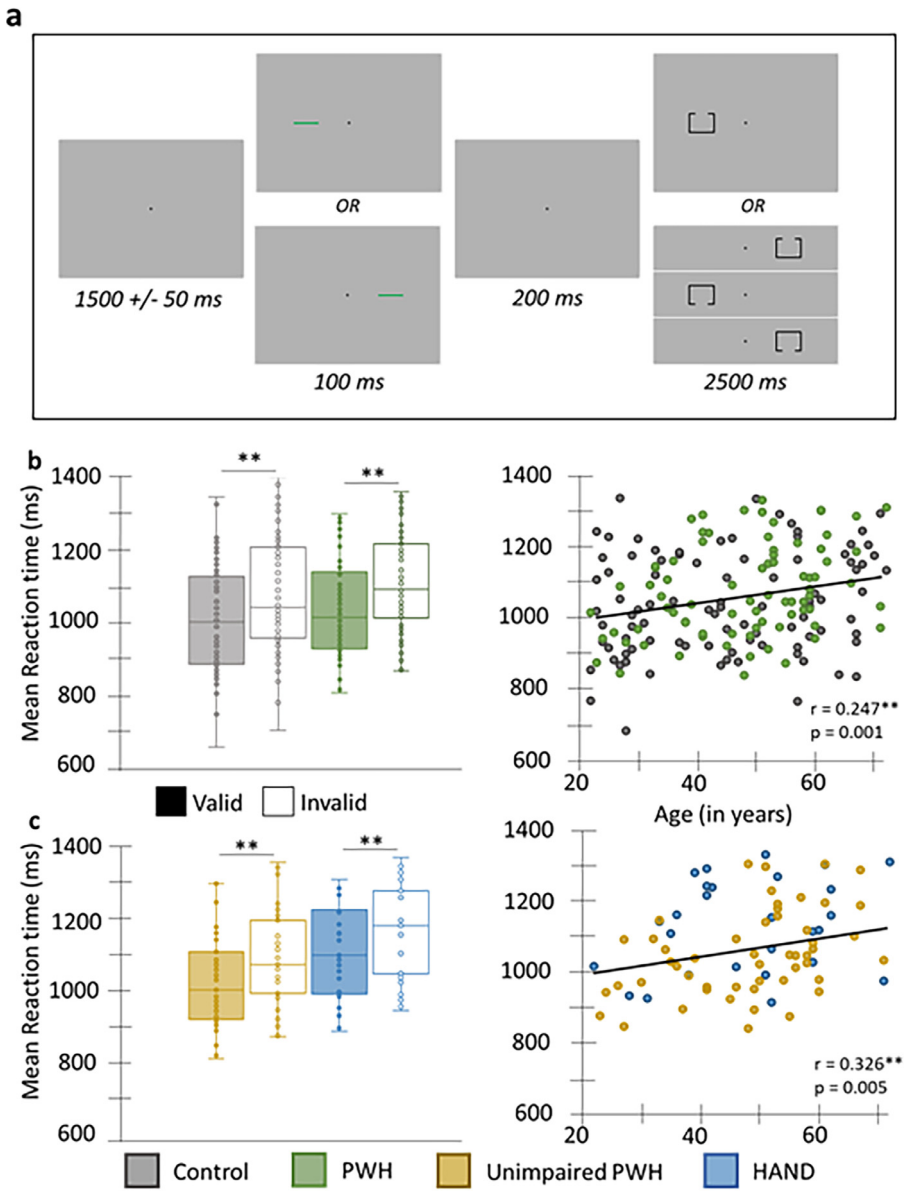

Fig. 2. Posner cueing task and behavioral performance. (**a**) A central crosshair was presented for 1500 ms (± 50 ms), followed by a cue (green bar) that appeared in either the left or right hemifield for 100 ms. Target presentation (box with opening at the top or bottom) was presented 200 ms after cue offset (300 ms from onset), in either hemifield for 2500 ms. The cue was predictive of the upcoming target location 50% of the time (i.e., "valid" condition) and was presented on opposite side from the target in remaining 50% of trials (i.e., "invalid" condition). Participants completed 200 trials and were instructed to respond as to whether the opening was on the bottom (right index finger) or top (right middle finger) of the box. Trials were pseudorandomized and counterbalanced in regard to target validity (valid or invalid), visual hemifield (left or right), and box opening (top or bottom). (**b**) Box and whisker plots showing the reaction time data in controls and PWH. Main effects of condition (valid vs. invalid) and age were observed. Scatterplots with mean reaction time (right) displayed on the y-axes and age on the x-axes indicated that participants across both groups responded slower with increasing age across both conditions. (**c**) Box and whisker plots showing the reaction time data in unimpaired PWH and participants with HAND. Main effects of condition (valid vs. invalid) and age were observed, similar to the analyses of PWH and controls. Scatterplots with mean reaction time (right) displayed on the y-axes and age on the x-axes indicated that all PWH responded slower with increasing age across both conditions. Note that reaction time was computed as the time from target onset (not cue onset) to button press. ** $p < .01$ [ANCOVA].(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

group by age interaction effects (F(2168) =0.974, $p = .380$) [ANCOVA]. For more information, see supplementary material (Table S1).

Artifact-free epochs were transformed into the time-frequency domain using complex demodulation [87], and the resulting spectral power estimations per sensor were averaged over trials to generate time-frequency plots of mean spectral density. These sensor-level data were normalized per time-frequency bin using the respective bin's baseline power, which was calculated as the mean power during the −600 to 0 ms baseline period. The specific time-frequency windows used for source reconstruction were determined by statistical analysis of the sensor-level spectrograms across all participants using the entire array of 204 gradiometers.

2.6. Sensor-level statistics

Briefly, each data point in the spectrogram was initially evaluated using a mass univariate approach based on the general linear model. To reduce the risk of false positive results while maintaining reasonable sensitivity, a 2-stage procedure was followed to control for Type-1 error. In the first stage, paired-sample t-tests against baseline were conducted on each data point, and the output spectrogram of t-values was thresholded at $p < .05$ to define time-frequency bins containing potentially statistically significant oscillatory deviations across all participants. In stage two, time-frequency bins that survived the $p < .05$ threshold were clustered. This clustering involved

taking the temporally and/or spectrally neighboring bins that were also above the threshold ($p < .05$), and deriving a cluster value by summing the t-values of all data points in the cluster using the BESA Statistics 2.0 software.

Nonparametric cluster-based permutation testing was then conducted using a monte-carlo approach to randomly sample participants and re-assign their active versus baseline data before recomputing the cluster sum values, which were eventually used to build a null distribution based on 10,000 permutations. The significance level of the observed clusters (from stage 1) were tested directly using this distribution [88,89]. Based on these analyses, the time-frequency windows that contained statistically significant oscillatory events across all participants and conditions were subjected to a beamforming analysis. A detailed description of this approach is available in a recent paper [90].

2.7. MEG source imaging

Cortical networks were imaged using the dynamic imaging of coherent sources (DICS) beamformer [91], which applies spatial filters in the time-frequency domain to calculate voxel-wise source power for the entire brain volume. The single images were derived from the cross-spectral densities of all combinations of MEG gradiometers averaged over the time-frequency range of interest, and the solution of the forward problem for each location on a grid specified by input voxel space. Following convention, we computed noise-normalized source power for each voxel per participant using active (i.e., task) and passive (i.e., baseline) periods of equal duration and bandwidth [92] at a resolution of $4.0 \times 4.0 \times 4.0$ mm. Such images are typically referred to as pseudo-t maps, with units (pseudo-t) that reflect noise-normalized power differences (i.e., active versus passive) per voxel. MEG pre-processing and imaging used the Brain Electrical Source Analysis (version 6.1) software.

2.8. Source-level statistics

Conditional whole-brain images per time-frequency response were subtracted (i.e., invalid−valid) within each participant to generate maps representing the validity effect (i.e., attention reallocation). To identify regions where the validity effect was significantly modulated by age, whole-brain correlation maps were computed between the voxel-wise validity effect maps and participant ages. These validity-by-age interaction maps were computed for each group individually (i.e., healthy controls, unimpaired PWH, and participants with HAND). From these maps, whole-brain bivariate correlation coefficient comparisons were computed using Fisher's Z-transformation, which provided a voxel-wise map of z-scores representing the normalized difference between each group in the age/validity effect relationship. The resulting maps were thresholded at $p < .005$ and adjusted for multiple comparisons using a spatial extent threshold (i.e., cluster restriction; $k = 300$ contiguous voxels) based on the theory of Gaussian random fields [93-95]. Finally, Pearson correlations were conducted among the neural activity maps and the behavioral reaction time validity effect for all three groups. Any value ±2.5 SD from the mean was considered an outlier and removed prior to statistical analyses.

3. Results

All 173 participants successfully completed the study (see Fig. 1), but two controls and one participant with HAND were excluded due to poor task performance (i.e., very delayed responses; 2.5 SD above the mean). Briefly, extremely long reaction times are often indicative of participants not performing the task correctly (i.e., lapses of attention, missing the stimulus onset, etc.) and can add substantial noise to the mean response time.

3.1. Clinical characteristics & behavioral effects

Assessment of the neuropsychological and Activities of Daily Living (ADL; [96]) functional data indicated that 28 of the PWH met the diagnostic criteria for HAND. Of these 28 participants with HAND, 20 were classified as having asymptomatic neurocognitive impairment (ANI), 6 were classified as having mild neurocognitive disorder (MND), and 2 were classified as having HIV-associated dementia (HAD) according to the Frascati criteria [84]. No major demographic variables differed between the three groups (Table 1).

An Analysis of Covariance comparing controls and PWH on reaction time revealed statistically significant main effects of condition ($F(1, 166) = 18.71$, $p < .001$) and age ($F(1, 166) = 11.185$, $p = .001$) [ANCOVA]. The main effect of condition indicated that participants responded more slowly during invalid relative to valid trials across all both groups (Fig. 2B) and the age effect revealed that participants were slower to respond to all trials with advancing age across both groups. Moreover, there was a trending condition by age interaction ($F(1, 166) = 3.60$, $p = .06$) and post-hoc testing showed a statistically significant correlation between age and the reaction time validity effect in only the control group ($r = 0.248$, $p = .017$) [Pearson correlation]. In other words, the slower responses during invalid relative to valid trials became greater with increasing age in controls. A similar statistical analysis was conducted on the accuracy data and this indicated a main effect of condition ($F(1, 166) = 4.47$, $p = .036$) [ANCOVA], which suggested that participants were more accurate in responding to valid as compared to invalid trials across both groups. No other main effects or interactions with accuracy were found. Similarly, comparing unimpaired PWH and participants with HAND on reaction time revealed statistically significant main effects of condition ($F(1, 74) = 17.34$, $p < .001$) and age ($F(1, 74) = 8.23$, $p = .005$) [ANCOVA]. As with the larger analysis comparing PWH and controls, the main effect of condition indicated that all participants responded more slowly during invalid relative to valid trials (Fig. 2C), and the age effect revealed that participants took longer to respond to all trials with advancing age across both PWH groups. No other effects were statistically significant. For a detailed information, see supplementary material (Tables S2, S3 and S4).

3.2. MEG sensor-level oscillatory analysis

While strong theta and alpha/beta responses were observed after cue onset, the goal of the current study was to examine oscillations related to the attentional reorienting process. Thus, our statistical analyses focused on neural activity during the target period (i.e., starting 300 ms after cue onset). These analyses revealed four spectrally specific oscillatory responses in gradiometers near the parietal, occipital, and frontal cortices across all participants and both conditions (Fig. 3). Briefly, during target presentation, a strong increase in the theta range (3−7 Hz) was observed from 350 to 700 ms ($p < .001$, corrected). This response partially overlapped in time with robust decreases in the alpha (8−14 Hz; 350−950 ms, $p < .001$, corrected) and beta ranges (14−22 Hz; 350−950 ms, $p < .001$, corrected). Finally, a strong gamma increase (46−58 Hz; 850−1450 ms, $p < .001$, corrected) [Paired-sample *t*-test]. was observed and this oscillatory response was most prominent in sensors near the occipital cortices (Fig. 3).

3.3. Ageing with HIV: impact on attentional reorienting

To identify regions where the validity effect was significantly modulated by age within each group, we computed whole-brain "validity effect" maps by subtracting validly-cued from invalidly-cued maps in a voxel-wise manner, and then performed correlations using these whole-brain maps and the respective age of each participant. To examine whether the resulting cortical responses differed

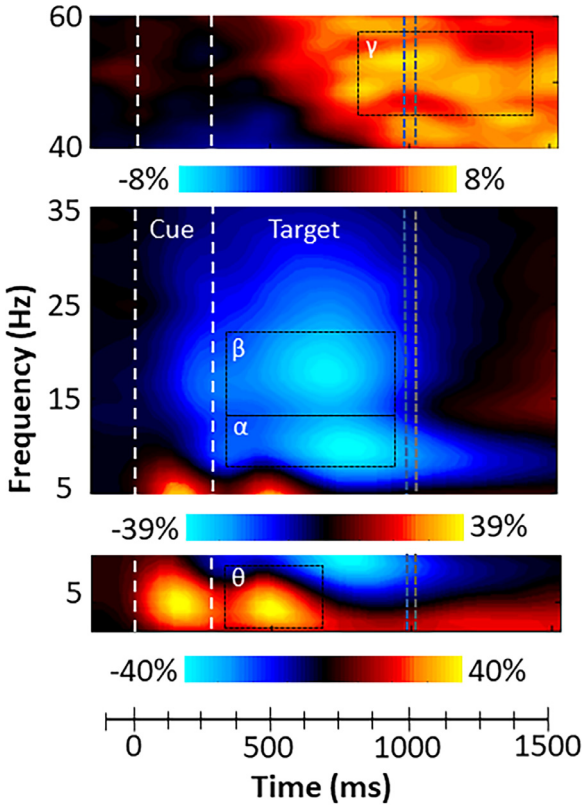

Fig. 3. Sensor level time frequency analysis. Grand averaged spectrograms for two sensors near parietal cortices with time (ms) displayed on the *x*-axis and frequency (Hz) denoted on the *y*-axis. Power is shown in percentage units relative to the baseline period (−600 to 0 ms), with a color scale bar beneath each spectrogram. The data per spectrogram have been averaged across all trials and participants. Note that statistical analyses focused on the target period (i.e., after 300 ms). **(Bottom)** A strong increase in theta (3–7 Hz) power was observed following cue onset and during target processing (350–700 ms). **(Middle)**: Strong decreases in alpha (8–14 Hz, 350–950 ms) and beta (14–22 Hz, 350–950 ms) power were also observed after the onset of the target. **(Top)**: Robust increases in gamma (46–58 Hz) activity occurred during later target processing (850–1450 ms). All four oscillatory responses statistically differed from baseline activity in the spectral and temporal windows listed above and in the text ($p < .001$, corrected) [Paired *t*-test]. These time-frequency windows are indicated using the black dotted line boundaries. Blue and grey dotted lines represent the reaction times for valid and invalid trials across all three groups, respectively.(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

between controls and PWH (i.e., unimpaired PWH and HAND groups collapsed), we applied Fisher's Z-transformation to the whole-brain correlation maps. Our results indicated statistically significant differences in the age-related trajectory of the theta validity effect in the left prefrontal region between the two groups ($p < .005$, corrected) [Fisher's Z], such that controls exhibited a statistically significant but weak positive correlation between the theta validity effect and age in this region ($r = 0.268$, $p = .01$), while PWH exhibited a marginal negative correlation with age ($r = -0.214$, $p = .07$; Fig. 4) [Pearson's correlation].

In regard to the validity effect in the alpha bandwidth range, age-related group differences were observed in the left parietal ($p < .005$, corrected), right cuneus ($p < .005$, corrected), and right frontal eye fields (FEF; $p < .005$, corrected) [Fisher's Z]. Briefly, in left parietal cortices, the neural validity effect was positively associated with age in controls ($r = 0.375$, $p < .001$) indicating that advancing age was associated with smaller alpha validity effects in this region, while PWH exhibited a statistically non-significant negative relationship between the alpha validity effect and age ($r = 0.155$, $p = .198$) [Pearson correlation]. A similar pattern of alpha responses was observed in the right cuneus, although the correlation in controls was only trending

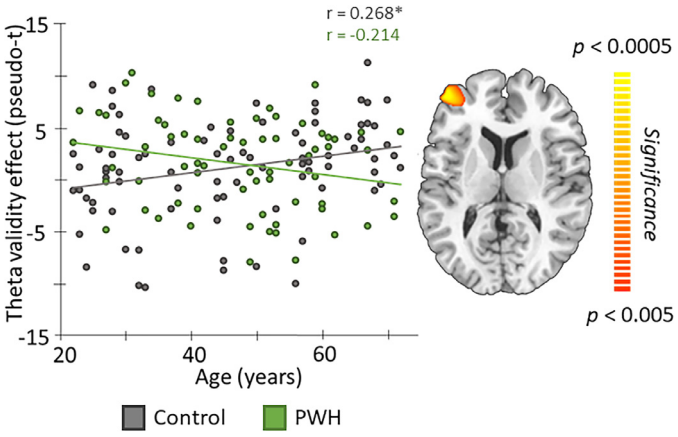

Fig. 4. Age-related theta validity effects in Controls and PWH. Validity maps (invalid–valid trials) were computed for each participant and were correlated with age in each group. We then compared these maps after Fisher's Z transformation to identify regions where the correlation differed statistically between controls and PWH (unimpaired and HAND groups collapsed), which revealed a cluster in the left prefrontal cortices (right). To determine the directionality, we extracted the peak voxel value in each participant, and these are shown in the scatterplot. In the scatterplot, age (in years) is represented on x-axis and the theta validity effect (3–7 Hz) in the prefrontal cortices is plotted on the y-axis in pseudo-t units, with the line of best-fit overlaid for each group. Controls exhibited a statistically significant positive correlation between the theta validity effect and age in the left prefrontal region (grey), which differed from PWH who exhibited a statistically non-significant negative correlation (green). * $p < .05$ [Pearson correlation].(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

($r = 0.206$, $p = .053$). Conversely, in the right FEF, PWH showed a statistically significant negative correlation between the alpha validity effect and age ($r = -0.310$, $p = .008$), indicating that the alpha validity effect became stronger (i.e., more negative relative to baseline) in PWH as a function of age (Fig. 5), while controls exhibited no relationship ($r = 0.038$, $p = .722$) [Pearson correlation] between the alpha validity effect and age in this brain region.

Finally, the relationship between beta validity effects and age differed between the groups in the dorsal left prefrontal cortices ($p < .005$, corrected), such that a robust positive correlation between the beta validity effect and age was observed in controls ($r = 0.30$, $p = .004$), while PWH exhibited the opposite relationship ($r = -0.319$, $p = .006$; Fig. 6) [Pearson correlation]. Since oscillatory beta responses in this brain area are generally negative (i.e., are decreases relative to baseline), these findings indicate that the responses became weaker with increasing age in controls, whereas they became stronger with increasing age in PWH. No other age-by-validity effect group differences were observed between controls and PWH.

To identify whether these neural validity effects were linked with behavioral performance, we computed Pearson correlation coefficients using the reaction time data and peak voxel values from the neural findings described above. These analyses revealed statistically significant positive associations in controls, such that alpha validity effects became smaller as reaction time validity effects increased in the left parietal and right FEF regions where alpha group differences were observed (left parietal region: $r = 0.255$, $p = .017$; right FEFs: $r = 0.364$, $p < .001$; Fig. 5B [Pearson correlation]. A marginal correlation was also observed for alpha in the right cuneus of controls ($r = 0.190$, $p = .08$) [Pearson correlation]. These alpha relationships were not statistically significant in PWH and effects in other spectral windows (e.g., theta) were not statistically significant in either group (all $ps > 0.05$) [Pearson correlation].

3.4. Cognitive status modulates the impact of ageing in HIV

To determine whether age-related changes in attentional reorienting (i.e., the cue validity effect) differed as a function of cognitive

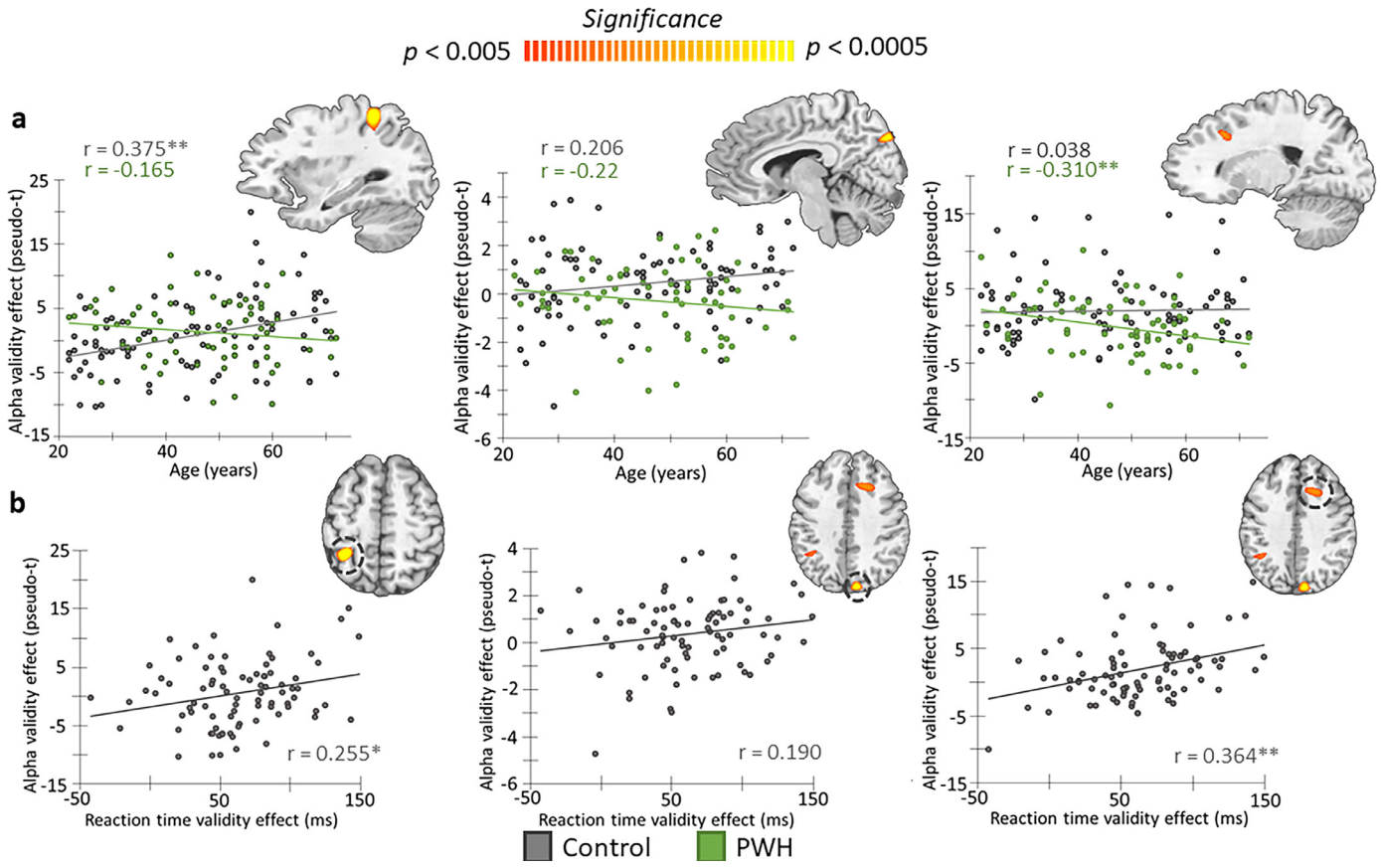

Fig. 5. Age-related Alpha validity effects in Controls and PWH and their relationship to reaction time. (a) As in Fig. 4, validity maps (i.e., invalid−valid) were computed and correlated with age in each group (controls and PWH), then Fisher's Z transformation was applied to determine whether the correlation between alpha (8−14 Hz) validity effects and age differed between controls and PWH (unimpaired and HAND collapsed). These analyses revealed group differences in the left parietal, right cuneus, and right frontal eye fields (FEF). Post hoc analysis showed that the left parietal validity effect (left) was positively correlated with age in controls, but negatively leading (statistically non-significant) in PWH. A similar pattern was observed in the right cuneus (middle), although the correlation was only trending. In contrast, alpha correlations validity was found to have a strong negative association with age in PWH in the right FEF (right), while controls showed no relationship with age in this region. **(b)** Pearson correlational analysis between alpha validity maps in the left parietal, right cuneus and right FEFs showed statistically significant positive associations between the alpha and reaction time validity effects in left parietal regions and right FEFs. Black dotted circles in the images above each scatterplot indicate the relevant region.* $p < .05$. ** $p < .01$ [Pearson correlation].

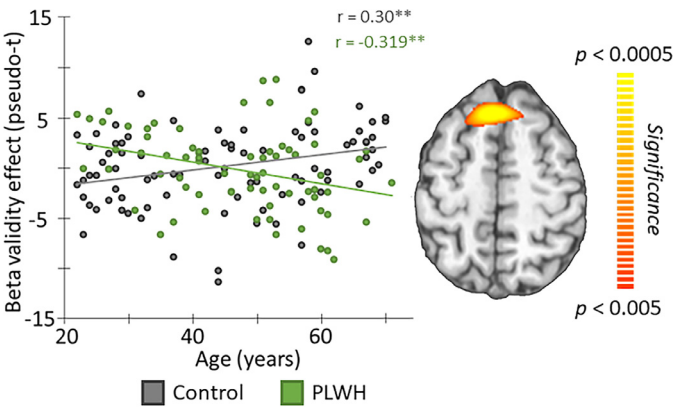

Fig. 6. Age-related beta validity effects in Controls and PWH. As in Figs. 4 and 5, validity maps (invalid − valid trials) were computed for each participant and were correlated with age in each group. Fisher's Z transformation was then applied to identify regions where the correlation differed statistically between controls and PWH (unimpaired and HAND groups collapsed). Age (in years) is represented on *x*-axis and the beta validity effect (14−22 Hz) in the left dorsolateral prefrontal cortices is plotted on the *y*-axis in pseudo-t units, with the line of best-fit overlaid for each group. Controls exhibited a positive correlation between the beta validity effect and age in the left dorsolateral prefrontal region (grey), while PWH showed a strong statistically significant negative association between the validity effect and age in the same region. ** $p < .01$ [Pearson correlation].

status in PWH, Fisher's Z-transformed whole-brain correlation maps of unimpaired PWH and participants with HAND were compared. Interestingly, we found statistically significant results only in the gamma range (46−58 Hz, 850−1450 ms). Our results showed that the impact of age on gamma validity effects differed between unimpaired PWH and those with HAND in the left temporoparietal ($p < .005$, corrected), left inferior frontal gyrus (IFG; $p < .005$, corrected), and the right lateral prefrontal cortex ($p < .005$, corrected; Fig. 7) [Fisher's Z]. In all three regions, neural validity effect scores of participants with HAND were found to be positively associated with ageing (left temporoparietal: $r = 0.624$, $p = .001$; left IFG: $r = 0.614$, $p = .001$; right prefrontal cortex: $r = 0.627$, $p = .001$) [Pearson correlation], such that the validity effect in the gamma bandwidth range became larger as age increased. In contrast, unimpaired PWH exhibited statistically non-significant negatively leading correlations between gamma validity effect and age in these regions (Fig. 7). For reference, we also plotted the best-fit lines for uninfected controls, and like unimpaired PWH, there were no statistically significant age-by-gamma validity effects in these brain regions.

Finally, since the three groups differed statistically in years of education and BDI scores (both $ps < 0.001$) [ANOVA], we re-tested statistically significant findings using these variables as covariates of no interest to mitigate their possibly confounding effects. Including these covariates in the analyses did not change the findings; all statistically significant findings remained.

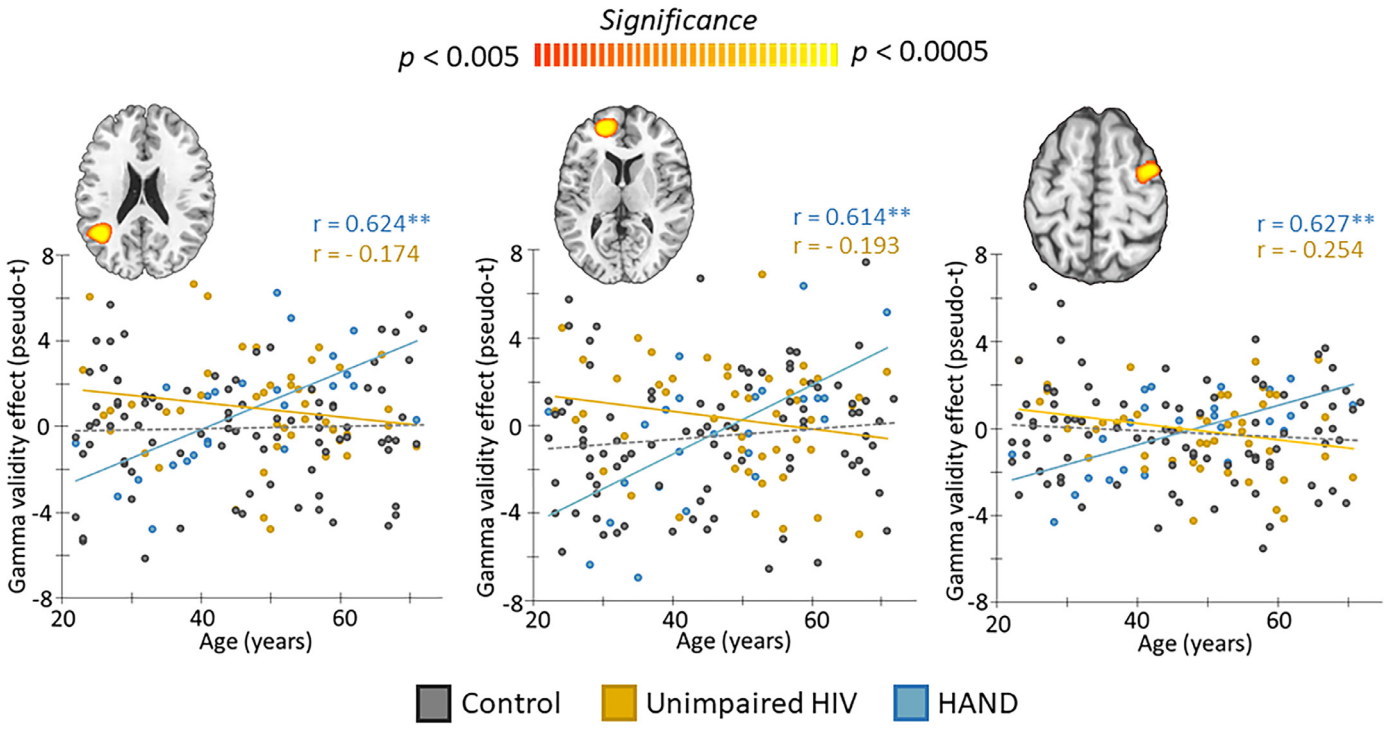

Fig. 7. Age-related gamma validity effects in unimpaired PWH and HAND groups. Validity maps (i.e., invalid−valid) were computed and correlated with age in each group (unimpaired PWH and HAND), then Fisher's Z transformation was applied to determine whether the correlation between gamma (46−58 Hz) validity effects and age differed between unimpaired PWH and HAND groups. For reference, best line fits for controls are also plotted (grey). These analyses revealed statistically significant group differences in the left temporoparietal (left), left inferior frontal gyrus (middle), and right lateral prefrontal cortex (right). In all three regions, adults with HAND exhibited a strong positive association between the gamma validity effect and increasing age (blue), and these statistically differed from unimpaired PWH (yellow). ** $p < .01$ [Pearson correlation].(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

In this study, we combined state-of-the-art MEG imaging and a well-established cued attention task to investigate how ageing differentially modulates the neural oscillatory dynamics serving attentional reorienting in PWH and controls. Critically, we found that age-related changes in the multi-spectral neural responses serving attentional reorienting statistically differed between the two groups across a network of brain regions that previous normative studies have identified as critical to attention function. Such age-related differences included both theta and beta oscillations in the left prefrontal cortices, as well as alpha activity in the left parietal, right cuneus, and right FEFs. Further, within the PWH group, we found that age-related changes in gamma oscillatory activity statistically differed between the cognitively unimpaired and HAND groups in the left temporoparietal area, left IFG, and right lateral prefrontal cortices. Finally, age-related alterations in alpha activity in left parietal and right FEFs were statistically correlated with behavioral performance (i.e., reaction time) in controls, but not PWH. These findings and their implications are discussed below in further detail.

Our behavioral findings aligned well with the previous literature, with all three groups (controls, unimpaired PWH, and HAND) responding slower to invalid trials as compared to valid ones. Moreover, in controls, ageing accentuated this reaction time validity effect. This increased processing time with ageing, especially in the case of invalid trials, has been widely supported by past studies. Across all trials (valid and invalid), ageing was associated with prolonged reaction times and decreased accuracy in both groups, which likely indicates slower overall decision making and general age-related declines and is consistent with prior literature [97].

In regard to the MEG data, we found that age-related changes in prefrontal theta activity during attentional reorienting distinguished PWH from controls. Specifically, we found that theta oscillatory responses (i.e., synchronizations) were largely equivalent during valid and invalid trials in younger controls, but with increasing age the difference between the two (i.e., the validity effect) increased, with invalid trials being associated with stronger theta responses. Previous studies have repeatedly tied prefrontal theta activity to attentional reorienting towards goal-relevant stimuli [53,98,99] and its modulation with ageing [100,101], and thus these results are congruent with previous reports. In contrast, PWH exhibited a different trajectory of prefrontal theta activity with increasing age, as young PWH showed stronger theta responses on invalid relative to valid trials, but with increasing age this pattern reversed and PWH responded equally or slightly more strongly to valid trials. To our knowledge, this is the first study of attentional reorienting in PWH, but it should be noted that other studies have found prefrontal theta aberrations in the context of cognitive interference [31] and ageing [33] in PWH. Further, such reports of theta aberrations in PWH have not been limited to the prefrontal cortices [37,39].

Beyond theta, age dependent changes in alpha and beta activity in essential nodes of the dorsal and ventral attention networks (DAN and VAN) robustly differentiated controls from PWH. Specifically, weaker alpha validity effects were found in left parietal cortex and right cuneus (trending) with advancing age in controls, while PWH exhibited the opposite pattern with advancing age in the right FEF and no effect in the other two regions. In controls, alpha responses were stronger (i.e., more negative relative to baseline) in the invalid relative to valid condition during young adulthood, and this difference converged with increasing age and actually reversed late in life. Interestingly, in controls, the strength of the validity effect in all three group-difference regions (i.e., left parietal, right cuneus, and right FEF) was positively correlated with the reaction time validity effect. Thus, this age-related change in the strength of alpha during attentional reorienting likely has at least an indirect effect on reaction time and thus the speed of the reorienting process. Beyond alpha, a

similar pattern of age-related responses was observed for beta activity in the left prefrontal cortices. Essentially, prefrontal beta oscillations were stronger (i.e., more negative relative to baseline) during invalid relative to valid trials in young adults, and this effect dissipated with increasing age and eventually reversed in older controls. PWH exhibited the opposite pattern of increasing prefrontal beta responses during invalid relative to valid trials with increasing age. These distinct patterns of neural activity serving attention reorientation with ageing between controls and PWH may aid in understanding the neural basis of cognitive decline in PWH. As stated previously, the DAN and VAN are known to have distinctive but collaborative roles in attentional reallocation, and the prefrontal, FEF, cuneus, and parietal regions have been widely associated with the top-down modulation of attention and selection of goal-oriented stimuli [54,102-111]. Additionally, attentional disengagement from a point and re-engaging on a relevant stimulus is considered to be at least partially driven by parietal neural activity [58,112-114]. Of note, aberrant activity in neuronal populations within DLPFC and the right FEF have been reported previously during visual processing in PWH, and such activity was correlated with neuropsychological performance [36]. Further, cognitive deficits in such patients are known to correlate with thinning of prefrontal and parietal cortical regions [115], and such findings of altered cortical thickness in these regions was recently extended to PWH who are receiving cART [116]. Interestingly, a recent study linked gamma oscillatory activity and local cortical thickness in healthy adults [117], although clearly further work is needed and showing this relationship in PWH would be a major step forward. Several of the regions identified here have also been previously shown to exhibit premature-ageing in HIV [118], but further work is needed to understand the precise mechanism.

Finally, one of our most interesting findings was the distinct ageing trajectory observed in unimpaired PWH versus those with HAND. Specifically, we observed stronger increases in gamma activity within the temporoparietal, left IFG, and right prefrontal cortices during invalid relative to valid trials as a function of ageing in adults with HAND, while unimpaired PWH and controls showed no relationship between ageing and gamma activity during attentional reorienting. Both the temporoparietal and IFG are key components of the VAN, critical for reallocation of attention by interrupting and resetting ongoing activity [53,56,119]. Thus, increased gamma activity in HAND during reorienting may reflect a compensatory mechanism with increasing age, such that those with HAND recruit brain reserve networks in VAN cortices to a comparatively greater extent during high attentional demands. A large body of literature focuses on compensatory processes in older adults [68,120,121], as well as in pathological conditions like diabetes [122,123] and HIV [37,76], and/or a similar framework may be at play here. Our behavioral findings would certainly support such a conclusion.

To close, we evaluated the impact of ageing with HIV on the neural oscillations serving attentional reorienting using MEG and the cued attention task. We observed distinct ageing trajectories for the neural oscillations serving attentional reorienting in controls and PWH, and in some cases within PWH depending on their cognitive status. We propose these findings hold important implications for understanding altered attention function and ageing phenotypes in PWH. One of our most interesting findings was that age-related changes in gamma oscillations within critical nodes of the VAN distinguished unimpaired PWH from those with HAND. These findings could have important implications for unraveling the complex pathophysiology of HAND and predicting its trajectory in PWH, as well as expanding on a more basic understanding of how the neural dynamics serving attentional reorienting are uniquely altered by ageing with HIV. Although the current study did not clearly show that HIV causes accelerated ageing, it certainly does support an altered ageing trajectory in PWH.

Before closing, it is important to acknowledge several limitations, which should be kept in mind when assessing the implications of the work and could be considered targets in future studies. First, our study was cross-sectional and the trajectories that we illuminate are limited in that regard. Employing a longitudinal design in this context would significantly enhance the veracity of the study and confidence in the overall conclusions. Secondly, we did not remove the potential neural activity secondary to saccades, which might have contributed to noise especially in the gamma band range within the temporal region [124]; thus, some of our findings should be interpreted with caution. Moreover, our sample had virologic suppression, reported minimal depressive symptoms, and were otherwise healthy for a community sample of PWH. While this is a strength in some ways (i.e., fewer confounding factors), it introduces some selection bias and somewhat limits generalization to PWH with clinical depression and other psychiatric comorbidities, which are common in PWH [125]. Similarly, substance use, especially cannabis use, is also prevalent in PWH and was minimal in our study [126]. Additionally, PWH are more likely to suffer from other clinical diseases affecting cardiovascular, renal, and peripheral vascular system [127], along with side effects of cART and possibly drug interactions [128]. Thus, future studies should consider incorporating those with more elevated depressive symptoms and consider the value of including PWH with other common comorbidities. Lastly, matching in this study did not include other potentially relevant factors such as cardiovascular disease risk factors, socioeconomic status, access to healthcare, or other lifestyle factors.

Finally, it is worth noting that the underlying molecular mechanisms of altered ageing phenotypes in neuroHIV are not understood, and future work should start to address this to provide greater contextualization for human findings like those reported here. Such multidisciplinary research extending across multiple levels is sure to bring new insights on the ageing process in PWH, and help establish protocols to enhance physical health, mental health, and cognitive processing across the lifespan in this population.

Contributors

Y.A.: drafting the manuscript and figures, analysis of data, design of the study; A.I.W.: acquisition and analysis of data, design of the study; J.O.: acquisition and analysis of data; C.E.M.: acquisition and analysis of data; P.E.M.: acquisition and analysis of data; B.J.L.: acquisition and analysis of data; M.D.S.: acquisition and analysis of data; H. S.F.: conception and design of the study; S.S.: conception and design of the study; T.W.W.: conception and design of the study, drafting of the manuscript, acquisition of funding. All authors contributed in revising the manuscript and take responsibility for its content.

Data sharing statement

The data that support the findings of this study are available from the corresponding author, Dr Tony W. Wilson, upon reasonable request.

Declaration of Competing Interest

Dr. Swindells reports research grants to her institution from the National Institutes of Health and ViiV Healthcare, with the ViiV healthcare support being unrelated to this work. Dr. Fox reports grants from the National Institutes of Health and the Michael J. Fox Foundation. Ms. O'Neill reports grants from the National Institutes of Health, National Science Foundation, Janssen Scientific, Gilead Science, and grants and personal fees from ViiV Healthcare; the support from Janssen Scientific, Gilead Science, and ViiV Healthcare was for projects separate from and outside of the submitted work. Drs. Wilson, Arif, and Wiesman report research grants to their institution

from the National Institutes of Health and the National Science Foundation. Dr. May reports research grants to her institution from the National Institutes of Health. Mr. Lew, Ms. Embury, and Ms. Schantell report research grants to their institution from the National Institutes of Health and the National Science Foundation. There were no other financial, commercial or institutional conflicts of interests to report.

Acknowledgments

The authors would like to acknowledge the enormous contribution of Kevin R. Robertson, PhD, professor of neurology and director of the AIDS Neurological center at the University of North Carolina at Chapel Hill. Dr. Robertson designed and analyzed all the neuropsychological testing, and sadly died during the conduct of the study. We would also like to thank our participants for volunteering.

This work was primarily supported by the National Institute of Mental Health (MH103220, MH116782, MH118013, and MH062261), the National Institute for aging (AG055332), the National Institute of General Medical Sciences (GM130447), the National Institute on Drug Abuse (DA041917, DA047828, and DA048713), and the National Science Foundation (#1539067). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ebiom.2020.103065.

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