Aberrant occipital dynamics differentiate HIV-infected patients with and without cognitive impairment

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Combination antiretroviral therapies have revolutionized the treatment of HIV infection, and many patients now enjoy a lifespan equal to that of the general population. However, HIV-associated neurocognitive disorders (HAND) remain a major health concern, with between 30% and 70% of all HIV-infected patients developing cognitive impairments during their life time. One important feature of HAND is visuo-perceptual deficits, but the systems-level neural dynamics underlying these impairments are poorly understood. In the current study, we use magnetoencephalography and advanced time series analyses to examine these neural dynamics during a visuospatial processing task in a group of HIV-infected patients without HAND (n = 25), patients with HAND (n = 18), and a group of demographically-matched uninfected controls (n = 24). All participants completed a thorough neuropsychological assessment, and underwent magnetoencephalography and structural MRI protocols. In agreement with previous studies, patients with HAND performed significantly worse than HIV-infected patients without HAND and controls on the cognitive task, in terms of increased reaction time and decreased accuracy. Our magnetoencephalography results demonstrated that both spontaneous and neural oscillatory activity within the occipital cortices were affected by HIV infection, and that these patterns predicted behavioural performance (i.e. accuracy) on the task. Specifically, spontaneous neural activity in the alpha (8–16 Hz) and gamma (52–70 Hz) bands during the prestimulus baseline period, as well as oscillatory theta responses (4–8 Hz) during task performance were aberrant in HIV-infected patients, with both spontaneous alpha and oscillatory theta activity significantly predicting accuracy on the task and neuropsychological performance outside of the magnetoencephalography scanner. Importantly, these rhythmic patterns of population-level neural activity also distinguished patients by HAND status, such that spontaneous alpha activity in patients with HAND was elevated relative to HIV-infected patients without HAND and controls. In contrast, HIV-infected patients with and without HAND had increased spontaneous gamma compared to controls. Finally, there was a stepwise decrease in oscillatory theta activity as a function of disease severity, such that the response diminished from controls to patients without HAND to patients with HAND. Interestingly, the strength of the relationship between this theta response and accuracy also dissociated patient groups in a similar manner (controls > HIV with no HAND > HIV with HAND), indicating a reduced coupling between neurophysiology and behaviour in HIV-infected patients. This study provides the first neuroimaging evidence of a dissociation between HIV-infected patients with and without HAND, and these findings shed new light on the neural bases of cognitive impairment in HIV infection.

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Introduction

Although combination antiretroviral therapies have greatly decreased mortality due to HIV infection, HIV-associated neurocognitive disorders (HAND) remain prevalent in this population, greatly decrease the quality of life of those affected, and represent a significant health concern (Clifford and Ances, 2013). The key features of HAND are cognitive impairments, which include notable deficits in attention, working memory, motor function, and visual perception (Woods et al., 2009; Wilson et al., 2013a, b, 2017b). Unfortunately, the neural mechanisms underlying these deficits are poorly understood at a systems-level. A more macro-level approach to this issue is probably essential, as large-scale white matter abnormalities have been repeatedly linked to HIV-related neurocognitive impairments (Heindel et al., 1994; Filippi et al., 2001; Ances and Hammoud, 2014), signifying the likelihood of impaired network-level function. Understanding the neural bases of these deficits is of major importance, as it could lead to earlier and more accurate diagnoses, more precise prognoses, as well as a more comprehensive understanding of the disease.

Previous structural neuroimaging studies of HIV infection have indicated progressive thinning of the grey matter in posterior cortices (Aylward et al., 1995; Stout et al., 1998), and that these neuropathological changes begin in the asymptomatic stages of the infection. Further, at least some of this degeneration continues even during effective treatment with combination antiretroviral therapies (Ances and Hammoud, 2014). Generalized degradation of grey matter in these regions, and in particular the posterior parietal cortices, would be expected to affect the visual attention and visuo-perceptual abilities of these patients, as these regions have been robustly implicated in the neural mapping of salience in visual space (Posner and Petersen, 1990; Colby and Goldberg, 1999; Bisley and Goldberg, 2010). Furthermore, as mentioned above, the structural integrity of white matter tracts has been found to be compromised in HIV infection (Heindel et al., 1994; Ances and Hammoud, 2014), particularly tracts involving prefrontal and parieto-occipital regions (Filippi et al., 2001). Such structural abnormalities would likely affect both local and distant functional communication between key neural regions, and have been previously linked with dysfunction on common cognitive tasks (Tate et al., 2010).

Functional imaging studies have also reported impairments in visuo-perceptual and visual attention networks in HIV-infected adults, and these have generally been in agreement with the structural data. For instance, in early studies, Chang and colleagues found that HIV-infected patients exhibit markedly increased functional MRI activation in lateral occipital, posterior parietal, and prefrontal regions during attentional processing (Chang et al., 2001, 2004), which suggested aberrant signalling at the systems-level, or perhaps compensatory processing. More recently, corruption of parietal and fronto-visual functional connectivity in the resting state has been reported in HIV-infected patients (Becker et al., 2012; Thomas et al., 2013), and these fronto-visual networks align particularly closely with those that are compromised in advanced age (Thomas et al., 2013). However, surprisingly, few functional neuroimaging studies have examined whether the neural activity of patients with HAND can be distinguished from that of unimpaired HIV-infected patients, and no research has been aimed at investigating this potential dissociation through the lens of oscillatory neural activity. Neural oscillations have been found to functionally organize the processing of visual stimuli in the occipital cortices, and to play a central role in visual attention function (Fries et al., 2001; Tallon-Baudry et al., 2005; Vidal et al., 2006; Doesburg et al., 2007; Handel et al., 2011; Landau and Fries, 2012; Koelewijn et al., 2013; Jensen et al., 2014; Szczepanski et al., 2014; Landau et al., 2015; Marshall et al., 2015; Fellrath et al., 2016; Kwon et al., 2017; Wiesman et al., 2017). Specifically, oscillatory activity in the theta (4–7 Hz), alpha (8–14 Hz), and gamma (30+ Hz) rhythms has been found to regulate divergent components of visual processing (Gray and Singer, 1989; Başar et al., 2001; Edden et al., 2009; Handel et al., 2011; Koelewijn et al., 2013; Muthukumaraswamy and Singh, 2013; Nikolić et al., 2013; Landau et al., 2015; Fellrath et al., 2016; Mayer et al., 2016; Wiesman et al., 2017; Wilson et al., 2017a), and thus could provide novel insight into the mechanisms that underlie attention deficits in HIV-infected patients, while also serving as a marker for the presence of HAND, and potentially a sensitive prognostic indicator.

Herein, we examine the neural dynamics underlying aberrant visuospatial processing in HIV-infected patients without HAND, patients with HAND, and a group of demographically-matched control participants. All participants completed an extensive neuropsychological
Materials and methods

Participants

We enrolled 24 uninfected adult controls (23 right-handed; 13 males), 25 HIV-infected adults (24 right-handed; 15 males), and 18 adults with HAND (16 right-handed; 13 males) from a large ongoing study of the effects of ageing in HIV infection, for a grand total of 67 participants in the study. Selected participants were all middle age [range = 32–55 years old; mean = 44.16; standard deviation (SD) = 7.05] to minimize the impact of ageing, and all three groups were matched on age, sex, handedness, ethnicity, and educational level. Group demographics and neuropsychological profiles are reported in Table 1. The HAND group was composed of three subtypes based on the Frascati criteria (Antinori et al., 2007), and this distribution is reported in the results. All HIV-infected participants were receiving effective combination antiretroviral therapies and all but two had undetectable viremia (<20 copies/ml). Exclusion criteria included any medical illness affecting CNS function (other than HIV infection/HAND), any neurological disorder (other than HAND), history of head trauma, and current substance abuse. The Institutional Review Board at the University of Nebraska Medical Center reviewed and approved this investigation. Written informed consent was obtained from each participant following detailed description of the study. All participants completed the same experimental protocol.

Neuropsychological testing

All participants underwent a battery of neuropsychological assessments, with raw scores for each participant being converted to demographically-adjusted z-scores using published normative data (Heaton et al., 2004). This battery adhered to the recommendations of the Frascati consensus (Antinori et al., 2007) and assessed multiple functional domains, including fine motor (grooved pegboard), language (WRAT 4 reading), verbal learning and memory (Hopkins Verbal Learning Test – Revised), speed of processing (Trailmaking-A, digit symbol), attention and working memory (Symbol Search, Stroop word), and executive functioning (verbal fluency, Stroop interference, and Trailmaking-B). Using these assessments and activities of daily living, patients were rated on a scale of 0 to 3 as having no cognitive impairment (0), HIV-associated asymptomatic neurocognitive impairment (1), HIV-associated mild neurocognitive disorder (2), or HIV-associated dementia (3) according to the Frascati guidelines. HIV-infected individuals with an impairment rating of 1 or higher were included as a part of the HAND cohort, while those with a rating of zero were included as a part of the HIV-infected (no HAND) cohort. These HAND severity rankings were also used in subsequent Spearman rank-order correlation analyses, to examine relationships among task performance and neuropsychological markers. Composite scores for each functional domain were also computed using multiple assessments and the standardized z-scores described above.

MEG experimental paradigm

We used a visuospatial discrimination task, termed ‘Vis-Attend’ (Fig. 1A), to engage visual attention circuitry. During this task, participants were seated in a magnetically-shielded room and told to fixate on a crosshair presented centrally. After a variable interstimulus interval (range: 1900–2100 ms), an 8 × 8 grid was presented for 800 ms at one of four positions relative to the fixation: above right, below right, above left, or below and to the left. The left/right orientations were defined as a lateral offset of 75% of the grid from the centre of fixation. Participants were instructed to respond via button press with their right hand as to whether the grid was positioned to the left (index finger) or right (middle finger) of the fixation point upon presentation of the grid. Each participant performed 240 repetitions of the task concurrent with MEG recording.

MEG data acquisition, co-registration, and preprocessing

MEG signals were sampled at 1 kHz with an acquisition bandwidth of 0.1–330 Hz using a 306-sensor Elekta MEG system equipped with 204 planar gradiometers and 102 magnetometers. All data were corrected for head movement, subjected to a noise reduction method (Taulu and Simola, 2006), and co-registered to high-resolution structural MRI. For a detailed account of the data acquisition, co-registration, and preprocessing steps used in this study, please refer to the Supplementary material.
Figure 1 Experimental paradigm and behavioural results. (A) An illustration of the visuospatial discrimination task paradigm. Each trial was composed of two periods: (1) a fixation period lasting 2000 ms (variable interstimulus interval: 1900–2100 ms), 400 ms of which functioned as the baseline; and (2) a stimulus-presentation period lasting 800 ms and consisting of the appearance of a checkered grid in one of four locations. Participants were required to indicate by button press the laterality (left or right) of the stimulus position relative to the fixation point. (B) Behavioural results from the visuospatial task, with participant group denoted on the x-axes. Reaction time (in ms) is displayed on the y-axis of the graph on the left, and accuracy (in % correct) is displayed on the y-axis of the graph to the right. *P < 0.05, **P < 0.01.

Table 1 Group-wise demographic and neuropsychological profiles

|                        | Group means | P-value |
|------------------------|-------------|---------|
|                        | Controls    | HIV     | HAND    |
| Demographics           |             |         |         |
| Age                    | 43.17       | 44.60   | 44.89   | 0.688   |
| Education, years       | 16.71       | 15.64   | 15.17   | 0.328   |
| Gender, % males        | 54.17       | 60.00   | 72.22   | 0.500   |
| Handedness, % right-handed | 95.83   | 96.00   | 88.89   | 0.572   |
| Neuropsychology**      |             |         |         |
| Motor                  | −0.15       | −0.02   | −0.96   | 0.014   |
| Verbal                 | 0.00        | 0.07    | −1.38   | <0.001  |
| Memory                 | 0.20        | 0.09    | −0.83   | <0.001  |
| Executive function     | 0.22        | 0.01    | −0.89   | <0.001  |
| Speed of processing    | 0.14        | 0.25    | −0.95   | <0.001  |
| Attention              | 0.29        | 0.06    | −1.24   | <0.001  |
| Task performance        |             |         |         |
| Reaction time, ms      | 598.04      | 633.45  | 693.70  | <0.001  |
| Accuracy, % correct    | 97.66       | 98.06   | 94.67   | 0.007   |

**All neuropsychology scores are functional domain composite z-scores standardized using published normative data (see ‘Neuropsychological testing’ section).
**MEG time-frequency transformation and sensor-level statistics**

The continuous magnetic time series was divided into 2700 ms epochs, with the baseline extending from −400 to 0 ms prior to stimulus onset. Epochs containing artefacts were rejected using a fixed threshold method, supplemented with visual inspection. An average of 213.24 (SD = 12.37) trials per participant were used for further analysis, and the mean number of trials per participant did not significantly differ between groups (control: 214.17; HIV: 214.88; HAND: 209.72). To examine the spectrally-specific neural responses to the visuospatial discrimination task, the artefact-free epochs were next transformed into the time-frequency domain, 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 using the mean baseline data, which was defined as the mean power during the −400 to 0 ms time period. The specific time-frequency windows used for subsequent source imaging were determined by a stringent statistical analysis of the sensor-level spectrograms across the entire array of gradiometers (Supplementary material). Based on these analyses, the time-frequency windows that contained significant oscillatory events across all participants were subjected to an advanced source-imaging analysis.

**MEG source imaging and statistics**

Cortical networks were imaged through an extension of the linearly constrained minimum variance vector beamformer (Gross et al., 2001), which applies spatial filters to time-frequency sensor data to calculate voxel-wise source power for the entire brain volume. 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. To identify peak voxels, grand averages were computed using the pseudo-t maps from all participants. Virtual sensor (i.e. voxel time series) data were computed by applying the sensor-weighting matrix derived through the forward computation to the preprocessed signal vector, which yielded a time series for each source vector centred in the voxel of interest (see below). These time series were in absolute units (not relative to baseline) and were averaged across both hemispheres, since we did not hypothesize hemispheric effects, into one voxel time series per time-frequency component per participant. Importantly, as both the active and passive (i.e. baseline) time periods are utilized to compute covariance in the beamformer analysis, this approach allows analysis and interpretation of data from not only the post-stimulus active period, but also from the prestimulus baseline period.

**Statistical analysis**

Omnibus MANOVA tests, with follow-on one-way ANOVAs and post hoc testing were used to determine whether neural activity differed by group. To facilitate the evaluation and comparison of these effects, Bayes Factors ($BF_{10}$) were also computed for each ANOVA and post hoc test using JASP (Amsterdam, The Netherlands). Briefly, as opposed to a frequentist statistical approach, where one simply rejects or fails to reject the null hypothesis using arbitrary cut-offs (i.e. $P$-values), Bayes Factors represent the likelihood of the alternative hypothesis producing the same observed pattern in the data, and thereby facilitate the comparison of distinct effects that are only marginally different. To examine the predictive capacity of basal and relative neural dynamics on task performance and neuropsychology, separate linear regression models were computed using reaction time, accuracy, and the three composite neuropsychological scores expected to be essential to performance of the task, respectively, on basal (i.e. prestimulus) amplitude and relative pseudo-t measures where there were significant between-groups differences. When hypotheses dictated, we further examined these predictions within each group using Pearson product-moment correlation coefficients. Fisher’s $z$ transformation was then used to identify significant differences between these group-wise correlation coefficients. All tests were two-tailed, and an alpha level of $P < 0.05$ was considered statistically significant. All statistical analyses were performed in SPSS (Chicago, Illinois, USA), unless otherwise stated.

**Results**

In brief, the results presented herein show that the oscillatory coding of visual stimulus processing is aberrant in HIV-infected patients compared to controls, and that these abnormalities often distinguish patients with and without neurocognitive impairments. After first describing the neuropsychological testing and behavioural MEG task results, we identify the neural time-frequency responses that serve visuospatial discrimination during our task (see ‘Frequency-specific neural responses in occipital, parietal and motor cortices’ section). We then image these responses to dissect the effect of HIV infection and HAND on the functional neuroanatomy generating these responses (see ‘HIV infection and HIV-associated neurocognitive disorders differentially affect visual neuronal dynamics’ section). Finally, to determine whether these aberrant patterns of neural activity relate to behaviour, we examine their relationship with both task-performance and composite neuropsychology scores (see ‘Visual neural dynamics predict task performance’ section).

**Behaviour and neuropsychology**

Neuropsychological and functional assessments indicated that 18 HIV-infected participants were HAND-positive; this included 11 with asymptomatic neurocognitive impairment, three with HIV-associated mild neurocognitive disorder, and four with HIV-associated dementia. One-way ANOVAs revealed that both the accuracy [$F(2,62) = 5.41$, $P = 0.007$, $BF_{10} = 6.30$] and reaction time [$F(2,63) = 8.33$, $P < 0.001$, $BF_{10} = 48.10$] measures in the visuospatial discrimination task were significantly different between groups (Fig. 1B). Post hoc analyses revealed that participants with HAND were significantly slower and less accurate on the task than both HIV-infected non-HAND [reaction time: $t(40) = 2.56$, $P = 0.022$, $BF_{10} = 2.74$; accuracy:
Frequency-specific neural responses in occipital, parietal and motor cortices

MEG analyses were performed only on significant oscillatory events that began in the time window preceding the mean reaction time across all participants, so as to focus on responses underlying visuospatial attention and discrimination, rather than other processes inherent to the later portions of our task (i.e. motor initiation, response/error-checking, etc.). To identify the neural responses related to task performance, the sensor-level MEG data were transformed into the time-frequency domain, and time-frequency windows of interest were determined through a data-driven statistical approach. In agreement with previous studies of visuospatial processing, the task elicited significant responses within four distinct spectral windows (Fig. 2A; all $P < 0.001$, corrected). Specifically, early and transient increases in power were observed in the theta ($4–8$ Hz) band between 100 and 500 ms, followed by a sustained decrease in alpha activity ($8–16$ Hz) between 300 and 700 ms. Temporally coincident with these low-frequency responses was a sustained increase in power in the gamma ($52–70$ Hz) range between 350 and 750 ms. Additionally, in more anterior and superior sensors over the left hemisphere, a decrease was observed in the beta ($20–30$ Hz) band between 200 and 600 ms. Finally, it should be noted that the thresholds used to display the sensor-level responses in Fig. 2A vary substantially (between 8% and 80%) to enhance visualization, as the power of neural responses often differ across distinct frequency bands. For a more complete view of the temporal, spectral, and spatial extent of these responses, refer to Supplementary Fig. 1.

To determine the cortical origins of these responses, the time-frequency windows specified above were imaged using a beamforming approach (Fig. 2B, insets), which was computed across the entire array of gradiometers. Congruent with previous visuospatial attention studies, the theta and gamma power increases originated bilaterally in the posterior primary visual areas, while the decrease in alpha activity was generated by more lateral, parieto-occipital cortices bilaterally. Finally, the decrease in beta activity was centered on the hand-knob region of the left precentral gyrus (contralateral to the hand used for the button pad).

For statistical analysis, we extracted the pseudo-$t$ values from the peak voxel of each cluster in the occipital and motor cortices, which was defined as the voxel with the maximum amplitude value within each spatially distinct cluster. The MNI coordinates for each grand average peak voxel location, as well as the individual group-wise MNI peak voxel coordinates, are reported in Supplementary Table 1. Importantly, the peak coordinates for each group (per response) were similar, and thus the same grand average peak voxels were used for the extraction of pseudo-$t$ values across all participants. These values represent the relative increase in neural activity from baseline at the specified voxel across the time-frequency window of interest. Moreover, to evaluate the temporal dynamics more precisely, peak voxel time series were extracted from the same voxel in each of the clusters (Fig. 2B, line graphs). Since we did not have hypotheses about hemispheric effects, we averaged the pseudo-$t$ values and the time series across the bilateral visual responses within each frequency range per participant. Note that no averaging of responses was performed in the beta band, as the observed neural response was not bilateral. This resulted in a single time series of response amplitude per frequency (i.e. theta, alpha, and gamma) per participant. Finally, to determine whether HIV infection and HAND status significantly affected basal (i.e. spontaneous) levels of activity at each spatially- and spectrally-defined peak, we averaged the absolute amplitude time series across the baseline period ($–400$ ms to 0 ms) to derive a single prestimulus value per frequency for each participant. This basal amplitude value and the baseline-relative oscillatory pseudo-$t$ value, per frequency per participant, were used in all subsequent analyses. Note that both values correspond to the same voxels per frequency. Outliers were excluded at this stage based on a fixed threshold of $\pm 2$ SD from the mean, to reduce the impact of errors in reconstruction of the virtual sensor data.

HIV infection and HIV-associated neurocognitive disorders differentially affect visual neuronal dynamics

To evaluate broader effects (e.g. group differences in basal versus oscillatory dynamics), as well as more focal effects (e.g. group differences across different frequencies), prestimulus and pseudo-$t$ values were first compared separately between groups using multivariate analysis of variance (MANOVA) models. These comparisons were then followed by one-way ANOVAs testing for between group differences in frequency. Significant one-way models were then tested post hoc using Fisher’s LSD.

The omnibus MANOVA for oscillatory activity (across frequency-specific responses) was marginally significant ($F(8,100) = 1.719, P = 0.103$); however, subsequent one-way ANOVAs for each response showed that the visual theta response differed between
Figure 2 Frequency-specific neural responses serving visuospatial processing. (A) Spectral time course of occipital neural responses at the sensor level. Time (in ms) is denoted on the x-axes, with 0 ms defined as the onset of the visual stimulus, and frequency (in Hz) shown on the y-axes. The colour scale bar for per cent change from baseline is shown beneath each plot. Note that the thresholds vary greatly across responses, as the power of neural activity differs in distinct frequency bands. (B) Peak voxel time series for each significant time-frequency response, with source reconstructions inlayed on each respective plot. Note that the data for occipital responses were averaged across hemispheres since there were no laterality hypotheses. For each time series, time (in ms) is denoted on the x-axis, with 0 ms defined as the onset of the visual stimulus, and relative amplitude (in % of baseline) is denoted on the y-axis. The respective colour scale legend for each inlaid source map is displayed to the right.
groups \( F(2,53) = 5.45, P = 0.007, BF_{10} = 6.74; \text{ Fig. 3} \). Post hoc testing revealed a HIV-related decrease in oscillatory theta, such that HIV-infected participants exhibited a decrease that approached significance compared to controls \( t(39) = -1.90, P = 0.065, BF_{10} = 1.00 \), while participants with HAND had substantially decreased responses compared to controls \( t(35) = -3.26, P = 0.002, BF_{10} = 23.93 \). Interestingly, the oscillatory (baseline-relative) visual gamma response also exhibited a pattern of marginal significance \( F(2,53) = 2.97, P = 0.060, BF_{10} = 1.23 \), and exploratory post hoc tests revealed that participants with HAND exhibited significantly lower responses \( t(35) = -2.26, P = 0.030, BF_{10} = 1.23 \), while HIV-infected participants exhibited a non-significant effect in the same direction \( t(39) = -1.80, P = 0.080, BF_{10} = 0.828 \).

The omnibus MANOVA for prestimulus spontaneous activity indicated a significant difference between HIV-infected participants, participants with HAND, and controls \( [\text{Wilks’ Lambda} = 0.712, F(8,104) = 2.41, P = 0.020] \). Subsequent one-way ANOVAs for each response showed that this effect was significant for the alpha \( F(2,55) = 4.34, P = 0.018, BF_{10} = 2.94 \) and gamma \( F(2,55) = 4.73, P = 0.013, BF_{10} = 4.32 \) visual responses, but not the theta visual response \( F(2,55) = 2.24, P = 0.116, BF_{10} = 0.70 \) nor the beta motor response \( F(2,55) = 1.98, P = 0.149, BF_{10} = 0.59 \); Fig. 4). Post hoc tests revealed that participants with HAND exhibited significantly increased spontaneous alpha activity in the parieto-occipital cortices compared to HIV-infected participants \( t(34) = 2.79, P = 0.009, BF_{10} = 3.81 \) and controls \( t(36) = 2.35, P = 0.024, BF_{10} = 1.74 \), whereas HIV-infected participants and controls did not differ on this measure \( t(40) = 0.53, P = 0.599, BF_{10} = 0.36 \). In the gamma band, post hoc testing revealed that both participants with HAND \( t(36) = 2.38, P = 0.023, BF_{10} = 3.61 \) and HIV-infected participants \( t(40) = 2.81, P = 0.008, BF_{10} = 7.42 \) had significantly elevated spontaneous gamma activity in visual cortices compared to controls, but did not significantly differ from each other \( t(34) = 0.26, P = 0.796, BF_{10} = 0.33 \).

Visual neural dynamics predict task performance and neuropsychology

Lastly, we investigated whether the neural dynamics described above predicted behaviour or neuropsychology. To examine whether these measures predicted behaviour on the task, reaction time and accuracy were each regressed on prestimulus spontaneous alpha and gamma, as well as oscillatory visual theta responses, individually. Both spontaneous alpha \( R = -0.26, P = 0.040 \) and oscillatory theta activity \( R = -0.29, P = 0.019 \) were found to significantly predict accuracy on the task. Next, these relationships were further probed by correlating these two neurophysiological measures (i.e. spontaneous alpha amplitude and oscillatory theta activity) with accuracy within each participant group separately (Fig. 5). Interestingly, the oscillatory theta response correlated significantly with accuracy only in the control group \( r = 0.65, P = 0.001 \), whereas spontaneous alpha amplitude did not correlate with accuracy within any group. These differences (i.e. between group-wise correlation coefficients) were significant, such that the relationship between the oscillatory theta response and task accuracy for the control group was more positive than that for the HIV-infected group \( z = 2.13, P = 0.033 \), as well as the HAND group \( z = 3.61, P < 0.001 \). A non-significant trend was also found for the same relationship between the HIV-infected and HAND groups \( z = 1.67, P = 0.095 \). As a means to externally validate the relationship between our significant neurophysiological measures and attention function, we also probed whether these neural dynamics predicted performance on specific neuropsychological indices.
Since the attention, executive function, and speed of processing composite scores would be those most likely to be central to task performance, we regressed each of these scores individually on the same neural dynamics reported above. Interestingly, two of the composite scores were selectively predicted by differing neural dynamics. Briefly, prestimulus alpha activity significantly predicted executive function scores ($R = 0.30$, $P = 0.022$), such that as spontaneous alpha activity increased, scores on the executive function tests decreased, while oscillatory theta responses exhibited a significant relationship with the attention composite score in the opposite direction ($R = 0.27$, $P = 0.039$). The direction of both of these relationships would be as expected given our central neurophysiological findings.

**Discussion**

Through these experiments and analyses, we have provided evidence that HIV infection and HAND status differentially affect neural oscillations and rhythmic activity serving visuospatial discrimination abilities in the adult human brain, and that these neural responses are directly related to behavioural and neuropsychological performance. This study is the first to investigate the oscillatory neural dynamics underlying visuospatial attention and processing deficits in an HIV-infected population, and the first to dissociate these dynamics according to HAND status. In addition, this study involves, to our knowledge, the largest sample of HIV-infected participants ever included in an MEG study, which is essential because of the heterogeneous nature of the disease. By applying state-of-the-art neurophysiological imaging, voxel time series, and statistical analyses to MEG data, we found aberrant patterns of occipital neural activity in three distinct neural rhythms in HIV-infected patients. These aberrant patterns included both spontaneous activity during the prestimulus baseline, and task-induced oscillatory responses during visuospatial processing. In combination, these neurophysiological
In this study, aberrations dissociated HIV-infected participants with and without HAND. Further, one of the MEG responses (i.e., oscillatory theta) significantly predicted behavioural performance on the task, and the strength of this relationship decreased in a stepwise fashion according to disease severity (i.e., the strength of the relationship diminished from control to HIV-infected to HAND participants), signalling a deficient coupling of neurophysiology to behaviour in these patients. Finally, we found that oscillatory theta activity predicted attention function on independent tests across the sample, while the same was true for spontaneous alpha and executive function, which together strongly support the veracity of our MEG results. Broadly, these findings confirm our hypotheses that HIV-infected participants with and without HAND differ from controls in oscillatory frequencies that are commonly known to index recognition and encoding of stimulus features (i.e., in the theta and gamma bands), whereas only those participants with HAND exhibit differences from controls in the alpha band, which is typically associated with ‘top-down’ inhibitory processes.

**Computational significance of spectrally-specific neural responses**

The spectrally-specific neural oscillatory responses observed in this study are all robustly supported by previous literature. The theta-band synchronization that we observed in the posterior visual cortices has been widely accepted as an initial component of stimulus recognition (Başar-Eroğlu et al., 1992; Başar et al., 2001), while the alpha desynchronization observed in parieto-occipital regions has been tied to top-down inhibitory release in visual circuits (Handel et al., 2011; Spaak et al., 2014). Likewise, the gamma synchronization has been linked to more fine-scale encoding of visual stimulus features (Busch et al., 2004; Hoogenboom et al., 2006; Muthukumaraswamy and Singh, 2013). Further, components of these oscillatory dynamics have been robustly linked to distinct aspects of behavioural performance on tasks similar to that used here (van Dijk et al., 2008; Edden et al., 2009; Handel et al., 2011). Specifically, responses in the theta-band commonly predict measures of target-detection accuracy (Landau et al., 2015), alpha-band activity typically relates to measures of reaction time (van Dijk et al., 2008), and oscillatory activity in the gamma-band is thought to index more ‘fine-scale’ components of stimulus appraisal (Muthukumaraswamy and Singh, 2013), such as spatial orientation (Edden et al., 2009). Finally, the robust decrease in beta band amplitude in the ‘hand-knob’ region of the left primary motor cortex has been extensively documented, and represents motor planning and/or execution processes (Jurkiewicz et al., 2006; Cheyne et al., 2008; Heinrichs-Graham and Wilson, 2015, 2016). In agreement with our findings, this beta response is known to be heavily lateralized.

**Effects of HIV infection and HIV-associated neurocognitive disorders on frequency-specific neural responses**

Visuo-perceptual and attention deficits in HIV-infected patients have been well documented, but the underlying pathophysiology remains poorly understood, especially in regard to differences between HIV-infected patients with and without HAND. Interestingly, in this study we found that HIV-infected participants with and without HAND had clear differences in spectrally-specific spontaneous and oscillatory neural activity. The HIV-infected participants without HAND exhibited significantly elevated spontaneous gamma activity during the baseline, and a marginally significant trend towards decreased oscillatory theta activity as compared to controls. Similarly, participants with HAND also exhibited elevated spontaneous gamma during the baseline and had a robust decrease in oscillatory theta compared to controls. As previously discussed, activity in the theta and gamma bands are thought to support task accuracy and stimulus component discrimination, respectively, and so these neurophysiological aberrations are directly relevant to the visuo-perceptual and attention deficits reported in HIV-infected populations.

As mentioned above, only participants diagnosed with HAND had aberrant spontaneous activity in the
alpha-band. Importantly, these increased levels of spontaneous occipital alpha during the baseline carried over into the stimulus presentation and response periods. Since the strength of alpha activity has been widely linked to the inhibition of irrelevant visual stimuli, this basal increase in alpha may represent a key functional dissociation between HIV infection and HAND. Supporting this concept, deviations in parieto-occipital alpha activity have been reported in ageing populations (Proskovec et al., 2016), as well as a number of neurological disorders affecting cognition (Osipova et al., 2005; Başar and Güntekin, 2013; Wiesman et al., 2016). Interestingly, a recent study of working memory in HIV-infected individuals also found aberrant alpha-frequency activity in parieto-occipital cortex (Wilson et al., 2017b); however, a smaller sample size in that study made it infeasible to distinguish between participants with and without HAND. Likewise, abnormal alpha activity in the prefrontal cortices has also been reported in HIV-infected older adults (Wilson et al., 2015), but again limited sample size precluded HAND-specific comparisons.

**Effects of HIV infection and HIV-associated neurocognitive disorders on behavioural performance**

Consistent with previous investigations of the neuropsychological sequelae of neuro-HIV, HIV-infected participants with and without HAND performed significantly worse on our visuospatial task than controls. Specifically, participants in the HAND group, but not the HIV-infected group, were significantly less accurate in their responses than controls, while both HIV-infected groups were significantly slower in their time to respond. Interestingly, only theta oscillatory responses were significantly correlated with task performance, and upon further investigation the strength of this response decreased with increasing disease severity. In other words, the relationship between accuracy and oscillatory theta activity was strongest in controls, weaker in HIV-infected participants without HAND, and weakest in those with HAND. This finding may signal that HIV-induced CNS injuries more prominently affect theta circuitry, and that these injuries are progressive and eventually lead to observable HAND. Theta oscillations are known to play a key role in neuronal coding during information processing (Lisman and Jensen, 2013), which may be a critical factor that heightens the impact of this alteration and underpins the associated behavioural outcome (i.e. decreased task accuracy).

In contrast, oscillatory theta responses and spontaneous alpha activity predicted executive function and attention-related composite scores, respectively, of the neuropsychological battery. These findings provide convergent evidence of a functional distinction between neural activity in these rhythms, as well as key insights into the meaning behind the neural abnormalities exhibited by the patient groups in this study. Specifically, across our sample, theta oscillations were found to significantly predict performance on the attention composite, which is broadly consistent with the existing literature connecting theta activity to alertness and attention function (Demiralp and Başar, 1992; Başar et al., 2001; Jensen and Tesche, 2002; Lisman and Jensen, 2013; Landau et al., 2015; Fellrath et al., 2016). Our finding of a progressively decreased response in this frequency from controls to those with HAND bolsters the conceptualization that this atypical pattern of neural activity reflects a deficient attention system in patients with HIV and, more notably, HAND. Intriguingly, spontaneous alpha levels predicted only the executive function composite scores, supporting the idea that this frequency is associated with active inhibition of irrelevant environmental information.

Further, this direct neuropsychological connection also supports the notion that the uniquely elevated spontaneous alpha activity in the HAND group represents a functional deficiency in executive function, which is specific to those HIV-infected patients with neurocognitive impairments.

**Conclusions and future directions**

En masse, these findings shed light on the complex neurophysiological consequences of HIV infection, as well as the divergent population-level neural codes supporting visual perception and visual attention in HIV-infected patients with and without cognitive impairments (i.e. HAND). More specifically, we found that HIV-infected patients exhibit general aberrations in visual cortical processing associated with ‘bottom-up’ stimulus recognition and feature encoding, whereas patients with HAND exhibit an additional deficit in the neural activity associated with the ‘top-down’ process of inhibiting irrelevant sensory input.

Before closing, it is important to point out some limitations of our study. For instance, although our statistical analyses revealed a fascinating relationship between oscillatory theta activity and task accuracy, it is likely that the admittedly low difficulty of our task precluded the detection of other relationships between neurophysiology and behaviour that might have been present. Further, a great deal of work still remains in elucidating the origin of these impairments, and future research might be aimed at examining these neural markers in a longitudinal study with a focus on the impact of ageing and specific metabolic factors. Additionally, although the functional dissociations reported here are intriguing, the causative factors behind them remain unknown. Indeed, the aberrant patterns of neural activity reported here could be resultant of a loss of grey matter integrity, abnormalities in white matter connections between relevant neocortical regions, dysfunctional regulation of cortical activity by phylogenetically ‘older’ structures, or some combination of these factors. Further, whether these abnormalities are progressive, or represent a
legacy effect of neuronal damage that occurred after infection but before combination antiretroviral therapies initiation remains unknown. Future investigations into the structural and molecular covariates that predict and influence the functional neural dynamics reported here will be essential in gaining a comprehensive understanding of cognitive impairment in HIV infection. Despite these limitations, our findings substantially illuminate the neurophysiological underpinnings of visuo-perceptual and visual attention impairments in patients infected with HIV, as well as the dynamic neural codes that support normative cognitive function in health and disease.

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Supplementary material

Supplementary material is available at Brain online.

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