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The electrophysiology of neuroHIV: A systematic review of EEG and MEG studies in people with HIV infection since the advent of highly-active antiretroviral therapy

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HIGHLIGHTS

- EEG differences are present in HIV+ compared to HIV− groups, even with well-controlled infection.
- Cognitive ability of persons living with HIV is associated with electrophysiological differences.
- Electrophysiological variables show promise as biomarkers for brain dysfunction in HIV.

ABSTRACT

Objective: The Human Immunodeficiency Virus (HIV) has an impact on the brain, even when the infection is well-controlled with modern highly-active antiretroviral therapy (HAART). While dementia is rare in those on HAART, milder cognitive impairment is common. The causes, patterns, and evolution of brain dysfunction in people living with HIV remain uncertain. We evaluate whether electrophysiological methods provide informative measures of brain dysfunction in this population.
Methods: A systematic literature search identified studies that used EEG or MEG to evaluate persons living with HIV published between 1996 (when HAART became available) and 2016.
Results: Twenty-eight studies were identified. Most involved small samples, and all but four were cross-sectional. Reduced amplitude of Event Related Potentials and decreased power in the alpha band at rest were the most frequent differences between people with and without HIV infection. Of the 16 studies that also assessed cognitive ability, 13 found a significant relationship between cognition and electrophysiological changes in the HIV+ groups. Five of those studies also reported a significant relationship with current immunosuppression, suggesting a direct effect of HIV on the brain. There were few longitudinal studies; whether these electrophysiological changes progress over time, or respond to treatment, remains unclear.
Conclusions: EEG and MEG can provide useful information about brain dysfunction in people with HIV infection, but more consistent assessments of both cognition and EEG patterns, as well as longitudinal studies with larger, better characterized samples are needed.
Significance: This is the first systematic review of electrophysiological findings in HIV since the availability of HAART. EEG and MEG measures are sensitive to brain dysfunction in this population, and could complement other approaches in improving the assessment, understanding and treatment of neurocognitive disorders in HIV.

1. Introduction

Highly active antiretroviral therapy (HAART) has dramatically improved the life expectancy of people living with the human immunodeficiency virus (HIV) (Nakagawa et al., 2013). However, even with excellent immune recovery, up to 45% of patients with

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HIV suffer from HIV-associated neurocognitive disorder (HAND) (Heaton et al., 2011). These cognitive deficits are typically mild, making clinical diagnosis difficult (Heaton et al., 2010) and patients may not be fully aware of their cognitive deficits (Chiao et al., 2013). Further, it is likely that brain changes occur before overt symptoms. A direct measure of brain function may be more sensitive to very early changes, and could provide insights into the nature and causes of brain injury in HIV, as well as serving diagnostic or prognostic purposes.

Structural, functional, and molecular neuroimaging have been applied in HIV, including multimodal MRI, magnetic resonance spectroscopy, and positron emission tomography. These imaging modalities have provided evidence of changes in brain energy metabolism, inflammation, gray and white mater integrity, and cerebral blood flow or neurotransmitter homeostasis in people with HIV infection compared to those without HIV. Recent opinion papers and systematic reviews summarize this literature, which is still evolving, with a need for larger samples and longitudinal studies (see Tucker et al., 2004; Holt et al., 2012; Ances and Hammoud, 2014; Plessis et al., 2014; Thompson and Jahanshad, 2015; Hakkers et al., 2017).

Although the variety of methods and heterogeneity of samples limit general conclusions, there is converging support for effects in subcortical and white matter structures, with regional cortical atrophy and inflammation also reported. There is no consensus on the causes of these differences, with evidence for direct effects of HIV infection in the brain, indirect effects through systemic inflammation or cerebrovascular injury, perhaps 'accelerated aging' or antiretroviral toxicity, as well as influences from common comorbidities, including mental health conditions, vascular disease, and substance use (Ellis et al., 2007; Alfahad and Nath, 2013; Bonnet et al., 2013; Clifford and Ances, 2013).

These imaging findings are consistent with the common patterns of cognitive impairment, with inattention, psychomotor slowing and executive dysfunction as dominant features (Lewis et al., 2003; Baldewicz et al., 2004; Plessis et al., 2014). One emerging view is that HIV leads to a degradation of brain network function, perhaps through a combination of white and grey matter injury, with higher order cognitive abilities and processing speed the first to be affected (Thomas et al., 2013, 2015; DeVaughn et al., 2015; Ortega et al., 2015).

Electrophysiological methods, whether EEG or MEG, can assess changes in brain activity arising from the summation of postsynaptic potentials with millisecond accuracy (Luck, 2014) and could detect early changes in the synchronization of brain activity relevant to network degradation accounts of cognitive impairment in HIV. Furthermore, EEG (if not MEG) is cheaper and more widely clinically available than the other neuroimaging modalities studied to date. Most HIV care occurs in resource-poor settings (nearly 70% in sub-Saharan Africa (World Health Organization, 2016)). Robust EEG biomarkers of HIV effects on the brain might thus have particular research and clinical value.

Given the seemingly good match between electrophysiological measurement capabilities and the presumed anatomical basis of brain dysfunction related to HIV, and the practical advantages of the wider availability of EEG, it is perhaps surprising that this method has received less attention in neuroHIV research. No systematic review of electrophysiological studies in HIV has been undertaken since Comi and colleagues evaluated the clinical utility of ERPs in the detection of neurological complications of HIV in 1996 (Comi et al., 1996). In their pre-HAART era review, focusing mainly on patients with AIDS, the authors suggested that ERPs could reveal early functional abnormalities before these were detectable on structural MRI. A report a few years later summarized 14 ERP studies, as well as reporting new findings from 10 patients with HIV (Polich et al., 2000). These authors emphasised characteristic ERP patterns that could potentially distinguish between HIV+ and HIV− participants but identified inadequate descriptions of the methods and non-optimal technical approaches as limitations of much of that work.

We undertook a systematic review of EEG and MEG studies in people with HIV infection since the availability of HAART with the following specific aims. (1) Assess the extent and quality of current evidence for electrophysiological differences in HIV+ compared to HIV− groups in cross-sectional studies. (2) Determine whether these electrophysiological variables consistently relate to HIV clinical variables, co-morbidities, or medication effects in people with HIV. (3) Determine whether these electrophysiological variables relate to cognitive performance or real life function in people with HIV. (4) Finally, we asked whether there was evidence for changes in electrophysiological activity in HIV+ individuals over time, or following interventions.

2. Methods

Strategies for the literature search were developed with the advice of a health sciences librarian following the PRISMA guidelines (Moher et al., 2009). Potentially relevant studies were identified using the databases Embase, PubMed and Scopus considering all studies published since the development of HAART, i.e., from 1996 to October 2016, without any language restrictions. Text words and MeSH headings were used for the search. These were first developed in Embase and then adapted for the other databases. Appendix A lists the search terms. The retrieved articles were screened for repetitions and organized in an Endnote x7 library for further assessment. All abstracts were first evaluated by one of the authors to exclude irrelevant or case studies. The remaining articles were reviewed in full, to assess whether they met inclusion or exclusion criteria, and to characterize the risk of bias at the study level. Studies with incomplete outcome data or reporting biases were classified as high risk. For example, articles that described one technique in the Methods section, but reported results from a different method, or reports of ERPs that did not conform to standard reporting procedures that allow judgment of the quality of the data (e.g. as recommended by Woodman, 2010) were considered high risk. Studies that did not match HIV+ and HIV− groups on potentially relevant variables, such as education, were identified as having a potential risk of bias.

2.1. Criteria for study inclusion

Included studies were published in peer-reviewed journals and used quantitative analysis of either electroencephalography or magnetoencephalography in persons living with HIV, without gender restrictions. Both cross-sectional and longitudinal studies with any length of follow up were included. Studies of spectral and connectivity analysis as well as ERP studies were considered. For studies to be included, participants had to be recruited after the widespread availability of HAART, i.e. 1996 or later. There were no restrictions with regards to the aims of the studies.

2.2. Criteria for study exclusion

Studies were excluded if EEG or MEG was used to assess HIV comorbidities other than cognitive impairment: e.g., leukoencephalopathy, epilepsy, or sleep disorders, or if EEG/MEG was used for clinical diagnosis rather than to address a research question. Studies of groups not taking HAART were excluded. Editorials, commentaries, reviews, or case studies were also excluded, as were studies that investigated only auditory brainstem responses (ABR) or somatosensory evoked potentials. Studies classified as having a

high risk of selective reporting bias, as described above, were also excluded.

3. Results

558 non-repeated studies were identified in the primary search. No additional papers were found by cross-referencing. A total of 28 studies met the inclusion and exclusion criteria described above. Fig. 1 shows the flowchart of study selection.

Fig. 2 summarizes the methodologies and designs used in the reviewed papers. Most of the studies used EEG (78.5%, $n = 22$) in a cross-sectional design (85.7%, $n = 24$). All made comparisons between people living with HIV and an HIV− control group, with three of those also making comparisons within the HIV+ group (10.7%, $n = 3$). Four studies used a longitudinal design: In a series of studies, Babiloni et al. (2015, 2016a,b) focused on the longitudinal effects of antiretroviral therapy on resting-state EEG (RS-EEG) after HAART initiation, and Becker et al. (2012a,b) estimated the test re-test reliability of frequency magnitudes measured with MEG over a 24-week period in groups of 10 HIV+ and 7 control participants.

The sample sizes of the included studies varied widely, ranging from 10 HIV+ and 7 controls to 146 HIV+ and 92 controls, see Fig. 3B. However, the majority of studies involved samples of fewer than 30 people. Reviewed studies report data from participants between 33 and 58 years of age in the case of persons living with HIV and between 20 and 59 years for controls. A distribution of the mean ages and sample sizes is shown in Fig. 3. As expected for studies conducted in the HAART era, participants typically were not severely immunosuppressed at the time of testing. Studies reported average current CD4 values greater than 330 cells/mm^3 ranging to 772 cells/mm^3 (Fig. 3C). On average, 64% (SD = 37%) of the participants were male. No study assessed real life function in the HIV+ or control group.

3.1. Cross-sectional studies comparing HIV+ and HIV− groups

The 24 studies that carried out cross-sectional comparisons of electrophysiological differences in HIV+ and HIV− groups are listed in Table 1. Most of the studies attempted to match the groups on age and years of education. Twenty of the 24 studies matched the groups for age. In the other 4 studies, control participants were significantly younger than the HIV+ group (Table 1; Fig. 3). Sixteen studies matched on years of education, while 2 studies had significant differences in education levels between groups, with persons living with HIV having fewer years of education, and 6 studies did not report any information in this regard.

The electrophysiological differences between HIV+ and HIV− groups in the reviewed studies took two main approaches: examining the power or connectivity of specific frequency bands based on spectral analysis, or the amplitude and latency of ERPs.

Table 2 shows the studies that measured the power of different frequency bands at rest (eyes open or closed) or while participants performed a task. Alpha power measured at rest with eyes closed was reported as significantly diminished for the HIV+ group compared with controls in all 3 studies that performed this analysis. Other power analysis results were more inconsistent or were not reported reliably across studies. An additional study by Wilson and colleagues in 2013 investigated beta activity associated with movement planning (pre-movement beta desynchronization) in 12 HIV+ and 12 healthy control participants (Wilson et al., 2013b). Power analysis at 12–28 Hz showed that HIV+ participants had stronger desynchronization in the right dorsolateral and medial prefrontal cortex and the left inferior frontal gyrus. On the other hand, the desynchronization was weaker for HIV+ participants in the right and left precentral gyri and the supplementary motor area. Finally, Becker et al. (2012a,b) investigated functional connectivity using RS-MEG with eyes open and closed (5 min) in a sample of 10 HIV+ individuals and 8 controls. The authors reported that functional connectivity measured as the mutual information shared between all pairs of sensors could distinguish these two groups.

Table 3 summarizes studies that measured ERPs. No study reported reductions in the latency of ERP components in the HIV group when compared to controls, while 3 out of 5 studies found increases in the latency of the P300. Most studies found decreases in the amplitude of ERPs for HIV+ participants compared to controls. This effect was most reliably replicated for the P300, an ERP believed to reflect stimulus categorization and working memory updating (Polich, 2007), commonly evoked with oddball paradigms. All six studies that investigated the P300 found diminished amplitude for participants with HIV+, suggesting that neural coor-

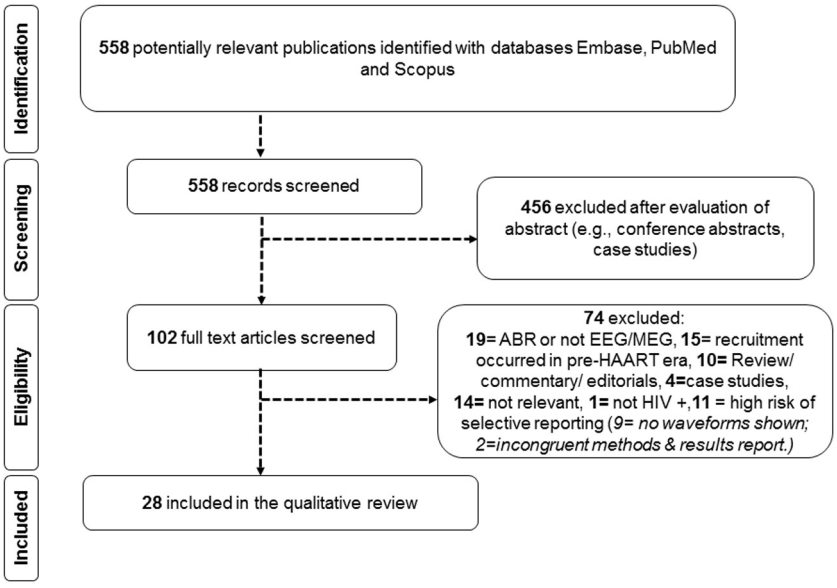

Fig. 1. Flow diagram illustrating the steps in study selection.

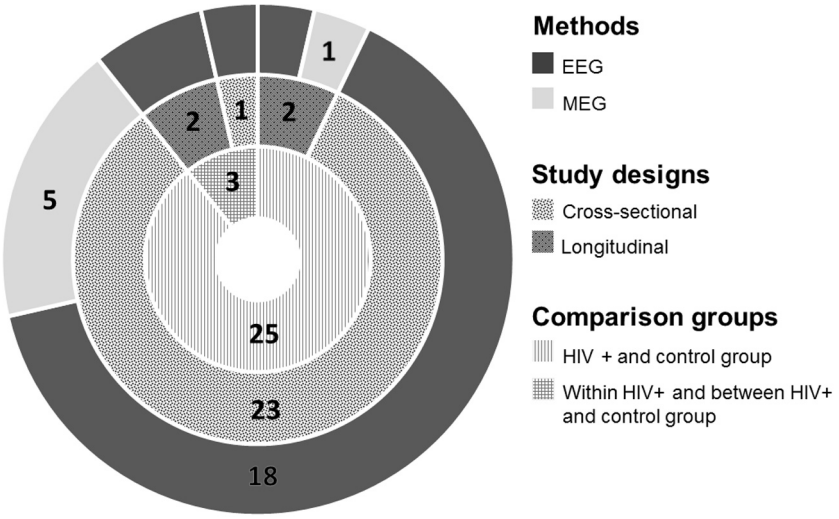

Fig. 2. Overview of the methods and study designs used in the reviewed literature. Numbers indicate the number of studies using each method and design.

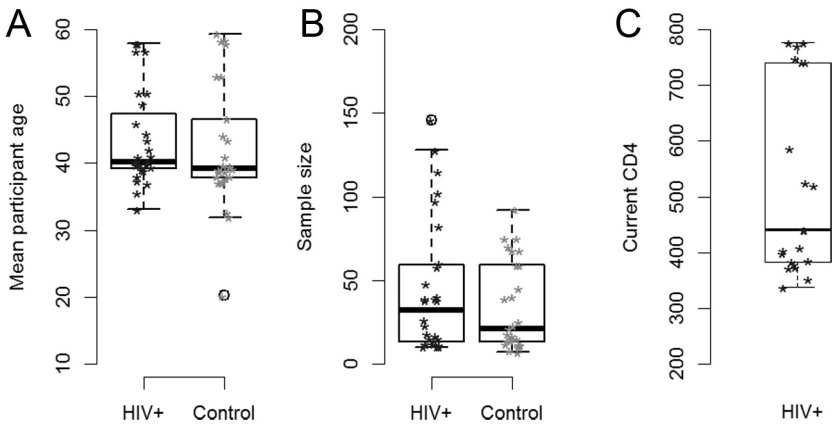

Fig. 3. Box and whisker plots summarizing the sample characteristics, across all reviewed studies reporting these data. Panel A shows the mean participant age in each study, by HIV serostatus. Panel B shows the sample size of each group across studies. Panel C shows the mean current CD4 count in the HIV+ group in each study, as an indicator of on-going immunosuppression.

dination required for these cognitive processes might be less efficient in HIV+individuals. Other ERP components related to attention and early sensory processing (N100, P100 (Vogel and Luck, 2000)), discrimination and evaluation of intrinsic characteristics of stimuli (P200 (Hillyard and Anllo-Vento, 1998)) or semantic categorization, (N400 (Kutas and Federmeier, 2011)), were studied less often. Thus, more evidence is needed to draw strong conclusions about whether these differ consistently between HIV+ participants and controls.

Of note, most ERP studies included HIV+ participants 40 years of age or older, in whom cognitive deficits are more evident (Heaton et al., 2010), and the healthy control groups in these studies were not always matched in age. This is important for between group comparisons of the ERP amplitudes, since the amplitude of ERP components, such as the P300, have been shown to decrease with age even in healthy populations (Polich, 2012). Studies not matched for age were not included in Tables 2 and 3.

3.1.1. Relationship between electrophysiological and HIV-related clinical variables

Ninety-three percent of the studies ($n = 26$) indicated that HIV related clinical variables were assessed, although 2 did not report the corresponding values. Most studies reported the current CD4 count (Fig. 3), with current viral load and nadir CD4 count reported less often. Only 46% ($n = 13$) of all studies tested for a relationship between any of these clinical variables and the EEG/MEG measurements. Nine of those 13 studies found a significant association between viral load, current CD4, or duration of infection and the EEG or MEG variable of interest. Details are found in Table 1.

In sum, reports of HIV clinical variables were not always complete. More systematic reporting of clinical variables, including current and nadir CD4 count, and viral load as well as their relationship with electrophysiological variables, if any, would facilitate the synthesis of this literature, going forward.

3.1.2. Effects of HAART or co-morbidities on electrophysiological variables

Nine studies reported no difference in comorbid conditions present in the HIV+ and control groups, and 7 did not address this issue. In the studies that reported differences, co-morbidities found at higher rates in the HIV+ groups included depression, any psychiatric diagnosis, anxiety disorders, or childhood conduct disorders. A series of studies by Bauer and Shanley (2006), Bauer (2008a,b, 2011, 2013) additionally reported conditions that interacted with HIV status when assessing its effects on electrophysiological measurements: family history of alcoholism, major depression, or bipolar disorder, family history of substance abuse or dependence, and antisocial personality disorder. Finally, only one of the studies con-

Table 1
Summary of cross-sectional and between group studies. Abbreviations: (–) = non reported or non-tested, BDI = Beck Depression Inventory, CNS = Central Nervous System, CNV = Contingent Negativity Variation, DLPFC = dorsolateral prefrontal cortex, FEF = frontal eye field, HVLT-R = Hopkins Verbal Learning Test-Revised, IFG = inferior frontal gyrus, LPP = Later Positive Potential, MMSE = Mini Mental State Examination, mPFC = medial prefrontal cortex, ns = no significant differences found, RS-EEG/MEG = resting state EEG/MEG, RT = reaction time, SMA = supplementary motor area, PCC = posterior cingulate cortex.

Authors	Sample Size (Mean Age ± SD)		% male HIV+	Cognitive Assessment	Mean current CD4 (SD)	Design/Task	Main Results (significant differences for HIV+ group compared to HIV− group)	Cognitive-physiological relationship	Clinical Assessment-physiological relationship	Limitations
	HIV+	HIV−								
1. Babiloni et al. (2012)	18 (38 ± 2)	18 (39 ± 2)	83	Delayed recall of Rey figures & Prose Memory, Trail Making Test A&B, MMSE	587 (318)	Cortical EEG sources measure in eyes-closed RS	More delta (2–4 Hz) power frontal and central-parietal; Less widespread alpha1 (8–10 Hz) and alpha2 (10–12 Hz) power	MMSE score used as a covariate as it differed between the HIV+ and control group	CD4 positively correlated with the magnitude of global alpha 1 and 2	
2. Babiloni et al. (2014)	128 (43 ± 1)	75 (47 ± 2)	78	Prose Memory Test delayed recall, 1-min verbal fluency, Trail Making Test A & B and MMSE	519 (30)	RS-EEG, eyes closed	More delta (2–4 Hz) and theta (4–8 Hz) frontal, parietal & occipital power in HIV+ on HAART vs. controls. Widespread alpha 1 (8–10.5 Hz) and alpha 2 (10.5–12 Hz) decreased in HIV+ off HAART < HIV on HAART < controls. Beta 1 (13–20 Hz) parietal, occipital and temporal lower in HIV+ on HAART vs. controls. Beta 2 (20–30 Hz) temporal lower in HIV+ on HAART vs. controls	Score on Rey delayed recall correlated significantly with increase in alpha 1 in HIV+ on HAART	Higher CD4 count and medication start normalized alpha and delta power	
3.Babiloni et al., (2016c)	82 (40 ± 1)	59 (9 ± 2)	100	MMSE and neuropsychological tests of memory, executive function and attention	441 (29)	RS-EEG, eyes closed	Reduction in posterior alpha 1 and 3 and increase in parietal delta. Parietal delta/ alpha ratio discriminated healthy from HIV+ treatment naïve	HIV+ with abnormal EEG delta/alpha ratio had lower MMSE vs. those with normal ratio	HIV+ with abnormal EEG delta/alpha ratio had lower CD4 count	
4. Bauer (2008a)	60 (39 ± 6)	75 (37 ± 7)	56	Kaufman Brief Intelligence Test	399 (88)	ERP, cognitive conflict/control task	Smaller frontal Slow Potential amplitude, only when HIV+ had no family history of alcoholism, major depression, or bipolar disorder	(–)	(–)	HIV+ reported a larger number of childhood conduct disorder symptoms
5. Bauer (2008b)	115 (40 ± 6)	70 (37 ± 7)	50	Verbal IQ	386 (265)	ERP, Stroop color-word task to evoke P300	Smaller frontal P300 amplitude in HIV+ with family history of substance abuse or dependence	ns	(–)	HIV+ participants were significantly older
6. Bauer (2011)	102 (40 ± 6)	68 (38 ± 7)	54	(–)	351 (242)	ERP, visual oddball paradigm	Longer frontal P300 latency. Effect greater if HIV+ were overweight. Smaller P300 amplitude reported for HIV+ and substance abuse treatment history	(–)	(–)	Conduct disorder more common in HIV+ group
7. Bauer (2013)	146 (4 ± 1)	92 (39 ± 1)	55	(–)	379 (64)	EEG, visual oddball	Decreased frontal theta (3–7 Hz) event evoked oscillation only if HIV+ patients had no family history of substance dependence. More CNS penetrant HAART increased theta power only in patients without this family history	(–)	HIV+ group split by CNS penetration of HAART	HIV+ groups were slightly older, less educated, and had more depression symptoms
8. Bauer and Shanley (2006)	97 (42 ± 6)	68 (39 ± 7)	57	(–)	372 (63)	ERP, visual oddball	Smaller frontal P300 amplitude for HIV+ off HAART when there is no comorbid antisocial personality disorder	(–)	(–)	HIV+ participants on HAART were older (age used as covariate). HIV+ off HAART were significantly more depressed. Education not reported

(*continued on next page*)

Table 1 (*continued*)

Authors	Sample Size (Mean Age ± SD)		% male HIV+	Cognitive Assessment	Mean current CD4 (SD)	Design/Task	Main Results (significant differences for HIV+ group compared to HIV− group)	Cognitive-physiological relationship	Clinical Assessment-physiological relationship	Limitations
	HIV+	HIV−								
9. Becker et al., (2012a)	10 (51 ± 5)	8 (53 ± 7)	95	Assessed cognitive/functional domains following Frascati classification.	777 (268)	RS-MEG; 5 min with eyes open followed by 5 min with eyes closed	Functional connectivity (measured by the mean of mutual information, MI, between each 2 pairs of electrodes) differentiated HIV+ from control participants	Executive domain rating was associated with the MI value	ns	
10. Becker et al. (2013)	15 (57 ± 5)	15 (58 ± 6)	73	Grooved pegboard, WRAT 4 reading, HVLT-R Trail making-A and B, digit symbol	772 (281)[a]	RS-MEG eyes open, 6 min	Smaller beta oscillations (14–30 Hz) in SMA, PCC and paracentral and superior parietal lobule	HVLT-R score correlated with amplitude of beta responses in the PC; Stroop interference correlated with amplitude in the left and right SMA	ns	Education not reported
11. Chao et al. (2003)	39 (44 ± 8)	39 (46 ± 7)	(–)	Trail-Making Test A&B, California Verbal Learning, Grooved Pegboard, Symbol Digit	403 (217)	ERP, reaction time task, button press when signal appears	Central CNV significantly smaller for HIV+	Correlation between CNV amplitude and RT of task found only in the control group, ns in any of the HIV+ groups. HIV+ group divided (undetectable vs detectable (>50 copies/ml) viral load	Ns differences between 2 HIV+ groups	
12. Chao et al. (2004)	15 (44 ± 8)	15 (45 ± 8)	(–)	(–)	440 (203)	ERP, auditory oddball	Smaller P200, P3a and P3b amplitudes, longer central-parietal P3a latency	(–)	(–)	Depression (BDI) used as covariate
13. Costa et al. (1997)	11 (33 ± 6)	11 (33 ± 6)	0	Shipley abstraction, Stroop, Trail Making A&B, Figural Memory Delay	525 (375)	EEG, semantic task/phonetic letter task	Ns differences in any frequency: delta, theta, alpha or beta	(–)	(–)	Psychiatric diagnoses more common, more depression symptoms in HIV+
14. Fletcher et al. (1997)	38 (40 ± 6)	23 (38 ± 7)	100	Rey-Osterreith Complex Figure, Trail Making Test A&B, Symbol Digit, Controlled Oral Word Association	CD4% 7 (6.3)	RS-EEG, eyes closed	Widespread decrease in alpha frequency coherence (7–13 Hz) in severely cognitively impaired HIV + vs. HIV−. No differences unimpaired/ moderately impaired HIV+ vs HIV−	Global impairment score correlated negatively with decreased coherence in severely impaired HIV+		
15. Kremer et al. (2016)	40 (4 ± 9)	Normative data n = 106	58	(–)	54% had CD4 < 500	RS-EEG, eyes closed	Interhemispheric asymmetry in the normal range in HIV+. Central theta alpha and beta asymmetries were higher for those with depressive symptoms, females had greater asymmetry than males	(–)	(–)	Education not reported
16. McIntosh et al. (2015)	26 (36 ± 5)	25 (32 ± 6)	0	Vocabulary, block design, digit span and letter number sequencing of the WAIS	409 (220)[a]	ERP, visual stimulation: negative and neural images	Larger P200 amplitude, smaller LPP	(-)	Longer infection was associated with increased reduction in LLP amplitude	HIV+ were older
17. Nielsen-Bohlman et al. (2002)	39 (40 ± 4)	21 (40 ± 7)	(–)	Shipley abstraction, Stroop color word, Trail Making A&B, Symbol Digit	(–)	ERP, lexical decision task	Smaller N400 amplitude at electrodes Cz and Pz	N400 difference wave amplitude correlated with attention score	(–)	
18. Polich and Basho (2002a,b)	14 (41)	14 (41)	93	(–)	(–)	ERP, auditory oddball	Smaller P3a amplitude at midline electrodes	(–)	(–)	

19. Polich et al. (2000)	10 (37)	10 (20)	83	(–)	(–)	EEG & ERP, auditory oddball	Smaller central-parietal N100 amplitude; longer N200 latency. P300 longer latency and smaller amplitude. Delta (1–4 Hz) and theta (4–8 Hz) power larger frontally and smaller at central and parietal locations, alpha-1 (7.5–9.5 Hz) and alpha-2 (9.5–12.5 Hz) smaller in central-parietal locations	(–)	P300 latency increased as viral load increased	
20. Tartar et al. (2004)	23 (range 18–35)	11		Trail making A&B, Digit Span and HVLT	(–)	ERP, auditory oddball	Smaller P300 amplitude	ns	(–)	
21. Tartar et al. (2014)	12 (37 ± 6)	14 (37 ± 6)	0	MMSE, Boston naming test, grooved pegboard, finger tapping	>200	Affective priming (negative vs. neutral pictures,)	Smaller N100 and LPP amplitudes (at electrodes Cz and Pz)	Neuropsychological performance correlated with magnitude of change in LPP (positive vs. negative)	(–)	Groups differed in BDI score
22. Wilson et al. (2013a)	12 (58 ± 5)	11 (59 ± 9)	74	Grooved pegboard, WRAT 4, HVLT-R, Trail making A&B	741 (252)[a]	MEG, visual processing, checkerboard-pattern square was presented	HIV+ had less synchrony (6–12 Hz) between 50–225 ms post stimulation in the rDLPFC, FEF and PCC	HVLT-R correlated positively with the amplitude of neural activity in the rFEF rDLPFC	(–)	Education not reported
23. Wilson et al. (2013b)	12 (58 ± 5)	12 (58 ± 5)	75	Neuropsychological tests including Grooved Pegboard and Trail Making Test B	741 (252)[a]	MEG, Finger tapping task. Measured event related desynchronization that peaks before movement	Pre-movement beta desynchronization (12–28 Hz): HIV− had significantly stronger responses in precentral gyrus and SMA and HIV+ had significantly stronger responses in the DLPFC and left IFG	Performance on grooved pegboard correlated with beta activity in left pre-central gyrus and SMA, trail making A correlated with activity in left IFG and B in mPFC and rDLPFC	ns	Education not reported
24. Wilson et al. (2015)	17 (57 ± 6)	17 (58 ± 6)	76	Grooved pegboard, WRAT 4 reading, HVLT-R, Trail making-A and B, Stroop	748 (301)	MEG, tactile stimulation applied in 2nd digit of right hand	Less theta (4–8 Hz) activity in left postcentral gyrus, alpha (8–14 Hz): greater activity in the left prefrontal cortex	Peak theta amplitude correlated positively with score on digit symbol. Peak alpha activity correlated negatively with scores on grooved pegboard and retention/delayed recall of HVLT-R	Nadir CD4 correlated with alpha activity, duration of HIV diagnosis and HAART associated with theta activity amplitude	Education not reported

[a] Approximations calculated based on reported range.

Table 2
Summary of resting state (RS) and task based EEG and MEG studies that compared spectral power in HIV+ and control participants. The table displays the number of studies that assessed power differences at rest with eyes closed and open, and those that calculated spectral power while participants performed a behavioral task. The tasks performed were: a = auditory oddball, b = visual oddball, c = tactile stimulation, d = visual stimulation, e = phonetic letter and simple and complex semantic task. The ↑, ↓ and ns columns indicate the number of studies reporting increases, decreases or no significant differences between HIV+ and HIV− groups. See Table 1 for details on the topography of the effects. The numbers in superscript refer to the numbering of the studies in Table 1.

Frequency band		RS-EEG eyes closed				RS-EEG eyes open				Task based EEG			
		Studies assessing differences	Power differences in HIV+ vs. HIV−			Studies assessing differences	Power differences in HIV+ vs. HIV−			Studies assessing differences	Power differences in HIV+ vs. HIV−		
			↑	↓	ns		↑	↓	ns		↑	↓	ns
Gamma: 30–50 Hz		–	–	–	1^{10}		–	–	1	–	–	–	–
Theta: 3–7 Hz	Frontal	$2^{1,2}$	–	–	2	1^{10}	–	–	1	$2^{13,19}$	**1**[a]	–	1^{e}
	Central parietal	$2^{1,2}$	–	–	2	1^{10}	–	–	1	$4^{7,13,19,24}$	–	**2**[a,c]	$2^{b,e}$
	Temporal	1^{2}	–	1	–	–	–	–	–	–	–	–	–
Delta: 1–4 Hz	Frontal	$2^{1,2}$	**1**	–	1	1^{10}	–	–	1	$2^{13,19}$	**1**[a]	–	1^{e}
	Central parietal	$2^{1,2}$	**2**	–	–	1^{10}	–	–	1	$2^{13,19}$	–	**1**[a]	1^{e}
alpha1 & 2: 7.5–12.5 Hz		$3^{1,2,3}$	–	**3**	–	1^{10}	–	–	1	$4^{13,19,22,24}$	**1**[c]	**2**[a,d]	1^{e}
beta: 14–28 Hz		2^{1}	–	**1**	1	1^{10}	–	**1**	–	$2^{13,19}$	–	–	$2^{e,a}$

sidered factors related to antiretroviral medication in their analyses. Bauer (2013) categorized HIV+ individuals in groups considering the degree of central nervous system (CNS) penetration of their antiretroviral regimen. The group taking a regimen with very good penetration had significantly less decrease in theta power (3–7 Hz), i.e., their power was closer to that of controls, compared to those taking regimens with good to poor CNS penetration.

3.2. Relationship between electrophysiological variables and cognition

While 71% (n = 20) of the studies reported the cognitive status of participants, the tests used for cognitive assessment varied widely, and in several cases were incompletely reported. For example, some studies reported the tests performed without providing results, or provided only general descriptions of the cognitive domains assessed. Sixteen studies tested for relationships between the cognitive status of participants and electrophysiological measurements. Of those, 13 studies found significant relationships between the cognitive status of HIV+ participants and one or more of the electrophysiological variables. Most of these studies used correlation analyses to estimate the extent to which poorer cognitive performance was associated with degraded or altered electrophysiological measurements in HIV+ participants, compared to controls. In general, these studies indicated that either disconnection, decreases in ERP amplitude or abnormal power in specific frequency bands, compared to healthy controls, were associated with weaker cognitive performance. None of the reviewed studies attempted to link the electrophysiological findings to any aspect of real life function. Details are provided in Table 1.

3.3. Changes in electrophysiological variables over time or after interventions

Four studies used longitudinal designs, all evaluating the stability of electrophysiological activity at rest in people with HIV. Becker et al. (2012a,b) evaluated the possible use of RS-MEG (5 min eyes open and 5 closed) as a biomarker of brain abnormalities in HIV. Test-retest reliability of MEG power in different frequency bands was measured in a sample of 10 HIV+ and 7 HIV− participants at baseline and after 24 weeks. The authors reported effects of HIV on right occipital and frontal gamma (30–50 Hz) power. Theta to gamma ratio was related to cognitive performance regardless of HIV serostatus, whereby participants with worse performance had higher ratios than those with better performance. A median stability of r = 0.82 over time (measured as interclass correlation) was found for the eyes closed measurements in the whole sample.

A series of studies by Babiloni and colleagues provide further insights on the longitudinal changes of RS-EEG activity. The first study recorded RS-EEG with eyes closed, four times over an interval of 5 months (Babiloni et al., 2015). Activity was first recorded at baseline in 38 HIV+ participants who were naïve to antiretroviral treatment, and recording sessions were repeated 4 weeks, 8 weeks and 5 months after HAART initiation. Data from 40 age-matched and cognitively normal healthy controls, i.e., performing in the normal range on a battery of neuropsychological tests, were collected following the same procedures. After 5 months, the HIV+ participants were categorized as responders or mild responders to treatment based on changes in their CD4 count: responders were those with an increase of greater than 100 CD4 cells/μl (n = 20). The HIV+ group had increased central delta (2–4 Hz) sources and decreased alpha 1 (8–10.5 Hz at parietal, occipital, temporal and limbic areas) and alpha 2 (10.5–13 Hz at parietal, occipital and temporal areas) at baseline, compared to controls. Furthermore, HAART responders had increased occipital alpha 1 and alpha 2 sources when compared with mild-responders after 5 months of HAART. Responders

Table 3
Summary of the number of event related potential (ERP) studies that compared the latency and/or amplitude of components between HIV+ participants and healthy controls. The ↑, ↓ and ns columns indicate the number of studies that found increases, decreases or non–significant differences in amplitude/latency between HIV+ and HIV− groups. The listed ERPs were evoked using standard visual or auditory stimulation, such as oddball, Stroop and cognitive control tasks. See Table 1 for details of the tasks used and the topography of the ERP components. The numbers in superscript refer to the numbering of the studies in Table 1. LPP = late positive potential, CNV = contingent negative variation.

Component	Studies assessing latency	Latency differences in HIV+ vs. HIV−			Studies assessing amplitude	Amplitude differences in HIV+ vs. HIV−		
		↑	↓	ns		↑	↓	ns
N100	$3^{12,19,20}$	–	–	3	$4^{12,19,20,21}$	–	**2**	2
N200	1^{19}	**1**	–	–	1^{19}	–	–	1
P100	1^{12}	–	–	1	1^{12}	–	–	1
P200	$2^{12,19}$	–	–	2	$2^{12,19}$	–	**1**	1
P300	$5^{6,12,18,19,20}$	**3**	–	2	$6^{6,8,12,18,19,20}$	–	**6**	–
N400	1^{17}	–	–	1	1^{17}	–	**1**	–
LPP	–	–	–	–	$2^{20,21}$	–	**1**	1
Slow Potential (700–1100 ms)	–	–	–	–	1^{4}	–	**1**	–
CNV	–	–	–	–	1^{11}	–	**1**	–

also had decreased parietal delta sources at baseline when compared to non-responders. The authors found no significant interactions between these electrophysiological findings and cognitive ability in the HIV+ group. Education was not reported.

The normalizing effects of HAART initiation on delta and alpha source activity were replicated in a second study (Babiloni et al., 2016b). Compared with an age matched group of 59 healthy adults (mean age 39 years), 48 HAART naïve HIV+ participants had higher parietal delta and lower limbic alpha 1, 2 and 3 (parietal, occipital, temporal, and limbic) sources. The ratio between delta and alpha 3 source activity was used to calculate a z-score at baseline. Only the subgroup of HIV participants that differed from the control group at baseline showed normalization of delta (decrease) and alpha 1 (increase) power after 5 months on HAART. CD4 count at baseline correlated significantly with the global delta source activity. Although scores on the Mini Mental State Examination (MMSE) were significantly lower for HIV+ participants compared to controls at baseline, these didn't correlate with EEG sources, nor did MMSE scores change after HAART initiation. The HIV+ HAART naïve group was less educated than the HIV− group.

In their most recent study, Babiloni and colleagues investigated the effect of 2 different HAART regimens in 2 groups of HAART naïve HIV+ participants (Babiloni et al., 2016a). Concordant with their previous results, both HIV+ groups showed decreased alpha at baseline. After 5 months of HAART, one treatment group had an increase in frontal and temporal delta sources (i.e., not tending toward normal, as in their previous studies), increased parietal, occipital temporal and limbic alpha 2 and 3 power as well as decrease in parietal and limbic theta. The other group showed decreased theta power, tending toward normal. Neuropsychological testing before and after 5 months of HAART revealed significant improvement in the Rey figure delayed recall task for both groups. A limitation of this study is that the HIV+ participants were not randomly assigned to the two different HAART regimes, so participants differed in medical co-morbidities at baseline.

4. Discussion

The aim of this systematic review was to qualitatively summarize electrophysiological findings in people living with HIV studied in the HAART era. We were interested in whether there were reliable differences between HIV+ and HIV− groups in specific EEG or MEG indices, whether these were explained by HIV variables, or by comorbidities or medications, and whether they predicted cognitive performance.

We found that there has been relatively little work using EEG or MEG to study brain function in people living with HIV since the widespread availability of HAART, with only 28 studies published over 20 years. Most of that work involved small samples, and much of it either did not characterize or did not control for relevant variables. Nevertheless, the findings suggest that electrophysiological measures can provide insight into the mechanisms of brain dysfunction in HIV, providing information about the timing and coordination of brain activity (Ishii and Canuet, 2014) that may be particularly pertinent for testing network accounts of cognitive dysfunction (Hawellek et al., 2011; Meehan and Bressler, 2012). Two electrophysiological variables most reliably distinguished HIV+ participants from HIV− controls: alpha activity and P300 amplitude.

Widespread alpha, recorded most often at rest with eyes closed, was consistently shown to be significantly reduced in HIV+ participants (Babiloni et al., 2012, 2014, 2015, 2016b,c). Central, parietal and frontal alpha power was also shown to be reduced in HIV+ participants while they performed an auditory oddball task or were presented with visual stimulation (Polich et al., 2000; Wilson et al., 2013a). Considering that alpha band oscillations are the dominant oscillations at rest with eyes closed, the comparison of this frequency between groups might have more statistical power than other bands and differences might thus be detected most easily, even in small samples. Decreased alpha power has previously been identified in persons with mild cognitive impairment due to prodromal Alzheimer's disease (van der Hiele et al., 2007; Jackson and Snyder, 2008; Babiloni et al., 2009, 2013).

Some studies also found frontal and central parietal delta recorded at rest was increased in HIV+ compared to HIV− groups (Babiloni et al., 2012, 2014), an effect also previously reported in patients with Alzheimer's disease, where it is thought to reflect functional disconnection between cortical regions (Jeong, 2004). A recent study reported that, considered together, participants with either mild cognitive impairment or Alzheimer's disease had lower cortical gray matter volumes that correlated with the amount of decreased alpha and increased delta sources (Babiloni et al., 2013). Mild cognitive impairment-related changes in subcortical grey matter volumes have also been associated with EEG indices (such as alpha 3/alpha 2 and theta/gamma ratios) (Moretti et al., 2012). Both cortical and subcortical volumes have been shown to be reduced in HIV+ compared to HIV− groups, even in the HAART era (Sanford et al., 2017). Thus, while non-specific, resting state power in one or more frequency bands seems a good candidate biomarker for brain health status in HIV, with face validity for HIV-related brain dysfunction that could reflect a breakdown of cortico-cortical or cortico-subcortical networks, or loss of cortical volume. Further work relating structural MRI and EEG measures in the same participants will be useful in testing these ideas.

The field would also benefit from more work exploring the connectivity and integrity of neural networks in people with HIV infec-

tion. Although only employed in one study to date, connectivity analysis (using the mutual information shared between pairs of MEG sensors (Becker et al., 2012a)) seems promising to further explore the effects of HIV on cognition (Thomas et al., 2013; DeVaughn et al., 2015). More work is needed to establish the most appropriate analyses and variables in this regard.

The reviewed ERP studies found that persons living with HIV had, in general, significantly smaller amplitudes and larger latencies in ERP components when compared to healthy control groups, with the P300 showing the most consistent results. These patterns suggest that post-stimulus information processing might be less synchronized or slower. Findings of larger latencies and smaller amplitudes have been observed in other neurological conditions marked by mild cognitive impairment (e.g., Olichney et al., 2011; Papaliagkas et al., 2011). For instance, prolonged ERP latencies in components like the N200, a component thought to reflect early stimulus discrimination under control-demanding conditions, have also been reported as indicators of risk for developing mild cognitive impairment on a neurodegenerative basis (Howe, 2014).

The P300, evoked by auditory oddball (Polich et al., 2000; Polich and Basho, 2002a; Chao et al., 2004; Tartar et al., 2004) visual oddball (Bauer and Shanley, 2006; Bauer, 2011) or visual Stroop (Bauer, 2008b) tasks, showed diminished amplitudes and/or longer latencies in HIV+ groups in 6 studies. However, experimental designs evoking this potential were also the most commonly used among the reviewed studies. Thus, the P300 seems to be a good candidate for a sensitive (although non-specific) ERP biomarker, but comparative work studying other potentials is needed to establish whether there might be better alternatives.

The extent to which the observed differences in neurophysiological variables are due directly to HIV-related brain injury, or reflect brain dysfunction related to comorbidities, aging, or neurotoxic effects of treatment, or early neurodegenerative changes as observed in other forms of age-related mild cognitive impairment remains to be firmly established. In this regard, some of the reviewed studies found that electrophysiological differences were associated with indicators of the severity of HIV-related immunosuppression. This was the case even when HIV+ participants had, on average, current CD4 counts greater than 300 cells/mm^3 and, in some studies, CD4 counts within the normal range. This observation is in line with findings from other imaging techniques showing brain changes in HIV+ individuals even when current CD4 counts are similar to those of healthy participants (Clifford and Ances, 2013; Vera et al., 2016). However, only 13 of the reviewed EEG/MEG studies tested for such relationships. Others did not aim to link electrophysiological findings with HIV-related clinical variables or did not report the immune status of HIV+ participants.

Fuller reporting of HIV clinical variables and their relationship with electrophysiological findings would be advantageous to address the specific effects of HIV on the brain in these chronically ill patients. For instance, establishing if there are effects of past level of immunosuppression, as indexed by nadir CD4 count, or the size of the latent viral reservoir, indicated by time between HIV diagnosis and initiation of HAART (Ananworanich et al., 2015) on EEG measures would contribute to a better understanding of the biological basis of the electrophysiological findings in this population. Importantly, these measures have been shown to be more predictive of MRI abnormalities and cognitive impairment compared with current CD4 count (Jernigan et al., 2011). More generally, designs (with appropriate sample sizes) that address the potentially multiple variables contributing to brain health in HIV over time will be essential to disentangle direct and indirect effects of the infection.

Differences in electrophysiological variables were related to the cognitive status of participants as evaluated by various cognitive tests in 13 of 16 studies that assessed this relationship. This argues that electrophysiological patterns relate to clinically relevant brain changes. However, only 20/28 of the studies reported the type and results of the cognitive assessment performed. None directly tested whether EEG markers might be superior to cognitive assessment for detecting brain dysfunction, a claim that would likely require longitudinal designs (i.e. to establish whether EEG changes precede cognitive impairment), and a focus on clinically relevant neurocognitive outcomes, such as occupational status, medication adherence, or other indicators of real-life function.

Longitudinal designs will likely provide the most useful information as the field moves forward: electrophysiological changes that relate to cognitive decline, or that predict such decline, would be of both clinical and fundamental relevance. The present review identified only 4 longitudinal studies. The results are encouraging, but further information on the test-retest reliability of potential electrophysiological biomarkers in this population will be important, at a minimum.

Longitudinal work linked to interventions may provide valuable insights into the mechanisms (including the modifiability) of the electrophysiological changes associated with HIV infection. Importantly, longitudinal work would benefit from re-framing cognitive ability as a continuum (Mayo et al., 2016), rather than being bound to the existing categorical classification of cognitive impairment in HIV (Antinori et al., 2007), which is poorly suited to tracking change over time. It may be more informative to relate electrophysiological measures to cognitive ability considered as a continuous quantity, particularly if the aim is to detect the earliest signs of cognitive decline even in high functioning individuals (Brouillette et al., 2015).

Both EEG and MEG are promising candidates for detecting changes in brain function early and for clarifying the underlying causes of cognitive impairment in persons living with HIV. Furthermore, electrophysiological findings might serve as biomarkers for brain dysfunction with potential for research or clinical application. Electrophysiological measures could be useful even before the underlying mechanisms are fully established, if they can be shown to reflect clinically important brain dysfunction earlier, more cheaply or more sensitively than the existing gold standard of neuropsychological testing. However, comparisons of HIV+ with HIV− control groups, the most common design in the current literature, are limited. These groups may differ in myriad other ways (e.g. presence of medical or psychiatric comorbidities, medication use, substance use, socioeconomic status) that may not be addressed in the study design, especially if sample sizes are small (as most have been, to date), making a direct link to HIV infection difficult to draw. Adequately powered multivariate studies are needed to address the heterogeneity of HIV+ samples. Rather than comparing HIV+ to HIV− groups, it may be more pertinent to compare electrophysiological measures in people with HIV who vary in immune or cognitive status, or to examine the effects of potentially explanatory clinical or personal variables on such measures. Moreover, evidence from studies in biological psychiatry and other medical domains suggests that extreme comparisons, i.e., those of a perfect healthy control versus prototypical patients, are not the most useful for clinical application. The predictive value of a biomarker tends to decrease as evaluations move from extreme comparisons to ones that are more clinically relevant (Kapur et al., 2012). Thus, the search for predictors should focus on clinically relevant comparisons.

EEG holds particular promise as a potential biomarker, given its wider availability, compared to MRI or MEG, in the relatively resource-poor clinical settings where many people with HIV infection receive care. As HIV treatment moves toward the goal of viral eradication, characterizing the extent of the latent viral reservoir in the CNS takes on further importance (Joseph et al., 2016). An EEG

biomarker that indexed the extent of the latent viral reservoir in the CNS could be critical in this regard. There is clearly a need for more work directly testing EEG measures as potential biomarkers of brain dysfunction in HIV+ individuals. As with other neuroimaging approaches in the field of neuroHIV, MEG and EEG studies remain preliminary.

A biomarker for clinical use should contribute information about the risk, presence, severity, or absence of clinically relevant brain dysfunction in persons living with HIV. The present review shows that electrophysiological differences can be identified in people with HIV infection, but the clinical relevance of these observations remains to be established. Future work should include estimates of validity, reliability, sensitivity and specificity (Castellanos et al., 2013). Lacking that information, it is difficult to comment on which of these electrophysiological measures or combinations of measures are most promising. However, alpha power and P300 amplitude and latency are reasonable starting points that allow the greatest links to the current literature. Work comparing (or combining) EEG with information from other neuroimaging modalities would also be valuable.

The present systematic review suggests that neurophysiological imaging has a lot to offer in the field of neuroHIV. Temporal precision combined with accessibility in a range of healthcare settings makes these techniques good candidates for early detection of brain dysfunction in HIV, and for contributing to the assessment of cognitive symptoms in such patients. Studies assessing EEG/MEG oscillations at rest with eyes closed and those evaluating the amplitude of ERP components with onsets of 200 ms or later seem to have the most promise as potential biomarkers. However, there is a need for more work with rigorous designs, better clinical characterization, and adequate sample sizes to fully test candidate biomarkers against alternatives such as neuropsychological testing or structural neuroimaging, and to better understand the brain mechanisms, pathogenesis and prognostic relevance of observed EEG and MEG differences.

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Appendix A

(((((((("Acquired Immunodeficiency Syndrome" OR "AIDS"[ot] OR "Human Immunodeficiency Virus" OR "Acquired Immune Deficiency Syndrome")) OR ((((((((("HIV"[Mesh])) OR "HIV Infections"[Mesh:noexp]) OR "Acquired Immunodeficiency Syndrome"[Mesh])) OR "AIDS Arteritis, Central Nervous System"[Mesh]) OR "AIDS-Associated Nephropathy"[Mesh]) OR "AIDS Dementia Complex"[Mesh]) OR "AIDS-Related Complex"[Mesh]) OR "HIV Seropositivity"[Mesh])))) OR "HIV associated neurocognitive disorder" OR "Asymptomatic Neurocognitive Impairment" OR "Mild Neurocognitive Disorder" OR "HIV-associated Dementia" AND ((((((((((("Evoked Potentials"[Mesh:noexp]) OR "Contingent Negative Variation"[Mesh]) OR "Event-Related Potentials, P300"[Mesh]) OR "Evoked Potentials, Auditory"[Mesh]) OR "Evoked Potentials, Auditory, Brain Stem"[Mesh]) OR "Evoked Potentials, Motor"[Mesh]) OR "Evoked Potentials, Somatosensory"[Mesh]) OR "Evoked Potentials, Visual"[Mesh])) OR (("Event Related Potential*" OR ERP))) OR (("Electroencephalography"[Mesh]) OR "Magnetoencephalography"[Mesh] OR EEG OR MEG[tiab]))))) NOT hearing)) AND ("1996"[Date - Publication]: "3000"[Date - Publication]).

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