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CENTRAL NERVOUS SYSTEM AND COGNITION (S SPUDICH, SECTION EDITOR)

# Neurocognitive Phenotyping of HIV in the Era of Antiretroviral Therapy

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## Abstract

**Purpose of Review** This paper examines the theoretical and empirical basis for neurocognitive phenotyping of HIV.

**Recent Findings** The pattern of neurocognitive symptoms associated with HIV has traditionally been referred to as a "subcortical" phenotype. Recent concern has been raised that the neurocognitive phenotype in the post-ART era has changed to reflect the addition of cortical features, suggestive of synergistic age-related neurodegeneration. Empirical evidence reviewed in this paper suggests that, when present, HIV-related neurocognitive impairment in the post-ART era remains subcortical in nature, regardless of advanced age or treatment status. Persistent neurocognitive impairment among virally suppressed individuals may reflect a combination of HIV disease factors, pre-existing risk factors, and/or emergent health comorbidities such as subcortical ischemic vascular disease in older people living with HIV.

**Summary** An entrenchment of the subcortical neurocognitive phenotype of HIV appears to be unfolding in the post-ART era. Whether new neurocognitive subtypes of HIV exist in the current era requires additional research utilizing harmonized test protocols and advanced computational methods capable of deep phenotyping. Recommendations from other neurological disorders are provided.

**Keywords** HIV · Cognition · HAND · Phenotype

## Introduction

HIV-associated neurocognitive disorders (HAND) are believed to affect nearly one in two persons living with HIV (PLWH) [1–3]. While HAND is not a universal manifestation, the massive scale of the HIV epidemic translates into an estimated point prevalence of 18 million PLWH who meet current research criteria for HAND [2, 3]. In most cases, the symptoms are described as mild [3, 4]. However, individuals with minor neurocognitive impairment are at risk of cognitive decline when co-morbid health conditions are present, despite treatment with antiretroviral therapy (ART) [5]. More profound neurocognitive impairment has been reported among PLWH who reside in countries where access to healthcare is suboptimal [6]. According to one estimate, HIV is the leading cause of significant brain dysfunction in young adults in resource-restricted regions of the world [7]. These trends are alarming given the absence of a cure for the disease, and a growing body of evidence that neurocognitive symptoms persist in the context of suppressive ART.

Numerous studies demonstrate that treatment-induced viral suppression does not reverse brain abnormalities in chronically infected individuals [8, 9]. Additionally, initiation of ART may not be sufficient to prevent the development of new cerebral injury. Sanford et al. [10•] reported neuroimaging abnormalities in treatment-naïve individuals, but no evidence of progressive injury 6 months after suppressive treatment. By contrast, preliminary results from adults with acute HIV revealed progressive brain volume loss over a 2-year period despite initiation of suppressive ART during the first weeks of infection [11]. Long-term prospective studies are needed to determine whether individuals with either acute or more chronic infection are protected from de novo neurocognitive impairment.

PLWH on long-term suppressive ART are now expected to live as long as their uninfected peers. The life-saving benefits of ART introduce new health challenges including increased risk of synergistic or additive disease processes that have potential to alter the neurocognitive profile of HIV. This concern has been reported in the recent literature, noting that the

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neurocognitive phenotype of HIV has shifted towards a mixed subcortical-cortical pattern [12, 13•]. If substantiated, the change would implicate new disease mechanisms and neural substrates of neurocognitive symptoms, particularly Alzheimer's disease.

The current paper examines the theoretical and empirical basis for neurocognitive phenotyping of HIV, with attention directed at the pattern of neurocognitive impairment before and after the start of the ART era. The paper concludes with recommendations to guide future studies, including an example of deep phenotyping using unsupervised machine learning.

## Frontal-Subcortical Neurocognitive Phenotype of HIV

The neurocognitive phenotype of HIV has been described as "subcortical" since the beginning of the epidemic [14]. Independent of moderating factors (e.g., viral, host, cultural context), PLWH predominately exhibit slow motor speed, bradyphrenia, reduced learning efficiency, and/or executive dysfunction, with sparing of core language and memory consolidation skills [2, 15–17]. Impaired memory is believed to result from "upstream" abnormalities in attention, working memory, and/or executive function; amnestic memory dysfunction less uncommon [2, 14, 15].

The description of neurocognitive strengths of the disease identified in postmortem studies and weaknesses among PLWH aligns with the neuropathological features of HIV. Studies demonstrate high viral aggregation in the basal ganglia [18], and neuroimaging abnormalities in the white matter, caudate, and putamen in the early and later stages of HIV [9, 19–22]. Neuroimaging abnormalities in the cortex and diffuse disruption to network connectivity have also been reported in PLWH [23], particularly in advanced or untreated disease [24]. These cortical abnormalities likely reflect remote signatures of damage to interconnected subcortical regions rather than isolated injury in the cortical mantle. Recognition that a given brain injury can produce regional and remote functional abnormalities underscores the danger of using broad clinical phenotypes (cortical, subcortical, etc.) to infer specific anatomical substrates much less unique disease mechanisms. To this point, multiple neurologic and psychiatric conditions produce neurocognitive symptoms characteristic of a subcortical profile. Two that are highly relevant to HIV include subcortical ischemic vascular disease and depression as such, caution is warranted when applying subcortical or "cortical" phenotype labels because neither is defined by exclusive neuroanatomical models.

## Neurocognitive Symptoms in the Pre- and Post-ART Era

The pattern of neurocognitive symptoms associated with HIV before and after the introduction of ART was rigorously examined in two recent publications. In the first, Cysique et al. [25] reported more significant verbal learning impairment among PLWH in the post-ART era compared to the prior period. Nearly identical results were described by Heaton et al. [16], with the additional observation that motor dysfunction appeared less common in the current era when compared to the prior period. Importantly, both studies emphasized that poor learning, rather than loss of retained information, contributed to the expression of worse memory in the post-ART era. Indeed, close examination of the frequencies of delayed recall performance reported in both studies reveals high correspondence between the two treatment periods suggesting no major shift in the frequency of amnestic memory impairment typical of AD.

Outcomes from the studies above are consistent with the observations of brain disruption from Navia et al. [14] in the earliest days of the HIV epidemic, which included abnormal memory function among individuals with neuropathology confined to the basal ganglia and white matter, consistent with the aforementioned danger of inferring anatomical substrates from clinical descriptions. Memory, for example, is a complex phenomenon governed by multiple neural networks that harbor differential sensitivities to disease processes. Evidence of impairment in one component of memory does not ensure impairment across other memory systems, or the involvement of a common neural substrate. This complexity necessitates a standardized nomenclature to facilitate interpretation of neurocognitive performances.

## Recommendations for Future Research

Neuropsychology, perhaps more so than other disciplines, is riddled with inconsistent and nonspecific nomenclature. Significant differences in test selection, nomenclature for defining neurocognitive cognitive domains (e.g., working memory vs. short-term memory vs. executive function), assignment of individual tests to specific domains (e.g., verbal fluency as a measure of Language vs. Executive Function), and definitions of "impairment" (e.g., global deficit score, NPZ) are common [26–31]. Additionally, variability in methods to calculate global dysfunction contributes to the confusion because global scores derived from cognitive tests that assess a restricted brain network (e.g., average scores on tests of frontal function) are not comparable to "global" scores comprised of tests that examined heterogeneous brain networks. These challenges emphasize the need for a common methodology to quantify and describe neurocognitive impairment.

Specialty areas in neurology (AD, cerebrovascular disease, multiple sclerosis, etc.) and psychiatry (e.g., schizophrenia) benefit from common test batteries. By comparison, cognitive protocols in HIV studies are frequently designed and implemented on a study-by-study basis without pre-meditated efforts to support harmonization. Overcoming this challenge will require a

consensus panel comprised of experts with input from multiple stakeholders to select tests based on psychometrics (reliability, validity, ceiling, floor), real-world relevance, opportunity for international application, brevity, availability of multiple forms, cost, and task-sharing opportunities (i.e., administration by non-neuropsychologists). Table 1 provides an example from the vascular cognitive impairment literature [32], which provides recommendations for longer and shorter protocols.

It is important that a harmonized test battery for HIV includes domains/measures that are sensitive to diverse brain networks. While a central theme of the current paper is that available data point towards a persistent subcortical neurocognitive phenotype, there is high possibility that the pattern of neurocognitive symptoms will evolve in this population considering the expansive list of possible contributing factors. Recent studies identify potential causal pathways involving immune dysregulation (i.e., monocyte activation marker soluble CD163 [33, 34, 35•], increased levels of CD16 expressing monocytes [36], loss of CCR2 expressing non-classical monocytes [37], plasma and CSF levels of neopterin, MCP-1, lymphocyte markers such as IP-10 [38], viral reservoirs, iatrogenic effects of medications, health co-morbidities (hepatitis C, cardio/cerebrovascular disease), and confounding effects of mental health symptoms. It is possible, therefore, that the

**Table 1** Harmonized Neurocognitive Assessment Protocols

| Cognitive domain | Vascular harmonization battery | Modified for HIV harmonization |
|---|---|---|
| 60-minute battery | | |
| Premorbid function | – | Wide Range Achievement Test-IV |
| Focused attention | – | Digit Span Forward |
| | | *1-Back* |
| Working memory | Digit Span Forward | PASAT trial 1 |
| | Digit Span Backward | *LNS* |
| Fine motor speed | – | Finger Tapping |
| | | Grooved Pegboard |
| Psychomotor speed | – | SDMT |
| | | Color Trails 1 |
| Executive function[a] | Animal Fluency | Letter Fluency |
| | Letter Fluency | Action Fluency |
| | Color Trails 1 and 2 | Color Trails 2 |
| | | Go/No-Go |
| | | *Stroop Interference* |
| Visuomotor speed | SDMT | – |
| Language | BNT-15 | Animal Fluency |
| | | *BNT-15* |
| Visuospatial | Rey-Osterrieth CFT Copy | – |
| Memory | Rey-Osterrieth CFT | CVLT–2 |
| | HVLT-R | Alt: Rey AVLT |
| | Alt: CVLT-2 | |
| 30-minute battery | | |
| Psychomotor-executive function | Animal Fluency | Letter Fluency |
| | Letter Fluency | Action Fluency |
| | SDMT | Color Trails 1 and 2 |
| | | Stroop |
| | | Go/No-Go |
| Memory | HVLT-R | CVLT–2 learning and delay only |
| 5-minute battery# | | |
| Montreal Cognitive Assessment (MOCA) | 5-word registration, delayed recall and recognition; orientation, and letter fluency | MOCA |
| | | Color Trails 1 and 2 |

Italics represent tests that overlap with recommendations from the NIH Research Domain Criteria (RDoCS)

*PASAT* Paced Auditory Serial Addition Test (PASAT, trial 1 only), *SDMT* Symbol Digit Modalities Test, *BNT* Boston Naming Test (short form), *RCFT* Rey-Osterreith Complex Figure Test, *HVLT-R* Hopkins Verbal Learning Test-Revised, *CVLT-2* California Verbal Learning Test-2

[a] Alternative computer-administered measures from the EXAMINER

neurocognitive phenotype of HIV will become more variable, and more nuanced based on the combinations of individual and interactive risk factors for each person.

Research is also needed to leverage advances in computational methods such as machine learning algorithms. Cluster analyses identify intrinsic patterns that help to organize large data matrices. These methods offer a less biased approach to explore hidden features of clinical phenotypes. Unfortunately, few studies have employed cluster analyses to examine neurocognitive symptoms of HIV, and results from the existing studies are difficult to interpret due to lack of standardized methods of neurocognitive assessment. An advantage of machine learning is the opportunity to explore the underlying data structure of complex clinical phenotypes by applying algorithms that iteratively learn patterns within highly dimensional data. The result is a much deeper level of clinical description. An example of outcomes using the deep clustering program CorEx [39] is provided in Fig. 1. CorEx (correlational explanation) identifies hierarchical representations of data (i.e., phenotypes) using a mutual information criterion. When applied to neurocognitive performance, CorEx can help identify intrinsic patterns that are not evident using traditional correlational methods. Figure 1 depicts two neurocognitive phenotypes of chronic HIV. Additional methods for phenotype analyses include graphical modeling [40] and Rasche analysis [41] that have been applied

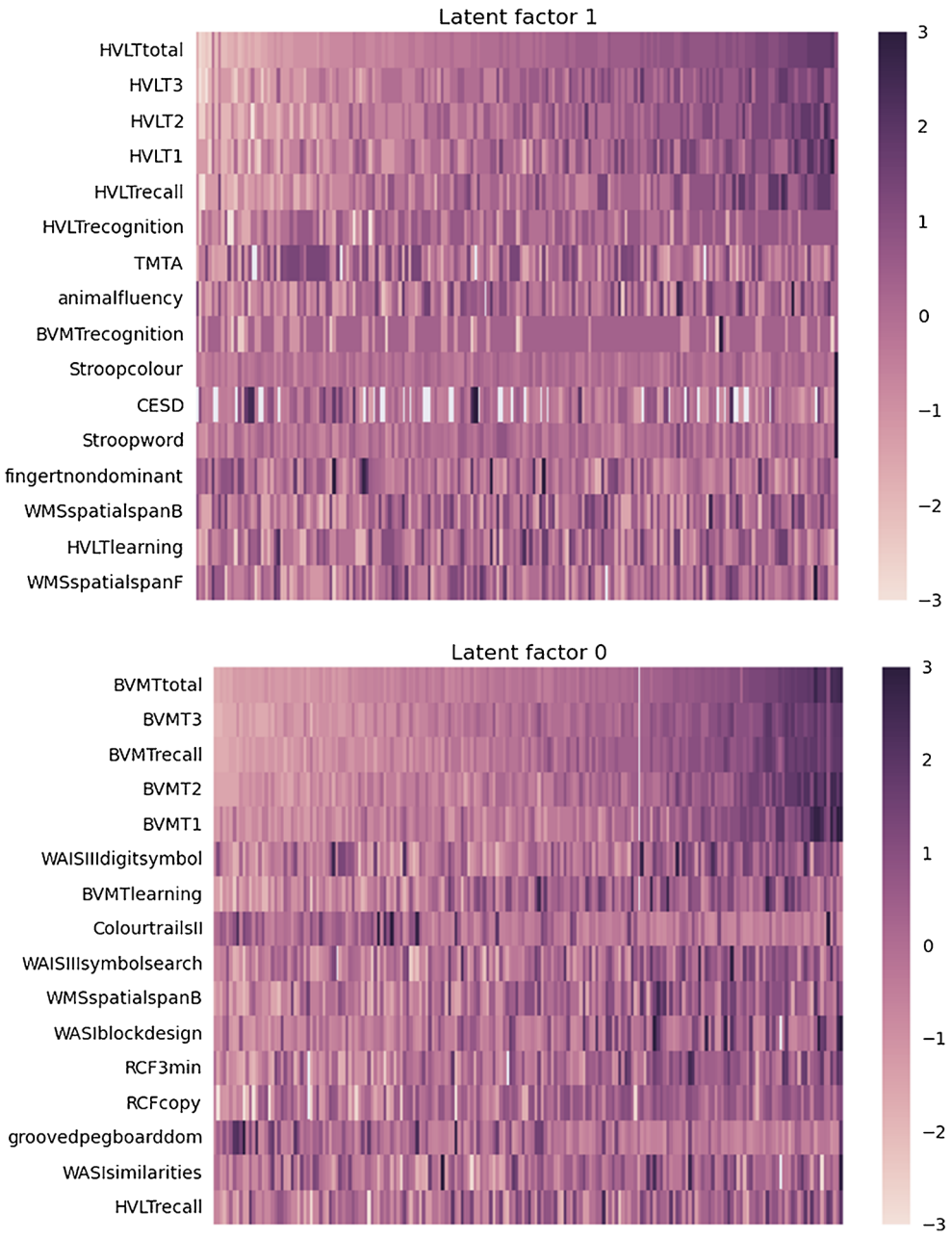


**Fig. 1** Deep phenotyping of neurocognitive performance in HIV. Heat maps depicting two deep phenotypes of neurocognitive performance in HIV. Top: verbal-dominant factor; Bottom: visual-dominant factor. Performances are depicted as raw scores

successfully in other neurological populations (e.g., stroke) and represent important methodological tools for deep phenotyping of HIV.

Finally, there is a significant need to enhance methods to quantify capacity to complete activities of daily living (ADLs) in PLWH. The degree to which cognitive symptoms interfere with ADLs is a critical component of current diagnostic criteria for neurocognitive impairment, including the Frascati criteria for HAND [3]. Despite the clinical relevance, accurate assessment of real-world function is challenging in both clinical and research settings. By default, the common approach in HIV involves the use of Western-based self-report scales that were developed for use in other populations, with insights provided by informants (spouses, adult children, life partners, etc.) familiar with the individual's prior and current functional capacity.

Not surprisingly, self-reported ADL measures are not well suited for most adult populations of PLWH, with even less relevance to pediatric cohorts and individuals residing in resource-restricted settings. Objective measures of ADL capacity that simulate real-world tasks (e.g., balancing a checking account) are viable alternatives for select adult populations [42, 43], but these methods require significant investment in assessment/scoring time and the tasks do not readily translate to international settings. More work is needed to develop brief yet sensitive objective measures of ADL capacity that have strong cultural relevance in both resource-enriched and resource-restricted settings. The latter may require a paradigm shift to address superordinate skills (e.g., transportation/navigation and bartering/trade) rather than the current focus on specific subordinate tasks (e.g., driving a car and balancing a checkbook).

## Conclusion

The neurocognitive phenotype of HIV remains subcortical in the post-ART era. Evidence does not support a shift towards a mixed cortical-subcortical phenotype at the present time. The neurocognitive phenotype may shift in the future, reflective of numerous candidate risk factors that persist in the context of long-term ART. Development of a common test protocol and use of standardized nomenclature will enhance data harmonization and create opportunities for deep neurocognitive phenotyping using advanced computational methods.

### Compliance with Ethics Standard

**Conflict of Interest** The authors declare that they have no conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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