Title
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Journal
AIDS, 35(1)

ISSN
0269-9370

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Publication Date
2021

DOI
10.1097/qad.0000000000002726

Peer reviewed

AIDS, Publish Ahead of Print
DOI: 10.1097/QAD.0000000000002726

Prepared for: AIDS

Body Word Count: 2308
Tables: 1

USING HEALTH TECHNOLOGY TO CAPTURE DIGITAL PHENOTYPING DATA IN HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS

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Conflict of Interest: Dr. Raeanne C. Moore is a co-founder of KeyWise AI, Inc. and a consultant for NeuroUX. The terms of these arrangements have been reviewed and approved by
the University of California San Diego in accordance with its conflict of interest policies. No other authors have conflicts of interest to report.

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Funding/Support: This work was supported by the National Institutes of Health (RCM, grant numbers NIMH K23MH105297, NIMH K23 MH107260 S1, NIA R01AG062387). Stipend support to MK is funded by the National Institute on Alcohol Abuse and Alcoholism award T32AA013525.

Keywords: Individualized medicine, mobile applications, wearable technologies, digital biomarkers, chronic illness, aging

INTRODUCTION

The ubiquity of smartphones is transforming health services and management of patient care to increase patient symptom tracking, accessibility to resources, and personalization of care [1]. Indeed, 81% of Americans own a smartphone, and ownership among ethnic minorities, who are disproportionally affected by HIV, is equally high [2]. Medical and public health practices supported by mobile devices allow medical professionals and caregivers to improve communication and patient symptom tracking as well as focus on individually tailored treatments and preventative care [3]. Mobile health technologies have proven efficacious in reducing disease burden among persons living with HIV (PWH), including strategies to improve medication adherence, increase retention in care, and facilitate social support systems [4-6]. Furthermore, several studies focusing on optimizing HIV care among populations with co-occurring HIV and substance use disorder have found promising success using mobile health technologies to promote adherence to antiretroviral (ART) medications [7-9].

Although mobile health interventions provide streamlined and lower cost alternatives to improve HIV-related health care, many published mobile phone tools, such as two-way text messaging or ecological momentary assessments (EMA), requires the user to actively engage with the device to provide input. While there are advantages of active engagement with an mHealth intervention, passive collection of digital data eliminates the need for active user engagement by collecting data continuously and objectively in the background, as a user goes about their daily activities [10]. For example, accelerometer along with gyroscope, GPS, WiFi, and smartphone microphone data have been used to detect physical activity and daily behaviors [10]. With the wealth of health-related data captured via passive, as well as active, digital health devices, researchers are able to develop and interpret a digital phenotype. Digital phenotyping, as defined first by Jukka-Pekka Onnela (2016), is the *"moment-by-moment quantification of the individual-level human phenotype in situ using data from personal digital devices"* [11]. Digital phenotyping can provide a comprehensive understanding of the specific symptomology and experience of disease that can impact diagnosis, treatment, and management of disease [12].

Considering the potential compounding effects of HIV and aging on the brain, older PWH are at a high risk for HIV-Associated Neurocognitive Disorders (HAND) and may be at increased risk for other age-related neurodegenerative diseases including Alzheimer's Disease (AD) and its precursor, amnestic mild cognitive impairment (aMCI) [13-15]. Identifying preclinical factors that can distinguish among those with HAND, AD, and aMCI is challenging due to considerable overlap in neuropsychological profiles [16]. Cognitive dysfunction among PWH has been associated with ART non-adherence, unemployment, increased dependence in activities of daily living, depressed mood, and increased risky behaviors [17, 18]. Considering the multisystem impact of aging, improving neuropsychological outcomes among aging PWH is a global mental and public health priority [19]. Furthermore, differentiating HAND from neurodegenerative disease pathology is critical to understanding the likelihood of cognitive impairment progression and for effectively providing targeted interventions.

Given the increased risk of neurocognitive impairments in PWH, mobile cognitive testing provides easily accessible alternatives to traditional neuropsychological evaluations and can potentially detect more nuanced neurocognitive changes [20]. Furthermore, advancements in innovative wearable devices and optimization of smart home systems allow for streamlined and continuous collection of clinical, physiological and ambient data relevant to brain health that may be suggestive of pre-clinical neurocognitive decline [21]. These novel methodologies may aid in the efforts to differentiate among HAND, aMCI and AD profiles by providing real-time and ecologically valid indications of an individual's neurocognitive and everyday functioning.

Active and passive digital health technologies can significantly improve the way researchers assess cognitive and everyday functioning by transitioning from traditional clinical assessments to digital assessments and continuously captured data from daily activities. Despite these benefits, there are numerous challenges and barriers to address before clinical implementation related to disentangling cognitive profiles among PWH, validating active and passive assessment tools, integrating sensor platforms, participant privacy, data security, interventional feasibility and ethical issues. Despite these challenges, dissemination of mobile cognitive testing and passive digital technologies is becoming more feasible, with significant efforts now focused on validating the psychometric properties of these tools (e.g., [22]).

The purpose of this brief review is to (1) discuss the utility of digital health assessment in evaluating cognitive trajectories among PWH, (2) review research designs amenable to integrating digital technologies, and (3) describe examples of challenges and barriers that may arise when implementing digital technologies into research designs.

DIGITAL HEALTH ASSESSMENT MEASURES

Active Engagement

Substantial evidence suggests an association between cognitive impairment and declines in everyday functioning among PWH; however, there are also cognitively healthy older adults with HIV that exhibit functional impairments on lab-based assessments and cognitively impaired older PWH that remain functionally unimpaired [17, 23]. These unexpected findings may reflect the need to investigate other real-world factors that may detrimentally affect functioning in aging PWH. Current research supports the feasibility of ecological momentary assessments (EMAs) to monitor real-world variability in mood, stress, social support, coping, everyday activities, substance use, and cognition among younger to older adults living with HIV [24-28]. For example, one study examined the validity of smartphone-based EMAs in relation to lab-based assessments of substance use among older adults with and without HIV and found that EMA-reported substance use was significantly correlated with lab-based assessments. This study additionally investigated real-time ecologically valid data to better understand predictors of health and behaviors and found effects of mood and pain on subsequent substance use such that greater anxious mood, happiness, and higher pain levels significantly affected substance use [29]. Furthermore, results from another study exploring substance use and pain using smartphone-based EMAs suggest a bidirectional association between pain and daily drinking and lower levels of daily worst pain with higher coping abilities [30]. Another study observed that older PWH spent substantial time at home, alone, and engaged in passive leisure activities (e.g., watching TV), and that greater time engaged in passive leisure activities correlated with worse cognitive functioning [25]. This last finding is consistent with research among persons with serious mental illness including schizophrenia that showed less productive activity, fewer social interactions, greater time at home and higher engagement in passive leisure activities in this group [31]. Thus, smartphone-delivered EMA may be a useful and feasible method to better understand variability and correlates of daily functioning among PWH.

Traditional assessment of cognition typically requires an in-person comprehensive neuropsychological evaluation that is time- and resource intensive, non-ecologically valid, and only represents a snapshot of a patient's cognitive abilities at the time of assessment. Traditional instruments are therefore unable to detect subtle, real-world declines in cognitive functioning. Advances in digitalizing traditional neuropsychological assessments may improve the sensitivity and specificity of clinical diagnoses at earlier stages of neurocognitive diseases via frequent and less burdensome digital assessments [20]. Growing research on validating mobile cognitive assessments suggests that mobile cognitive assessments are feasible and valid among older adults as well as adults with head injury, schizophrenia, and substance use disorders [32-36]. Furthermore, results of a validation study evaluating a smartphone-based cognitive impairment screener were promising with strong preliminary evidence indicating construct and criterion validity as well as high sensitivity to detect neurocognitive impairment among PWH [37].

Mobile cognitive assessments may serve as an adjunct to traditional neuropsychological testing. For example, mobile cognitive data collected via ecological momentary cognitive assessment (EMCA) methods can be aggregated and analyzed to examine temporal relationships between variability in cognition with indicators of, for example, everyday functioning (e.g., mood, activities of daily living, socially-engaging activities, physical activity, and passive leisure activities), sleep, physiological functioning, and social activity, among others [25]. Moreover, EMCA assessments may be able to serve as screening instruments to indicate whether a person needs a more comprehensive laboratory-based neuropsychological assessment. Overall, mobile cognitive assessments permit remote testing on a frequent or infrequent schedule in a person's natural environment, a design flexibility that is not afforded to traditional neuropsychological testing, and may therefore provide (1) more reliable indicators of early cognitive difficulties among older PWH that clinic-based tools cannot detect, and/or (2) identification of need for comprehensive in-person testing.

There are several challenges associated with traditional in-person neuropsychological evaluations that may be addressed using mobile cognitive testing. For instance, evaluating individual effort put forth during traditional neuropsychological evaluations to ensure interpretability remains a significant challenge. Mobile cognitive tests could integrate built-in metrics (e.g., reaction time) or embedded (e.g., symptom validity tests) effort measures to gauge the level of effort given to an assessment. Furthermore, smartphone cameras could potentially capture videos of pupillometry during task completion as an indicator of attentional allocation which could also serve as a measure of effort [38]. More analogous to traditional tests of effort, studies currently in preparation have preliminary evidence suggesting efficacy of a mobile assessment using a 6-item word list to evaluate effort in both cognitively healthy and impaired adults. Finally, individuals invested in their results may feel more motivated to provide their best effort on mobile cognitive tests as there is the potential to provide real-time performance feedback to individuals, allowing them to track changes in their cognitive health over time.

Passive Engagement

Examples of existing passive features that can be collected from digital health technologies are presented in Table 1. Technologies were selected based on the following: (1) experience using the product/tech in previous and/or ongoing studies; (2) knowledge of products/tech from colleagues, peer-reviewed papers, conference presentations etc.; (3) brief review of the literature on novel technologies and applications. This list is meant to be an informed sampling from the field, and this commentary should not be viewed as a substitute for a systematic review.

Smartphone functionality has the ability to passively collect a myriad of digital data streams from GPS/GIS, microphone, camera, accelerometry, phone usage metrics, and keyboard typing features. For example, preliminary evidence from one study suggests that symptoms related to pain and mood which were previously only captured via subjective self-report measures may be alternatively monitored by objective passive movement data (i.e., actigraphy) among PWH [39]. Furthermore, this study found that psychomotor and sleep patterns measured via wearable sensors were significantly predictive of pain severity, pain chronicity, and worry severity among PWH. Another recent study examined the feasibility and discriminant ability of continuously captured real-world data from a unified and unobtrusive monitoring platform to differentiate between participants with and without cognitive impairment. The study design spanned 12-weeks in which participants were monitored via consumer-grade smart devices (i.e., iPhone 7 plus, Apple Watch Series 2, iPad pro with smart keyboard, a Beddit sleep monitoring device, and all associated applications to collect sensor and phone-usage data). Domains assessed include gross motor function, autonomic nervous system, circadian rhythm, behavior, social engagement, cognitive control, attention, fine motor control, and language. Results indicate that the sensor platform was adequately able to differentiate between cognitively healthy controls and participants with cognitive impairment from a relatively short period of data collection (i.e., 12-weeks) [40]. Although passive metrics of cognition are still in the early stages of clinical validation, they hold promise in progressing researcher's ability to classify and detect early nuanced behavioral and cognitive changes associated with neurodegenerative diseases.

RESEARCH DESIGNS

Complex continuously collected data could be leveraged to understand the effects of comorbid conditions (e.g., substance use and psychiatric disorders) within the context of PWH and neurocognitive decline. Depending on the specific aims of the research study, digital health technologies can be appropriately integrated into research designs to understand complex relationships between everyday life activities, health indicators, and cognitive function. Digital health technologies offer the ability to have a myriad of study designs, including (for example): (1) burst; (2) longitudinal; (3) hybrid of burst and longitudinal designs. Burst designs are characterized by short and intensive assessment periods to capture high frequency data that are useful in understanding the effects of comorbidities as well as temporal relationships [41]. Burst designs typically range from an average of one day to approximately one month. Longitudinal designs offer continuous, objective, unobtrusive measures via sensors and devices to capture real-time data in the home or in everyday environments [42]. This design permits a continuous collection of comprehensive functional data over a longer span of time with minimal intrusion and burden. This approach offers insights into subtle intra-individual behavioral and lifestyle changes that could be indicative of early signs of neurodegenerative diseases. Finally, a hybrid of burst and longitudinal designs typically employs short periods of data collection over a longer span of time (e.g., two-week bursts every quarter for two years).

Prior research has used traditional neuropsychological evaluations to examine intra-individual variability in neurocognitive performance among PWH; however, mobile cognitive testing may potentially detect more nuanced neurocognitive changes [43]. Several research designs can be employed to investigate fluctuating patterns of neurocognition over time using mobile technology. Burst designs using active data collection (e.g., EMCA) can provide a wealth of information within a specified time period to examine associations between neurocognition, everyday functioning, and mood. Longitudinal designs, employing continuous and passively collected data, can be utilized to examine temporal relationships and predictors of neurocognitive performance using real-time data from everyday environments. Hybrid designs, that leverage both active and passively collected data, offers the ability to frequently assess neurocognition as well as everyday behaviors, lifestyle, and mood to evaluate intra-individual variability.

Thus far, studies have yet to assess intra-individual variability in neurocognition among PWH using digital health data. We conducted a literature search to assess the use digital assessments among PWH (Table 2). In order to identify articles for this non-systematic review of the literature, we searched the PubMed database using the following search terms “digital OR digital assessment OR mobile assessment”, AND “HIV.” Then, we reviewed the reference list for pertinence and compiled relevant articles. We also reviewed relevant articles reference lists to identify additional articles. Further, we restricted our searches to studies published in peer-reviewed English-language journals. No restrictions were placed on samples demographics or sample sizes.

CHALLENGES AND BARRIERS

Prior to implementing digital technologies into clinical practice, research is warranted to identify the potential mechanisms underlying the heterogeneity of aging, especially among populations at a higher risk for cognitive impairment such as PWH. Additionally, establishing validated assessment tools with normative data across demographic and clinical populations that are culturally- or language-unbiased remains a concern with traditional neuropsychological evaluations; without the consideration of factors associated with the usability of digital technologies and smartphones among older persons with comorbid conditions. Moreover, there are limited integrated platforms that have been developed and well-validated that incorporate passive data collection methods with active features to provide cohesive data on activities of daily living and patterns of behavior [44]. The lack of well-validated assessment tools to be implemented into clinical care could be due to, in part, funding limitations to support such studies. Considering there are a multitude of companies working on commercialized digital health products and platforms, researchers could work more closely with industry partners to develop complex analytic algorithms that can integrate large amounts of digital data and process it in a meaningful way in the context of early changes in cognition.

In order to transition from research settings to commercial use and clinical care, health-related digital technology platforms must be sustainable and scalable without driving up consumer and healthcare costs. Within the commercial market, there are extant start-up companies developing digital technology platforms marketed directly to the consumer; however, many lack extensive research validation and involvement of care providers and consumers in the product development process [45]. It is crucial on the part of the developer to engage clinicians and consumers when addressing the needs and concerns of both parties in order to develop an effective product. For example, one study that examined appraisals of the potential risks and barriers of participating in a texting-based research study found that participants were particularly concerned with information privacy, confidentiality, and data security; however, were more likely to participate if these concerns were appropriately addressed [46].

CONCLUSIONS

Despite these barriers, the ubiquity of digital health devices across the lifespan makes the dissemination of mobile health assessments increasingly feasible [2]. Furthermore, increased accessibility to digitally captured health metrics allows individuals to proactively monitor their own changes in health and behaviors. Digital phenotyping will continue to evolve as new technologies emerge, individuals engage with digital technologies in new ways, and advances in data analytics and artificial intelligence continue to improve. This type of research requires a multi-disciplinary approach, and could advance our understanding of the complex overlap in cognitive profiles among aging PWH.

Acknowledgements

* The San Diego HIV Neurobehavioral Research Center [HNRC] group is affiliated with the University of California, San Diego, the Naval Hospital, San Diego, and the Veterans Affairs San Diego Healthcare System, and includes: Director: Robert K. Heaton, Ph.D., Co-Director: Igor Grant, M.D.; Associate Directors: J. Hampton Atkinson, M.D., Ronald J. Ellis, M.D., Ph.D., and Scott Letendre, M.D.; Center Manager: Jennifer Iudicello, Ph.D.; Donald Franklin, Jr.; Melanie Sherman; NeuroAssessment Core: Ronald J. Ellis, M.D., Ph.D. (P.I.), Scott Letendre, M.D., Thomas D. Marcotte, Ph.D, Christine Fennema-Notestine, Ph.D., Debra Rosario, M.P.H., Matthew Dawson; NeuroBiology Core: Cristian Achim, M.D., Ph.D. (P.I.), Ana Sanchez, Ph.D., Adam Fields, Ph.D.; NeuroGerm Core: Sara Gianella Weibel, M.D. (P.I.), David M. Smith, M.D., Rob Knight, Ph.D., Scott Peterson, Ph.D.; Developmental Core: Scott Letendre, M.D. (P.I.), J. Allen McCutchan; Participant Accrual and Retention Unit: J. Hampton Atkinson, M.D. (P.I.) Susan Little, M.D., Jennifer Marquie-Beck, M.P.H.; Data Management and Information Systems Unit: Lucila Ohno-Machado, Ph.D. (P.I.), Clint Cushman; Statistics Unit: Ian Abramson, Ph.D. (P.I.), Florin Vaida, Ph.D. (Co-PI), Anya Umlauf, M.S., Bin Tang, M.S.

The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, nor the United States Government.

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Table 1. Examples of mobile tools for gathering digital phenotyping data

Device/App Name	Device Type	Operating System	Method	Data Type	Behavioral Features Collected
ActiGraph GT9X[a] [47-49]	Wrist Worn Wearable[b]	iOS & Android	-Operation: Passive -Data Transfer: Active	-Frequency: High -Continuity: Continuous	-Energy expenditure -Heart rate[c] -Metabolic rate -Physical activity -Sleep
Anti-social[d]	Smartphone Application	Android	-Operation: Passive -Data Transfer: Active	-Frequency: High -Continuity: Continuous	-Social activity
Apple Watch Series 4[a] [50-52]	Smartwatch	iOS	-Operation: Passive -Data Transfer: Active	-Frequency: High -Continuity: Continuous	-Heart rate -Fall detection -Physical activity -Sleep
BACtrack Skyn [53, 54]	Wrist Worn Wearable	iOS	-Operation: Passive -Data Transfer: Passive	-Frequency: Moderate -Continuity: Continuous	-Skin temperature -Transdermal alcohol concentration
BrainCheck[a] [55, 56]	Smartphone Application	iOS	-Operation: Active -Data Transfer: Passive	-Frequency: Low -Continuity: Intermittent	-Cognition
BiAffect [57, 58]	Smartphone Application	iOS & Android	-Operation: Passive -Data Transfer: Passive	-Frequency: High -Continuity: Continuous	-Cognition -Mood -Neuropsychiatric symptoms
Centrepoint Insight by ActiGraph[a,d]	Smartwatch	iOS & Android	-Operation: Passive -Data Transfer: Passive	-Frequency: High -Continuity: Continuous	-Metabolic rate -Physical activity -Sleep
Delta Cognitive Testing App[a]	Smartphone Application	iOS	-Operation: Active -Data Transfer: Passive	-Frequency: Low -Continuity: Intermittent	-Cognition -Speech/Language
E4 [59-61]	Smartwatch	iOS & Android	-Operation: Passive -Data Transfer: Passive	-Frequency: High -Continuity: Continuous	-Skin temperature -Electrodermal activity -Heart rate variability -Physical activity -Blood volume pulse
EmbracePlus [61]	Smartwatch	iOS & Android	-Operation: Passive -Data Transfer: Passive	-Frequency: High -Continuity: Continuous	-Blood volume pulse -Electrodermal activity -Heart rate variability -Inter-beat interval -Physical activity -Skin temperature
Fitbit [62, 63]	Smartwatch	iOS & Android	-Operation: Passive -Data Transfer: Active	-Frequency: High -Continuity: Continuous	-Calorie expenditure -GPS -Heart rate -Physical activity -Sleep
Garmin vivosmart [64, 65]	Smartwatch	iOS & Android	-Operation: Passive -Data Transfer: Passive	-Frequency: High -Continuity: Continuous	-Blood oxygen saturation -GPS -Heart rate variability -Physical activity

					-Sleep
GPS Logger [66]	Smartphone Application	Android	-Operation: Passive -Data Transfer: Active	-Frequency: Customizable -Continuity: Continuous	-GPS/navigation
KardiaMobile 6L[a] [67]	Smartphone Application	iOS & Android	-Operation: Active -Data Transfer: Passive	-Frequency: Low -Continuity: Intermittent	-6-Lead Electrocardiography
Mezurio [68]	Smartphone Application	iOS & Android	-Operation: Active -Data Transfer: Passive	-Frequency: High -Continuity: Intermittent	-Cognition -Fine motor control -Speech analysis
mindLAMP [69]	Smartphone Application	iOS & Android	-Operation: Active & Passive -Data Transfer: Passive	-Frequency: Low -Continuity: Intermittent	-EMA -Cognition -Phone sensor data
myTracks [66]	Smartphone Application	iOS	-Operation: Passive -Data Transfer: Passive	-Frequency: Customizable -Continuity: Continuous	-GPS/navigation
NeuroUX[d] [70]	Weblink to Smartphones	iOS & Android	-Operation: Active -Data Transfer: Passive	-Frequency: Low -Continuity: Intermittent	-Cognition -EMA -Integration with Fitbit -Well-being
Pillow Automatic Sleep Tracker[d]	Smartphone Application	iOS	-Operation: Passive -Data Transfer: Active	-Frequency: Moderate -Continuity: Intermittent	-Sleep

Note. Novel tools are released regularly and the presented list is not a comprehensive list of available tools; nor are they being promoted as we have not personally tested many of these tools. Interventions were not included as we are focused on digital assessment data for digital phenotyping.

[a]FDA-cleared or CE-certified

[b]ActiGraph GT9X can be worn on the wrist, waist, ankle, or thigh

[c]Heartrate measurement requires compatible Bluetooth Polar H7 or Polar H10 heart rate monitors

[d]This tool has not been validated in the current literature or has an ongoing validation study

Table 2. Literature review on the use of digital assessments among persons with HIV

Author/Year	Sample Size (*N*)	Study Location	Digital Assessment Method	Assessment Frequency
Anderson et al., 2016 [71]	39 PWH	Atlanta, Georgia	Novel Computerized Cognitive Assessment Device[e]	Once during study period
Campbell et al., 2020 [72]	67 PWH, 36 HIV-	San Diego, California	Mobile Color-Word Interference Test[a] and Mobile Verbal Learning Test[b]	Once/day for 14 days
Campbell et al., 2020 [73]	52 PWH, 32 HIV-	San Diego, California	ActiGraph GT9X Link[c]	Once/day for 5-14 days
Katzef et al., 2019 [74]	102 PWH, 112 HIV-	South Africa, Africa	Neuroscreen[d]	Once during study period
Moore et al., 2020 [22]	58 PWH, 32 HIV-	San Diego, California	Mobile Color-Word Interference Test[a]	Once/day for 14 days
Robbins et al., 2014 [37]	50 PWH	Manhattan, New York	Neuroscreen[d]	Once during study period
Robbins et al., 2018 [75]	102 PWH	South Africa, Africa	Neuroscreen[d]	Once during study period

Note. PWH = persons with HIV
[a]Mobile Color-Word Interference Test assesses the Stroop effect (i.e., cognitive inhibition)
[b]Mobile Verbal Learning Test assesses verbal learning
[c]ActiGraph GT9X Link contains an accelerometer, gyroscope, and magnetometer sensors
[d]Neuroscreen assesses processing speed, executive function, working memory, verbal learning and memory, and motor speed
[e]Novel Computerized Cognitive Assessment Device assesses processing speed, episodic memory, working memory, and executive function