Metabolic Brain Disease (2023) 38:1737–1747
https://doi.org/10.1007/s11011-022-01134-x

REVIEW ARTICLE

Remote monitoring of cognition in cirrhosis and encephalopathy: future opportunity and challenge

Adam P. Buckholz[1] · **Russell Rosenblatt**[1]

Received: 27 September 2022 / Accepted: 24 November 2022 / Published online: 12 December 2022

Abstract

Hepatic Encephalopathy (HE) is a critically important complication of chronic liver disease and portal hypertension, but especially in early covert stages remains underdiagnosed and a common cause of hospitalization and morbidity. Defined by often subtle neuropsychiatric changes, significant cognitive deficits have been extensively described. While traditional methods of assessment remain underutilized in practice and subject to significant confounding with other diseases, mobile technology has emerged as a potential future tool to provide simple and dynamic cognitive assessments. This review discusses the proliferation of cognitive assessment tools, describing possible applications in encephalopathy and the challenges such an implementation may face. There are significant potential advantages to assessing cognition in real time in order to aid early detection and intervention and provide a more realistic measurement of real-world function. Despite this, there are issues with reliability, privacy, applicability and more which must be addressed prior to wide proliferation and acceptance for clinical use. Regardless, the rapid uptake of mobile technology in healthcare is likely to have significant implications for the future management of encephalopathy and liver disease at large.

Keywords Encephalopathy · Portal hypertension · Remote monitoring · Mobile technology · Cognition · Liver disease

Introduction

Hepatic encephalopathy (HE) is an important cause of hospitalization, need for transplant, and death in those with chronic liver disease and cirrhosis. Additionally, it has a profound deleterious effect on patient wellbeing. Multiple prior studies have demonstrated the negative quality of life changes in HE including increased fall risk, caregiver burden, reduced employability, and reduced performance at tasks requiring concentration such as driving (Amodio et al. 2016). As a progressive, relapsing and remitting consequence of hepatic dysfunction and portal hypertension, HE is characterized by neuropsychiatric alterations with variable characteristics (Weissenborn 2019). One of the major manifestations of HE is altered cognition, which will be the focus of this review. Given the challenges of cognitive assessment in encephalopathy as well as the multiple factors that impact disease progression in HE, it's of considerable future interest to develop dynamic testing strategies. Herein we discuss the advances of remote monitoring of cognition in general and within HE specifically as well as potential applications in clinical practice and challenges therein.

Cognition in hepatic encephalopathy

Cognition in HE should be distinguished from consciousness, arousal, or psychiatric alterations. The classic West Haven criteria for grading of HE most readily assesses arousal and behavior in differentiating covert (stage 0 or 1) from overt (2–4) HE whereby a patient may progress to coma and death (Vilstrup et al. 2014). While there is significant interplay between arousal and cognition, the vast majority of HE in ambulatory medicine is covert encephalopathy (CHE), with no clear alterations in behavior or consciousness.

Cognition, which encompasses intellectual functions including thought, attention and intelligence as well as judgment and decision making, is altered at all grades of encephalopathy, with significant implications for patients

✉ Russell Rosenblatt
rur9017@med.cornell.edu

[1] NewYork-Presbyterian/Weill Cornell Medical College Division of Gastroenterology and Hepatology, New York, NY 10021, USA

with liver disease (Revlin 2013). The cognitive manifestations of liver disease have been described since Hippocrates (Amodio 2015) and remain a bedrock of disease assessment (Montagnese et al. 2022).

Attention, or vigilance, is a key component of cognition and has been repeatedly demonstrated to be diminished across the spectrum of HE (Weissenborn et al. 2001b) Both visual and auditory attention are diminished even in those with CHE, and functional studies of cerebral glucose metabolism demonstrate reduced utilization in those with encephalopathy (Lockwood et al. 2002). Attention deficits are captured by many of the currently utilized assessment tools in CHE, including the psychometric hepatic encephalopathy score (PHES), critical flicker frequency and Stroop (Felipo et al. 2012). Similarly, there is an ever-expanding body of research on the loss of fine motor skill and visuospatial abilities in progressive liver disease, as well as memory decline (Bahceci et al. 2005).

While historically considered reversible, the cognitive changes from recurrent episodes of HE or persistent covert encephalopathy (CHE) may be permanent in some patients even after transplantation or other reversal of portal hypertension. More recently, the chronic edema and oxidative stress of portal hypertension have been recognized to cause astrocyte senescence in those with HE preferentially (Görg et al. 2018). Senescence, or biological aging, is seen commonly in neurodegenerative diseases and correlates strongly with cerebral oxidative stress (Nagelhus et al. 2013). Such senescence may reduce synaptic potential in the brain, permanently reducing cognitive ability.

It is therefore of significant importance to identify cognitive changes early in order to prevent complications arising from altered cognition, such as vehicular accidents, and reverse the etiology. There has been great progress in the classification and management of overt HE. Despite this, we often fail to capture and intervene on subtle cognitive changes which, while not requiring hospitalization, may nonetheless cause detrimental effects in real time for far more patients than does overt disease. Adequate detection and early intervention are imperative to the future of liver disease care, and this review will focus on the potential for and challenges of remote cognitive assessment and monitoring in cirrhosis and encephalopathy.

Limitations of current cognitive assessment tools in HE

Given the importance of cognition for patient wellbeing, everyday functioning, and as a marker of progressive and potentially irreversible disease, there has been considerable focus on accurate measurement in cirrhosis. In fact, current HE guidelines suggest multimodal assessment of cognition via tests such as the Psychometric Hepatic Encephalopathy Score (PHES), Stroop, and critical flicker frequency. Despite the repeated validation of these tests, they are significantly underused in clinical practice. They are cumbersome, often unavailable outside of research settings, and, even when performed, are often misinterpreted. Additionally, these tests identify only altered cognition, without pointing to a precipitator and with significant risk of confounding (Amodio and Montagnese 2021).

Another significant weakness to in-office assessment of cognition is that it's widely accepted that cognition, and the ability to "think" more broadly, is dynamic. The PHES test must be performed under idealized conditions whereby patients are placed in a quiet room without distractions (Weissenborn et al. 2001a). This, however, is a poor simulation of the real world, and therefore fails to capture cognition in everyday life, where it is needed. Even under the same set of stressors, cognitive performance is not static throughout the day, as anyone who's had to accomplish a difficult task late in the evening can attest. Moreover, intraindividual cognitive ability, or the so-called noise that affects our cognition, may actually be prognostic of eventual permanent decline (Christensen et al. 2005). While understudied at this time, it would be no surprise if there was prognostic importance to intraindividual cognitive changes over the course of hepatic encephalopathy. A small study found that not only did those with minimal HE demonstrate reduced mean cognition when evaluated with the inhibitory control test (ICT), but they had increased intraindividual variability, especially when performing more complex tasks (Bisiacchi et al. 2014). As with all pen and paper studies, however, this variability was assessed in a laboratory setting, rather than in clinical practice much less real life.

Despite the many tools currently accepted to diagnose subtle cognitive changes in encephalopathy, they all suffer from lack of specificity and inter-test reliability. There is now ample literature describing the multitude of factors which can reduce cognition during any single assessment, including drugs (prescription and illicit), alcohol, concomitant neurological disease such as Alzheimer's or Parkinson's Disease, infection and electrolyte abnormalities. Likewise, mood disorders are common in cirrhosis and may cause similar findings to CHE without sharing a pathophysiologic basis or appropriate therapeutic direction. Whether these alterations are persistent or transient are poorly captured by a single test, and there may be significant discrepancy between test outcomes.

Emergence of mobile and wearable technology

Mobile technology has become ubiquitous in the developed world, with approximately 85% of Americans owning a phone with internet connectivity, often termed a

"smartphone" (Pew Research Center 2021). These devices, and others like them, have an almost constant bidirectional flow of data related to the consumer. Unsurprisingly, there has been keen interest in the applicability of mobile technology to healthcare, which now represents a greater than $90 billion annual industry globally (Lee and Lee 2020). Two major components of this expanding field are the use of smartphone-based applications and the use of wearable technology. Broadly speaking, wearable health technology is any mobile device which collects and integrates real time biometric or spatial data relating to the wearer (Rutherford 2010). The wide variety of commercial and research technologies are beyond the scope of this review, but several have reached the level of FDA approval (Steil et al. 2006) or clearance (Dhruva et al. 2021) for the diagnosis of medical conditions. Likewise, given that nearly all age ranges in the developed world use smartphone applications on a daily basis (Parasuraman et al. 2017), many health researchers have sought to develop applications specifically for the prevention, detection and monitoring of disease.

High frequency data collection in the setting of healthcare has the potential to produce a digital phenotype with dynamic information collected in a variety of settings and under true-to-life conditions (Torous et al. 2016). Such phenotypes are highly related to the fundamental goal of precision medicine, whereby diagnosis and management of medical conditions are derived from "n of 1" patient-centric data. Continuous monitoring leading to precision management strategies is highly attractive for its potential in cognition and cirrhosis (Fig. 1).

Applications of remote cognitive assessment in patients without cirrhosis

There has been some research into the use of mobile technology as a real-world test of a patient's status. Termed "ecological momentary assessment" (EMA), it relies on data collection as patients undergo their daily activities (ecological), in any given state (momentary). Such random assessments would provide not only a better understanding of average mental state, but also their variations in state (Sliwinski et al. 2018). Small studies have used EMA designs to evaluate ambulatory cognition as it relates to outcomes or disease states. In one, an ambulatory memory test with an aggregated cognitive score was more sensitive than laboratory testing for reduced hippocampal volume in pre-clinical Alzheimer's (Allard et al. 2014). The Stroop test, which has also been used in an ambulatory setting in cirrhosis, was found to be potentially useful in recovering addicts, with elevated attention bias predicting relapse events (Marhe et al. 2013). By using Stroop, the researchers were able to infer the participants' implicit cognitive state, increasing objectivity over subjective assessments of "focus" as relates to craving and likelihood of pending recidivism.

Research into mobile applications to assess attention, an important domain of cognition, has also proliferated in recent years, especially in aging and after traumatic brain injury. The FDA has cleared the Immediate Post-Concussion Assessment and Cognitive Test Quick Test (ImPACT QT) for assessment of cognitive functioning after concussion (Wallace et al. 2020). Using visual prompts and including modules such as reverse number counting, the approximately 5-min test allows athletes to test cognitive performance against established baselines. An additional FDA cleared device, the SWAY System (SWAY Medical Inc., Tulsa, OK) was developed to leverage cognitive testing (reaction time, impulse control and inspection time) combined with balance and physical reaction times using the embedded tri-axial accelerometers within mobile devices (Burghart et al. 2019).

Finally, mobile and wearable technology may be able to improve disease outcomes by fundamentally altering patient behavior. This has been termed "automated hovering", and constitutes a significant new horizon for healthcare intervention (Asch et al. 2012) given that a significant majority of patient decisions are made without direct input from a clinician. For example, in one pilot randomized study, a wearable fitness tracker that provided real time biometric data and feedback increased activity and reduced sedentary time in a group at risk for cardiovascular disease (Roberts et al. 2019). Such interventions rely on the control theory, whereby a discrepancy between desired and observed performance leads to both conscious and unconscious behavioral alteration (Hermsen et al. 2016). While the long-term durability of such interventions remains to be determined, the concept is nonetheless appealing, especially given the limited relative time available for direct healthcare interaction with patients.

Current and future uses of mobile technology in cirrhosis

Biometric data is of critical importance in chronic liver disease and cirrhosis. Guidelines for the prevention of variceal bleeding recommend close titration of resting heart rate with blood pressure. Reduced mobility may represent progressive frailty, worsening ascites, or progression of encephalopathy. Likewise, fractured sleep may signal CHE or any of the mood disorders known to be intrinsic to liver disease. Because of the multitude of physiologic changes seen in cirrhosis, there are ample potential applications for mobile technology in liver disease (Fig. 2).

Given the approximately 50% readmission rate for patients with cirrhosis discharged from the hospital, and the outsized proportion of these for encephalopathy, it is clear that current outpatient monitoring strategies are inadequate

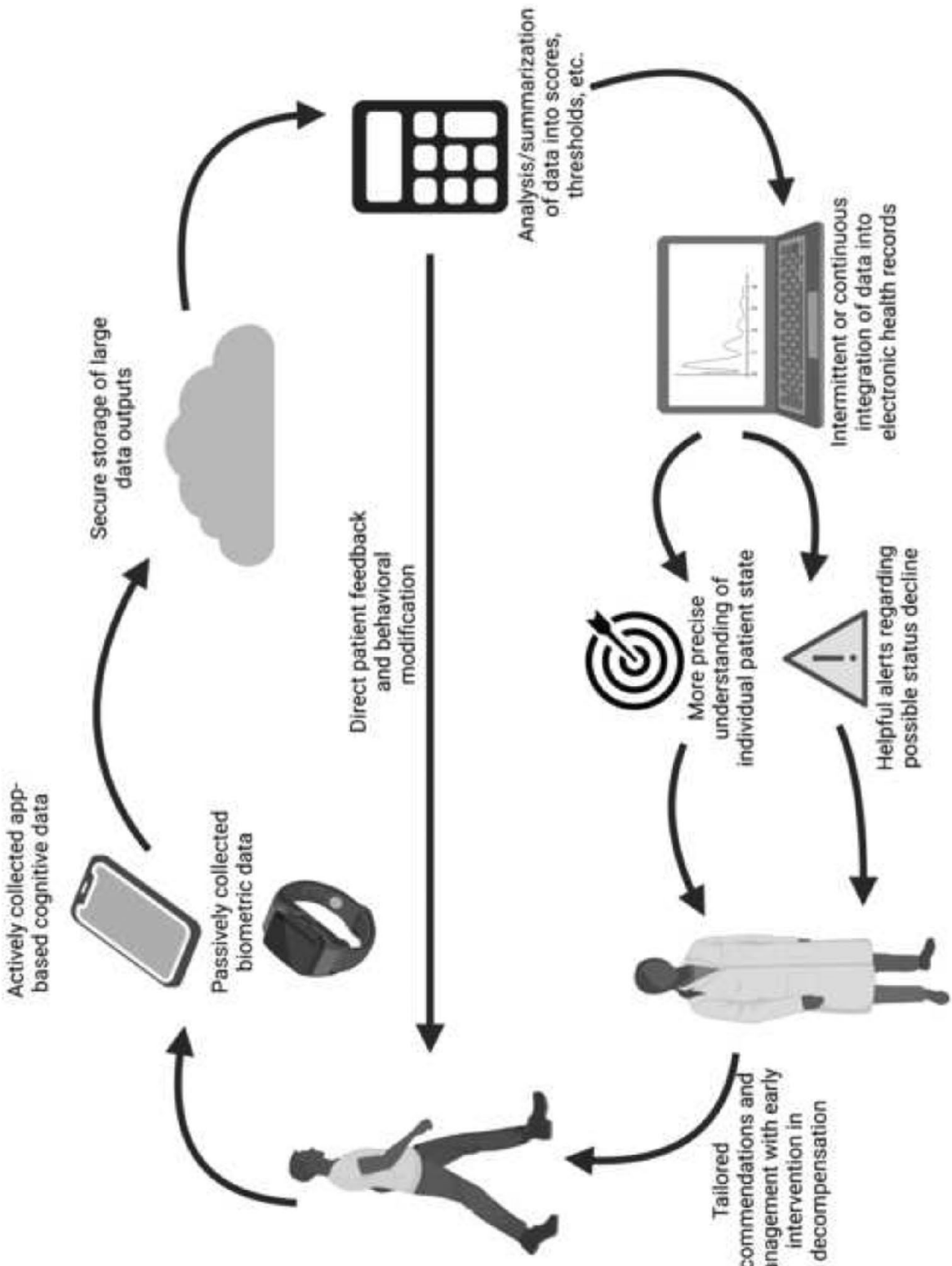

Fig. 1 Hypothetical use of a mobile health platform for cognitive assessment in cirrhosis, leveraging technology to better diagnose and manage encephalopathy. Created with Biorender.com

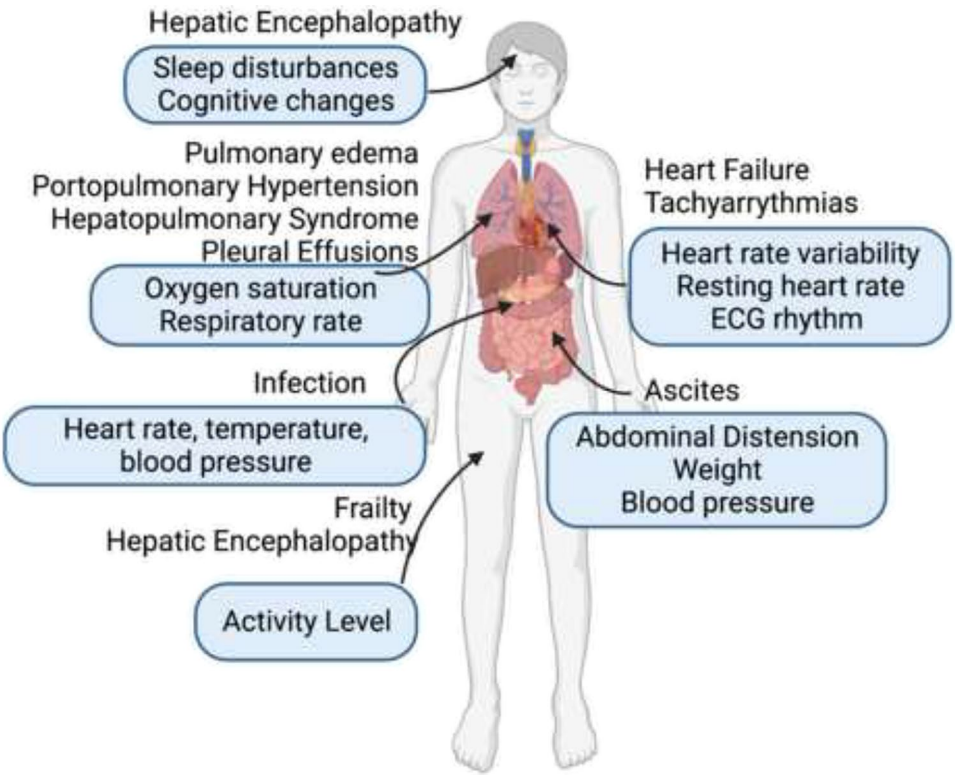

Fig. 2 Potential applications of mobile and wearable technology to detect various complications of cirrhosis

(Bajaj et al. 2016). In one study, patients with HE had a more than fourfold increased risk of 30-day readmission relative to those without (Sood and Wong 2019), and encephalopathy is responsible for up to one third of readmissions in patient with cirrhosis (Gaspar et al. 2019). Reasons for readmission are beyond the scope of this review, but may include medication non-adherence, infection, or lack of close follow up. Despite the high risk of many preventable causes of rehospitalization, there are no widely accepted tools to monitor at risk patients and prevent emergent readmission. Overall, the literature regarding mobile health and remote monitoring in cirrhosis remains relatively sparse (Fig. 3).

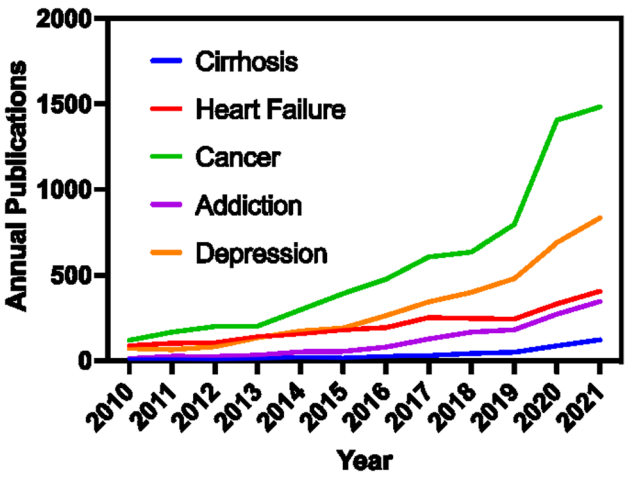

Fig. 3 Annual publications found in a pubmed.gov search for studies pertaining to "mobile health" and "remote monitoring" by disease state. While disease prevalence plays a role, cirrhosis continues to lag behind other diseases in proliferation of mobile technology

Several attempts have already been made to assess cognition using mobile technology. Most notably, the Stroop test has been converted into mobile format in the EncephalApp, which has been broadly validated for the detection of CHE. More recently, a short form of EncephalApp, named Quick-Stroop, has shown promise for detection of CHE with only one minute of patient engagement – making it a more practical test to be used in clinical practice (Acharya et al. 2022). Many other traditional pen/paper based neuropsychological assessments have been converted into computerized versions outside of the scope of cirrhosis. For cognitive impairment related to possible early Alzheimer's disease, one systematic review identified no less than 36 smartphone applications available for assessing attention, memory, executive function and/or visual special abilities (Charalambous et al. 2020). Some are simply conversions of previously published psychometric evaluations, such as the BrainTest, which is based on the Self-administered Gerocognitive Examination (SAGE) (Scharre et al. 2010). In many cases, the application publishers also include normative and validation data (Scharre et al. 2017).

Verbal fluency is another cognitive domain known to be negatively affected by encephalopathy (Randolph et al. 2009). Recent studies have validated use of simple fluency tests such as the Animal Naming Test for diagnosis of CHE

(Campagna et al. 2017). Such a test is simple, requires very little training to perform, and could be performed reasonably easily as a dynamic, mobile cognitive assessment (Moore et al. 2022). Further research has demonstrated slow speech in those with HE (Bloom et al. 2021), and while such technologies have yet to be assessed in cirrhosis, there are mobile applications being researched for real time assessment of fluency and speech rate (Aharonson et al. 2017). Several other mobile applications have been built to assess fluency and phonation for disease states such as Parkinson's Disease (Byrom et al. 2018a).

Wearable technology may also be a useful tool in dynamic assessment of cognitive state in HE. Electroencephalogram (EEG) alterations have been demonstrated to correlate to encephalopathy grades, but laboratory-based testing is too cumbersome for routine clinical use (Amodio et al. 2006). While it may never be feasible for long term ambulatory monitoring, so called "dry" lead EEG technology has been demonstrated to provide adequate approximation of real time neural activity (Hinrichs et al. 2020), potentially increasing its utility in encephalopathy. Dry lead EEG, which does not require specially applied, messy, and cumbersome gel for electrode placement, has rapidly increased interest in EEG technology for rapid cognitive assessment (Pei et al. 2018). For example, one study evaluating a dry lead EEG against established EEG technologies found comparable or even improved performance for cognitive assessment with visual evoked potentials (Hinrichs et al. 2020).

Use of remote assessment for positive interventions in cirrhosis

Another potential application of mobile cognitive tools in cirrhosis is to seek active cognitive improvement. Several commercially available applications have been extensively developed and marketed, including but not limited to Lumosity, Elevate Brain Training and NeuroNation. Interestingly, NeuroNation is now reimbursed by the national German health insurance (Byrom et al. 2018a). In another study, online cognitive training improved processing speed and cognitive flexibility in breast cancer survivors suffering from cognitive impairment after chemotherapy (Kesler et al. 2013). Such games have already been demonstrated to identify some of the same cognitive impairments as traditional tests for CHE (Tartaglione et al. 2014). While as yet no study has evaluated cognitive training in cirrhosis, future research could identify an important benefit.

Remote monitoring also has the potential to further elucidate the relationship between intraindividual cognitive variability and outcomes in encephalopathy. There is a known continuous decline in performance in neurocognitive assessment as encephalopathy progresses from covert to overt. Declining activity levels and changes in biometrics such as body temperature and heart rate could be combined with dynamic assessment of cognition to signal an impending overt episode, potentially initiating therapy prior to disease progression. Given the known amount of noise in a single assessment, it's important to better understand how variation from baseline and throughout the day may be correlating to a change in disease state. Such an assessment is possible only with mobile technology.

Similarly, it can potentially improve our understanding of how other determinants of cognition relate to function in HE, allowing targeted interventions. For example, circadian rhythm disruption and sleepiness are known to impact concentration and working memory (Manly et al. 2002), and those with HE have repeatedly been demonstrated to have disruptions in sleep architecture and quality (Labenz et al. 2018). Sleep measurement is a ubiquitous feature of many commercially available wearable technologies, and several publications have suggested that such measurements reasonably approximate four stage sleep detection with gold standard polysomnography (Chinoy et al. 2021; Miller et al. 2021). Passively collected sleep data serves as just one example of how mobile technology could help researchers and clinicians better understand the course of encephalopathy. Sleep is also an example of how clinicians could impact outcomes in encephalopathy through wearable technology. If it becomes clear, for example, that consistent bed and wake times are preferrable for those with CHE, a clinician could "prescribe" a certain time, and then rely on control theory and passive feedback to encourage patient adherence.

Challenges for implementation of remote monitoring of cognition

In a multi-disciplinary perspective paper following a workshop organized by the NIH's Big Data to Knowledge Centers of Excellence, the workshop participants outlined several tenets to implementing successful digital health programs, adapted in Table 1 below (Smuck et al. 2021). Full integration of such a program for cognition in cirrhosis is out of scope in this review, but several factors are worth considering for the challenges they may pose.

In order to be successfully implemented, the mobile health technology must be capable of performing its prescribed task. In the case of HE, this means assessing whether remote cognitive assessment outperforms, or at least approximates, the current testing practices. Test performance itself can be judged by many metrics, but key among them is discriminatory ability for the diagnosis of interest. This is often weighted against an accepted gold standard, which may or may not be an appropriate metric. Validation of mobile technology for

Table 1 Challenges and recommendations for successful implementation of digital health programs. Adapted from Smuck et al 2021 and derived from a multidisciplinary NIH Big Data Workshop and subsequent position paper

Clearly Defined Problem and Disease State
Integrated System of Healthcare Delivery
Technology support and service
Personalized Experience
Enhanced End User Experience
Aligned Payment and Reimbursement Models
Clinical Champions and Stakeholder Support

determining health indicators and outcomes is inevitable, with over 900 trials currently registered just within the United States at clinicaltrials.gov (Mitsi et al. 2022). Regulatory considerations are unlikely to be a significant barrier to accessing cognitive assessment tools, as most are likely to be classified as minimal potential for harm and clearable through an expedited 510(k) pathway in the United States or similar in the European Union and Canada (Byrom et al. 2018b).

Generally speaking, the practical validity of a clinical tool should follow the "three V's" of validation, including verification, analytical validity, and clinical validity (Goldsack et al. 2020). Verification evaluates the actual tool/sensor performance itself, insofar that it consistently generates an accurate reading of its intended biomarker. This could be acceleration, temperature, or attention and should be performed by the technology manufacturer, with published results available for clinicians and researchers. Analytical validation requires testing in human subjects to evaluate performance of the sensor for converting raw collected data into a meaningful metric (Witt et al. 2019). For example, validation may be performed to show that motion and accelerometry data can actually interpret gait velocity, or that temperature change, heart rate and motion can identify sleep duration. These should be tested against reference standards, for example polysomnography for sleep. Importantly, this analytical validation needs to be performed in each population of interest, and as companies are unlikely to expand their own validation studies beyond healthy volunteers, much of the burden will fall on clinicians and researchers. Finally, clinical validation applies an analytically valid tool to achieve a clinically meaningful endpoint. That endpoint could be whether ambulatory measurement of blood pressure impacts mortality, for example (Banegas et al. 2018). In the case of cognitive monitoring in HE, clinical validity may be whether an ambulatory assessment program reduces hospitalization for overt HE. As yet, there are no passive or active remote cognitive monitoring tools that have been clinically validated in cirrhosis.

Additionally, it's important that the technology be applied in a clearly defined patient population, a clearly defined disease state, and preferably clearly defined thresholds for action. One potential diagnosis sought by remote monitoring is the cognitive decline when patients transition from a covert or latent encephalopathy to an overt form requiring immediate medical attention, believed to be at an approximately 20% rate annually. In one pilot study, the Patient Buddy App was evaluated in a cirrhosis-specific context in an attempt to close some of this gap. The App was developed to improve provider and patient/caregiver communication across healthcare, and in this study its capabilities were enhanced by including simultaneous weekly use of EncephalApp and orientation questions, to be entered into the Buddy App. Likewise, the study team received alerts if patients were non-adherent to medications or failed to monitor sodium intake. In their short pilot study, the researchers identified 8 HE-related admissions (from 40 enrolled participants) which had been likely avoided by in app communication after assessments or alerts (Ganapathy et al. 2017). Overall, the app was well received but admission rates overall were similar to those previously published and overall usage and adherence was moderate at best. An illustrative example was recently published using mobile technology for ascites management (Bloom et al. 2020). In their study, they a weight increase of > 5 pounds over one week automatically triggered an email alert to providers, with high adherence on both the provider and patient side, and more than half of the alerts eliciting an intervention.

A common challenge when considering mobile or wearable technology is its reliability, whether within the device itself or in comparison with another. It's worth noting, however, that even presently accepted tools for measuring cognition are unreliable in some ways. Significant discordance between tests such as EncephalApp and PHES have been previously published (Duarte-Rojo et al. 2019). While it has not been significantly discussed in publication, it is unclear whether true technological reliability will be a limiting factor in implementing remote monitoring platforms.

An effective cognitive monitoring tool in encephalopathy will retain patient engagement, which will likely prove challenging. In one study evaluating mobile device proficiency in cirrhosis, 84.6% owned mobile devices and 61.5% were interested in personalized mobile health management programs (Ismond et al. 2021). The researchers found similar technical proficiency among those with cirrhosis compared to the general population. Interestingly, a history of HE was not associated with worse technical proficiency, but formal cognitive assessment was not performed in that study. Regardless, given the known sociodemographic challenges facing those with liver disease, a cognitive monitoring tool has the potential to widen the already present gap in outcomes based on access to technology and health

literacy (Reiners et al. 2019). Unfortunately, few studies have attempted to evaluate real world usage of cognitive monitoring in encephalopathy. In one prospective study, patients with cirrhosis were evaluated for usage of EncephalApp longitudinally, but only 32% actually completed a run of EncephalApp despite most expressing interest on enrollment (Louissant et al. 2020). There were multiple reasons cited for failure to complete, including technical difficulties, forgetting to use it, and recurrent admission. One recently presented study found that passively collected sleep data using commercially available wearable technology had higher (71.4%) participant adherence over a 6-month period (Buckholz et al. 2022), suggesting that perhaps passive data collection could improve some test performance. One solution posited by the Smuck et al. position paper was to incorporate "Apple genius bar" style technical support whereby trained staff members incorporate physician recommendations to assist patients in setting up and delivering appropriate data back to the physician. Passive data collection would require validation of indirect markers of cognition which has as yet not been performed. In a non-cirrhotic population, passively collected interactions with smart phones were strongly correlated with outcomes of neurocognitive testing (Dagum 2018).

Overall, it seems likely that increased points of contact for patients with healthcare, even digital healthcare, are likely to improve outcomes. A study conducted by the Oshsner health system found that blood pressure data collected at home with a loop feedback approach to a treating physician helped 71% of patients reach target blood pressure, compared to 31% with usual care (Milani et al. 2017). One potential barrier, however, is uptake by gastroenterologists. In comparison with other specialties, the providers most responsible for the management of patients with chronic liver disease are among the least likely to use telemedicine and mobile health technology. In one study, only 7.9% of gastroenterologists used telemedicine, the lowest of any specialty, albeit the study was conducted prior to the COVID-19 pandemic, so usage is undoubtedly higher in the present day (Kane and Gillis 2018). Overall, the COVID-19 pandemic has increased comfort level among both patients and providers with remote health technology, and payer models are adjusting to the new health landscape. For example, the Centers for Medicare and Medicaid Services in 2018 incorporated Current Procedural Terminology (CPT) code 99,091, which allows billing for physiologic and patient-generated digital health information (Smuck et al. 2021). Mobile technology applied appropriately may also reduce caregiver and physician burden, which is a major concern in the management of encephalopathy. A study performed in the Kaiser Permanente health system noted that electronic management of diabetes medication improved glycemic control and reduced direct physician workload by 35% (Zhou et al. 2017).

In order to achieve broad physician acceptance and patient benefit for a mobile health program, there must be efficient integration of the data into the electronic health record (EHR). It is likely unrealistic that healthcare providers will actively monitor all of the vast number of data points generated with mobile technology, and equally unrealistic that patients themselves can or would sift through to find meaningful metrics. By one estimate, over 400 wearables already have the ability to integrate into EHRs, but such a significant amount of data can overwhelm health system storage capacity (Kalid et al. 2017) and induce provider fatigue (Ramirez et al. 2018). Artificial technology may be a potential solution in the future, but such usage is in its infancy (Dinh-Le et al. 2019). This problem reiterates the need to have clearly defined thresholds for "alert" states and clearly outline mutual goals and recommendations with physicians and patients.

A final challenge regards the privacy concerns with using often proprietary mobile technology for patient care. The relative lack of regulatory oversight means that mobile health data faces significant transmission and storage concerns across healthcare. In one study by the United Kingdom's Health service, 66% of apps that were categorized as "trusted" for clinical use were transmitting data that was not properly encrypted, while 20% did not have any privacy policy at all (Huckvale et al. 2015). Moreover, the proliferation of entrepreneurially focused apps has the potential to create data silos (Mamlin and Tierney 2016), whereby there are so many different mobile applications that it's unrealistic to expect clinicians to understand privacy and safety policies for each. Similarly, many mobile health companies do not publicize proprietary algorithms used to obtain or interpret health biometrics, deepening distrust between researchers, clinicians and mobile health companies (Depner et al. 2020). To adequately integrate a mobile cognitive assessment platform in cirrhosis, improved transparency and strict data management strategies will need to crucial.

Conclusion

Hepatic encephalopathy remains a devastating complication of chronic liver disease, responsible for considerable morbidity and healthcare expenditure. Because the vast majority of HE is covert, cognitive assessment is a critical component of disease identification and management. However, current assessment tools are cumbersome and underutilized in clinical practice, and capture only an isolated and idealized moment in a patient's course. It's well understood that cognition is dynamic and changes can occur due to myriad factors. From both a research and clinical care standpoint, the proliferation of mobile healthcare may offer new insight into cognition in HE. While many mobile cognitive tools have been

developed, tested, and marketed, there has yet to be significant penetration within HE. While many questions remain as to how such tools can be validated and leveraged in cirrhosis, it's important that researchers embrace the challenge in order to modernize and improve cognitive assessment. Certainly, all advances within mobile health and wearable technology should be met with appropriate levels of scrutiny and caution until they're effectively validated. There is considerable research needed at all levels prior to true clinical implementation of such tools. Despite this, entrepreneurs, patients, healthcare providers, insurance companies and even government entities understand that mobile health will only continue to grow, and failing to capitalize on that growth within HE would represent a significant opportunity lost.

Author's contributions All authors contributed to the writing and editing of this review. The first draft was written primarily by Dr. Buckholz with conceptual and editing input from Dr. Rosenblatt.

Data availability Not applicable

Code availability Not applicable

Declarations

Ethics approval Not applicable

Consent to participate Not applicable

Consent for publication Not applicable

Conflicting/Competing interests The authors have no relevant financial or non-financial interests to disclose.

References

Acharya C, Shaw J, Duong N et al (2022) QuickStroop, a shortened version of encephalapp, detects covert hepatic encephalopathy with similar accuracy within one minute. Clin Gastroenterol Hepatol. https://doi.org/10.1016/J.CGH.2021.12.047

Aharonson V, Aharonson E, Raichlin-Levi K et al (2017) A real-time phoneme counting algorithm and application for speech rate monitoring. J Fluency Disord 51:60–68. https://doi.org/10.1016/J.JFLUDIS.2017.01.001

Allard M, Husky M, Catheline GL et al (2014) Mobile technologies in the early detection of cognitive decline. PLoS One 9. https://doi.org/10.1371/JOURNAL.PONE.0112197

Amodio P (2015) Hepatic encephalopathy: historical remarks. J Clin Exp Hepatol 5:S4. https://doi.org/10.1016/J.JCEH.2014.12.005

Amodio P, Montagnese S (2021) Lights and shadows in hepatic encephalopathy diagnosis. J Clin Med 10:1–10. https://doi.org/10.3390/JCM10020341

Amodio P, Pellegrini A, Ubiali E et al (2006) The EEG assessment of low-grade hepatic encephalopathy: comparison of an artificial neural network-expert system (ANNES) based evaluation with visual EEG readings and EEG spectral analysis. Clin Neurophysiol 117:2243–2251. https://doi.org/10.1016/J.CLINPH.2006.06.714

Amodio P, Montagnese S, Mullen K et al (2016) Where are we going? Translational research in hepatic encephalopathy. https://doi.org/10.1007/s11011-015-9728-3

Asch DA, Muller RW, Volpp KG (2012) Automated hovering in health care–watching over the 5000 hours. N Engl J Med 367:1–3. https://doi.org/10.1056/NEJMP1203869

Bahceci F, Yildirim B, Karincaoglu M et al (2005) Memory impairment in patients with cirrhosis. J Natl Med Assoc 97:213

Bajaj JS, Reddy KR, Tandon P et al (2016) The three-month readmission rate remains unacceptably high in a large north american cohort of cirrhotic patients. Hepatology 64:200. https://doi.org/10.1002/HEP.28414

Banegas JR, Ruilope LM, de la Sierra A et al (2018) Relationship between clinic and ambulatory blood-pressure measurements and mortality. N Engl J Med 378:1509–1520. https://doi.org/10.1056/NEJMOA1712231/SUPPL_FILE/NEJMOA1712231_DISCLOSURES.PDF

Bisiacchi P, Cona G, Tarantino V et al (2014) Assessing inter- and intra-individual cognitive variability in patients at risk for cognitive impairment: the case of minimal hepatic encephalopathy. Metab Brain Dis 29:945–953. https://doi.org/10.1007/S11011-014-9529-0

Bloom PP, Robin J, Xu M et al (2021) Hepatic encephalopathy is associated with slow speech on objective assessment. Am J Gastroenterol 116:1950–1953. https://doi.org/10.14309/AJG.0000000000001351

Bloom P, Wang T, Marx M et al (2020) A smartphone app to manage cirrhotic ascites among outpatients: feasibility study. JMIR Med Inform 8(9):e17770. https://doi.org/10.2196/17770; https://medinform.jmir.org/2020/9/e177708:e17770. Accessed Sept 2022

Buckholz A, Clarke LM, Paik P et al (2022) Sa1454: longitudinal monitoring of sleep in covert hepatic encephalopathy reveals significant fracturing and loss of rem. Gastroenterology 162:S-1174

Burghart M, Craig J, Radel J, Huisinga J (2019) Reliability and validity of a motion-based reaction time assessment using a mobile device. Appl Neuropsychol Adult 26:558. https://doi.org/10.1080/23279095.2018.1469491

Byrom B, McCarthy M, Schueler P, Muehlhausen W (2018a) Brain monitoring devices in neuroscience clinical research: the potential of remote monitoring using sensors, wearables, and mobile devices. Clin Pharmacol Ther 104:59. https://doi.org/10.1002/CPT.1077

Byrom B, Watson C, Doll H et al (2018b) Selection of and evidentiary considerations for wearable devices and their measurements for use in regulatory decision making: recommendations from the epro consortium. Value in Health 21:631–639. https://doi.org/10.1016/j.jval.2017.09.012

Campagna F, Montagnese S, Ridola L et al (2017) The animal naming test: An easy tool for the assessment of hepatic encephalopathy. Hepatology 66:198–208. https://doi.org/10.1002/HEP.29146/SUPPINFO

Charalambous AP, Pye A, Yeung WK et al (2020) Tools for app- and web-based self-testing of cognitive impairment: systematic search and evaluation. J Med Internet Res 22. https://doi.org/10.2196/14551

Chinoy ED, Cuellar JA, Huwa KE et al (2021) Performance of seven consumer sleep-tracking devices compared with polysomnography. Sleep 44. https://doi.org/10.1093/SLEEP/ZSAA291

Christensen H, Dear KBG, Anstey KJ et al (2005) Within-occasion intraindividual variability and preclinical diagnostic status: is intraindividual variability an indicator of mild cognitive impairment? Neuropsychology 19:309–317. https://doi.org/10.1037/0894-4105.19.3.309

Dagum P (2018) Digital biomarkers of cognitive function. npj Digital Medicine 1:1. https://doi.org/10.1038/s41746-018-0018-4 (1:1–3)
Depner CM, Cheng PC, Devine JK et al (2020) Wearable technologies for developing sleep and circadian biomarkers: a summary of workshop discussions. Sleep 43. https://doi.org/10.1093/SLEEP/ZSZ254
Dhruva SS, Shah ND, Vemulapalli S et al (2021) Heart watch study: protocol for a pragmatic randomised controlled trial. BMJ Open 11. https://doi.org/10.1136/BMJOPEN-2021-054550
Dinh-Le C, Chuang R, Chokshi S, Mann D (2019) Wearable health technology and electronic health record integration: scoping review and future directions. JMIR Mhealth Uhealth 7. https://doi.org/10.2196/12861
Duarte-Rojo A, Allampati S, Thacker LR et al (2019) Diagnosis of covert hepatic encephalopathy: a multi-center study testing the utility of single versus combined testing. Metab Brain Dis 34:289. https://doi.org/10.1007/S11011-018-0350-Z
Felipo V, Ordoño JF, Urios A et al (2012) Patients with minimal hepatic encephalopathy show impaired mismatch negativity correlating with reduced performance in attention tests. Hepatology 55:530–539. https://doi.org/10.1002/HEP.24704
Ganapathy D, Acharya C, Lachar J et al (2017) The patient buddy app can potentially prevent hepatic encephalopathy-related readmissions. Liver Int 37:1843–1851. https://doi.org/10.1111/LIV.13494
Gaspar R, Rodrigues S, Silva M et al (2019) Predictive models of mortality and hospital readmission of patients with decompensated liver cirrhosis. Dig Liver Dis 51:1423–1429. https://doi.org/10.1016/J.DLD.2019.03.016
Goldsack JC, Coravos A, Bakker JP et al (2020) Verification, analytical validation, and clinical validation (V3): the foundation of determining fit-for-purpose for Biometric Monitoring Technologies (BioMeTs). npj Digital Med 3:1. https://doi.org/10.1038/s41746-020-0260-4 (3:1–15)
Görg B, Karababa A, Häussinger D (2018) Hepatic encephalopathy and astrocyte senescence. J Clin Exp Hepatol 8:294. https://doi.org/10.1016/J.JCEH.2018.05.003
Hermsen S, Frost J, Renes RJ, Kerkhof P (2016) Using feedback through digital technology to disrupt and change habitual behavior: A critical review of current literature. Comput Human Behav 57:61–74. https://doi.org/10.1016/J.CHB.2015.12.023
Hinrichs H, Scholz M, Baum AK et al (2020) Comparison between a wireless dry electrode EEG system with a conventional wired wet electrode EEG system for clinical applications. Sci Rep 10:1. https://doi.org/10.1038/s41598-020-62154-0 (10:1–14)
Huckvale K, Prieto JT, Tilney M et al (2015) Unaddressed privacy risks in accredited health and wellness apps: a cross-sectional systematic assessment. BMC Med 13:EE. https://doi.org/10.1186/S12916-015-0444-Y
Ismond KP, Eslamparast T, Farhat K et al (2021) Assessing patient proficiency with internet-connected technology and their preferences for e-health in cirrhosis. J Med Syst 45:3. https://doi.org/10.1007/S10916-021-01746-3
Kalid N, Zaidan AA, Zaidan BB et al (2017) Based real time remote health monitoring systems: a review on patients prioritization and related "big data" using body sensors information and communication technology. J Med Syst 42. https://doi.org/10.1007/S10916-017-0883-4
Kane CK, Gillis K (2018) The use of telemedicine by physicians: still the exception rather than the rule. Health Aff (millwood) 37:1923–1930. https://doi.org/10.1377/HLTHAFF.2018.05077
Kesler S, Hadi Hosseini SM, Heckler C et al (2013) Cognitive training for improving executive function in chemotherapy-treated breast cancer survivors. Clin Breast Cancer 13:299. https://doi.org/10.1016/J.CLBC.2013.02.004
Labenz C, Baron JS, Toenges G et al (2018) Prospective evaluation of the impact of covert hepatic encephalopathy on quality of life and sleep in cirrhotic patients. Aliment Pharmacol Ther. https://doi.org/10.1111/apt.14824
Lee SM, Lee DH (2020) Healthcare wearable devices: an analysis of key factors for continuous use intention. Serv Bus 14:503. https://doi.org/10.1007/S11628-020-00428-3
Lockwood AH, Weissenborn K, Bokemeyer M et al (2002) Correlations between cerebral glucose metabolism and neuropsychological test performance in nonalcoholic cirrhotics. Metab Brain Dis 17:29–40. https://doi.org/10.1023/A:1014000313824
Louissant J, Lok A, Fortune BTE (2020) Acceptance and use of a smartphone application in cirrhosis. Liver International
Mamlin BW, Tierney WM (2016) The promise of information and communication technology in healthcare: extracting value from the chaos. Am J Med Sci 351:59–68. https://doi.org/10.1016/J.AMJMS.2015.10.015
Manly T, Lewis GH, Robertson IH et al (2002) Coffee in the cornflakes: time-of-day as a modulator of executive response control. Neuropsychologia 40:1–6. https://doi.org/10.1016/S0028-3932(01)00086-0
Marhe R, Waters AJ, van de Wetering BJM, Franken IHA (2013) Implicit and explicit drug-related cognitions during detoxification treatment are associated with drug relapse: an ecological momentary assessment study. J Consult Clin Psychol 81:1. https://doi.org/10.1037/A0030754
Milani Rv, Lavie CJ, Bober RM et al (2017) Improving hypertension control and patient engagement using digital tools. Am J Med 130:14–20. https://doi.org/10.1016/j.amjmed.2016.07.029
Miller DJ, Roach GD, Lastella M et al (2021) A validation study of a commercial wearable device to automatically detect and estimate sleep. Biosensors 11:185. https://doi.org/10.3390/BIOS11060185
Mitsi G, Grinnell T, Giordano S et al (2022) Implementing digital technologies in clinical trials: lessons learned. Innov Clin Neurosci 19:65
Montagnese S, Romero Gómez M, Larsen FS et al (2022) EASL clinical practice guidelines on the management of hepatic encephalopathy. J Hepatol 77:807–824. https://doi.org/10.1016/J.JHEP.2022.06.001/ATTACHMENT/BA9A0C8B-4FCE-4720-B8E6-330A4A4138D5/MMC1.PDF
Moore RC, Ackerman RA, Russell MT et al (2022) Feasibility and validity of ecological momentary cognitive testing among older adults with mild cognitive impairment. Front Digit Health 4. https://doi.org/10.3389/FDGTH.2022.946685
Nagelhus EA, Amiry-Moghaddam M, Bergersen LH et al (2013) The glia doctrine: addressing the role of glial cells in healthy brain ageing. Mech Ageing Dev 134:449–459. https://doi.org/10.1016/J.MAD.2013.10.001
Parasuraman S, Sam AT, Yee SWK et al (2017) Smartphone usage and increased risk of mobile phone addiction: A concurrent study. Int J Pharm Investig 7:125. https://doi.org/10.4103/JPHI.JPHI_56_17
Pei G, Wu J, Chen D et al (2018) Effects of an integrated neurofeedback system with dry electrodes: EEG acquisition and cognition assessment. Sensors (Basel) 18. https://doi.org/10.3390/S18103396
Pew Research Center (2021) Mobile Fact Sheet. In: Pew Research Center. https://www.pewresearch.org/internet/fact-sheet/mobile/. Accessed 29 Aug 2022
Ramirez M, Maranon R, Fu J et al (2018) Primary care provider adherence to an alert for intensification of diabetes blood pressure medications before and after the addition of a "chart closure" hard stop. J Am Med Inform Assoc 25:1167. https://doi.org/10.1093/JAMIA/OCY073
Randolph C, Hilsabeck R, Kato A et al (2009) Neuropsychological assessment of hepatic encephalopathy: ISHEN practice guidelines. Liver Int 29:629–635. https://doi.org/10.1111/J.1478-3231.2009.02009.X
Reiners F, Sturm J, Bouw LJW, Wouters EJM (2019) Sociodemographic factors influencing the use of ehealth in people with chronic diseases. Int J Environ Res Public Health 16. https://doi.org/10.3390/IJERPH16040645

Revlin Russell (2013) Cognition : theory and practice. Worth Publishers, p 640

Roberts LM, Jaeger BC, Baptista LC et al (2019) Wearable technology to reduce sedentary behavior and CVD risk in older adults: a pilot randomized clinical trial. Clin Interv Aging 14:1817–1828. https://doi.org/10.2147/CIA.S222655

Rutherford JJ (2010) Wearable technology. IEEE Eng Med Biol Mag 29:19–24. https://doi.org/10.1109/MEMB.2010.936550

Scharre DW, Chang SI, Murden RA et al (2010) Self-Administered Gerocognitive Examination (SAGE): a brief cognitive assessment Instrument for mild cognitive impairment (MCI) and early dementia. Alzheimer Dis Assoc Disord 24:64–71. https://doi.org/10.1097/WAD.0B013E3181B03277

Scharre DW, Chang SI, Nagaraja HN et al (2017) Digitally translated Self-Administered Gerocognitive Examination (eSAGE): relationship with its validated paper version, neuropsychological evaluations, and clinical assessments. Alzheimers Res Ther 9. https://doi.org/10.1186/S13195-017-0269-3

Sliwinski MJ, Mogle JA, Hyun J et al (2018) Reliability and validity of ambulatory cognitive assessments. Assessment 25:14. https://doi.org/10.1177/1073191116643164

Smuck M, Odonkor CA, Wilt JK et al (2021) The emerging clinical role of wearables: factors for successful implementation in healthcare. npj Digital Medicine 4:1. https://doi.org/10.1038/s41746-021-00418-3 (4:1–8)

Sood KT, Wong RJ (2019) Hepatic encephalopathy is a strong predictor of early hospital readmission among cirrhosis patients. J Clin Exp Hepatol 9:484. https://doi.org/10.1016/J.JCEH.2019.01.005

Steil GM, Rebrin K, Darwin C et al (2006) Feasibility of automating insulin delivery for the treatment of type 1 diabetes. Diabetes 55:3344–3350. https://doi.org/10.2337/DB06-0419

Tartaglione Ev, Derleth M, Yu L, Ioannou GN (2014) Can computerized brain training games be used to identify early cognitive impairment in cirrhosis? Am J Gastroenterol 109:316–323. https://doi.org/10.1038/AJG.2013.306

Torous J, Kiang Mv, Lorme J, Onnela JP (2016) New tools for new research in psychiatry: a scalable and customizable platform to empower data driven smartphone research. JMIR Ment Health 3. https://doi.org/10.2196/MENTAL.5165

Vilstrup H, Amodio P, Bajaj J et al (2014) Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American association for the study of liver diseases and the European association for the study of the liver. Hepatology 60. https://doi.org/10.1002/hep.27210

Wallace J, Schatz P, Covassin T, Iverson GL (2020) Brief iPad-based assessment of cognitive functioning with ImPACT® quick test: prevalence of low scores using multivariate base rates. Arch Clin Neuropsychol 35:1276–1282. https://doi.org/10.1093/ARCLIN/ACAA078

Weissenborn K (2019) Hepatic encephalopathy: definition, clinical grading and diagnostic principles. Drugs 79:5. https://doi.org/10.1007/S40265-018-1018-Z

Weissenborn K, Heidenreich S, Ennen J et al (2001b) Attention deficits in minimal hepatic encephalopathy. Metab Brain Dis 16:13–19. https://doi.org/10.1023/A:1011654210096

Weissenborn K, Ennen JC, Schomerus H, Rückert N, Hecker H (2001a) Neuropsychological characterization of hepatic encephalopathy. J Hepatol 34(5):768–773. https://doi.org/10.1016/s0168-8278(01)00026-5

Witt DR, Kellogg RA, Snyder MP, Dunn J (2019) Windows into human health through wearables data analytics. Curr Opin Biomed Eng 9:28–46. https://doi.org/10.1016/J.COBME.2019.01.001

Zhou YY, Kanter MH, Wang JJ, Garrido T (2017) Improved quality at kaiser permanente through e-mail between physicians and patients. 29:1370–1375. https://doi.org/10.1377/HLTHAFF.2010.0048