What Good are Digital Technologies in Alzheimer's Disease Research? — A Systematic Literature Review

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Introduction

- An estimated 47 million people worldwide were living with dementia in 2015. This prevalence is predicted to reach 76 million in 2030,[1] by which time the cost of caring for such individuals is estimated to reach $2 trillion (US dollars).[2] Alzheimer's disease (AD) is the most common type of dementia, and therefore presents a major humanistic and economic burden.
- There are no effective treatments to delay the onset or slow the progression of AD, and currently available therapies offer only moderate symptomatic relief.[3]
- There is increasing interest in the use of digital technologies, such as mobile/wearable devices and unobtrusive sensors, to collect data on subtle functional changes known, or suspected, to precede clinical onset of dementia.
- By providing such information, digital technologies could not only facilitate recognition of early signs of AD, but also improve recruitment and retention in clinical trials that are investigating disease-modifying treatments. Additionally, this could improve clinical outcomes and daily activities for individuals living with AD.
- Against this background, we aimed to review recently published real-world evidence to identify any trends in the use of digital technologies in AD research.

Objective

- To identify and summarize real-world evidence on the use of digital technologies in recent research on AD

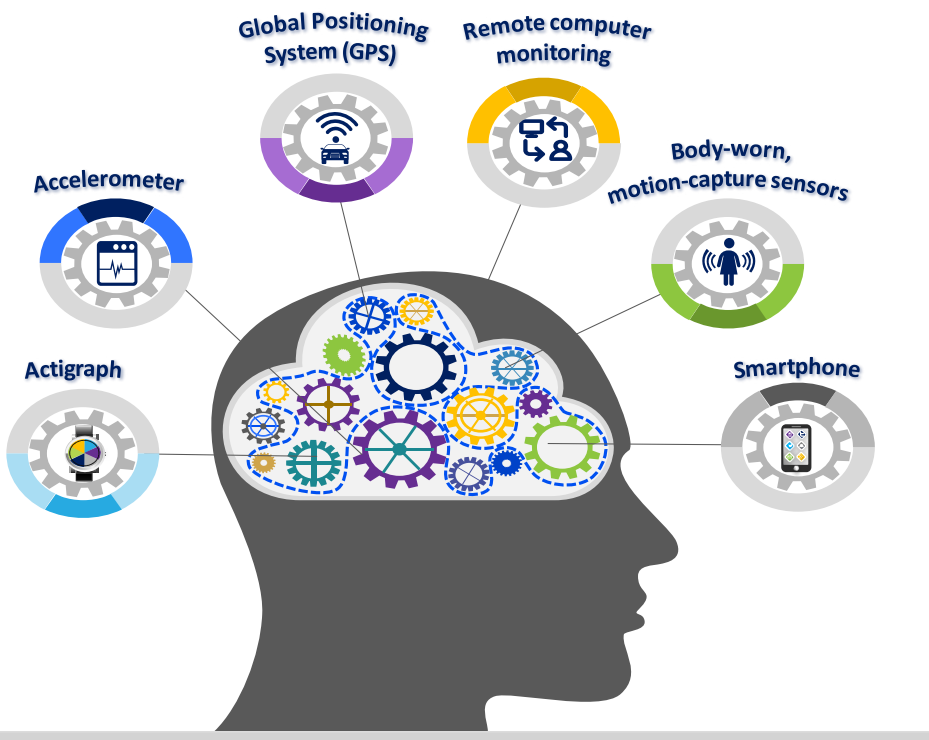
Methods

- A systematic literature review (SLR) was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[4]
- Searches were run in MEDLINE and Embase to capture articles published in English during the previous five years (1 January 2014 to 29 May 2019).
- To be included, studies had to be of observational design and report on digital technologies (e.g., mobile/wearable devices, sensors) being used to make objective measurements of outcomes (e.g., gait, sleep, physical activity) in patients with mild cognitive impairment (MCI), AD, or dementia.
- Abstract and full-text screening was undertaken independently by two reviewers, with any disagreement between them resolved by a third reviewer.
- For included studies, data on the type of digital technology used, outcomes measured, and study design were extracted into a pre-designed form and then summarized qualitatively.

Results

- The database searches yielded 532 unique records, of which 29 reported on the use of digital technologies to measure outcomes objectively in individuals with MCI, AD, or dementia.
- The digital technologies identified included wrist-worn actigraphs (n=11 studies), accelerometers (n=8), Global Positional System (GPS) tracking devices (n=3), smartphones (n=3), remote computer monitoring (n=3), and body-worn motion-capture sensors (n=1; Figure 1).

Figure 1. Digital Technologies



Abbreviation: GPS = Global Positioning System

Results (cont.)

- The different digital technologies collected data on gait (n=8), physical activity (n=8), sleep patterns (n=5), out-of-home mobility (n=3), computer use (n=3), and driving (n=2; Figure 2).

Figure 2. Results of Measuring Outcomes and Their Potential Impact

Gait

- In a longitudinal study of MCI,[5] use of accelerometers showed that certain changes in gait features (specifically, speed and symmetry) were significantly associated (both p<0.05) with subsequent development of AD over a three-year follow-up. Also, a cross-sectional study reported a significant association (p<0.05) between such accelerometric gait disturbances in MCI and white matter lesions on MRI, a known risk factor for AD.[6]
- In a study of individuals with mild AD at baseline, accelerometers measured a significant longitudinal decline in gait speed and step length (both p<0.05) over a two-year follow-up period.[7] Based on a seven-day in-home accelerometric gait assessment, another study found that gait speed and step length were significantly correlated (both p<0.05) with measures of global cognition in individuals with mild AD.[8]
- In two cross-sectional studies, accelerometric gait features allowed differentiation between MCI and AD.[9,10] However, the discriminative power of this assessment was weaker for distinguishing between MCI and healthy controls.[10,11]
- In a cohort of individuals with dementia, it was possible to grade the likelihood of experiencing falls in the short term (two months), midterm (four months), and long term (eight months), based on accelerometric gait parameters.[12]

Sleep patterns

- Across three cross-sectional studies, sleep-wake cycles measured by actigraphy revealed circadian disturbances in AD and dementia. Individuals with amyloid plaque pathology on PET imaging had significantly more circadian fragmentation than healthy controls (p=0.05).[13] Individuals with AD also had lower circadian amplitude (p=0.013) than did patients with MCI.[14] In addition, patients with early-onset dementia had greater rest-activity rhythm disturbances than cognitively intact adults (p=0.03).[15]
- One cross-sectional study found that individuals with AD had longer TST than did those with MCI (p<0.001).[16] Based on AD severity, defined by performance on a cognitive test, another cross-sectional study reported that those with moderate AD had longer TST than those with mild AD (p=0.02).[17]

Computer use

- Two longitudinal studies monitored computer use remotely for 12 to 36 months in individuals with MCI and healthy controls.[18,19] They showed that, over time, individuals with MCI used their computer on fewer days, had shorter daily usage, started usage later in the day, and had more day-to-day variability in usage (all p<0.05) compared to healthy controls.
- In a cross-sectional study that remotely monitored computer use over a week, individuals with MCI made significantly fewer total mouse movements (p<0.01), and the movements were more variable, less efficient, and separated by longer pauses (all p<0.05) compared to those made by healthy controls.[20]

Driving

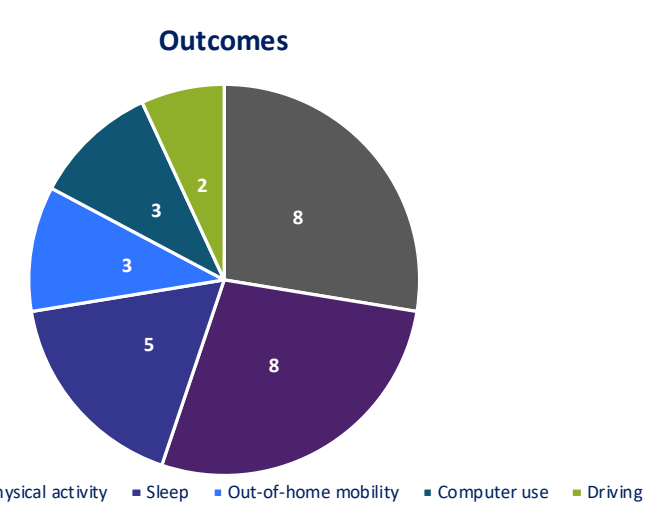
- In a longitudinal study of GPS-tracked driving, patients with pre-clinical AD (defined by amyloid plaque pathology on PET imaging) showed a greater decline over a 2.5-year follow-up period in the number of days driving per month and the number of trips between one and five miles compared to healthy controls.[21] However, another study reported no significant difference in the longitudinal change in GPS-monitored driving metrics (via smartphone) over a six-month period between individuals with MCI and cognitively healthy controls.[22]

Physical activity patterns

- Across six cross-sectional studies, individuals with MCI, AD, and dementia were less physically active than healthy controls according to actigraphy data.[23-28]
- Physical activity parameters derived from a 24-hour accelerometric assessment were an indicator of the future risk of falls in individuals with dementia.[29] Physical activity measured by actigraphy was also positively correlated with measures of apathy in dementia (p<0.05).[30]

Out-of-home mobility

- Three cross-sectional studies provided evidence for GPS-derived out-of-home mobility behaviors, distinguishing between MCI and AD and between AD and cognitively healthy controls.[31-22] Out-of-home mobility behaviors were also correlated with affective state in AD.[31,21]



Abbreviations: AD = Alzheimer's disease; GPS = Global Positioning System; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; PET = positron emission tomography; TST = total sleep time

- Twenty-two studies were cross-sectional and seven were longitudinal. Sample sizes ranged from 11 to 810 patients.
- Eight studies reported on outcomes in individuals with MCI, seven studies reported on individuals with AD, seven reported on both patient groups (MCI and AD), and seven reported on patients with dementia (not further defined) (Table 1).

Table 1. Outcomes in MCI, AD, and Dementia Populations

Outcome	MCI	AD	MCI and AD	Dementia*
Gait	3	2	2	1
Physical activity	1	1	1	5
Sleep	-	2	2	1
Out-of-home mobility	-	1	2	-
Driving	1	1	-	-
Computer use	3	-	-	-

Abbreviations: AD = Alzheimer's disease, MCI = mild cognitive impairment
*Patients reported to have dementia without further details provided

Conclusions

- While the use of digital technologies in AD research remains exploratory, this SLR highlights their potential use to:
  - Help the early detection of those at risk of developing AD
  - Discriminate between individuals at different stages of the disease
  - Provide key information on daily activities of those living with the disease
- Gait has been the most active area of research and is emerging as a potential diagnostic tool for cognitive decline. Preliminary evidence also suggests measures of driving, computer use, and out-of-home mobility might provide ecologically valid measures of subtle functional changes early in the disease process.
- Further research is needed to validate digital technologies as potential early markers of real-world functional changes in AD and to integrate them as recruitment tools and outcomes in clinical trials.
- As research continues, the opportunity for timely and economical data collection with digital technologies will need to be balanced against legal, data-privacy, and regulatory considerations.

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