Time is of the essence – early detection of incipient Alzheimer pathology

A commentary on "Association of Digital Clock Drawing with PET Amyloid and Tau Pathology in Normal Older Adults"

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With the possible advent of disease modifying treatment by targeting amyloid-beta metabolism or deposition, it becomes crucial to identify individuals at risk of Alzheimer's dementia as early as possible, preferably before the onset of overt cognitive impairment. Accessibility of screening in underserved areas will be needed despite a lack of neurological or neuropsychological expertise. Long wait times now common for dementia specialist care would be even more unacceptable if the wait meant delaying a disease modifying treatment. Given the prevalence of Alzheimer's disease and related disorders, such screening is likely to place high demands on the medical system.

New diagnostic developments continue to hold promise in expanding accessibility to early and accurate diagnosis of Alzheimer's disease and related disorders. Biomarkers such as PET scans or amyloid levels in CSF or serum may detect disease pathology and are increasingly required for a diagnosis of Alzheimer's pathology [1]. It is also necessary to screen for subtle cognitive changes, however, as the pathological changes indicated by physiological biomarkers do not always limit patient cognition or function [2]. Access to neurobehavioral status screening can be limited by geographical or other constraints. Digital testing may expand accessibility to cognitive assessment, especially if digital testing compares favourably to established tests and can predict the presence of underlying Alzheimer's pathology without the need of invasive or costly biomarker testing.

In this issue of neurology, Rentz and colleagues examine the value of a digital version of the well-established clock drawing test [3]. In this technological advance of the time-honoured clock draw, the use of a computerized pen allows analysis not only of the correctness of the clock's face and hands, but also analyses other, subtler features such as movement and spatial patterns, and thereby provides a much richer dataset than conventional clock draw scoring schema. The digital clock test has been commercially developed and has received FDA clearance, but requires a special pen with a camera and data needs to be uploaded to a server for analysis using machine-learning algorithms for feature extraction and comparison with reference data to infer abnormality.

As expected, the digital clock-drawing test was able to differentiate groups of AD dementia, mild-cognitive impairment and healthy controls. While slightly less effective than the Preclinical Alzheimer Cognitive Composite (PACC), the digital clock draw performed better than the conventional clock-drawing test. More interestingly, in the group of cognitively normal elderly controls with available PET data (n=143), the digital clock drawing test was better able to predict a cortical amyloid deposition. While the area-under-the-curve (0.72 compared to 0.62 for PACC) and the effect size (Cohen's D of 0.76) were both modest, this may be measured against the difference in time required for test administration (i.e., <5

minutes vs. 30 minutes). Digital clock results also weakly correlated with the amount of tau accumulation (especially in the entorhinal cortex, an early size of pathology in AD).

The digital clock drawing test may offer a rapid and relatively inexpensive cognitive screening tool which may expand the accessibility of a simple neurobehavioral status screening tool, and may ultimately find its way into more comprehensive screens such as the Mini-Cog or Montreal Cognitive Assessment [4, 5], both of which currently integrate a clock drawing. As the authors suggest, this may be especially feasible if the test could be administered using a more widely available device such as an electronic tablet. Strengths of the digital clock draw, then, include the promise of inexpensive, rapid, widely accessible screening, enhanced by the ability to incorporate many subtle features such as precise timing of pen movement throughout the patient's task performance.

While such subtlety may add to power, however, it may also be a weakness if it diminishes interpretability of test results. Ensuring that medical providers are comfortable using and interpreting the results provided by the underlying machine-learning algorithms may challenge implementation of this kind of new diagnostic technology. How can we ensure physicians have the training and ability to adequately understand, critically appraise, and clearly explain how these complex algorithms work? Without such an understanding, the physician-patient relationship may suffer due to the physician's role being reduced to uncritically relaying the conclusions of a computer. In the same way that physicians understand and explain the significance of the PET scans to which this digital clock draw is compared, we must be ready to interpret facets of the machine-learning algorithm, including more comprehensive subdomain scores. For example, when interpreting machine-learning research, physicians must consider descriptions of the overall analytic approach, information regarding algorithmic limitations, and any tests for systemic biases.

While some details may be lacking in this article, the authors have also built on and reference a more detailed description of the algorithms underlying the digital clock draw. The referenced article by Souillard-Mandar and colleagues clearly recognizes the need for intelligibility in machine-learning techniques [6]. Further demographic information about the training set would also be helpful, as some machine-learning algorithms have inadvertently and inscrutably integrated and reinforced societal biases [7]. Further information about how patient data are being identified, protected, and shared after being uploaded to a server would also reassure physicians keen on guarding patient confidentiality and health information. Further work is needed to determine which sub-scores and cognitive domains are most relevant to diagnostic performance at each stage of different diseases. For the detection of preclinical AD pathology as outlined above, performance may also be further boosted by combining information from other sources such as family history or APOE4 genotyping.

The clock draw test in this article may serve as an analogue for the increasingly digital face of medicine. In response to the need for timely diagnosis and possibly treatment of Alzheimer's and related disorders, and in today's time-strapped clinical environment, medical providers must be prepared to critically appraise and use digital screening and assessment tools in hopes of better detecting, slowing and stopping disease advancement.

References:

1. Jack CR, Jr., Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's & Dementia : the Journal of the Alzheimer's Association 2018;14:535-562.

2. Monsell SE, Mock C, Roe CM, et al. Comparison of symptomatic and asymptomatic persons with Alzheimer disease neuropathology. Neurology 2013;80:2121-2129.
3. Dorene M Rentz, Kathryn V Papp, Mayblyum DV, et al. Association of Digital Clock Drawing with PET Amyloid and Tau Pathology in Normal Older Adults. Neurology 2021.
4. Borson S, Scanlan JM, Chen P, Ganguli M. The Mini-Cog as a screen for dementia: validation in a population-based sample. Journal of the American Geriatrics Society 2003;51:1451-1454.
5. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society 2005;53:695-699.
6. Souillard-Mandar W, Davis R, Rudin C, et al. Learning Classification Models of Cognitive Conditions from Subtle Behaviors in the Digital Clock Drawing Test. Mach Learn 2016;102:393-441.
7. Char DS, Shah NH, Magnus D. Implementing Machine Learning in Health Care - Addressing Ethical Challenges. The New England Journal of Medicine 2018;378:981-983.