Using the Integrated Cognitive Assessment Platform (CognICA) to monitor changes in cognitive performance in patients with Alzheimer's Disease under disease-modifying therapy.

Seyed-Mahdi Khaligh-Razavi[1,*], Amirhossein Zarezadeh[1], Ruediger Stendel[2], Derk W. Krieger[2]

[1] Cognetivity Ltd, London, UK *seyed@cognetivity.com
[2] Mediclinic Parkview Hospital, Dubai, UAE

Introduction

Alzheimer's disease is a progressive and degenerative disorder that causes cognitive decline, and until recently had no cure. However, recently FDA-approved disease-modifying therapies (DMT) such as Aduhelm and Leqembi, have been developed to slow down the progression of this devastating condition. Both of these DMTs work by targeting a protein called beta-amyloid, which accumulates in the brains of people with Alzheimer's. By targeting this protein, the DMTs attempt to stop the progression of Alzheimer's disease, providing hope for patients and their families.

However, to accurately measure the impact of these therapies on patients' brain health and cognitive function, beyond the removal of beta-amyloid, it is important to track cognitive performance in these patients over time. This can be a challenge due to the complexity of the disease, as well as the difficulty in accurately measuring and monitoring changes in cognitive performance.

Here, we present a real-world study that demonstrates the effectiveness of Cognetivity's Integrated Cognitive Assessment (CognICA) in tracking cognitive function during treatment of Alzheimer's disease patients using Aducanumab. The study utilises CognICA, an AI-based digital biomarker of cognition, to monitor patients' cognitive performance every month, providing insight on the impact of Aducanumab in treating the disorder.

CognICA is a 5 minute computerised cognitive test that employs artificial intelligence, and is used as an inexpensive cognitive screening and monitoring tool. CognICA is independent of language and culture, free from practice effect, and has been utilised internationally in diverse populations [1-4]. CognICA is further shown to be cost saving to the health and social care payers, when used to screen primary care patients for dementia and perform initial triage in memory clinics [5].

Method

Patients, aged 55 and above, coming to the neurology clinic at Mediclinic Parkview Hospital in the UAE were screened for cognitive impairment using CongICA. 133 tests were completed to screen patients with cognitive complaints and/or at risk of dementia who came to the clinic; 13 individuals received a diagnosis of Alzheimer's Disease (AD). Five of these patients received *Aducanumab*, and were followed up monthly, using CongICA when they came to receive their dosage of the treatment. The clinical usability of CognICA was evaluated in identifying cognitive impairments and monitoring cognition in patients receiving Aducanumab treatment.

CognICA is a rapid visual categorisation task with backward masking, and has been described in detail in previous publications [1-4]. The test takes advantage of the human brain's strong reaction to animal stimuli [6-8]. One hundred natural images (50 of animals and 50 of not containing an animal) of various levels of difficulty are selected and are presented to the participant in rapid succession as shown in Figure 1.

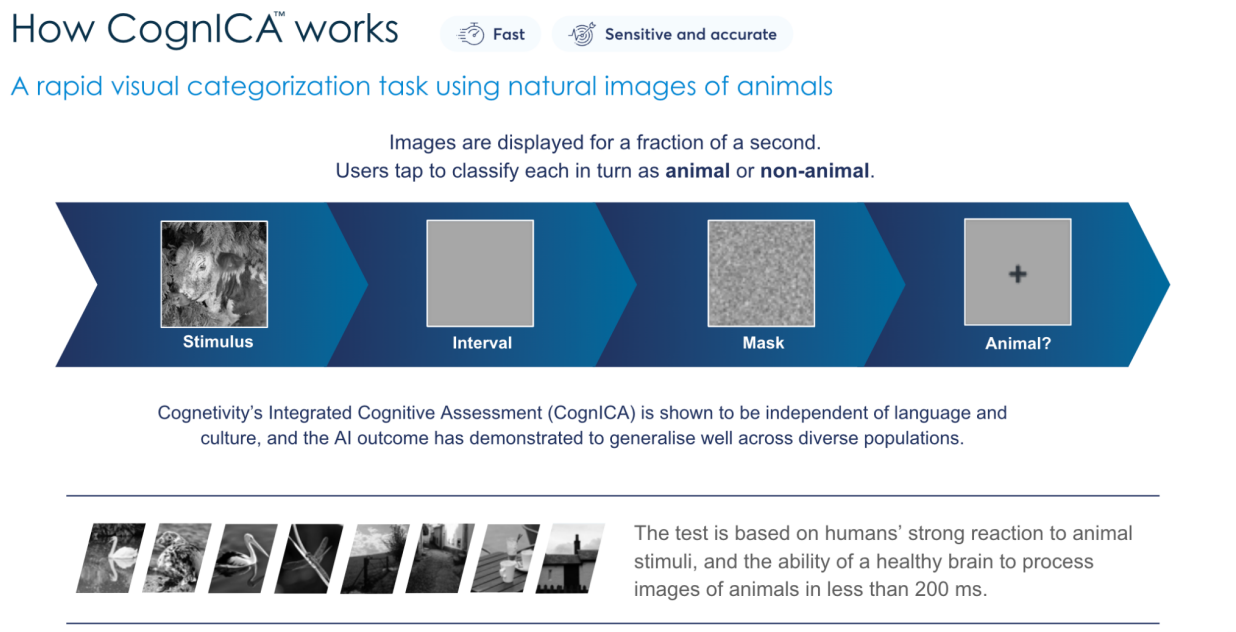

Figure 1. Description of Cognetivity's Integrated Cognitive Assessment (CognICA).

Result

The objective nature and high sensitivity and specificity of CognICA enabled the collection of multiple data points from patients, facilitating the identification of changes in cognition in very short intervals (e.g. monthly instead of six-monthly). This allows for a more comprehensive assessment of cognitive function over time, as well as being able to detect changes in cognition more quickly and accurately than the current standard of care. The study results showed that

patients who received Aducanumab did not experience a cognitive decline, as measured by CognICA, which is particularly noteworthy considering the absence of a practice effect in CognICA, and its high test-retest reliability [1,2,4] (Figure 2).

More specifically, two of the patients (P2 and P4) displayed significant cognitive improvement (Figure 2), while the cognitive performance of the other participants remained stable with no significant decline, compared to the baseline test. Changes in ICA index more than 5 points are considered clinically meaningful.

Table 1. Patients demographic and mean ICA index

	Number of Individuals	Number of tests	Mean Age (SD)	Gender (m)	Mean 1st ICA index (SD)	mean all ICA tests
Alzheimer's	13	36	71.3 (9.2)	9	43 (17.5)	49.4 (16.7)
Screening	84	98	54.5 (12.8)	52	67 (12)	66.5 (12.3)

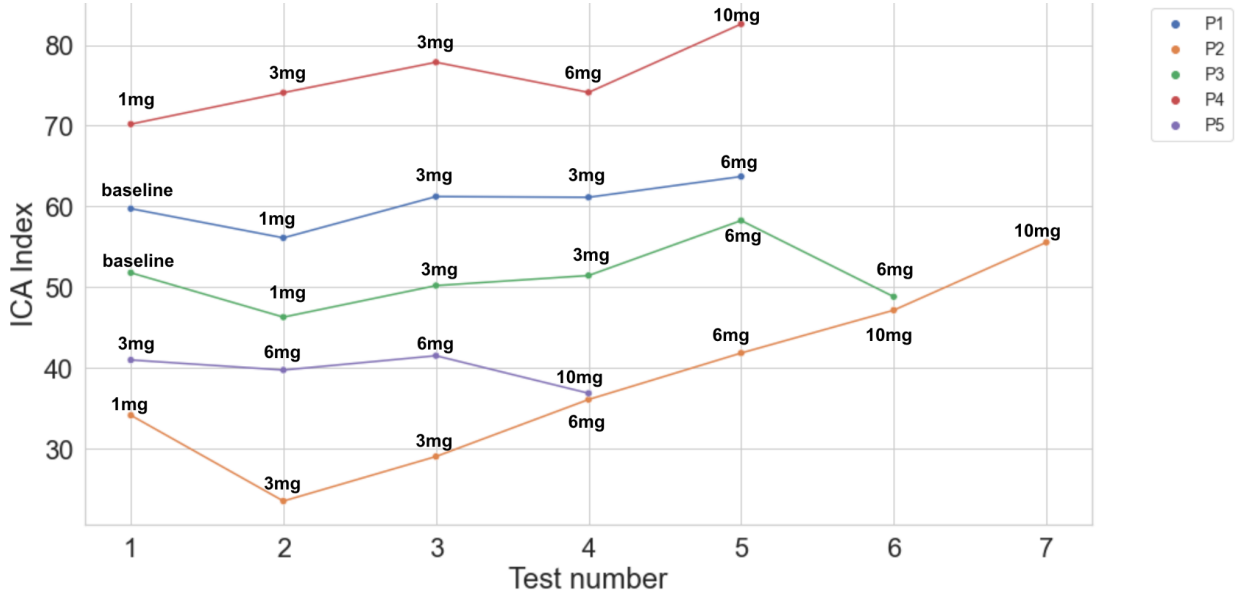

Figure 2. AD patients who received more than three dosages of aducanumab . Changes in the ICA Index are shown over time. Each line shows one individual, taking CognICA at baseline and then followed up monthly. In each session patients took CognICA prior to the infusion of Aducanumab. Dosages of Aducanumab are indicated in this figure for each session and patient.

Conclusions

Given CognICA's ease of use and rapid testing, CognICA was successfully utilised to screen for cognitive impairment as a routine process for individuals with cognitive complaints, or those at risk of developing dementia. The study presented evidence of the clinical usability of CognICA as a highly sensitive screening and monitoring tool to identify cognitive impairment and measure changes in cognitive abilities in response to Aducanemab. As disease-modifying therapies are becoming available for Alzheimer's Disease, it is becoming ever more essential to have access to sensitive tools for the quick assessment of patients with cognitive complaints or those at greater risk of developing AD. Moreover, it is of great importance to closely monitor how patients react to the treatment. CognICA offers an innovative and reliable approach to achieve these goals, thus providing an invaluable resource to clinicians and carers alike.

CognICA can be further used as an exploratory endpoint in AD clinical trials to pick up changes in cognitive function that otherwise go unnoticed because of the coarse resolution, and the ceiling effect of the existing cognitive assessment tools and ratings (such as CDR, MMSE and MoCA), that are typically used as primary and secondary endpoints. The higher resolution of the CongICA scale that goes beyond the current clinical recognition, can establish a meaningful relation between underlying pathological changes (such as changes in Aβ plaques) and quantifiable changes in cognitive performance. These are typically nuanced changes that are detected in real-life situations by caregivers, but the current standard practice lacks the sensitivity to detect and quantify them.

References

1. Khaligh-Razavi S-M, Habibi S, Sadeghi M, Marefat H, Khanbagi M, Nabavi SM, et al. Integrated Cognitive assessment: speed and accuracy of visual processing as a reliable proxy to cognitive performance. *Sci Rep*. (2019) 9:1102. Available online at: **http://www.nature.com/articles/s41598-018-37709-x**
2. Khaligh-Razavi S-M, Sadeghi M, Khanbagi M, Kalafatis C, Nabavi SMA. self-administered, artificial intelligence (AI) platform for cognitive assessment in multiple sclerosis (MS). *BMC Neurol.* (2020) 20:193. doi: 10.1186/s12883-020-01736-x
3. Karimi, H., Marefat, H., Khanbagi, M., Kalafatis, C., Modarres, M. H., Vahabi, Z., & Khaligh-Razavi, S. M. (2022). Temporal dynamics of animacy categorization in the brain of patients with mild cognitive impairment. *Plos one*, *17*(2), e0264058.
4. Kalafatis, C., Modarres, M. H., Apostolou, P., Marefat, H., Khanbagi, M., Karimi, H., ... & Khaligh-Razavi, S. M. (2021). Validity and Cultural Generalisability of a 5-Minute AI-Based, Computerised Cognitive Assessment in Mild Cognitive Impairment and Alzheimer's Dementia. Frontiers in Psychiatry, 1155.

5. Shore, J., Kalafatis, C., Modarres, M. H., & Khaligh-Razavi, S. M. (2022). Health Economic Analysis of the Integrated Cognitive Assessment Tool to Aid Dementia Diagnosis in the United Kingdom. *medRxiv*, 2022-05.
6. Kiani R, Esteky H, Mirpour K, Tanaka K. Object category structure in response patterns of neuronal population in monkey inferior temporal cortex. *J Neurophysiol.* (2007) 97:4296–309. doi: 10.1152/jn.00024.2007
7. Khaligh-Razavi, S. M., Cichy, R. M., Pantazis, D., & Oliva, A. (2018). Tracking the spatiotemporal neural dynamics of real-world object size and animacy in the human brain. *Journal of cognitive neuroscience*, *30*(11), 1559-1576.
8. Cichy RM, Pantazis D, Oliva A. Resolving human object recognition in space and time. *Nat Neurosci.* (2014) 17:455–62. doi: 10.1038/nn.3635