The majority of the neuropsychological tests used in ADNI are not suitable instruments for research in Preclinical Alzheimer’s Disease

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ABSTRACT

BACKGROUND: The search for substances to improve cognitive function and their age-related cognitive decline is dependent upon having instruments which can reliably measure such effects. For example research criteria for ‘practical’ Alzheimer’s disease (AD) include the requirement for sensitive measures of ‘psychomotor function’ to identify early clinical manifestations of AD. Spirling et al (2010). The Alzheimer’s Disease Neuroimaging Initiative (ADNI) employed widely used neuropsychological tests to identify the transition from normal aging to the earliest stages of memory loss through MCI/AD. The present analysis was to determine the utility of the ADNI tests for repeated administration in such research.

METHODS: Data from the control, amnestic MCI (MCI due to AD) and mild AD cohorts were downloaded from the ADNI database (20th February 2012) for the following tests: Rey Auditory Verbal Learning Test (AVLT), Logical Memory and Auditory Verbal Learning. A variety of methods were employed to establish the performance of the tests, including clinical trial simulations.

RESULTS: Data for up to 5 years were available for 226 non-demented controls aged 60 to 90. While the tests had good test-retest reliability and were able to differentiate the control, MCI, and AD cohorts extremely well, for the controls, no consistent pattern of clinical improvement was seen over the study period. Improvements occurred with repeated testing on most tests, some lasting to 5 years. The effect sizes of the improvements were variable in many cases.

CONCLUSIONS: The various analyses and clinical trial simulations conducted indicate that the neuropsychological tests used in ADNI would not perform well in clinical trials of compounds designed to reduce age-related cognitive decline or treat preclinical AD. While test-retest reliability is a necessary property for cognitive tests in this field, it is clearly not sufficient.

BACKGROUND

2011 Diagnostic guidelines for preclinical Alzheimer’s Disease

Trials in preclinical AD will involve repeated cognitive testing of middle aged and elderly individuals with generally normal cognitive function

METHODS

Data from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) Database

- Downloaded from ADNI database 19th February 2012
- 226 Healthy Controls (mean age 76 years range 60-90, MMSE 24-30)
- 234 amnestic MCI patients
- Administered a range of neuropsychological tests repeatedly over 5 years
  - Rey AVLT
  - WMS Logical 1H
  - Category Fluency
  - DSST
  - Digit Span

Analysis

- Data analysed using mixed-effects model repeated measures approach (MMRM) with SAD PROC MIXED
- Data are plotted as least squares means changes from study entry, with 95% confidence intervals (CI)
- Improvements are plotted to assess
- Where CIs do not cross zero line, improvement or impairment is significant

Sperling et al recognise the need for sensitive tests - do we need new ones or do we already have suitable tests?

Healthy Controls

AMNestic MCI Patients

DISCUSSION

Controls

- Over the 5 years, only delayed recall on the AVLT showed a significant deficit at any time point (5 yrs).
- 7 of the 12 task-measures showed significant improvements, 5 were still improved at 2 years and 3 at 5 years.
- The effect sizes of these improvements ranged from 0.25 to 0.72, 3 being small to medium effect sizes, 3 medium to large.
- All measures showed no evidence of impairment over the study, of these 3 measures showed improvements, for logical memory delayed this lasted 4 years.
- Only 1 measure (AVLT delayed recall) showed deficits from year 1 onwards, another (clock drawing) showed a deficit at year 1 and 3.
- Of the others, deficits were seen from 2 years for 1, and by 3 years for 4.

The tests are excellent for cross-sectional comparisons, but not repeated administration in the elderly controls or aMCI

However, the computerised tests had generally superior (lower) coefficients of variation, suggesting this may be a more important property of a test for detecting change with repeated testing.

CONCLUSIONS

- Large long-term clinical trials in preclinical AD are underway and many are being planned.
- These will involve populations comparable, or in several cases considerably younger than the ADNI cohort.
- The analyses presented here indicate that traditional neuropsychological tests are unlikely to prove suitable outcome measures in such trials.
- The opportunity to study large populations via the internet has applications to the various long-term patient registries being set up to study preclinical demerits.

REFERENCES