Are Traditional Neuropsychological Tests When Administered Repeatedly Suitable for Assessing Therapeutic Benefits to Cognitive Function in Clinical Trials?

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BACKGROUND

- Research criteria have been proposed (Sporting et al, 2011)
- Large long-term trials are underway in unimpaired individuals and many others are being planned
- Important requirements for tests in such trials are to be free of ceiling & floor effects while also sensitive to change over time when administered repeatedly

METHODS

- RESEARCH QUESTION 1
  How will neuropsychological tests as used in clinical trials perform over the long term?
  - Downloaded from ADNI database 19th September 2012
  - 249 non-cognitively impaired individuals
  - Mean age 76 years (range 60-90)
  - MMSE 24.30
  - Repeatedly administered a range of neuropsychological tests up to 6 years

- Ceiling Effects On Clock and Boston Naming Tasks
  - Clock Drawing & Copying Tasks: Range 0 to 5 - % at Baseline
  - Boston Naming Test: Score 0 to 24 - % scoring 25 to 30 at Baseline

- Performance on Episodic memory tests
  - Clock Drawing & Copying Tasks
  - Logical Delayed & Immediate 1, 2, 3, 4, 5, 6 0.25 - 0.53
  - Trails B 0.45
  - Trails A 0.22 - 0.31
  - Rey AVLT Recognition 0.44
  - Trail Making, Clock Task & Boston Naming Tests
  - Score 0 to 5 - % scoring 25 to 30 at Baseline

- RESEARCH QUESTION 2
  How will tests designed for repeated use in clinical trials perform over 5 years in a comparable population?

- THE CDR SYSTEM
  - The CDR System was designed for repeated use in clinical trials and has been used in almost 1400 trials since 1994
  - Validated Composite Scores:
    - Power of Attention: Derived from the sum of the speed scores from the 3 attention tasks
    - Quality of Working Memory: Derived from the sensitivity indices from the articulatory & spatial working memory tasks
    - Quality of Episodic Memory: Derived from the sensitivity indices from the three episodic recognition memory tests
    - Speed of Memory Retrieval: Derived by summing the speed scores from the two working memory tasks and three episodic recognition tasks

- SDMT
  - Speed of Retrieval from Memory
  - CONVERSION TO aMCI
    - 27 (11%) of the controls converted to aMCI during the study
    - Age of converters: 75.9 years v 75.7 years
    - 68% converters were male 53% of non-converters
    - 15 out of the 27 converters had at least one APOE4 allele, compared with 56 out of 222 non-converters (48% compared to 26%, p<0.05)
    - Converters were significantly impaired at baseline on a number of measures

- LOGICAL MEMORY - PARAGRAPH RECALL
  - 256 non-cognitively impaired normotensive individuals
  - Mean age 76 years (range 70-90)
  - MMSE 24.30
  - Repeatedly administered automated cognitive tests from the CDR System for up to 5 years

DISCUSSION

- The neuropsychological tests used in ADNI showed no evidence of consistent or statistically reliable decline over 6 years. In fact, 7 measures showed significant improvements, some lasting 6 years (effect sizes ranging from 0.27 to 0.72)
- This occurred despite yearly declines in cortical thickness and hippocampal volume being detected in this group, as well as 11% developing amnestic MCI during the study
- The CDR System tests designed for repeated did identify significant and consistent yearly patterns of decline over 5 years in a comparable population (effect sizes from 0.5 to 1.8)
- The majority of tests used in ADNI showed good test-retest reliability, whereas only 2 of the 4 CDR System measures showed good reliability
- However, the CDR System measures showed consistent declines over 5 years
- This indicates that test-retest reliability is not an essential criterion for test selection in long-term trials
- Alternatively, the inherent variability in the measures assessed by coefficients of variation may be a more suitable index

CONCLUSIONS

- The neuropsychological tests used in ADNI appeal for the purpose of assessing change when used repeatedly in long term trials involving non-impaired individuals
- Preclinical Alzheimer’s trials will require sensitive and reliable instruments to capture the potential opportunity for therapies to slow the rate of cognitive decline over extended periods
- Tests or test systems designed specifically for repeated use in clinical trials that properly constructed should prove more suitable in such studies
- Such tests, with sufficient validation data and demonstrated sensitivity to change over extended periods in non-impaired patients should prove acceptable to regulators for trials in early stage AD

REFERENCES

- Wesnes K et al (2013) The year by year changes in cognitive function in a non- postruption, population: ADNI-GO, a five year period. Journal of Alzheimer’s Disease 35S1: 81-91