

SUPPLEMENTAL DIGITAL CONTENT 1

Description of neuropsychological testing battery used in the Cognitive Impairment in HIV positive People in the European Region (CIPHER) study

Verbal fluency tests: Two semantic fluency executive function tests, the Controlled Oral Word Association Test (COWAT) ¹ and Category Fluency Test (CFT) ² were directly administered by researchers. The COWAT requires the participant to report as many words as possible (within certain rules, e.g. avoiding proper nouns) beginning with the letters C, F and L. Each of the three letters is presented in a 1-minute trial. The CFT requires the participant to name as many animals as they can in 1 minute. Both are tests of executive skills in their requirement to (i) develop a strategy to select category appropriate responses, (ii) selectively interrogate semantic memory and (iii) keep track of words already spoken to avoid repetition. Other cognitive skills, particularly language, are also tested and most available norms are for native English speakers.

CogState: This is a computerised cognitive test battery that has been compared against traditional NP tests in the background population, HIV positive subjects and other disease groups and clinical settings.³⁻⁷ It is largely self-completed, with supervising observers requiring only limited training, and is conducted on a standard desktop or laptop computer. All tests are adaptations of standard neuropsychological tests that can assess a range of cognitive domains including psychomotor speed, attention, decision-making, learning, monitoring, working memory and executive function. Most of the tests take the form of card games that are presented in succession on a green background. To help individuals attain optimal performance quickly, an instructional phase presents written instructions and visual and auditory feedback to interactively teach the rules for each task.

Once the participants have completed a sufficient number of practice trials to demonstrate awareness of the rules, the testing phase begins. Participants are required to respond with only 1-2 keys during the battery and an error bleep is made if an incorrect key is struck.

The following tests were included in the computerized cognitive test battery:

The **Detection** task is a brief (2-3 minute) test of visual attention, psychomotor function and speed of processing. To begin the task, the test supervisor presses the "Enter" key. A playing card is presented face-down in the centre of the screen. As soon as the card turns over, the study participant must press the "Yes" key. The study participant is encouraged to respond as quickly and accurately as they can. If the participant presses "Yes" before the card flips over or does not respond to a card that has flipped over in time, they will hear an error sound. The unit of measurement is the mean of the \log_{10} -transformed reaction times for correct responses. A lower score indicates better performance.

The **Identification** task is a brief (2-3 minute) test of psychomotor function, speed of processing and visual attention. To begin the task, the test supervisor presses the "Enter" key. A playing card is presented face-down in the centre of the screen. As soon as the card turns over, the study participant must decide whether the card is red or not. If it is red they should press "Yes", if it is not red they should press "No". The unit of measurement is the mean of the \log_{10} -transformed reaction times for correct responses. A lower score indicates better performance.

The **One Back Memory** task is a 5 minute test of working memory maintenance and attention. A sequence of playing cards are presented face-up, one at a time, in the centre of the screen. The study participant must decide as each card is presented whether it is

identical to the one before. If the card is identical to the one presented immediately before it, the subject should press the "Yes" key; if not, they should press the "No" key. The main unit of measurement is accuracy of performance as indicated as by the arcsine transformation of the square root of the proportion of correct responses. A higher score indicates better performance. A second measurement of speed can also be obtained, using the same units of measurement as the Detection and Identification tasks, where a lower score indicates better performance.

The **International Shopping List** task is a 30 minute test of verbal memory, learning and recall. A list of 12 items found in a supermarket is read to the study participant by the test supervisor. The words are read as they appear on the computer screen at a rate of one every two seconds. The participant is then given 1 minute to recall each item, and the test supervisor clicks the appropriate button on the screen. If the subject says a word that was not on the list, the test supervisor will click "Other Word". If the subject repeats a word, the test supervisor will click the corresponding button as many times as the word is said. The unit of measurement is accuracy of performance as measured by the total number of correct responses made in remembering the list. Two scores are generated, the first being an average of three consecutive trials with immediate recall (less than 3 minutes after presentation), the second being the result of a single trial with delayed recall (at least 20 minutes after presentation). Higher scores indicate better performance.

The **Groton Maze Learning and Recall** tasks are tests of executive function and spatial problem solving. Errors are made if the participant fails to exercise mental flexibility, rule execution and decision making skills. The study participant is shown a 10 by 10 grid of tiles on a computer screen. A 28-step pathway is hidden among these 100 possible locations. The start is indicated by a blue tile at the top left and the finish location is the

tile marked with a target sign at the bottom right of the grid. The study participant is instructed to move one step from the start location and then to continue, one tile at a time, toward the end (bottom right). The study participant moves by touching a tile next to their current location. After each move is made, the computer indicates whether this is correct by revealing a green tick (i.e. this is the next step in the pathway), or incorrect by revealing a red cross (i.e. this is not the next step in the pathway, or the subject has broken a rule, see below). If the choice is incorrect, the study participant must touch the last correct location and then make a different tile choice. The unit of measurement is the total number of errors, although measures of perseveration, speed, etc can also be obtained. Two scores are generated, the first being the total errors in 5 consecutive trials, the second being the result of a single trial at least 20 minutes after the initial 5 learning trials. A lower score indicates better performance.

REFERENCES

1. Ruff RM, Light RH, Parker SB, et al. Benton Controlled Oral Word Association Test: reliability and updated norms. *Arch Clin Neuropsychol*. 1996;11:329-338.
2. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Arch Clin Neuropsychol*. 1999;14:167-177.
3. Cysique LAJ, Maruff P, Darby D, et al. The assessment of cognitive function in advanced HIV-1 infection and AIDS dementia complex using a new computerised cognitive test battery. *Arch Clin Neuropsychol*. 2006;21:185-194.
4. Maruff P, Thomas E, Cysique LA, et al. Validity of the CogState brief battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. *Arch Clin Neuropsychol*. 2009;24:165-178.

5. Makdissi M, Collie A, Maruff P, et al. Computerised assessment of concussed Australian Rules footballers. *Br J Sports Med.* 2001;35:354-360.
6. Weaver Cargin J, Maruff P, Collie A, et al. Mild memory impairment in healthy older adults is distinct from normal aging. *Brain Cogn.* 2006;60:146-155.
7. Harrison J, Maruff P. Measuring the mind: assessing cognitive change in clinical drug trials. *Expert Rev Clin Pharmacol.* 2008;1:471-473.

SUPPLEMENTAL DIGITAL CONTENT 2

Description of functional assessment tool (instrumental activities of daily living scale or IADLS)

The IADLS is a pen-and-paper questionnaire completed by the participant, based on a questionnaire originally designed in the 1960s for observer-led assessment of elderly people.¹

The assessment comprises a question on each of a number of functional areas of daily life: housekeeping, maintaining finances, buying groceries, cooking, planning social activities, understanding reading materials and TV, transportation, using the telephone, home repairs, bathing, dressing, shopping for non-food items, laundry, taking medication, child care, and work. For each area, respondents are asked to grade their current ability level alongside their “best ever” ability, choosing from a list of 3 to 5 options. In this way, the number of areas with declining function can be enumerated. For most areas, this would be indicated by a deterioration between best ever and current ability level. For the purpose of this study, we also considered the most limited grading in bathing, dressing, housekeeping and cooking to always indicate a clinically relevant deterioration, even if the best ever was graded the same as current abilities. We also opted to ignore the child care responses as very few participants had child care responsibilities.

Respondents who noted deteriorations in their functional abilities were also asked to decide whether they felt such effects were caused by physical difficulties, neurocognitive impairment, or both. Deteriorations that were attributed solely to physical problems were not counted.

In applying the Frascati definition of HIV-associated neurocognitive disorder,² deterioration in at least 2 functional areas was required to fulfil the criteria for Mild Neurocognitive Disorder, and deterioration in at least 4 functional areas was required to fulfil the criteria for HIV-associated dementia.

REFERENCES

1. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*. 1969;9:179-186.
2. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007;69:1789-1799.