Supplementary data 1: Measures of neuropsychological assessment

Primary outcomes measures

The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) [1] includes the following 3 cognitive measures:

► The California Verbal Learning Test (CVLT) [2], a verbal memory and learning test which consists of 16 words presented in a fixed order to the participant over 5 consecutive trials. The 16 words contain 4 words in each of the 4 distinct categories. On each trial, participants are required to recall as many words as possible after each presentation of the list. The dependent variable is the total number of correct responses across the 5 trials.

► The Brief Visuo-spatial Memory Test (BVMT) [3], a visual memory and learning test which requires participants to encode six geometrical figures and memorize their precise location during a 10s presentation. Immediately afterwards, participants have to draw the memorized figures in the right location. The procedure is repeated three times. Depending on figure and exact location accuracy, a scoring from zero to two points for each figure is given. The total recall score consists of the sum of the participants’ scores of the three trials.

► The Symbol Digit Modalities Test (SDMT) [4], which provides an index of information processing speed, requires participants to orally substitute digits for geometric symbols shown in a key sequence of nine symbols as quickly as possible. The dependent variable is the number of digits correctly substituted for symbols in 90 seconds.

Secondary outcomes measures

Cognitive assessment

► Direct and forward digit spans will assess, respectively, short-term memory and working memory. Participants heard a list of digits with instructions to repeat the digits immediately in
the same order (direct span) or in the reverse order (forward). The task has six progressive levels of difficulty that start with two digits and build up to seven, with a pair of digit strings at each level. Participants had to repeat one string at each level correctly to proceed to the next level. Testing stopped when both strings at one level were incorrect. In each condition, the level of the span and the total number of correct responses will be measured.

- **Stroop Color-Word Test** [5,6] to assess the inhibition processing. Subjects are required to read three different tables as fast as possible. 1) in the two congruous condition, participants are required to name different colour patches and to read names of colours printed in black ink, 3) the third table, incongruent condition, participants are required to name the colour of the ink instead of reading the word. The performance is evaluated by the time to complete each part and the total number of errors.

- **Trail Making Test** [6,7], to assess reactive flexibility, through two conditions: Part A, the subject have to link numbers between 1 to 25, in ascending order, as quickly and as precisely as possible; Part B, the subject have to connect the items by alternating the numbers (1to 13) and the letters (A to L) in ascending order of the numbers and in the normal order of the alphabet (1A, 2B, 3C, …). The performance is evaluated by the time to complete each part and the total number of errors.

- **Categorical and phonemic verbal fluency** is used to assess spontaneous flexibility abilities. For 2 minutes, the subject is asked to produce the most words belonging, firstly, to a certain semantic category (Animals), then secondarily, starting with the same letter (P). Performance is assessed by the number of different words.

- **Tower of London (TOL)** [8] is a measure of planning ability. In this task, participants are presented with colored balls (red, yellow and blue) stacked vertically in three possible positions (the “start” state) and are instructed to move them one at a time until they match a given
configuration (the “goal” state). Each trial can vary in difficulty, requiring different numbers of moves. This test proposes a set of 12 problems with three or five moves. Difficult trials may also require moves that result in a series of configurations that do not match the “goal,” but that are required in order to solve the task (“subgoal chunks”). Dependent variables can include preplan times (i.e. time between task introduction and the first move), move times, excess moves made (i.e. number of moves exceeding the minimum needed to solve the task), and number of trials in which the task was completed with the minimum number of moves.

► Multiple Errands Test (MET)[9]: This test was designed to provide an ecologically valid, real world assessment of planning behavior. The MET is a semiquantitative task that provides patients with relatively unstructured, open-ended situations with multiple subgoals without the constraint, structure, and direction typical of clinical neuropsychological measures. In this version, participants had to do eleven errands in a downtown, with the following tasks and rules.

► The d2 test [10] is used to assess IPS and selective attention. The test consists of 14 trials. Each trial is a row with 47 “p” and “d” characters being disposed adjacent to one another. The characters have one to four dashes that are configured individually or in pairs above and/or below each letter. The target symbol is a “d” with two dashes (either two dashes above the “d,” two dashes below the “d,” or one dash above and one dash below the “d”). Thus, all other items are distracters. The participants’ task is to cancel out as many target symbols as possible, moving from left to right, with a time limit of 20 s per trial. No pauses are allowed between trials. Performance speed can be defined as the (average) number of items worked in all trial and the number of incorrect responses (error percentage).

► The Paced Auditory Serial Addition Test [11] is used to assess IPS and working memory. A serie of 61 singles digits from 1 to 9 were randomly delivered at presentation rates of one number every three seconds. Subject have to add each digit to the one immediately preceding it: the second had to be added to the first, the third to the second, and so on. The analysed
variables of the PASAT were the number (and the percentage) of correct additions (maximum score 60) and dyad scores (two consecutive correct answers, maximum score 59).

**Psychological assessment**

► *Subjective cognitive decline*: The McNair & Kahn scale (McNair) [12] a 39-item self-rated questionnaire was used to assess the perceived frequency of day-to-day cognitive difficulties. Participants were asked to rate how often they experience cognitive difficulties on a Likert scale ranging from 0 = never to 4 = most of the time. The total score ranges from 0 to 96, with higher score indicating more SCD.

► *Fast-Screen Beck Depression Inventory (BDI-FS)* [13] is a screening tool for depressive symptoms, which avoid the considerable overlap between the vegetative symptoms of depressive disorder and the neurological manifestations of MS (e.g., insomnia, fatigue, weight loss, poor concentration), containing 13 items.

► *State Trait Anxiety Inventory (STAI-Y)* [14]: this self-report questionnaire measures the presence and severity of current symptoms of anxiety and a generalised propensity to be anxious. There are two subscales: 20 items allocated to each of the State Anxiety (SAnxiety) and Trait Anxiety (T-Anxiety).

► *Visual Analog Scale (VAS) of Fatigue* is used to assess level of fatigue. This VAS is a horizontal line of 100 millimeters, oriented from left to right, on which the patient locates the intensity of his fatigue.
References


