


Executive Abilities as Reflected by Clock Hand Placement: Frontotemporal Dementia Versus Early-Onset Alzheimer Disease

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Abstract

The clock-drawing test (CDT) is widely used in clinical practice to diagnose and distinguish patients with dementia. It remains unclear, however, whether the CDT can distinguish among the early-onset dementias. Accordingly, we examined the ability of both quantitative and qualitative CDT analyses to distinguish behavioral variant frontotemporal dementia (bvFTD) and early-onset Alzheimer disease (eAD), the 2 most common neurodegenerative dementias with onset <65 years of age. We hypothesized that executive aspects of the CDT would discriminate between these 2 disorders. The study compared 15 patients with bvFTD and 16 patients with eAD on the CDT using 2 different scales and correlated the findings with neuropsychological testing and magnetic resonance imaging. The total CDT scores did not discriminate bvFTD and eAD; however, specific analysis of executive hand placement items successfully distinguished the groups, with eAD exhibiting greater errors than bvFTD. The performance on those executive hand placement items correlated with measures of naming as well as visuospatial and executive function. On tensor-based morphometry of the magnetic resonance images, executive hand placement correlated with right frontal volume. These findings suggest that lower performance on executive hand placement items occurs with involvement of the right dorsolateral frontal-parietal network for executive control in eAD, a network disproportionately affected in AD of early onset. Rather than the total performance on the clock task, the analysis of specific errors, such as executive hand placement, may be useful for early differentiation of eAD, bvFTD, and other conditions.

Keywords

Alzheimer disease, frontotemporal dementia, executive functioning

Introduction

The clock-drawing test (CDT) is a popular screening tool for cognitive impairment in clinical practice and dementia research and has also been increasingly part of neuropsychological assessments. It is a particularly useful cognitive screening instrument in the clinic because of its brevity and ease of administration. Investigators have documented correlations of the CDT with cognitive measures, including the Mini-Mental State Examination (MMSE)^{1,2} and executive function testing (such as The Executive Interview (EXIT-25)),² a bedside measure of executive control³. The CDT taps different neuropsychological domains.⁴⁻⁶ Originally, clinicians viewed it primarily as a visuospatial task; later studies revealed the crucial involvement of executive functions in completing a normal clock drawing.⁷

The CDT requires participants to draw a clock and set the hands to a specific time designated by the experimenter.⁸ Clinicians and investigators have used multiple variations of the CDT for assessment.⁸ The numerous scoring systems for

evaluating CDT performance range from highly specific and quantitative to highly qualitative approaches. Mendez et al specifically defined and scored 20 aspects of the clock drawing,¹

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while Rouleau et al scoring system also assessed qualitative aspects including visuospatial (clock size, graphic quality, and spatial organization) and executive (pull-to-stimulus, difficulty generating concepts, and perseverative responses) functions.⁹ These findings indicate that the specific items and errors in these CDT scoring systems reflect disturbances in different cognitive abilities.

Previous research has focused on specific errors on the CDT for the early differentiation of Alzheimer disease (AD), frontotemporal dementia (FTD), Huntington disease, and subcortical vascular dementia.⁹⁻¹¹ For instance, Blair et al compared CDT performance in patients with FTD and AD as well as patients without dementia (the FTD cohort included patients with behavioral variant FTD [bvFTD], progressive nonfluent aphasia, or semantic dementia).¹⁰ Their results showed that the patients with FTD performed better than the AD group and had fewer stimulus bound responses, conceptual deficits, and spatial or planning errors. The authors attributed these findings to better-preserved visuospatial skills and conceptual abilities on the CDT in patients with FTD compared to AD. Altogether, both global and error analysis of the CDT helped discriminate the FTD group from controls and patients with AD. However, these authors did not specifically evaluate bvFTD compared to early-onset AD (eAD), disorders that have onset in midlife and that may be confused with each other.¹²⁻¹⁴

On the CDT, the individual items that reflect executive abilities may be especially useful in the clinical evaluation of bvFTD versus AD. Executive deficits are among the most sensitive measures for distinguishing between dementia syndromes.^{15,16} Decisions about hand placement require the executive ability of abstracting the concept of time and its specific indication on an analog clock face. Moreover, prior work suggests that decisions about the placement of the hands reflect executive abilities and may be better at differentiating dementias, rather than the total CDT score.^{9,10}

With regard to neuroanatomical correlates of the CDT, several types of imaging evidence support the participation of both cortical and subcortical regions in the performance on the clock-drawing task,¹⁷ and a functional magnetic resonance imaging (fMRI) study found activation in both frontal and parietal regions.¹⁸ Still, only a handful of studies have examined how specific types of errors on the CDT are linked with the neuropathological localization of the disease.^{19,20}

The primary objective of this study was to identify specific error patterns on the CDT that may be useful in the differential diagnosis of bvFTD and eAD—the 2 most common early-onset neurodegenerative dementias. We were specifically interested in evaluating items that potentially reflected executive abilities. Our initial hypothesis was that—while patients with AD seem to have less preserved visuospatial skills and conceptual abilities compared to bvFTD¹⁰—executive hand placement errors would be more common in bvFTD than in AD. For the analysis of clock-drawing performance in our cohort, we chose 2 scoring systems, which we considered to be representative of the many available clock tests: Mendez's highly quantitative scale because it includes an in-depth single item analysis,¹ and Rouleau's scale

because of its detailed qualitative error analysis.⁹ For comparison, we correlated clock-drawing performance with the results of cognitive testing in several neuropsychological domains, especially executive functions. Finally—since there is little knowledge about the neural correlates of specific CDT error patterns in the context of the early differentiation of dementia subtypes^{17,19,20}—a secondary aim of this study was to investigate neuroanatomical associations between our findings and regional brain volumes on MRI in order to illustrate the neuroanatomical correlation of executive deficits on the CDT. This approach has been successfully used to study clinical correlates of brain changes in neurodegenerative disorders²¹⁻²³ and, unlike other whole-brain volumetric methods, does not require a segmentation step, thus avoiding potential errors in accurate tissue classification.

Methods

Participants

A total of 31 participants, 15 with bvFTD and 16 with eAD, were recruited from an outpatient behavioral neurology clinic in an academic university medical center. Participants with bvFTD met criteria for probable bvFTD based on revised International Consensus Criteria.²⁴ Participants with eAD were diagnosed according to the National Institute of Neurological and Communicable Disease and Stroke–Alzheimer's Disease and Related Disorders Association for clinically probable AD.²⁵

This prospective study was reviewed and approved by the local institutional review board (IRB), and study participants were enrolled according to IRB guidelines.

The following inclusion criteria were applied to both patients with bvFTD and eAD (exclusion criteria were violations of these criteria):

All individuals had to be able to understand and complete the procedures and to take part in the tests (including hearing and understanding instructions as well as basic visual abilities). All participants had to possess willingness and ability to provide informed consent. The competency of participants was evaluated using a competency assessment form for informed consent that involved explaining the study to the patients (and potential side effects) and then assessing whether they had understood their options and choices. All participants provided written informed consent whenever they were able to give acceptable answers. In the case that potential participants were not able to give acceptable answers, we had IRB approval to obtain assent from them and surrogate written consent from their legally authorized representative. All individuals had to be English speaking or having acquired English prior to age 13 and using it as their primary language. They had to be medically stable (defined as absence of active medical illness or changes in medical management that would interfere with the participant's ability to understand and participate in the study procedures). Participants could not have a neurological or psychiatric illness other than bvFTD or clinically probable AD. In

addition, absence of cortical infarctions, other cortical lesions, or significant subcortical lesions on brain MRI was demanded. Finally, we required the presence of a caregiver who could facilitate the participation in this project. Where there was more than 1 caregiver, we designated the closest relative as the main caregiver.

Procedures

Clock-drawing test. The participants completed an examination with a neurologist that included a clock-drawing task, for which each participant was presented with a sheet of paper and a pen and given the instruction “Draw the face of a clock, put in all the numbers, and put the hands to read ten minutes after eleven”.

Each clock drawing was separately evaluated by 2 independent raters blinded to the individual patient’s diagnosis using 2 different methods: a 20-item scale (Mendez et al, 1992¹) and a variation of Rouleau et al’s (1992) quantitative and qualitative scoring system⁹ that did not include a copy condition.

Mendez’s scoring system¹. Total scores as well as different cluster scores were calculated (scoring 1 point for each item if its description was fulfilled, and 0 points if it was not; scores were calculated for each cluster by adding up the single item scores; the total score was established by adding up the scores of all 20 items of Mendez’s scale¹); cluster A refers to items 1 to 3 (general description of the clock drawing); cluster B refers to items 4 to 15 (mainly referring to the clock numbers); and cluster C refers to items 16 to 20 (description of the clock hands). In addition, we extracted for further analysis 4 hand placement items where there was investigator consensus that they reflected executive function and added up their scores to an “executive hand placement score.” Such items had previously been described and suggested to correspond with executive difficulty on the CDT.^{1,2,26,27} The executive hand placement items included:

- Item 4: A “2” is present and is pointed out in some way for the time.
- Item 16: All hands radiate from the direction of a closure figure center.
- Item 18: There are exactly 2 distinct and separable hands.
- Item 19: All hands are totally within a closure figure.

Rouleau’s scoring system⁹. Total scores on the 10-point quantitative scale as well as different item scores were established (with item 1 referring to the integrity of the clock face, item 2 to presence and sequencing of the numbers, and item 3 to the presence and placement of the hands).⁹ Qualitative error analysis was also performed using Rouleau’s system.⁹

Neuropsychological testing. Standardized neuropsychological tests²⁸ were administered to the patients as follows: we assessed gross cognitive functioning (MMSE, Frontal Assessment Battery), attention (digit spans), language (a 20-item

version of the Boston Naming Test [BNT], “Animals” verbal fluency), visuospatial skills (Wechsler Adult Intelligence Scale—Block design, Beery-Buktenica Developmental Test of Visual-Motor Integration), verbal (Consortium to Establish a Registry for Alzheimer’s Disease [CERAD]), and nonverbal (Wechsler Memory Scale-III visual reproduction) memory as well as frontal-executive functions (Delis-Kaplan Executive Functioning System [DKEFS]: Proverbs and Design Fluency, “F words” verbal fluency). Three participants were administered a 15-item version of the BNT, while the remainder of the sample was given the 20-item version, and the 15-item scores were converted to a 20-item metric. The Pyramids and Palm Trees test was also administered.²⁹

Caregiver informant measures. A research assistant obtained information from the patients’ caregivers using the Washington University Clinical Dementia Rating (CDR)³⁰ Scale and the Functional Activity Questionnaire (FAQ).³¹

Neuroimaging data acquisition/tensor-based morphometry analyses. The participants underwent MRI using a standardized protocol on the same 1.5T Siemens Avanto MRI scanner. High-resolution T1-weighted 3D MRI scans were acquired in the coronal plane using a Magnetization Prepared Rapid Gradient Echo (MP-RAGE) sequence with the following acquisition parameters: repetition time = 2000 ms, echo time = 2.49 ms, inversion time = 900 ms, flip angle = 8°, slice thickness = 1 mm, 25.6 cm field of view, and voxel size = 1.0 × 1.0 × 1.0 mm³. An automated brain surface algorithm, along with manual editing, was applied using BrainSuite software³² in order to generate a deskulled brain volume with the scalp and meninges removed. To adjust for global differences in brain positioning and scale across individuals, all scans were linearly registered to the stereotaxic space defined by the International Consortium for Brain Mapping³³ with a 9-parameter transformation. Globally aligned images were resampled in an isotropic space of 230 voxels for each axis (x, y, and z) with a final voxel size of 1 mm³.

To quantify 3D patterns of volumetric brain differences for each participant, tensor-based morphometry (TBM) was applied to compute individual change maps, or Jacobian maps, by nonlinearly registering each individual scan to a template using a nonlinear inverse-consistent elastic intensity-based registration algorithm, with a built-in smoothing kernel, driven by a mutual information-based cost function (3D moment invariants), which has been previously described.³⁴ For each participant, a map of the Jacobian determinants was computed from the gradient of the deformation field to illustrate the voxel-wise expansion or contraction factors of relative volume differences between each individual and the template. Mean Jacobian values within the frontal lobes were computed for each participant to provide a numeric summary of regional volume. All results and statistical analyses are based on the TBM Jacobian maps.

All algorithms were developed at the Laboratory of Neuro Imaging (LONI) and were implemented using the LONI Pipeline.³⁵

Table 1. Participant Demographics and Clinical Baseline Data.

	BvFTD (n = 15), Mean (SD)	eAD (n = 16), Mean (SD)	P Value
Age at study enrollment, years	62.3 (9.6)	59.3 (5.4)	.29
Sex (male/female)	8/7	6/10	.38
Race (white/Asian)	14/1	15/1	.96
Estimated age at disease onset, years	58.5 (8.8)	55.8 (6.3)	.32
Years since disease onset	3.8 (3.3)	3.5 (2.1)	.76
Years of education	15.5 (2.3)	16.4 (2.3)	.31
Handedness ^a : right/left/ambidextrous	13/2/0	11/3/1	.51
MMSE (total score)	25.1 (4)	24.9 (4)	.93
FAQ (total score)	17.4 (6.7)	10 (6.4)	.004
CDR Sum Box	6.8 (2.1)	3.6 (1.6)	.00

Abbreviations: BvFTD, behavioral variant frontotemporal dementia; eAD, early-onset Alzheimer's disease; MMSE, Mini-Mental State Examination; FAQ, Functional Activity Questionnaire (data missing for 1 participant); CDR Sum Box, Clinical Dementia Rating Scale (Sum of Boxes).

^aData missing for one participant.

Descriptives and Statistical Analyses

Descriptive statistics and frequencies were outlined in each diagnostic group with respect to participant demographics, baseline clinical features, caregiver informant measures, neurocognitive tests, CDT parameters, and neuroimaging.

In order to assess interrater reliability on the CDT evaluation, kappa scores were calculated for all individual items on Mendez's,¹ and items 1 to 3 on Rouleau's⁹ quantitative scoring system and averages were computed.

Independent samples *t* test was used to determine group differences on demographic variables (including age, education, estimated age at disease onset, and time since disease onset), caregiver informant measures, most numeric CDT scores, and neuroimaging. With regard to the neurocognitive measures, independent samples *t* test was used for normally distributed data, while Mann-Whitney *U* test was applied to data that was not normally distributed.

Chi-square analysis was utilized to analyze differences in sex, race, and handedness as well as group differences for all individual items on Mendez's quantitative scoring system¹ (for the latter, analysis was performed adding the scores of both raters for every item) and qualitative CDT errors.

In addition, receiver operating characteristic (ROC) analysis was performed for the CDT total scores (for both scoring systems) and the executive hand placement score (for the latter, binary logistic regression was also performed) with regard to the differentiation of the 2 diagnostic groups. Partial correlations were performed to analyze the relations between the executive hand placement score, cognitive measures, and frontal lobe volume. All statistical analyses were carried out using SPSS 20/21.0.

Results

Participants—Baseline Characteristics

There were no significant group differences on any demographic variables including patient age, sex, race, estimated age at disease onset, years since disease onset, and years of education

between patients with bvFTD and eAD (see Table 1). The 2 groups also did not differ significantly with respect to clinical baseline characteristics such as handedness and the MMSE (total score); however, there was a significant difference on the CDR Sum of Boxes and FAQ (total score) with higher scores in the bvFTD group, indicating more functional impairment ($P < .01$ respectively, see Table 1). Concerning the global score on the CDR, no statistical analysis was performed due to the small sample size: 1 patient had a score of 0 in the eAD group (none in the bvFTD group), 2 patients with bvFTD and 9 patients with eAD had a score of 0.5, 10 patients with bvFTD and 6 patients with eAD had a score of 1 and 3 patients with bvFTD (none of the eAD) had a score of 2.

Neuropsychological Testing

The performance of both patients with bvFTD and eAD on neuropsychological testing is depicted in Table 2. There was no significant difference between both diagnostic groups with regard to the tests for gross cognitive screening, attention, language, visuospatial abilities as well as nonverbal memory. As expected, the patients with eAD showed worse performance ($P = .04$) on delayed free recall of the CERAD, a test of verbal memory, and the bvFTD group did worse concerning the DKEFS Proverbs Test ($P = .01$) as well as the Verbal Fluency ("F-words") test ($P = .004$), both measures of executive function. For Design Fluency, no significant group difference was noted with regard to "Total correct", but the patients with eAD had more rule violations ($P = .01$) and the patients with bvFTD showed more repeats ($P < .01$).

Clock-Drawing Test Performance

The average of the kappa scores for all individual items on Mendez's quantitative scoring system¹ was 0.64. When we excluded item 3 from the analysis because of a constant rating from 1 rater, this yielded an average kappa score of 0.68. This suggests good interrater agreement. Computing a similar analysis for items 1 to 3 of Rouleau's quantitative scoring system⁹

Table 2. Neuropsychological Testing.

Neurocognitive Task	n	BvFTD	n	eAD	P	Z ^a
MMSE, total score ^b	15	25.1 (4)	16	24.9 (4)	.93	
Frontal Assessment Battery (FAB), total score ^b	14	11.1 (5.2)	15	12.7 (4.1)	.39	
Digit Span Forward, longest # digits ^a	15	16.8	16	15.2	.59	−0.5
Mini-Boston Naming Test (20 item) ^a	15	14.2	16	17.7	.27	−1.1
Verbal Fluency, animals (total correct) ^a	14	15.4	16	15.6	.97	−0.04
WAIS-III Block design (total score) ^b	13	22.1 (13.1)	16	16.5 (12.4)	.25	
WAIS-III Block design (scaled score) ^b	13	7.1 (3.6)	16	5.6 (3.6)	.27	
Beery™ VMI (total correct) ^a	13	15.3	15	13.8	.63	−0.5
CERAD, delayed free recall, # correct ^a	15	19.3	16	12.9	.04	−2.0
CERAD, delayed recognition, # true positives ^a	14	14.9	16	16.1	.7	−0.39
WMS-III Visual Reproduction, immediate recall ^a	13	15	13	12	.3	−1.03
WMS-III Visual Reproduction, delayed recall ^a	12	14.3	13	11.9	.33	−0.99
Digit Span Backward, longest # digits ^a	15	14	16	17.9	.21	−1.3
Pyramids and Palm Trees (total correct) ^a	13	12	15	16.6	.14	−1.49
DKEFS Proverbs (correct # out of 8) ^a	15	11.7	16	20	.01	−2.6
Verbal Fluency, F words (total correct) ^a	14	10.6	16	19.8	<.01	−2.9
DKEFS Design Fluency	12		12			
Total correct ^b		16 (14.1)		13.7 (8)	.62	
Repeats ^a		18		7	<.01	−3.8
Rule violations ^b		3.6 (2.7)		6.9 (3.3)	.01	

Abbreviations: BvFTD, behavioral variant frontotemporal dementia; eAD, early-onset Alzheimer's disease; n, number of participants within group with available data; MMSE, Mini-Mental State Examination; WAIS, Wechsler Adult Intelligence Scale; Beery VMI (Beery–Buktenica Developmental Test of Visual-Motor Integration); CERAD, Consortium to Establish a Registry for Alzheimer's Disease; WMS, Wechsler Memory Scale; DKEFS, Delis–Kaplan Executive Functioning System.

^aMann-Whitney *U* test: mean rank, *P*- and *Z*-values reported.

^bIndependent samples *t* test: mean (SD) and *P* value reported.

Table 3. CDT Performance.

	BvFTD (n = 15), Mean (SD)	eAD (n = 16), Mean (SD)	P
Mendez's scoring system ¹			
Total score	17.4 (2.4)	16.1 (4.3)	.31 ^a
Cluster A score	2.8 (0.4)	2.6 (0.5)	.40 ^a
Cluster B score	10.4 (2.0)	9.9 (2.8)	.58 ^a
Cluster C score	4.2 (0.5)	3.6 (1.4)	.09 ^a
Executive hand placement score	3.6 (0.5)	2.7 (1.2)	.02 ^b
Rouleau's scoring system ⁹			
Total score	8.2 (2.2)	7.2 (2.5)	.26 ^a
Item 1 score (clock face)	1.9 (0.4)	1.7 (0.5)	.21 ^a
Item 2 score (numbers)	3.3 (1.2)	3.2 (1.0)	.84 ^a
Item 3 score (hands)	3.1 (0.9)	2.4 (1.4)	.11 ^a

Abbreviations: BvFTD, Behavioral variant frontotemporal dementia; eAD, early-onset Alzheimer disease.

^aIndependent samples *t* test.

^bMann-Whitney *U* test: *U* = 63, *Z* = −2.32, *P* = .02.

yielded an average kappa score of 0.504 (fair agreement). Thus, we created averages between both raters for all numerical clock items.

Mendez's scoring system¹. The overall results of both diagnostic groups on the Mendez's scoring system are included in Table 3. There were no significant differences between the bvFTD and the eAD groups on the total CDT score, the scores on clusters A to C, and the single items (with the exception of item 18 [*P* = .02], which was missed significantly more frequently in the eAD group).

Executive hand placement (see Figure 1): a significant difference between both diagnostic groups was detected for the executive hand placement score, with the patients having eAD performing worse than the patients having bvFTD (Mann-Whitney *U* test: *P* = .02). On ROC analysis, the area under the curve (AUC) was highest for the executive hand placement score (AUC = 0.74, *P* = .02) compared to the CDT total scores: AUC = 0.59, *P* = .41 (Mendez) and AUC = 0.63, *P* = .24 (Rouleau; see Figure 2).

A logistic regression analysis was conducted to predict group membership using the executive hand placement score

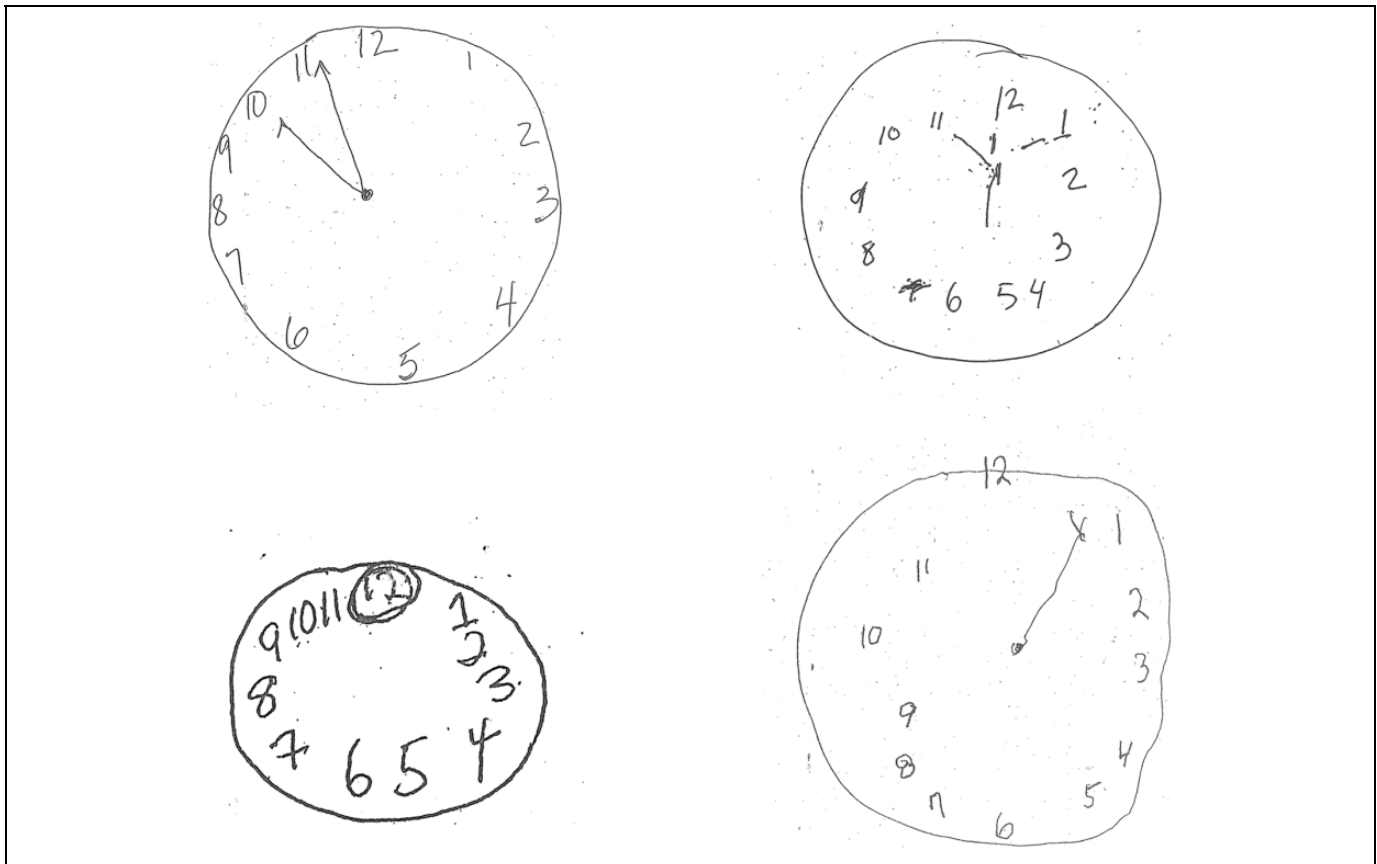


Figure 1. Examples of executive placement hand errors on the CDT in our cohort. Upper left, Concrete error with misplacement of the minute hand. Upper right, more than 2 hands are indicated. Lower left, absence of clock hands. Lower right, the hands do not radiate from the direction of a closure figure center.

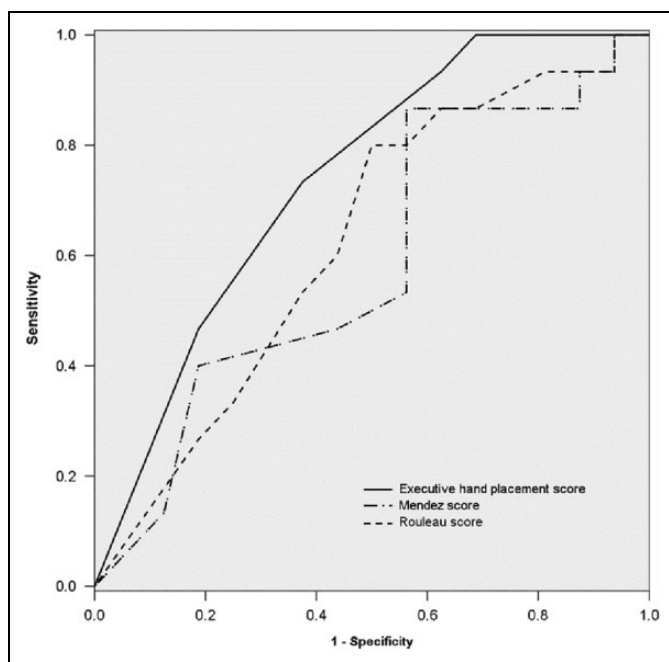


Figure 2. ROC analysis—areas under the curve (AUC). Executive hand placement score: AUC = 0.74, $P = .02$. Total score (Mendez): AUC = 0.59, $P = .41$. Total score (Rouleau): AUC = 0.63, $P = .24$.

and showed that using this score significantly distinguished the 2 diagnostic groups (model: $\chi^2 = 7.36$, $df = 1$, $P = .01$; variable [executive hand placement score]: $B = -1.36$, standard error = 0.65, Wald = 4.41, $df = 1$, $P = .04$, $\text{Exp}(B) = 0.26$, 95% confidence interval for $\text{Exp}(B)$: 0.07-0.91).

Rouleau's scoring system⁹. There were no significant group differences between diagnostic groups on the total score and the scores on items 1 to 3. In addition, there were no significant group differences on most qualitative errors except for graphic difficulties ($P = .03$), planning deficits ($P = .03$), and deficits in spatial layout of numbers ($P = .01$), which were worse in the patients with eAD versus the patients with bvFTD (according to 1 rater each).

Correlations Between the Executive Hand Placement Score and Cognitive Measures (Controlling for Age and Diagnosis)

There were significant positive correlations between the executive hand placement score and the Block design test (total score: $r = .61$, $P = .02$; scaled score: $r = .61$, $P = .02$), the Pyramids and Palm Trees test ($r = .61$, $P = .02$), and the 20-item version of the BNT ($r = .6$, $P = .03$), and a nonsignificant

positive trend with the “Animals” test of verbal fluency ($r = .52$, $P = .06$).

Correlations Between the Executive Hand Placement Score and Neuroimaging

Twenty-four participants (12 in each diagnostic group) underwent neuroimaging. The bvFTD group had significantly lower ($P < .01$) total frontal (mean \pm standard error [SD]: bvFTD: -0.9 ± 0.94 , eAD: 0.83 ± 1.2) and left frontal volume (mean \pm SD: bvFTD: -1.07 ± 1.4 , eAD: 1.22 ± 2.1) compared to the eAD group; the bvFTD group also had lower right frontal volume (mean \pm SD: bvFTD: -0.74 ± 2.1 , eAD: 0.46 ± 1.3), but the difference did not reach significance ($P = .1$). The only significant positive correlation between the executive hand placement score and neuroanatomical location was with right frontal volume (controlling for age and diagnostic group; $r = 0.59$, $P \leq .01$).

Discussion

This study compared 15 patients with bvFTD and 16 patients with eAD on the CDT using 2 different scales. The total CDT scores did not discriminate bvFTD and eAD; however, specific analysis of executive hand placement items successfully distinguished the groups, with eAD exhibiting greater errors than bvFTD. The performance on the executive hand placement items correlated with measures of naming as well as visuoexecutive function on neuropsychological testing. On TBM of the magnetic resonance images, executive hand placement correlated with right frontal volume.

Contrary to the findings of other studies,^{10,36} we found no significant differences between the diagnostic groups on the total scores and most item clusters (on both scoring systems). Altogether, using the 2 chosen scales in their original version did not result in relevant distinction between the 2 diagnostic groups. However, the specific analysis of the executive hand placement items distinguished bvFTD and eAD. Contrary to our initial hypothesis of greater executive difficulties among the patients with bvFTD, the patients with eAD exhibited greater errors than the bvFTD group on 4 specific items on Mendez's scale. These items corresponded to abnormalities on neuropsychological tests reflective of visuoexecutive dysfunction, such as the Block design test and Pyramids and Palm Trees test, and appeared to reflect executive aspects of clock hand placement.

Recent studies of eAD, in particular, are consistent with greater executive dysfunction compared to late-onset AD³⁷ and involvement of a dorsolateral frontal-parietal “executive-control” circuit.³⁸ Neuropsychological comparisons of eAD with late-onset disease demonstrate a greater decline in executive abilities in the early-onset form.³⁹⁻⁴¹ Moreover, investigations employing fMRI and FDG-PET (positron emission tomography with 2-deoxy-2-[¹⁸F]fluoro-D-glucose) measures indicate decreased connectivity of the frontal-parietal executive-control network in patients having eAD with a consequent effect on

executive abilities.^{37,42} Leyhe was able to show that patients with early AD could be discriminated from healthy control persons and participants with mild cognitive impairment solely by misplacement of the minute hand in clock drawing and clock setting, while patients with progressed AD showed significantly more impairment in all clock test variants.⁴³ Our findings are in line with those studies and indicate that clock hand placement requires executive function disproportionately affected in AD of early onset. These studies—along with our data—also illustrate the potential value of executive hand placement analysis, particularly of the minute hand, for the early diagnosis of AD.

So far, it has been difficult to establish a cognitive profile for patients with bvFTD, due to an important overlap in cognitive performance with patients having AD.⁴⁴

As expected, in our study, the patients with eAD showed worse performance on testing of verbal memory and the bvFTD group on measures of executive function.

Significant positive correlations were observed between the executive hand placement score and the Block design test (a measure of visuoexecutive function), as well as the Pyramids and Palm Trees test (that reflects semantic abilities and also has a visuoexecutive abstraction component), but no significant correlations were found with other neuropsychological measures felt to reflect executive abilities. In addition, there were positive correlations with some measures of language. This indicates that the executive hand cluster score mainly represents executive functions, but not exclusively, because the correct placement of the clock hands also requires a semantic concept of a clock, its hands, and time setting.

The analysis of neuroimaging showed an association between worse performance on the executive hand placement items and decreased right frontal volume. A prior study suggests the participation of both cortical and subcortical regions in the clock-drawing task,¹⁷ and a fMRI study found activation in both frontal and parietal regions.¹⁸ Still, only a handful of studies have examined how specific types of errors on the CDT are linked with neuroanatomy.^{19,20} Our study supports the findings of Matsuoka, who identified a significant positive correlation between a “hand score” (using the Rouleau scale) and regional cerebral blood flow in the right middle frontal gyrus (in addition to the bilateral parietal lobes, the right posterior temporal lobe, and the right occipital lobe) in patients with AD.²⁰

Alzheimer disease, particularly of early onset, involves the frontal lobes and related executive functions. Möller, for instance, characterized the involvement of the inferior frontal cortex in eAD.⁴⁵ The subcallosal medial prefrontal cortex has been delineated as a common site of frontal atrophy in both AD and FTD.⁴⁶ Ventre-Donney suggested that a spatial working memory task activated a dorsal pathway distributed between the parieto-occipital and dorsal prefrontal cortex, predominantly in the right hemisphere.⁴⁷ Other studies have suggested involvement of the frontoparietal network in visuo-motor⁴⁸ and attention control.⁴⁹ Possin described more repetition errors on the design fluency task in bvFTD compared to AD, which corresponds to

our findings.⁵⁰ These errors significantly correlated with atrophy in the right and left orbitofrontal cortex, the right and left superior frontal gyrus, the right inferior frontal gyrus, and the right striatum but did not correlate with volumes in any parietal or temporal lobe regions.⁵⁰ Specifically, the right and left lateral orbitofrontal cortex appeared to be crucial for preventing repetition errors.⁵⁰ Again, these authors also observed more correlations of these errors with the lateral prefrontal cortex and with the striatum in the right hemisphere,⁵⁰ which supports the view that right frontal systems are involved in visuoexecutive monitoring and disturbed in executive hand placement errors.^{51,52}

Altogether, these studies and our findings suggest that clock hand placement is a complex skill that requires not only visuospatial abilities but right frontal visuoexecutive functions as well.

There are several limitations of this study. First of all, the numbers of participants were relatively small. Nevertheless, they are sufficient to demonstrate statistically significant differences on the executive hand placement items and other measures. Second, the results were contrary to what was predicted. We interpret this as changes in the frontoparietal executive-control system discussed as part of eAD. Third, the determination of the executive hand placement items was arrived at by investigator consensus based on prior literature, rather than by correlation with executive neuropsychological tests. However, the neuropsychological tests included here may not have been sufficient or sensitive enough to detect changes in executive function. Fourth, the groups were not balanced for disease severity, which may have impacted our findings. Nevertheless, the fact that the bvFTD group was more severely affected than the eAD group, in the context of our findings would suggest an underestimation of the extent of executive impairment in the eAD group. Finally, the study was limited to 2 CDT scales. Clearly, there are many other scoring methods; however, it is not practical to examine all of them in one cohort. Instead, this study chose one representative quantitative and one representative qualitative scale.

In conclusion, hand placement on the CDT, together with other behavioral and cognitive findings, may be of use in the clinical setting for the early differential diagnosis of bvFTD and eAD. These findings are only preliminary. Further studies are needed on larger samples and other patients with dementia in order to evaluate the usefulness of the hand placement findings in the evaluation of other dementias and of older patients with dementia.

Authors' Note

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Declaration of Conflicting Interests

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