CLOX: an executive clock drawing task

Donald R Royall, Jeffrey A Cordes, Marsha Polk

Abstract

***Objective*—To describe a clock drawing task (CLOX) designed to elicit executive impairment and discriminate it from non-executive constructional failure.**

***Subjects*—90 elderly subjects were studied (45 elderly and well persons from the independent living apartments of a continuing care retirement community and 45 patients with probable Alzheimer's disease). The clock drawing performance of elderly patients was compared with that of 62 young adult controls.**

***Methods*—Subjects received the CLOX, an executive test (EXIT25), and the mini mental state examination (MMSE). The CLOX is divided into an unprompted task that is sensitive to executive control (CLOX1) and a copied version that is not (CLOX2). Between rater reliability (27 subjects) was high for both subtests.**

***Results*—In elderly subjects, CLOX subscores correlated strongly with cognitive severity (CLOX1: r=−0.83 *v* the EXIT25; CLOX2: r=0.85 *v* the MMSE). EXIT25 and MMSE scores predicted CLOX1 scores independently of age or education ($F(4,82)=50.7$, $p<0.001$; $R^2=0.71$). The EXIT25 accounted for 68% of CLOX1 variance. Only the MMSE significantly contributed to CLOX2 scores ($F(4,72)=57.2$, $p<0.001$; $R^2=0.74$). CLOX subscales discriminated between patients with Alzheimer's disease and elderly controls (83.1% of cases correctly classified; Wilkes' lambda=0.48, p<0.001), and between Alzheimer's disease subgroups with and without constructional impairment (91.9% of cases correctly classified; Wilkes' lambda=0.31, p<0.001).**

***Conclusions*—The CLOX is an internally consistent measure that is easy to administer and displays good inter-rater reliability. It is strongly associated with cognitive test scores. The pattern of CLOX failures may discriminate clinical dementia subgroups.**

(*J Neurol Neurosurg Psychiatry* 1998;**64**:588–594)

Keywords: dementia, Alzheimer's, executive, assessment

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Received 11 April 1997 and in revised form 29 July 1997
Accepted 3 October 1997

There is a growing interest in the potential of clock drawing tests (CDTs) as a screen for cognitive impairment.[1–7] CDTs have been found to correlate significantly with traditional cognitive measures[1 2 4 5] and to discriminate healthy from demented elderly patients.[8] The severity of clock drawing failures progresses over time in Alzheimer's disease, and correlates with longitudinal changes in cognitive testing.[5 9] Moreover, CDTs are rapid and well accepted.[5]

Unfortunately, CDTs still have both conceptual and practical limitations. Conceptually, clock drawing has been viewed as a visuospatial task, sensitive to right perietal pathology.[10–12] Recent studies undermine this notion, however. For example, CDT failure has been shown to be a state dependent feature of major depression.[13] Whereas Alzheimer's disease may be associated with signs of right hemispheric impairment (visual agnosia and apraxia), major depression generally is not. Failures of CDTs in non-cortically impaired subjects undermine a chiefly visuospatial conceptualisation of the CDT.[14]

Practical limitations arise from the fact that there is no consensus regarding CDT rating. This is a problem because a patient's performance may vary greatly as a function of the task itself. Patients with Alzheimer's disease have been reported who can construct perfectly adequate copies of a clock face, yet are unable to draw a clock when given a blank piece of paper to work from.[15] The available CDT rating schemes vary widely on the stimuli given to the subject, the time to which the clock is set, and the elements considered during scoring. Moreover, there are qualitative differences in how dementia subgroups fail a clock drawing task even if they are equated for overall severity of dementia.[9 15] These qualitative differences must be acknowledged in scoring a CDT if it is not to be biased by the presentation of a single dementia syndrome.[16]

We propose that the concept of "executive control" has the potential to greatly improve CDT interpretation. Executive control functions (ECFs) guide complex goal directed behaviour in the face of novel, irrelevant, or ambiguous environmental cues.[17 18] Examples of ECFs include goal selection, planning, motor sequencing, selective attention, and the self monitoring of a subject's current action plan. All are required by clock drawing. Impairment of ECF was added in 1994 to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition's definition of dementia.[19]

Neuropsychological test scores generally reflect the integrity of both the cognitive domain in question and its executive control. In the case of clock drawing, a subject's performance requires the separate analysis of visuoconstructional praxis and the executive control demanded by the testing paradigm. The relative variance in CDT performance explained by ECF remains to be determined. This is because (1) current CDT rating schemes are designed to elicit constructional

Table 1 Mean (SD) for selected clinical variables by group

Variable	*Young adult controls (n=62)*	*Independent living retirees (n=45)*	*Probable AD (n=45)*	*AD cases with MMSE constructional errors (n=19)*	*AD cases without MMSE constructional errors (n=26)*
Age (y)	24.4 (4.3)	76.0 (11.6)*	75.8 (8.5)*	73.8 (9.2)*	76.5 (7.9)*
Education (y)	14.6 (1.2)	14.9 (2.2)	12.7 (2.8)* ***	13.4 (2.1)* ***	12.2 (3.1)* ***
EXIT25	4.2 (2.2)	8.8 (3.7)*	26.8 (7.5)* ***	31.1 (6.9)* ***	23.7 (6.3)***‡‡‡
MMSE	29.3 (0.9)	29.1 (1.3)	16.4 (6.9)* ***	12.0 (6.7)* ***	19.7 (5.0)***‡‡‡
CLOX1	13.2 (1.6)	12.1 (2.6)*	4.6 (4.5)* ***	2.1 (3.3)* ***	6.5 (4.4)***‡‡‡
CLOX2	14.2 (1.2)	14.2 (1.0)	8.3 (5.3)* ***	3.4 (3.9)* ***	12.0 (2.4)***‡‡‡

AD=Alzheimer's disease.
*P<0.05 *v* young adults.
***P<0.001 *v* well elderly cases.
‡‡‡P<0.001 *v* patients with AD with MMSE constructional impairment.

failures rather than ECF related failures, (2) bedside mental status examinations are either indirectly sensitive to ECF failures or ignore them altogether, and (3) the possible qualitative differences in CDT failures arising from true constructional as opposed to ECF related pathology are not routinely assessed.[20] Although several authors have commented on the sensitivity of CDTs to "abstract" thinking or "complex behaviour", there have been no efforts to grade the CDT as an executive task, nor to divorce the executive control of clock drawing from drawing itself. We expect that a significant proportion of the variance in CDT failures is in fact the product of executive dyscontrol. In this paper, we describe a clock drawing task which has been designed specifically to discriminate executive and non-executive elements.

Methods

SUBJECTS

The CLOX instrument was first piloted in a sample of 62 young adult undergraduates (mean age 24.4 (SD 4.3) years) attending the University of Texas at San Antonio. This reference group was compared with 90 elderly subjects, selected from two clinical settings. Forty five were recruited from the independent living apartments of a large retirement community. All were free of depression and self reported impairment in activities of daily living. The mean geriatric depression scale (GDS short form)[21] score was 1.2 (SD 1.5). Scores >07/25 are considered "depressed". The mean independent activities of daily living score for this group was 13.7 (SD 0.77). We further required that these cases scored no less than 1.0 SD below the mean for *25* year old subjects on both the verbal and performance subscales of the Weschler adult intelligence scale. This helps to assure us that the elderly control group is free of incipient dementias. Less than 25% of independent living septuagenarians at this retirement community can pass this stringent criterion. Informed consent was obtained before the evaluation of both control groups.

The remaining 45 elderly subjects were outpatients diagnosed with probable Alzheimer's disease using National Institute of Neurological Communicative Disorders and Stroke (NINCDS) criteria.[22] All had undergone comprehensive geriatric assessments, including examination by a geropsychiatrist. Each received a history, physical examination, mental state examination, neuropsychological testing, and functional status evaluation. Clinical data were confirmed by family members or other available caregivers. All pertinent laboratory results and neuroimaging studies were reviewed. The patients with Alzheimer's disease were further divided into those with (n=19) and those without (n=26) gross constructional impairment on the mini mental state examination (MMSE). Table 1 compares these groups on selected clinical variables.

INSTRUMENTS

Subjects were interviewed by trained physicians using the CLOX, EXIT25, and MMSE. The CLOX was scored blind to the other instruments. Each instrument is briefly described below.

The executive clock drawing task (CLOX)

The CLOX has been divided into two parts to help discriminate the executive control of clock drawing from clock drawing itself. The patient is first instructed to draw a clock on the back of the CLOX form (see fig 3). He or she is instructed only to "Draw me a clock that says 1:45. Set the hands and numbers on the face so that a child could read them." The instructions can be repeated until they are clearly understood, but once the subject begins to draw no further assistance is allowed. The subject's performance is rated according to the CLOX directions, and scored as "CLOX1".

CLOX1 reflects performance in a novel and ambiguous situation. The patient is presented only with a blank surface and no further guidance regarding the task. He or she is responsible for choosing the clock's overall form (a digital or analog face, alarm clock, wrist watch, or wall clock, etc), its size, position on the paper, elements (hands, numbers, date indicators), the forms of these elements (hands as arrows, relative lengths, roman *v* arabic numerals, etc). Furthermore, the patient must also initiate and persist in clock drawing through a sequence of constructional actions (usually drawing the outer circle, followed by placing the numbers if any, followed by setting the time). Finally, he or she must monitor progress as the task unfolds, both anticipating (placing the 12, 6, 3, and 9 first) and/ or correcting errors as they occur.

It is just as important to note what a patient *does not do* during a clock drawing task. Our CLOX form and its verbal instructions have been designed to distract the subject with

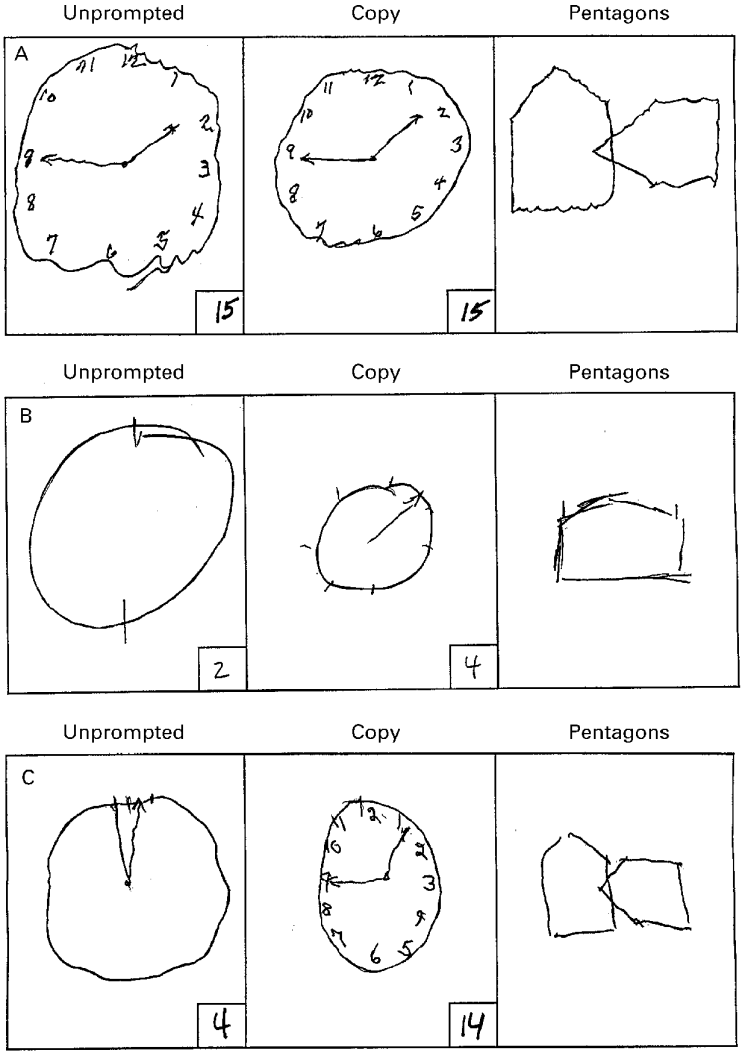

Figure 1 Qualitative differences in CLOX performance. in a normal elderly control, a patient with Alzheimer's disease, and a patient with non-cortical vascular disease. (A) An 82 year old elderly control. EXIT25=08/50 (scores>5/50 impaired), MMSE=29/30 (scores<24/30 impaired). (B) A 74 year old married white woman with Alzheimer's disease. EXIT25=21/50(24/50 comparable with six year old children or residents requiring skilled nursing), MMSE=12/30. (C) A 74 year old right handed white man with a history of coronary artery disease (status post myocardial infarction), hypertension, non-insulin dependent diabetes mellitus, and falls. EXIT22=24/50, MMSE=28/30.

strongly associated but irrelevant cues. The circle in the left lower corner is irrelevant to clock drawing when viewed from the reverse side of the form, but it tempts the patient to place their clock within its image. We chose the words "hand" and "face" because they are more strongly associated with body parts than clock elements, and may trigger semantic intrusions from their more common meanings. The number "45" does not appear on a typical clock face, and may intrude into the patient's construction in the form of a digital image (1:45) or hands pointing to the four or five o'clock positions. CLOX scores range from 0–15. Lower scores reflect greater impairment.

The CLOX's second step is a simple copying task. The examiner allows the patient to observe him or her drawing a clock in the circle provided on the scoring sheet. The examiner sets the hands again to "1:45", places the 12, 6, 3, and 9 first, and makes the hands into arrows. The patient is allowed to copy the examiner's clock. This clock is scored as "CLOX2". The difference between CLOX scores 1 and 2 is hypothesised to reflect the specific contribution of executive control versus visuospatial praxis to overall clock drawing performance assessed by CLOX1. Assuming that right parietal cortical function has not been compromised, lesions to the frontal systems controlling clock drawing should affect CLOX1 more than CLOX2. This could occur in major depression, non-cortical dementias, or frontal type dementias that spare posterior cortical regions. If the right cortical hemisphere is affected, both scores should suffer.

Figure 1 presents the clock drawing performance of a non-demented elderly control versus two demented patients who have been matched to their overall level of executive control. Each patient's pentagon drawing from the MMSE[23] has been included for comparison. Note that the pentagons in the MMSE are essentially a copying task that depends little on executive control.

Patient A is an independent elderly control. The presence of an essential tremor does not affect CLOX scoring. Patient B has Alzheimer's disease. Clock drawing is impaired in both unprompted and copy conditions. The MMSE has an inherent bias towards cortical type dementia features.[24] This is reflected by impairment in patient B's MMSE pentagons and total MMSE score. Patient C has a vascular dementia without cortical features. Only the unprompted clock drawing task is affected. This patient's MMSE pentagons and total MMSE score is within that instrument's normal range.

Table 2 Pearson product moment correlations for selected clinical variables

	Age	*Education*	*EXIT25*	*MMSE*	*CLOX1*
Education	0.05				
EXIT25	0.02	−0.40*			
MMSE	−0.05	0.39*	−0.92*		
CLOX1	−0.08	0.36*	−0.83*	0.82*	
CLOX2	−0.10	0.24*	−0.79*	0.85*	0.79*

*P<0.05.

THE EXECUTIVE INTERVIEW (EXIT25)

The EXIT25 is a bedside measure of executive control.[25 26] It defines the behavioural sequelae of executive dyscontrol and provides a standardised clinical encounter in which they can be observed. EXIT25 scores correlate well with other measures of ECF including the Wisconsin card sort (r=0.54), trail making part B (r=0.64), the test of sustained attention (time, r=0.82; errors, r=0.83) and Lezak's tinker toy test (r=0.57). EXIT25 scores also seem to correlate strongly with mesiofrontal cerebral blood flow by single photon emission computed tomography (SPECT).[27]

EXIT25 scores range from zero to 50. Higher scores suggest greater impairment. A cut off point of 15 out of 50 best discriminates non-demented elderly controls from both cortical and non-cortical dementing illness (SE=0.93, SP=0.83; area under receiver operating curve (ROC), c=0.93).[28] An EXIT25 cut off point of 10/50 best discriminates young adults with and without mesiofrontal perfusion

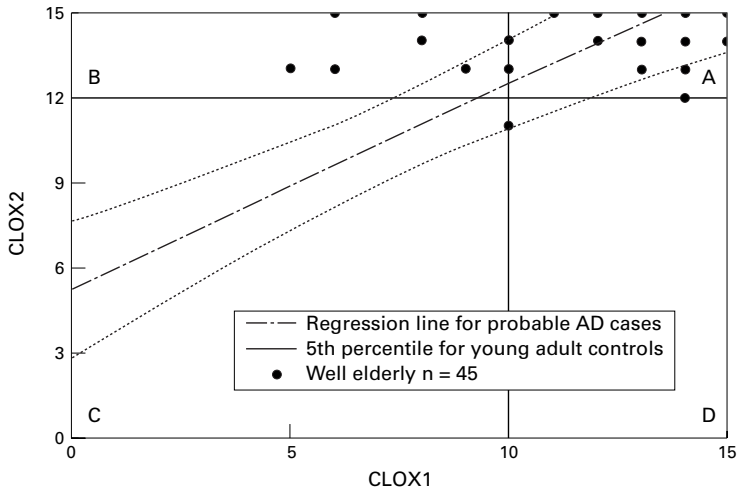

Figure 2 Scatterplot of CLOX1×CLOX2 scores for 45 independent and well elderly subjects. Regression line for 45 patients with probable Alzheimer's disease superimposed.

deficits after anterior cerebral artery aneurysmectomy.[27] The EXIT25 is more sensitive than the MMSE to early cognitive impairment and non-cortical dementia in elderly subjects.[24 26]

THE MINI MENTAL STATE EXAM (MMSE)

The MMSE is a familiar instrument.[23] It has been criticised for insensitivity in early dementia, and poorly educated subjects.[28] In our experience, the MMSE is also selectively biased against the detection of isolated frontal system disease.[24 29] We hypothesise that in the absence of posterior cortical type constructional impairment, CLOX scores will be more sensitive to dementia than the MMSE. The MMSE was obtained blind to the subjects' EXIT25 and CLOX scores.

Results

RELIABILITY

The internal consistency of the CLOX in this sample was high (Chronbach's α=0.82). Item total correlations ranged from r=0.32 to 0.77 (mean r=0.41). No item improved Chronbach's α if removed. The CLOX's between rater reliability was determined in a subset of 27 elderly subjects. The subjects' clocks were examined by two blind raters in the absence of clinical or demographic information. A high degree of between rater reliability was found (CLOX 1: r=0.94, CLOX 2: r=0.93; both p<0.001) (item 5 was excluded from this analysis).

CONSTRUCT VALIDITY

Scores for CLOX correlated strongly with cognitive impairment (EXIT25 and MMSE scores)(table 2). These instruments made significant contributions to CLOX1 scores after adjusting for age and education (F(4,82) =50.7, p<0.001; R^2=0.71). In a forward stepwise least squares regression model, the EXIT25 entered first, accounting for 68% of variance in CLOX1 scores (partial R^2=0.68). The MMSE entered next (partial R^2=0.03). Age did not contribute significantly to the model after adjusting for the EXIT25 and MMSE. Education failed to enter. By contrast, only the MMSE significantly contributeed to a similar model of CLOX2 scores (F(4,72) =57.2, p<0.001; R^2=0.74). It accounted for 72% of CLOX2 variance after adjusting for age and education. The EXIT25 failed to enter. Tolerance for these analyses was set to 0.15 to avoid possible multicolinearity.

The relative contributions of ECF (EXIT25) and constructional praxis to unprompted clock drawing (CLOX1) can be estimated by using CLOX2 scores as a proxy for constructional praxis. Together, the EXIT25 and CLOX2 explained 74% of the variance in CLOX1 scores (F(2,86)=120.98, p<0.001; R^2=0.74). The EXIT25 was responsible for 93% of the variance in CLOX1 scores (partial R^2=0.69).

DISCRIMINANT VALIDITY

We have examined the CLOX's ability to make two clinically important discriminations; firstly, between well elderly subjects and patients with Alzheimer's disease, and secondly, between Alzheimer's disease subgroups who present with and without gross constructional impairment. CLOX subscales discriminated Alzheimer's disease cases from elderly controls after adjusting for age, education, and MMSE test performance (MANCOVA: R(2,81)=3.6, p<0.03 (covarying age, education, and MMSE scores)). They did not discriminate these groups after adjusting for the EXIT25 ((MANCOVA: R(2,85)=1.7, NS) (covarying EXIT25 scores)).

In a discriminant model, the pattern of performance on the two CLOX subscales correctly identified 83.1% of cases (Wilkes' lambda =0.48; F(2,86)=46.27, p<0.0001). For comparison, 89.9% of cases were correctly identified by the combination of the EXIT25 and the MMSE (Wilkes' lambda=0.29; F(2,86)=103.80, p<0.0001).

However, patients with Alzheimer's disease are clinically heterogeneous. Specifically, Alzheimer's disease subgroups are known to exist that differ with respect to right hemispheric pathology.[30–32] Therefore, we used the qualitative evaluation of dementia (QED)[24] to divide the patients with Alzheimer's disease into those with (n=19) and without (n=26) grossly disorganised MMSE pentagons, to see if CLOX subscales could discriminate between them. These Alzheimer's disease subgroups differed in their EXIT25 and MMSE scores (table 1). However, CLOX2 scores discriminated between these groups after adjusting for these measures ((ANCOVA): F(1,33)=40.13, p<0.0001 (covarying EXIT25 and MMSE scores)). CLOX1 scores did not (ANCOVA: F(1,33)=0.61, NS). This suggests (1)that the constructional differences between these Alzheimer's disease subgroups cannot be attributed solely to general differences in dementia severity, and (2) that this difference is selectively detected by the CLOX2 paradigm. In a discriminant model, the pattern of performance on CLOX1 × CLOX2 subscales correctly classified 91.9% of these Alzheimer's disease subgroups (Wilkes' lambda =0.31; F(2,34)=37.8; p<0.001) This is remarkable

CLOX: An Executive Clock Drawing Task©

STEP 1: Turn this form over on a light colored surface so that the circle below is visible. Have the subject draw a clock on the back. Instruct him or her to **"Draw me a clock that says 1:45. Set the hands and numbers on the face so that a child could read them."** Repeat the instructions until they are clearly understood. Once the subject begins to draw no further assistance is allowed. Rate this clock (CLOX 1).

STEP 2: Return to this side and let the subject observe you draw a clock in the circle below. Place 12, 6, 3, & 9 first. Set the hands again to "1:45". Make the hands into arrows. Invite the subject to copy your clock in the lower right corner. Score this clock (CLOX 2).

RATING			
Organizational Elements	**Point Value**	**CLOX 1**	**CLOX 2**
Does figure resemble a clock?	1		
Outer Circle Present?	1		
Diameter >1 inch?	1		
All numbers inside the circle?	1		
12, 6, 3, & 9 placed first?	1		
Spacing Intact? (Symmetry on either side of the 12-6 axis?) If "yes" skip next.	2		
If spacing errors are present, are there signs of correction or erasure?	1		
Only Arabic numerals?	1		
Only numbers 1 - 12 among the Arabic numerals present?	1		
Sequence 1-12 intact? No omissions or intrusions.	1		
Only two hands present?	1		
All hands represented as arrows?	1		
Hour hand between 1 and 2 o'clock?	1		
Minute hand longer than hour?	1		
None of the following 1) hand pointing to 4 or 5 o' clock?	1		
2) "1:45" present?			
3) intrusions from "hand" or "face" present?			
4) any letters, words or pictures?			
5) any intrusion from circle below?	**TOTAL**		

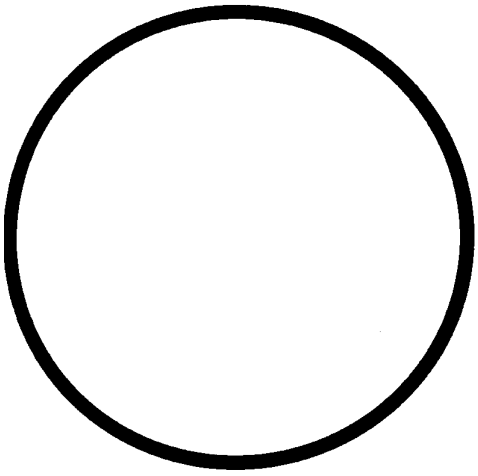

Figure 3

because the combination of EXIT25 and MMSE scores, which takes much longer (25–30 minutes) to administer, gave a less satisfactory performance (Wilkes' lambda =0.73; $F(2,34)=6.4$; $p<0.005$; 75.7% correctly identified).

INTERPRETING CLOX SCORES

CLOX scores were tightly distributed in young adult subjects (CLOX1 =13.2 (1.6); CLOX2 =14.2 (1.2) (table 1)). Thus, a CLOX1 score of 10/15, or a CLOX2 score of 12/15, represents the fifth percentile (2 SD below the mean) for the young adult reference group (fig 2). Cases presenting in box A of fig 2 have scored above the fifth percentile for young adult controls on both CLOX subscales. Cases in box B are below the fifth percentile for their unprompted CLOX1 score, but not the copied condition (CLOX2). Those in box D would have constructional>executive impairment.

Cases in box C have significant impairment relative to young adults on both CLOX subscales. The regression line for the 45 patients with NINCDS probable Alzheimer's disease enters this box from box A (fig 2). Cases presenting above this regression line have more executive impairment than would be expected for an average Alzheimer's disease case at that CLOX2 score. Cases presenting below this regression line would represent greater constructional impairment than could be expected for patients with Alzheimer's disease at similar CLOX1 scores. Figure 2 also presents the CLOX scores for the 45 elderly controls. It is immediately apparent that a significant fraction of this group (n=6, 14%) is presenting in box B (with relatively isolated executive impairment relative to both patients with Alzheimer's disease and young adult controls.

Discussion

In this study we have shown that a clock drawing task can be constructed that is both internally consistent and strongly associated with an executive test measure. We can confirm the impression of Huntzinger *et al*[33] that clock drawing would be useful to clinicians in busy outpatient practices. The CLOX is reliable, easy to administer, and well tolerated by elderly patients. Because many elderly adults are resistant or non-compliant with formal attempts to document their cognitive performance, a clock drawing assessment could improve testing compliance, especially in outpatient, community, and residential settings where professional examiners are not available.

We found that CLOX1 and CLOX2 scores were strongly associated with both the EXIT25 and MMSE. These associations persisted after adjusting for age and education, although education's range was limited by our sample frame.[34] Construct validity is suggested by the finding that the EXIT25 accounted for most of the variance in CLOX1 scores, after adjusting for the MMSE, whereas the opposite was found for CLOX2 scores.

Subject performance on CLOX subscales disclosed interesting information about both well elderly subjects and patients with Alzheimer's disease. Significant fractions of both groups presented below the fifth percentile for young adult controls on one or more CLOX subscales (n =37 (82%) of Alzheimer's disease cases; n =7 (16%) of controls). The pattern of these deficits in Alzheimer's disease suggests a generalised dementing illness. Twenty seven(60%) patients with Alzheimer's disease failed both CLOX subscales. By contrast, no controls presented below this threshold on both subtests.

The cognitive impairments we found in well elderly subjects suggest relatively isolated ECF impairment. Six (14%) elderly controls failed only the CLOX1 subscale, 12 (27%) failed the EXIT25 at 10/50. By contrast, only one elderly control (2.2%) failed the MMSE at 24/30. As Alzheimer's disease affects posterior cortical regions before invading the frontal cortex,[35] isolated ECF impairment is not likely to represent early Alzheimer's disease. On the contrary, many non-Alzheimer's disease medical disorders, including subcortical stroke, depression, polypharmacy, and hypothyroidism might be expected to affect ECFmore than posterior cortical function.[18 20] The CLOX may provide a practical means to screen for these "reversible" dementias in community settings.

However, independent of these diseases, there are also reports of (1) isolated age associated decline in ECF testing,[36 37] (2) disproportionate frontal system atrophy on MRI,[38] and (3) disproportionate frontal system hypometabolism by SPECT in healthy elderly controls relative to young adults.[39] These studies support the phenomenological overlap between well elderly subjects and those with isolated frontal system dementias.[40 41] The CLOX may provide a means of detecting this condition. In this study, only age, CLOX1, and EXIT25 scores discriminated between our young and elderly control groups.

The CLOX2 subtest, like traditional cognitive tests, implicitly targets posterior cortical deficits. Recent studies suggest that differences in right parietal metabolism discriminate Alzheimer's disease subgroups with and without constructional impairment.[32 42 43] CLOX2 scores discriminate Alzheimer's disease subgroups with and without gross constructional impairment, even after adjusting for severity of dementia, whereas the pattern of CLOX1/CLOX2 scores accurately classifies 91.9% of patients with Alzheimer's disease on this basis.

In this regard, our data are consistent with those obtained by Sawada *et al*.[44] They showed qualitative differences among patients with dementia for the pattern of SPECT perfusion deficits in the right parietal and frontal cortices. As we have noted, the patients with dementia differed from elderly and young adult controls in both indices. All patients with dementia showed frontal cortical hypometabolism relative to controls, but subsets among them differed with in right parietal perfusion. The relation of the CLOX to cortical pathology/perfusion has yet to be determined.

In summary, the CLOX is an internally consistent measure that is easy to administer and

displays good reliability between raters. It is strongly associated with both MMSE and EXIT25 scores. The pattern of clock drawing failures may be useful in the discrimination of clinically homogenous Alzheimer's disease groups, or in the discrimination of Alzheimer's disease from non-Alzheimer's disease cases. These issues remain to be explored in future studies.

We acknowledge the important cooperation and support we received from the Air Force Villages. This study was supported by a grant from the Freedom House Foundation of San Antonio, Texas, USA.

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