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Brain structural and cognitive correlates of clock drawing performance in Alzheimer's disease

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Abstract

The Clock Drawing Test (CDT) is widely used in the assessment of dementia and is known to be sensitive to the detection of deficits in neurodegenerative disorders such as Alzheimer's disease (AD). CDT performance is dependent not only on visuospatial and constructional abilities, but also on conceptual and executive functioning; therefore, it is likely to be mediated by multiple brain regions. The purpose of the present study was to identify component cognitive processes and regional cortical volumes that contribute to CDT performance in AD. In 29 patients with probable AD, CDT performance was significantly related to right-, but not left-hemisphere, regional gray matter volume. Specifically, CDT score correlated significantly with the right anterior and posterior superior temporal lobe volumes. CDT scores showed significant relationships with tests of semantic knowledge, executive function, and visuoconstruction, and receptive language. These results suggest that in AD patients, CDT performance is attributable to impairment in multiple cognitive domains but is related specifically to regional volume loss of right temporal cortex. (*JINS*, 1999, *5*, 502–509.)

Keywords: Alzheimer's disease, Clock drawing, Neuroimaging

INTRODUCTION

The Clock Drawing Test (CDT) is frequently used in the assessment of neurological diseases and is known to be sensitive to cognitive deficits in patients with neurodegenerative disorders such as Alzheimer's disease (AD; Mendez et al., 1992; Rouleau et al., 1992; Shulman et al., 1986; Sunderland et al., 1989). It is also useful in distinguishing disease processes from normal aging (Cahn et al., 1996; Freedman et al., 1994; Tuokko et al., 1992; Wolf-Klein et al., 1989) and for differentiating among neurodegenerative diseases (Rouleau et al., 1992). Performance on the CDT has been attributed to myriad cognitive component processes, such as executive functioning, semantic memory, and visuoconstruction, and to the integrity of different brain regions that are known to subserve these functions, including prefrontal, temporal, and parietal cortices (see Freedman et al., 1994, for review).

Historically, the CDT was proposed as a measure of visuospatial inattention, and some authors attribute poor performance to impaired visuospatial functioning (Mendez et al., 1992; Sunderland et al., 1989). More recently, however, a number of investigators have argued that performance on the CDT by AD patients is more strongly dependent on semantic memory and executive functioning than on visuospatial abilities (Libon et al., 1996; Rouleau et al., 1992; Tuokko et al., 1992). For example, Tuokko et al. (1992) suggest that impaired clock drawing abilities may be reflective of a decline in abstract thinking and reasoning abilities in AD patients. Based on the frequency of error types, including additions, omissions, and misplacements, these authors concluded that the deficits seen in the AD patients' clock drawings represented a fundamental impairment in their understanding of time representation. Similar conclusions were drawn by Rouleau and colleagues (Rouleau et al., 1992) who found that patients with AD were more likely than patients

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with Huntington's disease to make conceptual errors in their clock drawings. Conceptual errors were defined in this study as errors that reflect a "loss, or a deficit in accessing knowledge of the attributes, features, and meaning of a clock" (Rouleau et al., 1992, p. 75). Such errors included misrepresentation of the clock face or misrepresentation of the time on the clock. Rouleau and colleagues interpreted their findings as suggesting that the deficits seen in AD patients' clock drawings represented a breakdown in the semantic associations usually elicited with the word "clock."

Evidence that the CDT is sensitive to damage to diverse brain regions was provided by Freedman and colleagues (Freedman et al., 1994) from a review of patients with focal lesions. These authors reported that patients with right posterior lesions showed spatial disorganization while patients with right anterior lesions showed difficulty carrying out two aspects of the task simultaneously. Patients with left posterior damage made errors reflecting poor comprehension of the task and agraphia, while patients with left anterior lesions tended to make perseverative errors and showed difficulty with the sequencing demands of the task.

Several scoring systems and administration procedures have been devised to capture the different patterns of impairment produced by patients with various types of brain dysfunction. The drawing to command condition, in which the patient is asked to draw a clock face with the numbers and to set the hands to a particular time is thought to tap numerous cognitive abilities, including receptive language, memory, and executive functioning (Freedman et al., 1994). Freedman and colleagues have argued that the drawing to command condition places significant demands on memory and visual imagery, so damage to the temporal lobes will likely result in poor performance on this task (Freedman et al., 1994). Evidence for extraparietal contributions to clock drawing performance in AD is derived from a neuropathological study by Forstl and colleagues (Forstl et al., 1993). These authors demonstrated that poorer drawing performance in AD patients correlated with lower counts of large neurons in the parahippocampal gyrus and hippocampus, but not in the parietal lobe, suggesting that drawing disability in AD may not be specifically related to parietal lobe dysfunction. To the extent that hippocampal integrity in AD is reflective of dementia severity, this CDT–hippocampal relationship may simply signify nonspecific functional loss.

The goals of the present study were twofold. The first goal was to establish the relationship between clock drawing ability in AD patients and other specific cognitive processes likely to contribute to CDT performance. We hypothesized that CDT score would be positively correlated with tests that measure several component processes thought to mediate clock drawing performance: receptive language, visuoconstruction, semantic knowledge (defining the elements that comprise a clock and understanding time concepts), and executive function. The second goal was to examine the relationships between clock drawing performance and MRI-derived regional brain volumes in patients with AD. Based on the findings of Freedman and colleagues (Freedman et al., 1994), who outlined the specific impairments in CDT performance following focal brain damage and the known widespread cortical atrophy in AD, we hypothesized that CDT score would correlate significantly with gray matter volumes of the right and left hemisphere frontal lobe volumes, temporal lobe volumes and parietal lobe volumes.

METHODS

Research Participants

Participants included 29 patients (20 men, 9 women) recruited from the Geriatric Psychiatry Research Unit and National Institute of Mental Health Dementia Clinical Research Center of the Veterans Affairs Palo Alto Health Care System. All AD patients met the National Institute of Neurological and Communicative Disease and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD (Khachaturian, 1985; McKhann et al., 1984). Elderly normal control (NC) participants (19 men, 13 women) were included to provide comparison data for the CDT scores, but were not included in the MRI analyses. Screening for all participants included a psychiatric interview and medical examination (for full description, see Pfefferbaum et al., 1994). Participants were not included if they had any significant history of psychiatric or neurological disorder not related to their diagnosis (e.g., stroke, closed head injury), past or present alcohol abuse or dependence, or serious medical condition other than AD. There was no significant difference in age between the AD and NC groups, with the mean age of the patients being 70.7 ± 6.9 years and the mean age of the NC group being 68.8 ± 5.0 years ($t(59) = 1.5$, $p = .14$). On average, the AD patients completed 15.5 ± 3.5 years of education and obtained Dementia Rating Scale (DRS; Mattis, 1976, 1988) total scores of 109.2 ± 17.4, which falls into the severely impaired range for elderly individuals. Informed consent was obtained from all participants or their conservators.

Neuropsychological Tests

A 10-point scoring system (Table 1) was used to quantify the accuracy of the spatial arrangement of the numbers and setting of the hands. AD patients were given one of two test administrations (Freedman et al., 1994): the patient was asked to set the hands to either "ten after eleven," ($n = 18$) or to "three-thirty" ($n = 11$). The differences in clock settings were due to a change in our administration of this test over the several years taken to recruit these participants for our studies. The scoring system we employed was not designed to detect qualitative errors commonly seen in patients with AD (see Rouleau et al., 1992), but instead to provide an overall quantification of the patient's ability to represent time on a clock face. All control subjects received the instructions to set the hands for "three-thirty."

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Table 1. Scoring system for the Clock Drawing Test. Each item receives 1 point if accurately drawn

1. Circle
2. Any numbers
3. Numbers in the circle
4. 3,6,9,12 in correct spatial location (in or out of circle).
5. All numbers, 1–12, in correct place.
6. One or two hands (in or out of clock face).
7. One hand shorter than the other and hands drawn correctly.
8. 3 or 11 indicated somehow.
9. 2 or 6 indicated somehow.
10. Correct time indicated.

In addition to the CDT, patients were administered the Mini-Mental State Examination (MMSE; Folstein et al., 1975), Mattis Dementia Rating Scale (Mattis, 1976, 1988), and the National Adult Reading test (NART; Nelson, 1982). Tests from the neuropsychological battery that were chosen to represent the other cognitive functions thought to subserve clock drawing performance included: Animal Fluency (Goodglass & Kaplan, 1972), as a measure of semantic knowledge (see Salmon & Chan, 1994, for review), the Block Design (BD) subtest from the WAIS–R (Wechsler, 1981), as a measure of visuoconstructional skills, the Token Test (DeRenzi & Faglioni, 1978), as a measure of receptive language skills, the Verbal and Visual Memory Indices of the Wechsler Memory Scale–Revised (WMS–R; Wechsler, 1987) as measures of memory functioning, and the Initiation/Perseveration subtest of the DRS, as a measure of executive functioning. All AD patients were administered the neuropsychological battery within 2 months of their MRI scan.

MRI Methods

MRI images for the AD patients were scanned with 1.5T General Electric Signa scanners. Image acquisition procedures and parameters have been previously described in detail (Fama et al., 1997; Lim & Pfefferbaum, 1989; Pfefferbaum et al., 1994). Axial MR images were 5 mm thick (2.5 mm skip) and were acquired using a spin-echo sequence with a 24-cm field of view and a 256×256 matrix. Early (20 ms) and late (80 ms) echoes were obtained. All images were stored on magnetic tape and transferred to optical disks for analysis. For each patient, the index slice was identified as the most inferior slice above the level of the orbits, where the anterior horns of the lateral ventricles could be seen bilaterally. Seven consecutive slices, beginning with the section inferior to the index slice and proceeding superiorly, were analyzed for each patient. The index slice or the slice below it was used for quantification of the third ventricle.

All MRI films were reviewed by a neuroradiologist to exclude subjects with structural lesions. Each MRI slice was segmented into cerebrospinal fluid (CSF), gray matter, and white matter compartments, using a computerized, semi-automated image analysis technique (Lim & Pfefferbaum, 1989). To separate the cerebral hemispheres, a midline was drawn manually on each slice. Additionally, each slice was divided into an inner 55% region (to facilitate quantification of central CSF, which arose primarily but not exclusively from the lateral ventricles) and an outer 45% (to facilitate quantification of the cortical tissue volumes and sulcal CSF).

Regional divisions of the brain were divided according to anatomical landmarks and *a priori* geometric rules in an effort to achieve standardized images. Six geometrically defined cortical regions of interest (ROIs), which roughly corresponded to lobar anatomy were defined as follows: (1) *Prefrontal*: the most anterior quadrant of all seven slices; (2) *Frontal*: the anterior middle quadrant of slices 3 to 7; (3) *Anterior–Superior Temporal*: the anterior middle quadrant of Slices 1 and 2, which included the anterior superior temporal gyrus and the most posterior extents of the frontal lobes at the level of the superior temporal gyrus; (4) *Posterior–Superior Temporal*: the posterior middle quadrant of Slices 1 and 2, which included the posterior superior temporal gyrus and the anterior extents of the parietal lobes just above the superior temporal gyrus; (5) *Anterior Parietal*: the posterior middle quadrant of Slices 3 to 7; and (6) *Posterior Parietal–Occipital*: the most posterior quadrant of Slices 3 to 7, which also included much of the occipital lobes (Figure 1). In this analysis, only gray matter volumes were examined.

Statistical Analyses

A two-step regression analysis was used to correct the MRI volumes for normal variation due to head size and age (Mathalon et al., 1993; Pfefferbaum et al., 1994; Sullivan et al., 1995). The control group used for these corrections comprised 136 healthy community volunteers (95 men, 41 women; ages 20–84 years). The resulting head size- and age-corrected *Z* scores were calculated to have a mean of zero plus or minus 1 standard deviation in the normative sample. Greater abnormality was reflected by high CSF *Z* scores and low tissue *Z* scores in the AD group.

Correlational analyses were conducted using Pearson product-moment correlations. Multiple regression analyses examined the proportion of variance accounted for in the CDT score by lateralized MRI volumes and the incremental proportion of variance accounted for by one brain region over the other. In these models, the dependent variable was the CDT raw score, and the independent variables were the right or left regional MRI brain volumes.

RESULTS

AD and NC Performance on the CDT

First, we examined whether the AD patients in the two administration subgroups differed on any demographic or test measure. The patients in the two test administration groups

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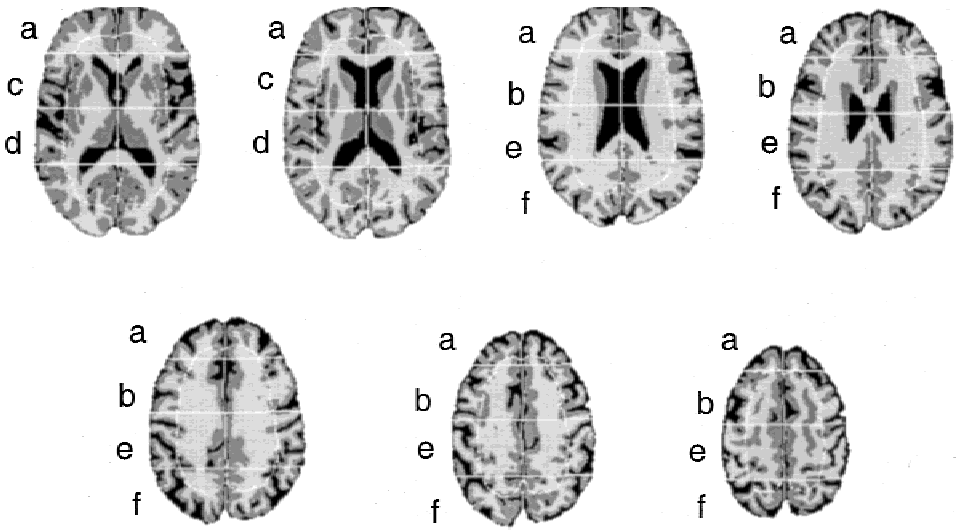

Fig. 1. Example of MR images, segmented into compartments of gray matter shown in dark gray, white matter shown in white, and CSF shown in black. The curved white lines mark the division of each section into the outer 45% for cortical measures and the inner 55% for ventricular measures. The vertical and horizontal white lines delineate the four quadrants used to define the cortical regional measures: *a* = prefrontal; *b* = frontal; *c* = anterior superior temporal; *d* = posterior superior temporal; *e* = anterior parietal; and *f* = posterior parietal–occipital.

did not differ in score on the MMSE ($p = .41$), DRS ($p = .18$), NART ($p = .59$), or CDT ($M = 5.8 \pm 2.2$ for the 3:30 setting; $M = 5.9 \pm 3.1$ for 11:10 setting). Further, analysis of covariance (ANCOVA) revealed that CDT score did not differ between the two test administration subgroups after controlling for DRS score ($p = .65$) and MMSE score ($p = .99$). Because there were not identifiable differences between the two AD groups in terms of demographics, disease severity, or test performance, the AD patients were considered as one group in all remaining analyses.

The mean CDT score of the total AD group was 5.9 ± 2.7, and the mean score of the NC group was 8.8 ± 1.6. The difference between the two groups was statistically significant ($t(59) = -5.19$, $p = .0001$). Examples of clocks drawn by AD patients are presented in Figure 2.

Bivariate Correlations Between CDT Scores and Component Motor and Cognitive Functions

These correlations revealed that lower CDT scores in the AD patients were significantly associated with worse visuoconstruction performance (Block Design: $r = .42$, $p = .03$), semantic knowledge (Animal Fluency: $r = .44$, $p = .02$), receptive language skills (Token Test: $r = .54$, $p = .006$), and executive function (Initiation/Perseveration: $r = .44$, $p = .02$). CDT score correlated significantly with the DRS total score, ($r = .50$, $p = .005$), but the MMSE score showed only a trend toward a significant relationship with CDT score ($r = .31$, $p = .10$). CDT score did not correlate significantly either with verbal memory, as assessed by the Verbal Memory Index of the WMS–R, ($r = .33$, $p > .10$) or with nonverbal memory, as assessed by the Visual Memory Index of the WMS–R ($r = .22$, $p > .10$).

Bivariate Correlations Between CDT Scores and MRI Volumes

Bivariate correlations (Table 2) indicated relationships between several right- but not left-hemisphere regional gray matter volumes and CDT score. Specifically, CDT score cor-

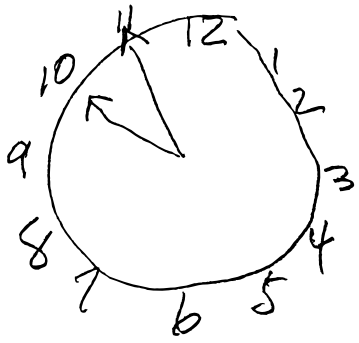

Fig. 2. The clock on the top received a score of 7 and the one on the bottom a score of 3.

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Table 2. Correlation matrix demonstrating relationships between right and left hemisphere regional gray matter volumes and clock drawing score

Hemisphere	Prefrontal	Frontal	Anterior superior temporal	Posterior superior temporal	Parietal	Parietal–occipital
Right	$r = .34$, $p = .07$	$r = .16$, $p = .39$	$r = .42$, $p = .02$	$r = .36$, $p = .05$	$r = .07$, $p = .72$	$r = .08$, $p = .68$
Left	$r = .11$, $p = .58$	$r = .02$, $p = .91$	$r = .05$, $p = .81$	$r = .22$, $p = .25$	$r = .11$, $p = .56$	$r = .06$, $p = .75$

related significantly with the right anterior–superior and posterior–superior temporal lobe volumes (Figure 3) and showed a trend towards an association with the right prefrontal gray matter volume.

Lateralized MRI Volume Predictors of CDT Performance

Because the bivariate correlations suggested selective relationships between CDT and right- but not left-hemisphere regional gray matter volumes, we used multiple regression analysis to test whether the significant relationships were unique, after accounting for the contributions of the left-hemisphere volumes. These analyses revealed that the right anterior–superior temporal gray matter volume was a unique significant predictor of CDT score ($p = .01$), after controlling for the variance accounted for by the left anterior–superior temporal gray matter volume. Neither the right prefrontal volume nor the right posterior–superior temporal volume was a significant independent predictor of CDT score after accounting for the contributions of the homologous regional volumes in the left hemisphere.

DISCUSSION

Historically, the CDT has been viewed as a measure of visuospatial and visuoconstructional ability. Recently, a number of studies have suggested that other cognitive functions, such as semantic knowledge and executive abilities, may underlie clock drawing performance in patients with AD (Forstl et al., 1993; Libon et al., 1996; Rouleau et al., 1996). The implication of this is that brain regions other than, or in addition to, the parietal lobe may subserve successful clock drawing performance. In the current study, clock drawing performance of AD patients correlated with right hemisphere gray matter volumes in the superior temporal lobe but not parietal regions of either hemisphere. These results appear to be consistent with the finding of Forstl and colleagues (Forstl et al., 1993) who reported that clock drawing performance in AD correlated with postmortem neuron counts in the parahippocampal gyrus and hippocampus, but not in the parietal lobe. In the context of AD, in which there is widespread gray matter volume deficits, this finding of a selective relationship does not suggest that the right superior temporal lobe is the only structure that contributes to clock drawing performance, but rather, that this structure

Table 3. Squared semipartial correlations between the right anterior–superior and right posterior–superior temporal lobe volumes and Clock Drawing Test score controlling for cognitive functions thought to underlie clock drawing performance

Volume and function	Squared semipartial correlation with CDT	p
Right anterior–superior temporal lobe controlling for:		
Visuoconstruction (Block Design)	.32	.002
Semantic knowledge (Animal Fluency)	.18	.028
Receptive language (Token Test)	.15	.055
Executive function (Initiation/Perseveration subtest)	.09	.09
Right posterior–superior temporal lobe controlling for:		
Visuoconstruction (Block Design)	.22	.014
Semantic knowledge (Animal Fluency)	.09	.093
Receptive language (Token Test)	.04	.265
Executive function (Initiation/Perseveration subtest)	.02	.365

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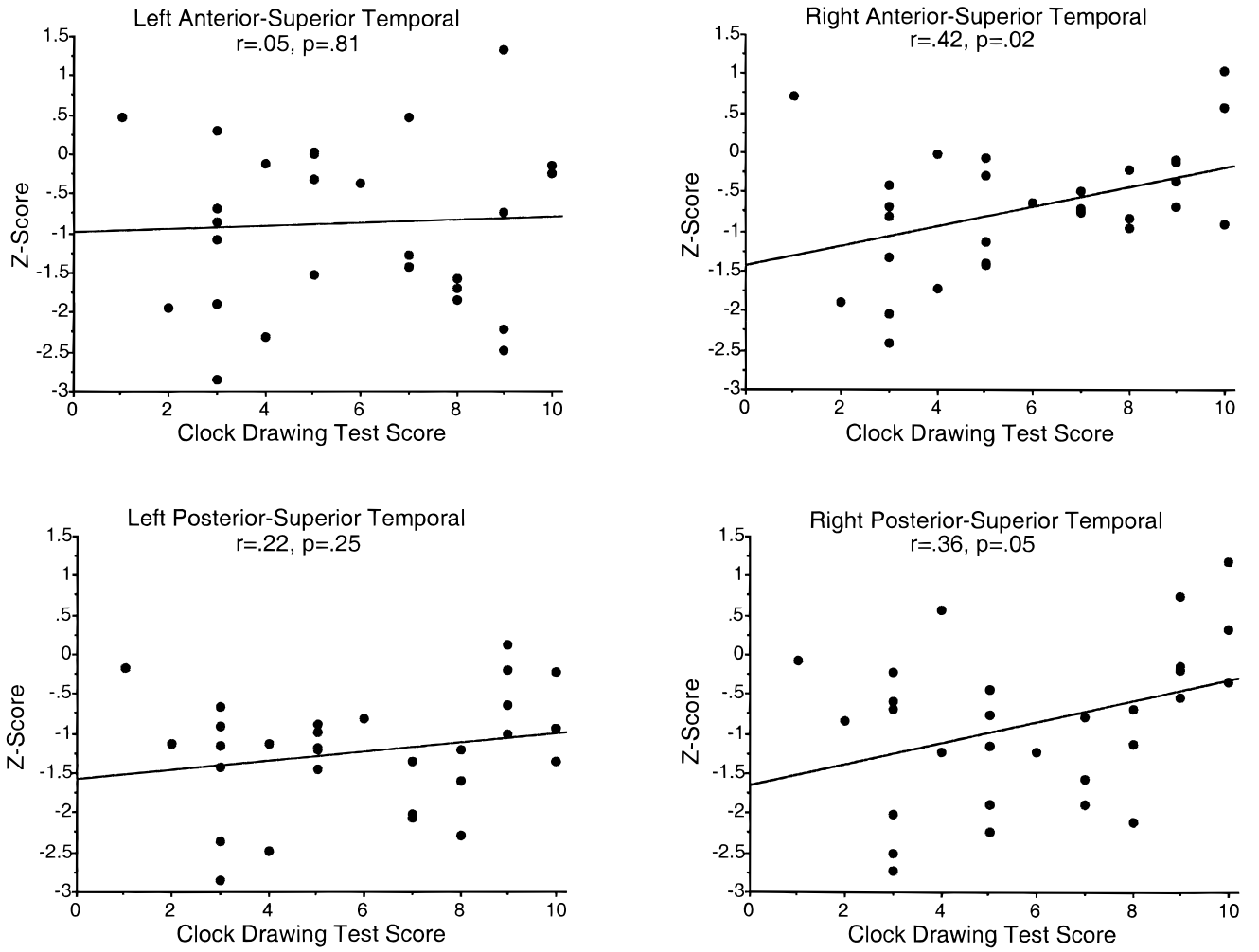

Fig. 3. Scatterplots depicting significant bivariate relationships between Clock Drawing Test Score and left and right hemisphere superior temporal gray matter volumes (*Z* scores).

has a significant independent relationship with clock drawing performance, after accounting for the contributions from the left hemisphere superior temporal lobe and a number of cognitive functions thought to subserve clock drawing performance.

An alternative interpretation of the findings is that the significant correlations between CDT score and the right hemisphere regional brain volumes reflect sensitivity of the CDT to brain areas that are disproportionately affected in AD. To investigate this possibility, we examined the relative differences between the mean right hemisphere regional gray matter volumes. Figure 4 displays the mean *Z* scores of the six MRI regional volumes of the right hemisphere in the AD patients. Paired *t* tests revealed that the mean posterior–superior temporal gray volume differed significantly from the mean frontal ($p = .05$) and posterior parietal–occipital volumes ($p = .05$). No other pairwise comparisons were statistically significant. Thus, although right anterior parietal volumes were as affected as the right temporal lobe volumes in these AD patients, they did not show a significant relationship with CDT score. Therefore, it appears that the CDT is not sensitive simply to general shrinkage of the cortical mantle, but to the volumes of selective brain regions.

Work by Hodges and colleagues (Graham & Hodges, 1997; Hodges et al., 1992a, 1992b) has supported the role of the temporal neocortex in semantic memory. While impairment in semantic memory is typically associated with left hemisphere damage, the current findings may support the role of the right temporal lobe in what Rouleau and colleagues referred to as "an impairment in retrieving visual images from semantic memory" (Rouleau et al., 1996). Hodges' studies of patients with semantic dementia has led to the hypothesis that lateral temporal lobe atrophy confined to the right hemisphere may cause impairment in nonverbally based knowledge, as opposed to impairment in verbal semantic knowledge seen in patients with left-sided pathology (Hodges, 1994). We speculate that if the right superior temporal gray matter supports some form of visual knowledge or memory, then the component of clock drawing that may be tapped in AD with the current scoring system is related to possible decline in the knowledge of the

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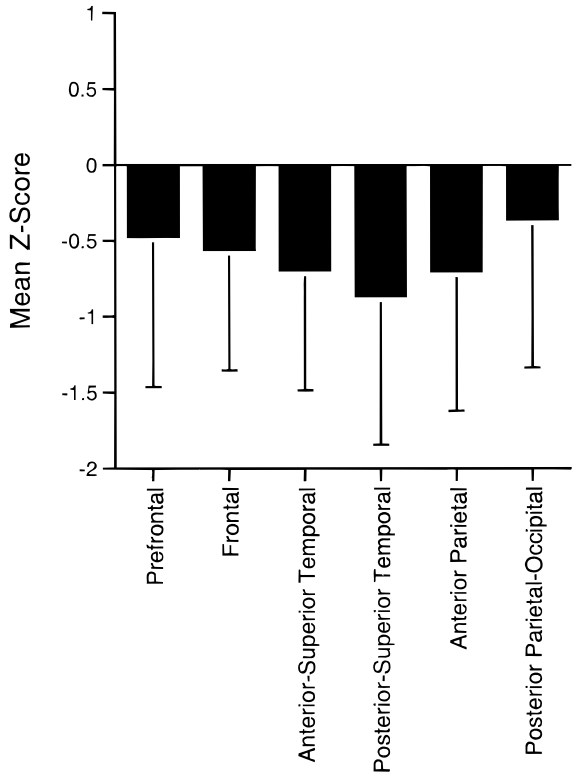

Fig. 4. Mean (*SD*) right hemisphere regional brain matter volumes (*Z* scores) of the AD patients. Greater abnormality is reflected by low *Z* scores.

attributes and features that comprise a clock face or in understanding of time concepts. While numerous studies have documented disturbances in semantic memory in patients with AD and semantic dementia (Chan et al., 1993; Hodges, 1994; Hodges et al., 1991; Johnson & Hermann, 1995; Martin & Fedio, 1983), few have examined the relationship between this deficit and degree or lateralization of cortical gray matter volume.

We hypothesized that CDT score would be significantly correlated with prefrontal cortical gray matter volumes, but the bivariate relationship only approached significance with the right prefrontal lobe volume. One explanation for this finding is that the current scoring system was not as sensitive to executive dysfunction as other systems. For example, the system used by Rouleau and colleagues (Rouleau et al., 1992) included a qualitative analysis that assessed planning errors, stimulus-bound responses, and perseverations. However, Rouleau and her colleagues (Rouleau et al., 1996) have recently argued that stimulus-bound responses (i.e., setting the hands to "10" and "11") may actually represent a semantic deficit rather than an executive one. The scoring system used in the current study is capable of reflecting executive dysfunction insofar as a patient who shows frontal–executive dysfunction might lose a point on Item #4 if impairment in planning disrupted the spatial arrangement of the numbers or on Item #10 if a stimulus-bound error resulted in improper hand setting.

The results of this study provide additional support for the theory that clock drawing performance taps numerous cognitive processes, including executive functioning, semantic knowledge, receptive language, and visuoconstructional ability. A question that remains to be answered is whether any of these cognitive component processes is a selective, or more accurate predictor of clock drawing performance after accounting for the contributions made by the others. Future studies with greater sample sizes and more specific scoring criteria are needed to address this issue.

There are a number of limitations to the current findings which deserve mention, including the use of two different time settings. It is possible that the two settings may elicit qualitatively different behaviors in patients with AD (Freedman et al., 1994); nonetheless, the purpose of the present study was to investigate the correlations between lateralized cortical volumes and a quantitative score of clock drawing performance that reflects knowledge and understanding of how to represent time on a clockface. The patients who were administered the two clock drawing procedures did not differ systematically on any demographic variable, however, and received similar scores on the CDT. The scoring system used in the current study quantifies spatial and conceptual processes, but is also capable of detecting errors in conceptualization and executive functioning. It is possible that other scoring systems may be more or less sensitive to these cognitive processes, and hence underlying regional brain volume variation, than was observed in this study. Another limitation of the current study is that we did not correct for multiple comparisons, and thus many of the relationships reported might not have reached statistical significance if we had applied a Bonferroni correction, for example. Finally, our sample of AD patients was overrepresented by men, which is likely a consequence of performing this study in a VA Medical Center. Additional studies using one clock setting and a larger sample of representative patients are needed to replicate the current findings.

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