Deficits in Controlled Processing May Predict Dementia: A Twin Study

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This study tested for differential patterns of cognitive decline in 33 twin pairs for which both were nondemented, but 1 member of the pair went on to develop dementia. Compared with their nondemented twin partners, twins who later developed dementia already showed poorer performance on tests of memory and attention, visuospatial–reasoning skills, and perceptual speed and the Mini-Mental State Examination (MMSE). The authors suggest that this cluster of tests reflects deficits in controlled rather than automatic cognitive processes. Nondemented twin partners of the twins who became demented were also compared with 33 matched controls selected from pairs in which both members remained nondemented. Nondemented twin partners scored lower than matched controls on tests of verbal ability, memory and attention, and perceptual speed and the MMSE. This finding indicates that nondemented twin partners of demented twins are at elevated risk themselves for becoming demented, and further suggests that certain areas of cognition are compromised prior to diagnosis of dementia.

Although normal aging is associated with decline in some areas of cognition (Salthouse, 1999), older adults who later develop dementia seem to demonstrate preclinical cognitive changes that can be discriminated from normal aging (e.g., Elias et al., 2000; Jacobs et al., 1995; Johansson & Zarit, 1997; La Rue & Jarvik, 1987; Nielsen, Lolk, Andersen, Andersen, & Krågh-Sorensen, 1999; Storandt, Botwinick, Danzinger, Berg, & Hughes, 1984). Although researchers agree that some signs of cognitive decline predict the onset of dementia long before its clinical onset (Fabrigoule et al., 1998; Flicker, Ferris, & Reisberg, 1991; La Rue & Jarvik, 1987; Linn et al., 1995; Nielsen et al., 1999), there is no clear evidence for which cognitive measures best identify those who will develop dementia. Preclinical signs of dementia have most often been associated with tests of verbal learning and delayed recall (Fox, Warrington, Agnew, & Rossor, 1998; Fabrigoule et al., 1998; Linn et al., 1995; Masur, Stiwinska, Lipton, Blau, & Crystal, 1994; Tierney et al., 1996), category verbal fluency (Dartigues et al., 1997; Fabrigoule et al., 1998; Masur et al., 1994; Monsch et al., 1992; Storandt et al., 1984), perceptual speed (Fabrigoule et al., 1998; Masur et al., 1994; Storandt et al., 1984), and attention or mental control (La Rue & Jarvik, 1986; Nielsen et al., 1999; Storandt et al., 1984; Tierney et al., 1996). Still, effect sizes tend to be small and findings inconsistent across studies even when identical measures are used.

Studies by Jorm (1986), Fabrigoule and colleagues (1998), and Amieva, Rouch-Leroyer, Fabrigoule, and Dartigues (2000) represent attempts to search for a pattern that could guide future research efforts and help clinicians distinguish early signs of dementia from normal aging. They suggest that the preclinical phase of dementia may be associated with cognitive deficits in controlled, but not automatic, processing (Shiffrin & Schneider, 1977). Controlled information processes rely on intact attentional resources and involve voluntary retrieval and integration of information. Automatic processes generally involve well-learned, spontaneous responses and require relatively less cognitive effort. This distinction may explain, for example, why some tests of verbal skills such as category verbal fluency and word finding seem to decline prior to dementia onset (e.g., Dartigues et al., 1997; Jacobs et al., 1995; Monsch et al., 1992; Storandt et al., 1984), whereas more automated verbal skills such as reading remain fairly intact (Fox et al., 1998; Monsch et al., 1992).

Over the past two decades, early and accurate detection of preclinical cognitive changes became of interest in dementia research (Masur et al., 1994). Early detection of dementia has also assumed greater medical value with the emergence of new preventive and treatment strategies. For example, use of antioxidants Vitamin C or E (Morris et al., 1998) and other oxidation inhibitors (Münch et al., 1998) may lower the risk of Alzheimer’s disease in healthy older adults. Early detection of developing dementia and consequent early implementation of treatment may slow down the neurodegenerative process and, in turn, delay dementia onset or slow down its progression.

Detection of early signs of dementia with cognitive tests has often been thwarted by the confounding effect of demographic variables such as age and education (e.g., Jacobs et al., 1995; Slooter et al., 1998). In addition, genetic factors may affect cognitive performance (Brandy et al., 1993; McClearn et al., 1997; Pedersen, Plomin, Nesselroade, & Helliwell, 1995).
Conclusions based on findings from twin studies may increase our confidence in accurate detection of predictors of dementia among cognitive tests. Twin comparisons enable researchers to control for genetic and environmental factors, including those affecting cognitive performance. In addition, twins are completely matched for age and gender (except for opposite fraternal twins), and tend to be similar in education (Lichtenstein, Pedersen, & McClearn, 1992).

Controlling for genetic factors affecting cognitive performance can be particularly important in dementia research. Twin researchers suggest that heritability for cognitive performance is high throughout adulthood (Bouchard, Lykken, McGue, Segal, & Tellegen, 1990; Finkel, Pedersen, & McGue, 1995; Finkel, Pedersen, Plomin, & McClearn, 1997; Patrick, 2000; Pedersen et al., 1992; Plomin, Pedersen, Lichtenstein, & McClearn, 1994), although heritability estimates seem to decrease in very old cohorts (Finkel et al., 1995, 1997; McClearn et al., 1997). Studies of specific cognitive abilities suggest heritabilities around 65% in older adult samples; for example, for tests of verbal skills (McClearn et al., 1997; Pedersen et al., 1992; Plomin et al., 1994; Swan et al., 1999), perceptual speed (McClearn et al., 1997; Pedersen et al., 1992), spatial skills (Pedersen et al., 1992), and memory (Finkel & McGue, 1993; McClearn et al., 1997), and Mini-Mental State Examination (MMSE) scores (Swan et al., 1990). High heritability of cognitive abilities means that monozygotic twin pairs are more similar than dizygotic twin pairs. However, dizygotic twins also have substantial intrapair correlations. Thus, within both monozygotic and dizygotic twins, the two members of the pair can be expected to show similar cognitive performance. If differences in cognition become noticeable in one member of the pair, these differences may signal pathological change.

In the present study, we investigated differences in cognitive performance in twin pairs who were initially nondemented, but in which one of the twins went on to develop dementia. We tested the hypothesis that the twin who would later become demented would score lower than the twin partner who continued to be nondemented on cognitive tests that predominantly involve controlled processing and require attention and unassisted retrieval of information. On the other hand, twin partners would score similarly on tests of automatic information processing for which performance is automated and/or retrieval cues are provided.

In addition, we compared the cognitive scores of the nondemented twin partners with the scores of matched individuals randomly selected from a pool of nondemented twin pairs. We know that concordance for dementia is quite high. For example, in the Bergem, Engedal, and Kringsen’s (1997) study of twins identified through the Norwegian Twin Register, probandwise concordance rates for all dementias combined was 70% for monozygotic twin pairs and 40% for dizygotic twin pairs. Concordance rates among twin pairs identified through the Swedish Twin Registry were 50% for monozygotic twin pairs and 30% for dizygotic twin pairs (Gatz et al., 1997). Therefore the nondemented twin partner of a demented twin can be regarded as being at elevated risk for dementia. This second comparison evaluated whether twins at higher risk for dementia differed from a comparison group of twins who were not at higher risk.

Methods

Sample

The demented twins and their twin partners were part of the Study of Dementia in Swedish Twins (Gatz et al., 1997) or members of the OCTO-Twin Study (McClearn et al., 1997). Both studies represent defined subsamples of the population-based Swedish Twin Registry (Cederlöf & Lorich, 1978).

The Study of Dementia in Swedish Twins identified cases from the Swedish Adoption/Twin Study of Aging (SATSA), a longitudinal study of personality, health, and aging among same-gender twins (Pedersen et al., 1991). SATSA includes all pairs from the twin registry who indicated having been reared apart and a matched sample who were reared together. SATSA data collection included in-person cognitive assessments on a 3-year rolling schedule. For purposes of the dementia study, all twins identified for the SATSA sample born in 1935 or previously were included, if one or both members of the pair were alive in 1987, whether or not they had responded to SATSA data collection efforts ($N = 1,978$). Baseline screening took place in 1987 and 1988, with the final 20% completed by 1991, and incident cases were identified at each additional data collection.

The OCTO-Twin Study enrolled all twin pairs aged 80 and older if both members of the pair were alive during the first wave of data collection in 1991–1994 ($N = 702$). Three waves of data collection including in-person cognitive assessment took place at 2-year intervals. Cases of dementia were identified at each of the waves.

Screening Procedures

Case ascertainment in the Study of Dementia in Swedish Twins used a two-stage process. Participants were screened for dementia using either the MMSE (Folstein, Folstein, & McHugh, 1975) or telephone screening protocol (Gatz et al., 1995). Those identified by screening as suspected cases of dementia were evaluated by an assessment team employing a nurse, a psychologist, and a physician. The protocol parallels Consortium to Establish a Registry for Alzheimer’s Disease procedures for physical and neurological evaluations, laboratory tests, neuropsychological testing, and neuroimaging (Morris et al., 1989). Findings were presented at a consensus diagnosis conference, attended by the clinicians and chaired by a psychologist who had not met the twin; diagnoses were assigned following Diagnostic and Statistical Manual of Mental Disorder (3rd ed., rev.) criteria for dementia (American Psychiatric Association, 1987), National Institute of Neurological and Communicative Disorders and
Stroke (NINCDS)/Alzheimer’s Disease and Related Disorders Association (ADRDA) criteria for probable and possible Alzheimer’s disease (McKahn et al., 1984) and—once available—National Institute of Neurological Disorders and Stroke—Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia (Roman et al., 1993). Twin partners of probands were given an identical clinical workup. If the twin partners were deceased, their diagnostic assessment included informant interviews and review of medical records, including death certificates. Cases and twin partners were followed longitudinally every 18 months, with postmortem neuropathological examination for any who died. Autopsy confirmation of diagnosis was available for 25 cases.

Case ascertainment from the OCTO-Twin sample entailed a review of MMSE scores and cognitive performance information collected from all twins, whether or not they were demented. The battery paralleled that used in the Study of Dementia in Swedish Twins. For those suspected of dementia, the same informant protocol was followed, medical records were reviewed, and a consensus diagnosis assigned by a physician and psychologist. The same psychologist chaired the diagnostic conferences for both samples.

As part of the informed consent procedure participants (or their proxy) were asked what information they wished to receive. If requested, the physician provided a report of the clinical evaluation to the participant’s health clinic with any comments about findings deserving follow-up. Participants were also informed that, in the case of significant finding requiring immediate attention, they and their primary physician would be notified.

In all, 33 twin pairs were identified in which both twins were initially diagnosed as nondemented but the pair became discordant for dementia during longitudinal follow-up. The nondemented twin partner was required to remain nondemented and alive for a minimum of 3 years counting from the year of dementia onset in the preclinical twin. Out of the 33 nondemented twin partners, two became demented 5 and 6 years, respectively, from dementia onset of the preclinical twin. In both cases, the nondemented twin partner was tested 7 years prior to dementia onset.

One control was matched to each of the 33 pairs by forming a pool of all potential matches based on age (± 3 years), gender, and zygosity. Then we randomly chose one control using a table of random numbers. The procedure also assured that no twin pairs had both members in the control sample, assuring independence of the data. To be included in the pool, both twin partners had to (a) have participated in at least two waves of testing, (b) stay nondemented and alive for at least 3 years after age of onset of the matched proband, and (c) match a discordant twin pair in gender, zygosity, and age at cognitive testing conducted by SATSA or OCTO-Twin. The first of three waves of cognitive testing was used for controls taken from OCTO-Twin. Controls from SATSA were included in the pool if their chronological age at one of the first two waves of cognitive testing corresponded to the age at testing of a discordant pair.

Table 1 presents demographic characteristics of the sample. The age at testing for both the preclinical and nonde-mented twin partners ranged from 60 to 88 years (M age = 78.1 years for preclinical twins and 78.2 years for nonde-mented twin partners). Matched controls were tested between ages 61 and 87 (M age = 78.1 years). The average age of onset in the preclinical twins was 80.1 years (SD = 6.6 years); the mean time difference between test administration and clinical dementia onset was 2.0 years (SD = .87 years). The preclinical twins were tested between 1 and 4 years before dementia onset. Fifty-eight percent of the preclinical twins were later diagnosed with Alzheimer’s disease; 18%, with vascular dementia; 6%, with mixed dementia; 3%, with secondary dementia (e.g., Parkinson’s disease or hydrocephalus); and 15%, with other dementias.

The education variable was scored on a 5-point scale from 1 (Compulsory, about 6 years of school) to 5 (University). On average, the participants attained slightly more than the compulsory elementary school education, with no significant differences between the groups. Seventy percent of the twin pairs were female and 30% were male; 36% were monozygotic and 64% were dizygotic. Matched controls were selected such that gender and zygosity corresponded precisely to that of the twin pairs who later became discordant for dementia. Because the sample included dizygotic twins, the results reflect only partial control of heritable factors.

**Measures**

Tests of verbal ability included a Swedish version of the Wechsler Adult Intelligence Scale (WAIS) Information subtest (Jonsson & Molander, 1964) and Synonyms, a forced-choice vocabulary test from the Swedish Dureman—Sälde Battery (Dureman, Kebran, & Osterberg, 1971). Visuospatial—reasoning measures included Koh’s Block Design (Dureman et al., 1971), similar to the WAIS Block Design subtest, and Figure Logic (Dureman et al., 1971), a matrix test in which the correct design must be chosen to complete a series. Perceptual speed was assessed using Figure Identification (Dureman et al., 1971), a timed pattern-matching test, and Symbol Digit Test, a task in which participants verbally indicate which digits correspond to a row of symbols, similar to the Digit Symbol test from the WAIS.
Tests of memory and attention included Digit Span Forward and Digit Span Backward and Thurstone’s Picture Memory. Digit Span Forward and Digit Span Backward were scored separately as the highest number of digits repeated correctly (Jonsson & Molander, 1964). Thurstone’s Picture Memory is a test of recognition memory of drawings of common items such as a truck and a table (Dureman et al., 1971). All tests were taken from standard batteries, with reliability coefficients ranging from .82 for Thurstone’s Picture Memory to .96 for Figure Identification (Pedersen et al., 1992).

A brief mental status screening test was included: the MMSE (Folstein et al., 1975) with an extension of the three-item recall task. The participants who were unable to recall all three items were given a recognition test for any missed items. The recognition test entailed providing the correct item and two distractors. Correct responses were each scored 0.5 points. The addition of the recognition component was prompted by the same modification used by the Alzheimer’s Disease Research Center at University of Southern California (S. H. Zarit, personal communication, November 9, 1992).

Analyses
Initially, we examined differences in baseline cognitive performance between those twins who later became demented and their nondemented twin partners using paired sample t tests. We also calculated Cohen’s (1977) d statistic using the formula for estimating effect sizes in studies with correlated designs (Dunlap, Cortina, Vaslow, & Burke, 1996). To corroborate our findings with a more stringent statistical method, we conducted conditional logistic regression analyses for case-control studies (Guo et al., 2000), controlling for age and education differences. For these analyses, we used the SAS Program Version 8 (SAS Institute, 1996). To corroborate our findings with a more stringent statistical method, we conducted conditional logistic regression analyses for case-control studies (Guo et al., 2000), controlling for age and education differences. For these analyses, we used the SAS Program Version 8 (SAS Institute, 1996). To corroborate our findings with a more stringent statistical method, we conducted conditional logistic regression analyses for case-control studies (Guo et al., 2000), controlling for age and education differences. For these analyses, we used the SAS Program Version 8 (SAS Institute, 1996).

RESULTS

Preclinical Twins Versus Nondemented Twin Partners
Cognitive scores of preclinical twins were consistently lower than the scores of their nondemented twin partners, although only some of the score differences were statistically significant (see Table 2).

Paired t-test analyses yielded no significant differences on the two measures of verbal ability—WAIS Information and WAIS Synonyms. The results for the tests of memory and attention were incongruent. Preclinical twins performed worse than their nondemented twin partners on one test of memory and attention—Thurstone’s Picture Memory test, t(22) = 2.21, d = .73, p < .05, but not Digit Span Forward and Digit Span Backward. Similarly, although preclinical

<table>
<thead>
<tr>
<th>Test</th>
<th>Preclinical Twins</th>
<th>Nondemented Twin Partners</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Verbal Skills</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information</td>
<td>22.79</td>
<td>11.09</td>
</tr>
<tr>
<td>Synonyms</td>
<td>14.10</td>
<td>6.82</td>
</tr>
<tr>
<td>Visuospatial–Reasoning Skills</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Figure Logic</td>
<td>12.90</td>
<td>5.96</td>
</tr>
<tr>
<td>Block Design</td>
<td>9.00</td>
<td>6.51</td>
</tr>
<tr>
<td>Perceptual Speed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symbol Digit</td>
<td>20.00</td>
<td>11.46</td>
</tr>
<tr>
<td>Figure Identification</td>
<td>19.05</td>
<td>7.74</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span Forward</td>
<td>5.30</td>
<td>0.92</td>
</tr>
<tr>
<td>Digit Span Backward</td>
<td>3.12</td>
<td>1.39</td>
</tr>
<tr>
<td>Thurstone Picture Memory</td>
<td>17.52</td>
<td>5.73</td>
</tr>
<tr>
<td>MMSE</td>
<td>26.08</td>
<td>2.90</td>
</tr>
</tbody>
</table>

Note: Cohen’s d statistic for correlated designs; OR = odds ratio, adjusted for age and education; CI = 95% confidence interval; MMSE = Mini-Mental State Examination.

*p < .05; **p < .01.
COGNITION AND DEMENTIA IN TWINS

Table 3. Means, Standard Deviations, t-Test Values, and Adjusted Odds Ratios for Nondemented Twin Partners and Matched Controls

<table>
<thead>
<tr>
<th>Test</th>
<th>N of pairs</th>
<th>Nondemented Twin Partners</th>
<th>Matched Controls</th>
<th>r test (df)</th>
<th>Cohen’s d</th>
<th>OR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td></td>
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<tr>
<td>Verbal Skills</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information</td>
<td>33</td>
<td>25.67</td>
<td>9.41</td>
<td>30.00</td>
<td>9.41</td>
<td>2.20* (32)</td>
<td>0.51</td>
</tr>
<tr>
<td>Synonyms</td>
<td>31</td>
<td>15.29</td>
<td>6.02</td>
<td>17.68</td>
<td>6.02</td>
<td>1.44 (30)</td>
<td>0.40</td>
</tr>
<tr>
<td>Visuospatial–Reasoning Skills</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Figure Logic</td>
<td>30</td>
<td>15.23</td>
<td>5.10</td>
<td>16.87</td>
<td>3.67</td>
<td>1.69 (29)</td>
<td>0.36</td>
</tr>
<tr>
<td>Block Design</td>
<td>31</td>
<td>13.90</td>
<td>6.59</td>
<td>16.06</td>
<td>7.12</td>
<td>1.34 (30)</td>
<td>0.32</td>
</tr>
<tr>
<td>Perceptual Speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symbol Digit</td>
<td>29</td>
<td>26.48</td>
<td>10.62</td>
<td>32.79</td>
<td>11.17</td>
<td>2.91** (28)</td>
<td>0.58</td>
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<tr>
<td>Figure Identification</td>
<td>25</td>
<td>21.00</td>
<td>9.44</td>
<td>22.04</td>
<td>9.96</td>
<td>0.64 (24)</td>
<td>0.11</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span Forward</td>
<td>33</td>
<td>5.70</td>
<td>1.47</td>
<td>5.82</td>
<td>1.18</td>
<td>0.40 (32)</td>
<td>0.09</td>
</tr>
<tr>
<td>Digit Span Backward</td>
<td>33</td>
<td>3.44</td>
<td>1.66</td>
<td>4.00</td>
<td>1.83</td>
<td>1.24 (32)</td>
<td>0.32</td>
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<tr>
<td>Thurstone Picture Memory</td>
<td>25</td>
<td>20.56</td>
<td>3.69</td>
<td>23.12</td>
<td>4.06</td>
<td>2.61* (24)</td>
<td>0.66</td>
</tr>
<tr>
<td>MMSE</td>
<td>33</td>
<td>27.74</td>
<td>2.11</td>
<td>28.70</td>
<td>1.30</td>
<td>1.38 (32)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Note: Cohen’s d statistic for correlated designs; OR = odds ratio, adjusted for age and education; CI = 95% confidence interval; MMSE = Mini-Mental State Examination.

*p < .05; **p < .01.

Twins scored significantly lower than their nondemented twin partners on Block Design, \( t(28) = 3.71, d = .74, p < .01 \), and no differences were found on Figure Logic. Preclinical twins scored low on both tests of perceptual speed—Symbol Digit, \( t(23) = 3.25, d = .57, p < .01 \), and Figure Identification, \( t(20) = 2.32, d = .43, p < .05 \). Finally, preclinical twins showed significantly lower scores on the MMSE, \( t(32) = 3.70, d = .64, p < .01 \).

Odds ratios adjusted for age and education yielded the same results as paired-sample \( t \) tests reported above (see Table 2) with the exception of Thurstone’s Picture Memory, for which the difference between preclinical twins and their nondemented twin partners was reduced to only a statistical trend (\( p = .070 \)).

Correlation coefficients indicated no association between either mean age at testing or zygosity with intrapair cognitive score differences for any of the measures. Correlation coefficients ranged from .25 to .17 for intrapair mean education and cognitive measures. The correlation coefficients ranged from .24 to .29 for age differences and .17 for intrapair mean education and cognitive measures.

**Discussion**

Our comparison of twins who later became demented and their twin partners who remained nondemented provides important evidence for preclinical demonstration of dementia. We assume that twins would generally be similar on cognitive tests and that intrapair differences reflect preclinical decline in the twin who became demented. Our results imply that multiple cognitive areas may be affected prior to dementia onset. Moreover, even in cases in which results were not significant, preclinical twins showed trends of scoring lower than their nondemented twin partners. These trends were consistent across all cognitive tests (see Figure 1). In addition, nondemented twin partners tended to score lower than a matched sample of controls.

We found that tests of memory and attention, perceptual speed, and visuospatial–reasoning identified correctly the twin who went on to be diagnosed with dementia. Memory and attention measures are among the best predictors of dementia (e.g., Jacobs et al., 1995; Johansson & Zarit, 1997; Nielsen et al., 1999; Rubin et al., 1998; Storandt et al., 1984; Tierney et al., 1996). Therefore, our finding that Thurstone’s Picture Memory test predicts dementia may be expected in spite of some opposing evidence. Some researchers argue that primary memory (Elias et al., 2000; Linn et al., 1995) or cued recall (Grober, Lipton, Hall,
trolled and automatic processing to pathological cognitive

cination of Shiffrin and Schneider’s (1977) theory of con-
to neurodegeneration. Similarly, Jorm (1986), in his appli-
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to decline in dementia. On the other hand, tasks requiring a

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to determine the sensitivity of a cognitive test to preclinical
deficits in perceptual speed may exist in perceptual
speed and visuospatial–reasoning skills is supported by previ-
ous research. Preclinical deficits in perceptual speed are well
documented (Amieva et al., 2000; Fabrigoule et al., 1998; Masur et al., 1994; Storandt et al., 1984). Several studies also reported that visuospatial–reasoning skills (Elias et al., 2000; Fabrigoule et al., 1998; Fox, Warrington, Agnew, and Rossor, 1998; Jacobs et al., 1995) may deteriorate prior to dementia onset. Although our results are based on measures that are similar but not identical to the tests used in other studies, our findings still seem to substantiate the existence of multiple cognitive deficits in the preclinical phase of dementia.

Fabrigoule and colleagues (1998) and Amieva et al. (2000) suggested that the sensitivity of a cognitive test to preclinical deterioration may not depend on a specific cognitive area involved in a task. Instead, it may depend on attentional and executive demands of each task regardless of the specific cognitive area involved. Moscovitch and Umiltà (1990) suggested that tasks requiring selective attention involve voluntary, “executive” processes and are prone to decline in dementia. On the other hand, tasks requiring a specific or well-learned response involve mandatory, modular, or autonomous processes and tend to be more resistant to neurodegeneration. Similarly, Jorm (1986), in his application of Shiffrin and Schneider’s (1977) theory of controlled and automatic processing to pathological cognitive

changes in older adults, proposed that controlled but not automatic processes predict dementia onset.

The controlled–automatic processing theoretical framework may shed some light on the seeming divergence of our results. For example, although both Block Design and Figure Logic assess visuospatial–reasoning skills, they may require different cognitive processing. In Figure Logic, participants are given several options from which to choose; therefore, their response is cued and hence more automatic. However, more centralized, controlled cognitive processes may be involved in Block Design for which accurate performance requires initiation of active retrieval plans (Jorm, 1986) and controlled cognitive manipulation. Our results indicate that cognitive performance may vary depending on what underlying processes are involved in the performance of a task.

Tests of perceptual speed may be especially useful in detecting early signs of dementia. Moscovitch (1992) identified perceptual speed as an important aspect of memory retrieval on more complex tasks. Fabrigoule and colleagues (1998) found that perceptual speed contributed to performance on tests that best predicted dementia because of its controlled processing component. Our finding that both measures of perceptual speed—Symbol Digit and Figure Identification—predict dementia complements the conclusions of Fabrigoule and colleagues (1998) and the hypothesis proposed by Jorm (1986) that deterioration of controlled cognitive processes is the first sign of dementia.

Several twin studies imply that perceptual speed may play an important role in detecting cognitive deficits in nondemented older adults because of its relatively high dependency on age and shared genetic factors. For example, Finkel and colleagues (1997) found perceptual speed a main cross-sectional indicator of cognitive deficits in older adults. Finkel and Pedersen (2000) concluded that the relation between cognitive abilities and perceptual speed is mediated primarily by genetic predisposition. Both McClearn and colleagues (1997) and Pedersen and colleagues (1992) reported relatively high heritability ratings for perceptual speed. Age and genetic predisposition seem to account for a relatively large portion of variance on tests of perceptual speed. Therefore, on average we would expect to find minimal intrapair differences on the measures of perceptual speed. Our results, however, indicate that twins in a preclinical phase of dementia score significantly lower than their nondemented twin partners on both tests of perceptual speed. Because previous research with nondemented twins seems to preclude such a finding, we may presume that the deficits in perceptual speed found here reflect the true predictive ability of perceptual speed in the preclinical phase of dementia.

Previous research provides some support for the applicability of the controlled–automatic theoretical framework to preclinical detection of dementia. For example, measures with the most stringent requirements on attentional resources such as some tests of memory (Fox et al., 1998; Jacobs et al., 1995; Linn et al., 1995; Nielsen et al., 1999; Tierney et al., 1996) and tests of visuospatial abilities (Fabrigoule et al., 1998; Masur et al., 1994), attention or mental control (La Rue & Jarvik, 1986; Nielsen et al., 1999;
Storandt et al., 1984; Tierney et al., 1996), and category verbal fluency (Dartigues et al., 1997; Masur et al., 1994; Nielsen et al., 1999) were most often cited as good predictors of dementia. On the other hand, tests that involve automatic information processing such as reading (Fox et al., 1998) or letter fluency (Monsch et al., 1992) may not be sensitive to early signs of dementia.

Similarly, we found only nonsignificant deficits among preclinical twins on tests of verbal skills—Information and Synonyms. Both these tests assess well-learned verbal ability with limited demands on controlled cognitive processing and, therefore, may not be sensitive to preclinical signs of dementia.

MMSE seemed to be a good determinant of incipient dementia in preclinical twins (see Table 2). Because MMSE is composed of multiple tests and assesses both controlled and automatic processes, this finding is somewhat more difficult to explain within the controlled–automatic framework. Nevertheless, the finding indicates that MMSE may be a valuable tool in assessing early dementia.

The comparison analyses of nondemented twin partners and matched controls yielded similar results to analyses of the preclinical and nondemented twins (see Figure 1). Paired t tests showed significant differences on five measures for preclinical twins and their twin partners. Nondemented twin partners and matched controls differed on three of these five measures plus Information. Whereas nondemented twin partners performed similarly to preclinical twins on Information, they performed worse on this test than matched controls. Black Design and Figure Identification were the only two tests on which differences were found between nondemented twins and their preclinical twin partners but not between nondemented twin partners and matched controls.

There are two ways to explain this pattern of results. First, it is possible that in spite of selective demonstration of dementia within twin pairs, accelerated change in cognitive functioning may occur in both preclinical and nondemented twin partners because of shared genetic and/or environmental factors. Second, because we were not able to assess twin pairs longitudinally, it may be that the inherently lower intellectual level in some twin pairs predetermines relatively poor performance on some cognitive tests independently of age and education. Incipient dementia in the preclinical twins may further exacerbate the low cognitive performance. In any case, similarity of findings in the two sets of analyses seems to converge in pointing to particular sorts of cognitive deficits that presage dementia.

Several limitations of the present study should be addressed. First, our sample included both mono- and dizygotic twin pairs. Sample size precluded separate analyses by zygosity. Because intrapair similarity should be greater for monozygotic than for dizygotic pairs, one might predict a more pronounced preclinical effect for monozygotic than for dizygotic pairs. We did establish in our sample that zygosity of twin pairs was not significantly associated with intrapair differences on any of the cognitive measures, suggesting that there were not major differences by zygosity that were hidden by the combined sample. Nonetheless, assessing differences in dizygotic twin pairs may still attenuate our conclusions regarding control for possible genetic influences. Second, we used a relatively small sample of participants in the study. As a result, we can be less certain about our findings in terms of their general application. Both of these limitations stem partly from the fact that obtaining a sample of twins who later develop dementia is difficult. In a study similar to ours, La Rue and Jarvik (1987) assessed preclinical signs of dementia in twins but were not able to use a twin design in their data analyses because of not having sufficient numbers of complete twin pairs. Third, the present analyses combine various types of dementia. It is possible that separate analyses with different types of dementia would find distinct profiles among preclinical twins. However, we do not have sufficient pairs eligible for such comparisons. Fourth, we used cognitive measures that varied in score range. For example, Figure Logic has a restricted range and low internal consistency (Pedersen et al., 1992). Consequently, a test with a greater score range may yield significant results that are not due to its greater sensitivity to incipient dementia but to a larger spread of scores. On the other hand, these tests may be more appropriate for preclinical dementia research because they alleviate the possibility of floor or ceiling effects. Fifth, we used only a limited range of cognitive tests in this study. For example, it would be helpful to assess preclinical changes on tests of secondary memory or verbal learning. Such tests were previously found to predict dementia (e.g., Elias et al., 2000; Fox et al., 1998; Nielsen et al., 1999) but were not available prospectively in the SATSA assessment battery.

Sixth, the preclinical interval in our sample was relatively short. La Rue and Jarvik (1987) or Elias and colleagues (2000) used preclinical intervals that spanned to up to 22 years before clinical dementia onset. Assessment earlier before dementia onset may enhance the chances to discern true premorbid signs from early mild dementia, especially considering that the exact dementia onset is difficult to determine. Finally, we know that two of the nondemented twin partners of demented twins became demented themselves after 5 and 6 years, respectively. It seemed possible that the reason that nondemented twin partners scored lower than matched controls was that these two individuals depressed the mean scores for the nondemented twin-partner sample. However, excluding these two nondemented twin partners did not change the results.

In summary, our findings indicate that some cognitive tests may be more sensitive to developing dementia than others. The results seem to go along with the notion proposed by Jorm (1986) that a preclinical phase of dementia is characterized by deterioration of the central, controlled cognitive processes, whereas automatic processes remain relatively preserved. Because of small effect sizes and a small sample size in the present study, the results and implications of this study should be regarded with caution. Additional research using a larger pool of participants is needed to further evaluate the utility of the controlled–automatic processes framework in identifying preclinical dementia. Nonetheless, by assessing cognitive change in twin pairs, our study was the first to enable the distinction of premorbid signs of dementia and shared genetic or environmental factors.
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PSYCHOLOGY and AGING—Sanders-Brown Center on Aging and University of Kentucky Chandler Medical Center: invites applications from psychologists with interest and expertise in normal and abnormal age-associated changes in cognition for a tenure-track position at the assistant professor level in the Regular Title Series. This individual would have an academic appointment in a related department in the College of Medicine. This individual would join a large Center on Aging that includes a NIA-funded Alzheimer’s Disease Research Center and a number of NIH-funded individual research grants and program projects. The successful candidate will be expected to have or establish an independent extramural-funded research program as well as participate in the multidisciplinary programs developed by the Center.

Interested candidates should submit a letter of interest, a detailed curriculum vitae, and letters from three references to: William R. Markesbery, M.D., Professor of Neurology, Pathology and Director, Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536.

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