Non-mnestic Cognitive Function in the Scopolamine Model of Alzheimer’s Disease

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The contribution of cholinergic dysfunction to the non-mnestic cognitive impairments associated with senile dementia of the Alzheimer type (SDAT) was investigated. Scopolamine (0.5 mg) was administered intravenously to 12 healthy individuals, and their performance on selected subtests of the Wechsler Adult Intelligence Scale — Revised (WAIS-R), and on additional non-mnestic neuropsychological tests were compared to that of 12 healthy control participants. The results demonstrate that scopolamine does impair performance on components of the WAIS-R, but that the Fuld WAIS-R profile does not have a cholinergic basis. Scopolamine did not impair performance on verbal fluency, the Token Test, Judgment of Line Orientation, finger tapping, the Modified Card Sorting Test, or the Mini-Mental State Examination. The results do not support the hypothesis that the cholinergic system contributes to the non-mnestic impairments in SDAT.

INTRODUCTION

The extent to which the well-documented changes in the cholinergic system accompanying senile dementia of the Alzheimer type (SDAT) (for reviews see Crawford et al., 1990; Kasa et al., 1997) account for the symptoms of this disease continues to be a matter of debate. One approach to resolve this issue has been to examine the effects of temporary muscarinic receptor blockade on the performance of healthy people on neuropsychological tests sensitive to dementia. According to this approach, if muscarinic receptor blockers like scopolamine mimic the cognitive impairments of SDAT when they are administered to healthy individuals, then the cholinergic dysfunction characteristic of SDAT may be the physiological basis for these cognitive impairments. In fact, there is considerable evidence that muscarinic receptor blockers like scopolamine do mimic some aspects of the memory difficulties seen in SDAT (Broks et al., 1988; Caine et al., 1981; Kopelman and Corn, 1988; Obonsawin et al., 1996; Rusted and Warburton, 1988), and these results raise the possibility that the dysfunctional cholinergic system may be responsible for the memory difficulties in SDAT. However, these results are difficult to interpret. Whereas it is possible that cholinergic dysfunction does contribute to the memory problems in dementia, it is not clear that the administration of scopolamine provides a good model for SDAT. Indeed, an important weakness of the scopolamine model of SDAT is that it is difficult to evaluate the result of a scopolamine challenge because the validity of the scopolamine model remains to be established. Nevertheless, the effects of scopolamine on memory tasks have generated considerable research into the physiological basis of the cognitive...
impairments of SDAT, and its effects on other cognitive functions deserve investigation.

The effects of scopolamine on non-mnestic cognitive tasks sensitive to SDAT have received less attention. Many of the relevant investigations have focused on the effects of scopolamine on the performance of tests of language function and of general intellectual ability. Most authors have not reported any effect of scopolamine on the performance of tests of language function, but the range of functions assessed has been narrow. There is some consensus that scopolamine has no effect on object naming (Flicker et al., 1990, 1992; Zemishlany and Thorne, 1991), but there is evidence that scopolamine impairs the performance of young participants on some spelling tests (Aarsland et al., 1994). Performance on tests of verbal fluency is impaired in individuals with SDAT (Christensen et al., 1992; Miller, 1984; Rosen, 1980), but there is less agreement about the effects of scopolamine on verbal fluency. Many authors have reported no effect of scopolamine on verbal fluency (Beatty et al., 1985; Dunne, 1990; Kopelman and Corn, 1988; Zemishlany and Thorne, 1991), some authors have reported that scopolamine decreases performance on verbal fluency (Aarsland et al., 1994; Molchan et al., 1992; Sunderland et al., 1987) and yet other authors have reported that scopolamine improves performance on the verbal fluency task (Dunne, 1993; Lines et al., 1991). It appears that the effects of scopolamine on tests of language function sensitive to SDAT remain unresolved.

The effects of scopolamine on the performance on tests of general intellectual ability have been predominantly investigated with the Wechsler Adult Intelligence Scale, both the original (WAIS) and revised (WAIS-R) versions. Fuld (1984) reported that 53 per cent of participants who had been administered scopolamine showed a characteristic pattern of performance on the subtests of the WAIS. This pattern has come to be called the Fuld profile. Only 18 per cent of the control participants in Fuld’s (1984) study showed the profile. There is some evidence that this profile is more likely to occur in people with SDAT but not other forms of dementia (Brinkman and Braun, 1984; Fuld, 1984). These results provided support for the hypothesis that cholinergic dysfunction in SDAT was contributing substantially to the dementia. Many subsequent investigators of the profile have used the revised version of the Scale, the WAIS-R. The rate of occurrence of the profile in both versions of the WAIS is not significantly different (Filley et al., 1987). The evidence appears to indicate that the profile occurs specifically in conditions of cholinergic dysfunction such as SDAT, and occurs rarely in other populations, such as the healthy elderly (Satz et al., 1987, 1990; Tuokko and Crockett, 1987), or individuals suffering from head trauma (Heinrichs and Celinski, 1987), from schizophrenia or affective disorders (Ryan and Paolo, 1989), or from dementia secondary to AIDS (van Gorp et al., 1990).

The potential importance of the Fuld profile is eclipsed by two unresolved issues. The first issue is that until now, there has been no prospective study examining whether the profile does indeed occur in healthy individuals during muscarinic receptor blockade. Fuld’s (1984) report consisted only of a retrospective examination of data collected by Drachman and Leavitt (1974). The second issue is the inconsistency with which other investigators have been able to detect the occurrence of the profile in individuals with Alzheimer’s disease. Fuld (1984), Brinkman and Braun (1984) and Filley et al. (1987) have all reported that the profile occurs in 45–60 per cent of individuals with SDAT. However, Gfeller and Rankin (1991), Goldman et al. (1992) and Massman and Bigler (1993) have not been able to replicate these results. The occurrence of the profile in Alzheimer’s disease is still a matter of debate, and evidence for the cholinergic basis of the profile remains unreplicated.

The aim of the present study was to test the prediction that the performance of healthy individuals after scopolamine administration would be similar to the performance of individuals with SDAT on neuropsychological tests sensitive to a wide range of functions: word generation, auditory verbal comprehension, executive function, and motor performance. The present study is also the first prospective study to examine the claim that the administration of scopolamine gives rise to the Fuld profile on subtests of the WAIS-R. Performance on all the neuropsychological tests chosen is known to be impaired in SDAT.

MATERIALS AND METHODS

Participants

Twenty-four healthy participants (Table 1) took part in the study. Participants were only accepted
into the study after undergoing a thorough medical examination and providing signed, informed medical consent. Participants had abstained from alcohol (for 24 h) and from coffee and tea (for 12 h) prior to the experimental session. They received an honorarium for their participation. The study was approved by the Joint Ethical Committee of the Grampian Health Board and the University of Aberdeen.

**Scopolamine administration**

Twelve of the healthy participants received an intravenous injection of scopolamine (0.5 mg) in saline, and 12 participants were injected with an equal volume of saline. Both groups were matched for age, sex, and intellectual ability, based on their performance on the National Adult Reading Test (Nelson, 1982) and the Standard Progressive Matrices (Raven, 1958) (Table 1). Participants were paired on the basis of these indices, and randomly allocated to one of the two groups by one of the authors not involved in the drug administration procedure (DMP). Group membership was only revealed to the investigator carrying out the injection a few minutes prior to the injection. All tests were administered by MO, who remained blind to the group allocation until testing was completed. The dose was not corrected for body size, as previous work by Safer and Allen (1971) had suggested that such corrections resulted in more variable effects of the drug. Neuropsychological testing began 45 min after scopolamine administration, and continued for approximately 150 min. This time period reflected the period of peak effectiveness of intravenously administered scopolamine, according to evidence presented by Safer and Allan (1971).

**Physiological index of central cholinergic blockade**

The change in visual near point was assessed once before injection and at regular fixed intervals during the 5 h following injection. The change in visual near point has been used previously as an index of muscarinic receptor blockade (Kopelman and Corn, 1988). Its use is based on the fact that 0.6 mg of scopolamine, but not equal doses of atropinergic drugs, induces changes in visual near point (Brown, 1990), and the assumption that the ocular effects of scopolamine must be due to its ability to penetrate the CNS more readily than other antimuscarinic drugs. To measure the visual near point, participants were required to look into a modified lenticular stereoscope. The lenses were removed from the eyepieces, and the original shaft was replaced with a graduated shaft that had been lengthened to extend to 730 mm from the eyes. A sample of prose was fixed to the stereogram holder, and the holder was moved progressively closer to the subject’s eyes by sliding it on the shaft. The subject indicated the point at which the text was out of focus. The final score was the distance of the card (in cm) from the eyes when the subject indicated that the text was out of focus.

**Neuropsychological tests**

All participants received the following neuropsychological tests to assess a variety of non-mnestic functions.

1. The Controlled Oral Word Association Test (COWAT), or verbal fluency task, was administered as described by Benton and Hamsher (1976, 1978) and Goodglass and Kaplan (1972) to assess word generation (language and executive functions). The letters F, A and S were used, and participants were asked to generate as many words as possible for each letter. Sixty seconds were allowed for each letter. The score is the total number of words correctly produced over the 3 min period. Many authors have reported that individuals with SDAT are impaired on this task.

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Table 1. Summary description of participants

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>Scopolamine (0.5 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Age (mean years ± SD)</td>
<td>40.83 ± 12.55</td>
<td>43.67 ± 13.41</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>20–63</td>
<td>21–64</td>
</tr>
<tr>
<td>Sex ratio (m:f)</td>
<td>3:9</td>
<td>3:9</td>
</tr>
<tr>
<td>NART score (mean ± SD)</td>
<td>35.09 ± 7.23</td>
<td>38.25 ± 5.82</td>
</tr>
<tr>
<td>Raven’s matrices score (mean ± SD)</td>
<td>51.17 ± 7.81</td>
<td>51.42 ± 6.82</td>
</tr>
</tbody>
</table>

(Christensen et al., 1992; Miller, 1984; Rosen, 1980).

(2) To assess language function, a shortened, 16-item version of the *Token Test* was administered and scored according to the instructions provided by Spellacy and Spreen (1969). Participants were presented with plastic tokens varying in size, shape and colour. They were then given instructions to carry out different tasks with these tokens. The instructions increased in complexity as the task progressed. The performance of individuals with SDAT is impaired on the *Token Test* (Emery, 1985; Faber-Langendoen et al., 1988; Thompson, 1987).

(3) The *Judgment of Line Orientation Test* was administered and scored according to Benton et al. (1983) to assess perceptual function. Participants were shown two practice and 30 test items from a test booklet. Each item of the test consists of two components: a stimulus on the top page of the booklet, and an array of 11 possible responses on the bottom page of the booklet. The subject was required to choose two responses from the array on the bottom page that have the same orientation as the two stimulus lines on the top of the page. The performance of individuals with Alzheimer’s disease has been reported to be impaired on this task (Eslinger and Benton, 1983; Eslinger et al., 1985; Ska et al., 1990).

(4) The *Modified Card Sorting Test* is thought to measure the ability to form concepts and the ability to shift cognitive set. Like the COWAT, it is thought to assess the integrity of frontal lobe function (Parker and Crawford, 1992). Participants are required to sort cards according to specific dimensions (colour, number and shape), and to change the sorting rule on a cue provided by the examiner. It was administered and scored according to the method described by Nelson (1976). The performance of individuals with dementia is impaired on this task (Bondi et al., 1993; Hart et al., 1988).

(5) The *Finger Tapping* task assesses manual dexterity and fine motor control. Participants were required to tap a mechanical counter (Lafayette Instruments Co.). The number of times the counter was tapped in 10 s was recorded. Administration and scoring was carried out according to the suggestions provided by the manual accompanying the finger-tapper. The final score was the average number of taps over five trials. These five trials were selected in one of two ways. If the subject completed five consecutive trials within a five-point range, no additional trials were required and the average of these five trials was taken. The maximum number of trials allowed was ten. If there were not five consecutive trials within a five-point range, the final score was the average of the five highest trials. The required number of trials were completed for both the dominant and non-dominant hand.

In comparison to the performance of age-matched healthy individuals, the performance of individuals with dementia is impaired on this task (Ott et al., 1995).

(6) The cognitive state of the participants was assessed according to the *Mini-Mental State Examination* (MMSE), as described by Folstein et al. (1975).

(7) In addition, all participants received the seven subtests of the WAIS-R that form part of the Fuld WAIS-R profile: Information, Digit Span, Vocabulary, Similarities, Block Design, Object Assembly and Digit Symbol. The seven subtests were administered according to the instructions provided in Wechsler (1981). Tests were administered in the following order: Information, Block Design, Digit Span, Object Assembly, Vocabulary, Digit Symbol, Mini-Mental State Examination, Similarities, Finger Tapping (dominant hand), COWAT, Token Test, finger-tapping (non-dominant), Judgment of Line Orientation and MCST.

RESULTS

Visual near point

The change in visual near point for both groups is presented in Figure 1. Although there was no significant group effect (*F*(1,22) = 1.76, *p* = 0.199), there was a significant within-participants effect of time (*F*(3,66) = 15.07, *p* < 0.001), and a significant interaction between group and time (*F*(3,66) = 4.76, *p* = 0.005). The two groups therefore differed in the change in visual near point over the course of the experiment.

WAIS-R subtests and the Fuld profile

The performance of the participants on the WAIS-R subtests are shown in Table 2. Because we compared the performance of participants on seven subtests with *t*-tests, we applied a Bonferroni
correction to change the significance level from 0.05 to 0.007. The performance of the participants in the scopolamine group was lower than that of participants in the control group on only one subtest, Block Design. There was no significant difference between the two groups on any of the other subtests. Only one of the 12 participants in the scopolamine group showed the Fuld profile, and none of the 12 participants in the control group did. This apparent small difference is not statistically significant according to Fisher's Exact Probability ($p = 0.50$).

**Neuropsychological tests of cognitive function**

The aim of this section was to see if individuals who were administered scopolamine would show a pattern of performance that reflected some aspects of dementia, especially dementia of the type associated with SDAT. The results from the neuropsychological tests are summarised in Table 3. T-tests demonstrated no significant differences between the participants in the control group and those receiving scopolamine on the verbal fluency, Judgment of Line Orientation, the Token Test, Finger Tapping or the MMSE. Mann–Whitney U tests demonstrated no significant differences between the two groups on either of the two indices of the Modified Card Sorting Test.

**DISCUSSION**

The aims of the present study were to test the hypothesis that scopolamine impairs the performance of...
healthy individuals on non-mnestic neuropsychological tests known to be sensitive to SDAT, and to verify the cholinergic basis of the Fuld profile. The results indicate that (i) the Fuld WAIS or WAIS-R profile is not a marker for impaired function of the central cholinergic system, but performance on individual subtests of the WAIS-R may be affected by scopolamine, and (ii) the performance of healthy participants after administration of scopolamine does not resemble the performance of individuals with SDAT on neuropsychological tests of non-mnestic cognitive function (verbal fluency, the Token Test, Finger Tapping, and the MCST).

The origins of the Fuld profile lie in the scopolamine model of SDAT and can be traced to a report by Fuld (1984) who conducted a retrospective examination of the performance on the WAIS of healthy participants who had been administered scopolamine in a previous study (Drachman and Leavitt, 1972, 1974). The present study is the first prospective study to investigate the cholinergic basis of the profile. The results do provide evidence that muscarinic receptor blockade impairs performance on the Block Design subtest of the WAIS-R, but do not provide evidence to substantiate the claim that cholinergic blockade leads to the characteristic profile reported by Fuld (1984).

Previous studies reporting the occurrence of the Fuld profile in individuals with SDAT were conducted with participants up to the ages of 83 (Fuld, 1984), and 86 years (Brinkman and Braun, 1984), despite the fact that norms for the WAIS-R are only available for individuals up to the age of 74. It is not clear in either report if the age of participants who do show the profile is different from the age of participants who do not show the profile, nor is there any explanation in these reports on how the age-corrected scores for the participants over 74 were obtained. In the absence of such information, one can only assume that the subtest scores of participants up to the age of 86 years of age were corrected for age with norms intended for participants between the ages of 70 and 74 years of age. If this is indeed the case, then the reports on the occurrence of the cholinergic WAIS-R profile in dementia may not be reliable. Given the results of the present study, and the use of inappropriate norms to support the existence of the cholinergic WAIS-R profile in SDAT, we do not recommend the use of this profile to investigate the presence of cholinergic dysfunction.

The administration of scopolamine to healthy individuals did not affect performance on any of the other neuropsychological measures. To certify that scopolamine did indeed cause blockade of central muscarinic receptors, we monitored changes in visual near point. Changes in visual near point during cholinergic blockade have been interpreted as reflecting blockade of central muscarinic receptors (Kopelman and Corn, 1988). Our results indicate a progressive increase in central muscarinic receptor blockade during neuropsychological testing, but do not indicate any increase in the occurrence of the Fuld profile, or any impairment of performance on the neuropsychological tasks.

Table 3. Effects of scopolamine on performance on tests of neuropsychological function (mean ± SD)

<table>
<thead>
<tr>
<th>Test</th>
<th>Control</th>
<th>Scopolamine</th>
<th>t/U</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Fluency*</td>
<td>39.08 ± 6.17</td>
<td>46.75 ± 14.30</td>
<td>-1.71</td>
<td>0.102</td>
</tr>
<tr>
<td>Judgment of Line Orientation*</td>
<td>24.92 ± 2.54</td>
<td>21.58 ± 5.38</td>
<td>1.94</td>
<td>0.065</td>
</tr>
<tr>
<td>Token Test*</td>
<td>77.75 ± 0.45</td>
<td>77.33 ± 1.15</td>
<td>1.16</td>
<td>0.257</td>
</tr>
<tr>
<td>Finger Tapping*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant hand</td>
<td>42.40 ± 7.57</td>
<td>44.88 ± 4.95</td>
<td>-0.95</td>
<td>0.352</td>
</tr>
<tr>
<td>Non-dominant hand</td>
<td>45.34 ± 18.34</td>
<td>39.17 ± 4.54</td>
<td>1.13</td>
<td>0.270</td>
</tr>
<tr>
<td>MMSE*</td>
<td>28.67 ± 1.30</td>
<td>27.92 ± 2.27</td>
<td>0.99</td>
<td>0.332</td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of categories</td>
<td>5.00 ± 1.95</td>
<td>4.42 ± 1.68</td>
<td>49.0</td>
<td>0.198</td>
</tr>
<tr>
<td>% perseverative errors</td>
<td>20.34 ± 30.50</td>
<td>25.40 ± 20.33</td>
<td>52.0</td>
<td>0.266</td>
</tr>
</tbody>
</table>

*The two experimental conditions were compared with a t-test.
†The two experimental conditions were compared with a Mann–Whitney U test.
The lack of effect of scopolamine on the verbal fluency test resemble the results obtained in some previous studies (Beatty et al., 1986; Curran et al., 1991; Dunne, 1990; Kopelman and Corn, 1988; Zemishlany and Thorne, 1991), although there are some reports that scopolamine impairs (Aarsland et al., 1994; Molchan et al., 1992; Sunderland et al., 1987) or even improves performance on the task (Dunne, 1993; Lines et al., 1991). The reasons for these discrepancies remain unclear. Curran et al. (1991) speculate that only higher doses of scopolamine impair performance on verbal fluency. Their speculation is based on the results obtained by Sunderland et al. (1987) in which only the higher dose (0.5 mg) but not the lower doses (0.1 and 0.25 mg) of scopolamine impaired performance on verbal fluency in elderly participants. However, Molchan et al. (1992) reported that 0.5 mg of scopolamine impairs performance on the verbal fluency task in elderly (mean age of 66.5) but not young (mean age of 27) participants. These results raise the possibility that the inconsistent results of past studies may be due in part to differences in the age of the participants.

The only effect of scopolamine appears to be on the Block Design subtest of the WAIS-R, but the scopolamine-induced impairment resembles an age-associated more than a dementia-associated impairment. Previous investigators have commented that scopolamine-induced memory impairments resemble age-associated rather than dementia-associated changes in function (Bartus et al., 1982; Coyle et al., 1983; Drachman and Leavitt, 1974; Flicker et al., 1990). There is considerable evidence for changes in cholinergic function with ageing (Dunnet, 1991; Gallagher and Colombo, 1995; Gottfries, 1990). Decreases in choline uptake, acetylcholine synthesis, choline acetyltransferase activity, transmitter release, muscarinic receptor density, volume and number of cholinergic neurons have all been reported to be associated with ageing in humans and other species (Bowen, 1984; Davies, 1978; Freund, 1980; Gibson and Peterson, 1981; McGeer and McGeer, 1981; Mesulam et al., 1987; Meyer et al., 1984). However, our knowledge of the contribution of the cholinergic system to the changes in cognition accompanying ageing is far from complete.

The results of the present study do not provide any support for the hypothesis that the well-recognised changes in cholinergic system function in SDAT are contributing to the cognitive impairments in that condition, but two points must be borne in mind when considering these results. Firstly, the range of non-mnestic psychological functions tested in this study was broader than in past studies, but was by no means exhaustive. It is possible that scopolamine does affect the performance on other non-mnestic tests that are also sensitive to SDAT (e.g. Aarsland et al., 1994). Secondly, the scopolamine model may not be an adequate test of this hypothesis. The dissimilarity between the known mechanism of action of scopolamine and the known pathophysiology of SDAT is such that comparisons between scopolamine-induced impairments and impairments associated with dementia must be interpreted with caution. Scopolamine causes cholinergic dysfunction by temporarily blocking muscarinic receptors on all target neurons of the brain, including receptors in the cerebral cortex, amygdala, hippocampus and thalamus, and receptors on the cerebral vasculature. During receptor blockade with scopolamine, the target cells are still functional, but do not receive cholinergic input. In contrast, dysfunction of the cholinergic cells of Ch4 and Ch5 in SDAT is accompanied by the death of target neurons in the cerebral cortex and hippocampus. It is still not clear whether cell loss in the cortex precedes or follows from cell loss in Ch4 (Cullen et al., 1997; Mesulam, 1991). In contrast to temporary muscarinic receptor blockade, cholinergic dysfunction in dementia is progressively degenerative and permanent, affects both muscarinic and nicotinic receptors, and is accompanied by the death of cortical and hippocampal target cells. The importance of the differences between the mechanism of action of scopolamine and the pathophysiology of SDAT is emphasized by the ability of cholinergic agonists like physostigmine and tacrine to reverse or diminish the effects of scopolamine (Ghoneim and Mewaldt, 1977; Kirkby et al., 1996; Mewaldt and Ghoneim, 1979; Murray and Cross, 1991; Riekkinen et al., 1991; Tsukada et al., 1997), but have minimal effects on alleviating the dementia associated with SDAT (Crawford et al., 1992; Eagger et al., 1991; Farlow et al., 1992; Freeman and Dawson, 1991; Sahakian et al., 1993).

Two unresolved issues arise from the scopolamine model of SDAT. The first is the issue of whether the cholinergic system dysfunction associated with SDAT contributes significantly to the symptoms of dementia. The second is the issue of whether scopolamine administration provides an adequate model of the cholinergic system.
dysfunction of SDAT. Both the differences between the mechanism of action of scopolamine and the pathophysiology of SDAT, and the inability of scopolamine to mimic many of the non-mnestic impairments of SDAT, raise serious questions about the scopolamine model. The principal evidence that provides support for the scopolamine model of SDAT is the similarity between the memory impairments induced by scopolamine and the memory impairments associated with SDAT (Broks et al., 1988; Caine et al., 1981; Kopelman and Corn, 1988; Obonsawin et al., 1996; Rusted and Warburton, 1988). These results imply that the scopolamine model of SDAT is a valid one, and that cholinergic dysfunction underlies some of the memory problems in SDAT. However, the memory difficulties in SDAT may be explained more parsimoniously by the progressive deterioration of other structures of the brain associated with memory, like the hippocampus. More recently, Cummings and Kaufer (1996) have suggested that cholinergic dysfunction may be the basis for some of the neuropsychiatric symptoms associated with SDAT, but there has been little research on this issue. The validity of the scopolamine model of dementia remains to be determined, but the results of the present study do not provide support for the hypothesis that cholinergic dysfunction is the basis for the non-mnestic cognitive impairments in SDAT.

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