Neuropsychologia 49 (2011) 1897–1902

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

False item recognition in patients with Alzheimer's disease

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ARTICLE INFO

Article history:
Received 22 November 2010
Received in revised form 9 March 2011
Accepted 11 March 2011
Available online 17 March 2011

Keywords:
Alzheimer's disease
Familiarity
Memory
Recognition
Recollection

ABSTRACT

Recent evidence suggests that patients with Alzheimer's disease (AD), as compared with normal individuals, exhibit increased false recognition by stimulus repetition in the Deese–Roediger–McDermott (DRM) task or associative recognition memory tasks, probably due to impaired recollection-based monitoring. However, because of possible alternative explanations for the findings of these previous studies, the evidence for impaired recollection-based monitoring in AD patients remains inconclusive. In this study, we employed stimulus repetition in old/new recognition judgments of single-item picture memory without a factor of association between the stimuli and examined whether AD patients showed increased false item recognition as compared with healthy controls. AD patients and healthy controls studied single-item pictures presented either once or three times. They were later asked to make an old/new recognition judgment in response to (a) Same pictures, pictures identical to those seen at encoding, (b) Similar lures, novel pictures similar to but not identical to those seen at encoding, and (c) Dissimilar lures, novel pictures not similar to those seen at encoding. For Same pictures, repeated presentation of stimuli increased the proportion of "old" responses in both groups. For Similar lures, repeated presentation of stimuli increased the rate of "old" responses in AD patients but not in control subjects. The results of the present study clearly demonstrated elevated false recognition by stimulus repetition in single-item recognition in AD patients. The present findings strongly support the view that AD patients are impaired in their ability to use item-specific recollection in order to avoid false recognition.

1. Introduction

One of the more prominent cognitive problems observed in Alzheimer's disease (AD) is the decline in episodic memory (Salmon and Bondi, 2009), the type of memory that allows one to remember past occurrences in one's life (Tulving, 2001). The episodic memory impairments observed in AD patients are mainly characterized by the failure to retrieve desired information, but at times, AD patients also suffer from memory distortion. The memory distortion in AD patients can sometimes be extreme, as in syndromes of delusional misidentification (e.g., Abe et al., 2007; for review, see Forstl et al., 1994). Therefore, an understanding of memory distortion in AD patients is clinically important; however, the underlying mechanisms remain to be fully elucidated.

One approach to evaluating memory distortion is assessment of false recognition in cognitive memory tasks. False recognition is a process whereby people incorrectly claim that they have recently seen or heard a stimulus that they have not actually encountered (Underwood, 1965). One of the most common tasks for assessment of false recognition is the Deese–Roediger–McDermott (DRM) task (Deese, 1959; Roediger and McDermott, 1995; for review, see Gallo, 2010) in which false recognition of non-studied lures is elicited by having subjects study lists of associates. For example, using a modified version of the DRM paradigm in which study and test trials were repeated five times, Budson, Daffner, Desikan, & Schacter (2000) reported that false recognition increased in AD patients, decreased in young adults, and fluctuated in older adults.

The findings of Budson et al. (2000) can be interpreted as indicating that impaired retrieval monitoring processes in AD patients would cause memory distortion (Schacter, Norman, & Koutstaal, 1998a). More specifically, recall-to-reject processes, where recall (or recollection) opposes familiarity in recognition memory tasks (see Yonelinas, 2002), might be impaired in AD patients. Here, "recall" refers to the ability to retrieve previously experienced information in response to some retrieval cue, and recollection is defined as the mental reinstatement of experienced events during which unique details of memory are recalled. Familiarity is a mental awareness that an event has been experienced previously without the unique details or mental reinstatement of the event (Gardiner,

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doi:10.1016/j.neuropsychologia.2011.03.015

1988; Jacoby, 1991; Mandler, 1980; Skinner and Fernandes, 2007). In the study of Budson et al. (2000), owing to the multiple study/test sessions, control subjects may have increased their recollection of the studied items, determined that the related lures were not presented, and hence rejected these lures as non-studied items. AD patients might be unable to use such a recollection-based monitoring process to reduce false recognition. In line with this idea, some previous studies have reported that AD patients have impaired recall or recollection relative to familiarity. For instance, Bartok et al. (1997) reported that AD patients tend to be impaired more in recall than in recognition tests. Dalla Barba (1997) showed that recollection-based recognition is more affected than familiarity-based recognition in AD patients. These findings suggest that AD patients perform poorly on tasks in which recall or recollection is necessary to oppose familiarity-based false recognition.

However, as Gallo, Sullivan, Daffner, Schacter, & Budson (2004) have pointed out, there are other possible explanations, such as impairment of source memory (e.g., Dalla Barba, Nedjam, & DuBois, 1999; Multhaup and Balota, 1997; Smith and Knight, 2002). In the repeated study/test sessions, the subject needs to monitor several sources of information, including whether the related lure was in the study list, in the test list, or whether it was only imagined (Budson et al., 2002; Kensinger and Schacter, 1999; Schacter, Verfaellie, Anes, & Racine, 1998b). Another possible explanation would be the impairment in remembering the associations between items and list-contexts. If the subjects can successfully remember the list-context in which they studied the item, they may reject the unstudied related lures more effectively.

To test the impaired recall-to-reject hypothesis for false recognition in AD patients without contamination of deficits in source memory, Gallo et al. (2004) used an associative recognition memory task in which subjects studied pairs of unrelated words and were later asked to distinguish between these same studied pairs (intact) and new pairs that contained either rearranged studied words (rearranged) or non-studied words (non-studied). During the study period, the pairs were presented either once or three times. The results showed that repetition increased the hits to intact pairs in both AD and control groups, but repetition increased false alarms to rearranged pairs only in the AD group. Gallo et al. (2004) suggested that repetition increases the familiarity of the words in both rearranged and intact pairs; however, only the control subjects were able to counter this familiarity by recalling the originally studied pairs, which is consistent with the recall-to-reject hypothesis.

As Gallo et al. (2004) noted, however, their findings may also be explained by an impaired memory for associations, although they did not ascribe their findings to deficits in source memory. Repetition of word pairs during a study task may enhance familiarity for test words in both intact and rearranged pairs, such that the discrimination between intact and rearranged pairs depends on the memory for the specific association formed during the task. More specifically, in the task used by Gallo et al. (2004), subjects need to recollect associations between two words in order to make an accurate recognition memory judgment. Here, it should be noted that both of the tasks used in Budson et al. (2000) and Gallo et al. (2004) required the subjects to recollect some kind of associations, namely, item-to-list-context association in Budson et al. (2000) and item-to-item associations in Gallo et al. (2004). Thus, from the previous studies on false recognition in AD patients, the evidence for impaired recollection-based monitoring in AD patients remains inconclusive due to possible alternative explanations, especially associative memory account.

To provide strong evidence supporting the impaired recall-to-reject hypothesis, we investigated false recognition in AD patients using a different kind of item-recognition task from those used in previous studies. Prior studies have used semantically related word lists (Budson et al., 2000), phonologically related word lists (Budson, Sullivan, Daffner, & Schacter, 2003b), or categorized color photographs (Budson et al., 2003a). In the present study, we used previously presented pictures (Same pictures), novel pictures similar to previously presented pictures (Similar lures), and novel pictures not similar to previously presented pictures (Dissimilar lures) as experimental stimuli for the recognition memory task. The experimental paradigm using these stimuli, which have often been reported in previous studies (e.g., Garoff, Slotnick, & Schacter, 2005; Kensinger, Garoff-Eaton, & Schacter, 2007a, 2007b; Kensinger and Schacter, 2007), was suitable for our investigation because it allowed us to measure changes in the ability to discriminate Same pictures from Similar lures (i.e., item-specific recollection) by stimulus repetition without the element of source memory or associative memory. The aim of the present study was to determine whether AD patients would show increased false recognition in response to Similar lures by stimulus repetition and to provide strong evidence supporting the impaired recall-to-reject hypothesis in AD patients.

Table 1
Demographic data (mean ± SD) for the AD patients and the healthy controls.

	AD patients ($n = 18$)	Controls ($n = 18$)	p-Value
Age	74.5 (4.6)	74.8 (4.2)	$p > 0.1$
Sex (female/male)	14/4	11/7	$p > 0.1$
Education	10.7 (2.1)	10.9 (1.8)	$p > 0.1$
MMSE	24.4 (2.1)	28.0 (1.7)	$p < 0.001$

The chi-squared test was used for the gender ratio, and the t-test was used for the remaining variables. Standard deviations are in parentheses. MMSE, Mini-Mental State Examination.

2. Materials and methods

2.1. Participants

Eighteen patients with a clinical diagnosis of probable AD (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria; McKhann et al., 1984) and 18 healthy elderly adults participated in the experiment. AD patients were recruited from the clinical population at Tohoku University Hospital. Each of these patients was assessed by one or more board-certified neurologists with expertise in diagnosing dementia. Elderly adults who had no history of neurological or psychiatric diseases were recruited from the local community via an advertisement. The exclusion criteria for both groups were a medical history of neurological disease (e.g., stroke, head injury, and epilepsy) or psychiatric illness (e.g., schizophrenia and manic depression) and a documented or suspected history of alcohol or drug abuse. In addition, because we intended to study patients with mild AD, patients who scored less than 20 on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) were excluded. Healthy participants who scored less than 24 (a cutoff level for a diagnosis of dementia) on the MMSE were also excluded. All participants had normal or corrected-to-normal vision. At the time of the study, none of the patients was being or had been treated with specific medication, such as anti-acetylcholinesterase agents. The elderly adults were matched to the patients for gender (4 male and 14 female patients vs. 7 male and 11 female elderly adults), age (patient mean = 74.5 years, range = 67–87 years; elderly adult mean = 74.8 years, range = 67–82 years), and education (patient mean = 10.7 years, range = 8–14 years; elderly adult mean = 10.9 years, range = 8–14 years). The study was approved by the Ethical Committee of Tohoku University and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants or their caregivers when appropriate. The demographic data of each group are summarized in Table 1.

2.2. Stimuli

We prepared color photographs of 120 common living things and 120 common inanimate objects, which were used in our previous study (Hashimoto et al., in press). These photographs consisted of 60 pairs of different photographs of the same living things and 60 pairs of different photographs of the same inanimate objects. These pairs were divided into three sets (i.e., 40 pairs each) of an equal number of animate and inanimate stimuli. The first members of two sets (80 stimuli) were used as study items in the study phase, and the first members of the other set (40 stimuli) were used as distracters in the test phase. The assignment of these three stimuli sets to either study or to the test phase was counterbalanced across subjects. Of the two sets used in the study phase, the first members of one set (40 stimuli)

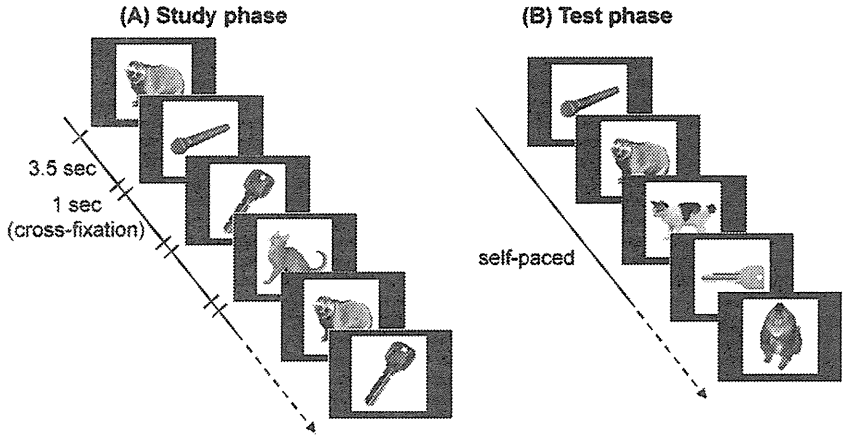

Fig. 1. The experimental design, which involved (A) a study phase and (B) a test phase. (A) During the study phase, participants were asked to judge whether each photograph represented a living or a non-living thing and to memorize each photograph. Half of the stimuli were presented once, and the remaining stimuli were presented three times. (B) During the test phase, participants were asked to judge whether each stimulus was new or old. They were requested to indicate "old" if the stimulus was presented as it was during the study phase and "new" if the stimulus was a non-studied object or was presented with different perceptual details from the studied object.

were used as target items to be recognized later in the test phase (for the "Same" condition, see below for details), whereas the second members of the other set (40 stimuli) were used as target items to induce false recognition in the test phase (for the "Similar" condition, see below for details). The assignment of the first and second members of the stimulus sets to either the "Same" or the "Similar" condition was also counterbalanced across subjects.

2.3. Procedure

The experiment consisted of an intentional study phase followed by the recognition memory test phase that required the participants to indicate whether the presented stimulus had been studied. Before the experiment, the participants were given a thorough explanation of the task procedure and were familiarized with the task by completing a short practice session. To ensure that the participants comprehended the task procedure, they were required to explain the instructions to an experimenter in their own words.

During the study phase (Fig. 1A), the subjects were presented with a total of 80 stimuli. Each stimulus was presented for 3.5 s with an interstimulus interval of one second during which a fixation point (a cross) was constantly presented. Half of these 80 stimuli were presented once, and the other half were presented three times. Therefore, the total number of trials was 160. The stimuli were presented one by one in a randomized order. The subjects were then asked to indicate whether the stimulus represented an animate or inanimate object by pressing buttons and were asked to memorize each stimulus for the later recognition memory test.

During the test phase, the subjects performed an old/new recognition task in a self-paced manner (Fig. 1B). Five different kinds of stimulus type were presented: (a) 20 stimuli that had been presented once during the study phase (Same-1× stimuli), (b) 20 novel stimuli similar to the 20 that had been presented once during the study phase (Similar-1× stimuli), (c) 20 stimuli that had been presented three times during the study phase (Same-3× stimuli), (d) 20 novel stimuli similar to the 20 that had been presented three times during the study phase (Similar-3× stimuli), and (e) 40 novel stimuli not similar to the 80 that had been presented during the study phase (Dissimilar stimuli). These stimuli were presented one by one in a randomized order. The subjects were asked to indicate whether they had studied each stimulus by pressing buttons. After each trial, the experimenter initiated the next trial by pressing a button.

3. Results

3.1. Demographic data

Comparisons of demographic data between the two groups were performed using the χ^2 test for gender ratio and the t-test for other components (Table 1). There were no significant differences in age ($t(34) = 0.227$, $p > 0.1$), gender ($\chi^2 = 1.178$, $p > 0.1$) or education ($t(34) = 0.260$, $p > 0.1$). On the MMSE scores, the AD patients scored significantly lower than the healthy controls ($t(34) = 5.621$, $p < 0.001$).

3.2. Recognition memory test

The mean proportion of "old" responses for all types of stimuli in the two groups is summarized in Table 2. First, we performed a 2 (stimuli: Same and Similar) × 2 (repetition: 1× and 3×) analysis of variance (ANOVA) for the AD patient data. We found significant main effects of stimuli ($F(1,17) = 145.040$, $p < 0.001$) and repetition ($F(1,17) = 55.148$, $p < 0.001$) with no interaction between the two factors ($F(1,17) = 0.491$, $p > 0.1$). This indicates that the repeated presentation of stimuli increased the rate of "old" responses to both Same pictures (true recognition) and Similar lures (false recognition) in AD patients.

We then performed a 2 (stimuli: Same and Similar) × 2 (repetition: 1× and 3×) ANOVA for the healthy control data. We found significant main effects of stimuli ($F(1,17) = 141.760$, $p < 0.001$) and repetition ($F(1,17) = 25.159$, $p < 0.001$) with a significant interaction between the two factors ($F(1,17) = 38.597$, $p < 0.001$). Post-hoc tests revealed a significant difference in the proportion of "old" responses for Same pictures between the single and repeated presentations ($t(17) = 9.301$, $p < 0.001$), whereas there was no significant difference for Similar lures between the single and repeated presentations ($t(17) = 0.452$, $p > 0.1$). This indicates that the repeated presentation of stimuli increased the rate of "old" responses to Same pictures (true recognition) but not to Similar lures (false recognition) in control subjects.

To further compare performance across the groups, two types of memory indices were calculated: memory for items and memory for perceptual details. The memory index for items (MI) was calculated as the difference between hits to Same pictures and false alarms to Dissimilar lures. This difference reflects the participants' ability to correctly discriminate Same pictures from Dissimilar lures. The memory index for perceptual details (MD) was calculated

Table 2
Mean proportions of "old" responses for each stimulus type.

Stimulus type	AD patients ($n = 18$)	Controls ($n = 18$)
Same-1×	70.0 (19.7)	75.3 (11.6)
Same-3×	87.5 (13.0)	95.8 (5.5)
Similar-1×	50.3 (19.8)	43.1 (13.5)
Similar-3×	65.0 (18.9)	44.4 (14.7)
Dissimilar	30.3 (20.3)	10.8 (7.2)

Standard deviations are in parentheses.

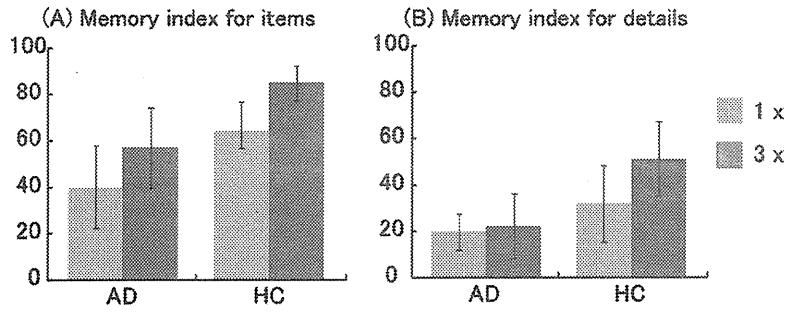

Fig. 2. Two memory indices for recognition memory in the two groups. (A) The memory index for items was calculated as the difference between the proportion of hits to Same pictures and the proportion of false alarms to Dissimilar lures. (B) The memory index for details was calculated as the difference between the proportion of hits to Same pictures and the proportion of false alarms to Similar lures. Error bars represent standard deviations. AD, patients with AD; HC, healthy controls.

as the difference between hits to Same pictures and false alarms to Similar lures. This difference reflects the participant's ability to correctly discriminate Same pictures from Similar lures. These measures were used over other measures of discrimination (d' or A') because they tend to be more sensitive (Snodgrass and Corwin, 1988) and because they may be more appropriate for recognition memory tests that investigate recall-to-reject processes (e.g., Gallo et al., 2004). These measures are also useful in that they reflect a subject's memory regardless of whether he or she has a liberal or conservative response bias (i.e., extremely high rate of "old" or "new" responses) derived from individual differences.

Fig. 2 shows the MI and MD for each group. A 2 (group: AD patients and healthy controls) × 2 (repetition: 1× and 3×) ANOVA was conducted separately for each type of memory index. For the MI, there were significant main effects of group ($F(1,34) = 34.994$, $p < 0.001$) and repetition ($F(1,34) = 94.150$, $p < 0.001$) without an interaction between the two factors ($F(1,34) = 0.607$, $p > 0.1$). The lack of interaction indicates that the ability of the AD patients and the healthy controls to discriminate Same pictures from Dissimilar lures was affected by stimulus repetition in a similar manner.

A different pattern emerged in the analysis of the MD. There were significant main effects of group ($F(1,34) = 27.806$, $p < 0.001$) and repetition ($F(1,34) = 19.079$, $p < 0.001$) with a significant interaction between the two factors ($F(1,34) = 10.641$, $p < 0.005$). Post-hoc tests revealed that AD patients did not show a difference between the single and repeated presentations ($t(17) = 0.701$, $p > 0.1$), whereas the healthy controls showed a higher index in the repeated presentation than in the single presentation ($t(17) = 6.213$, $p < 0.001$). This indicates that the ability of the AD patients and the healthy controls to discriminate Same pictures from Similar lures was differentially affected by stimulus repetition.

Finally, we examined whether AD patients were less susceptible to similarity-based false recognition than were healthy controls, especially in the Similar-1× condition. This analysis was inspired by previous findings that AD patients were less susceptible to false recognition in response to lure stimuli after a single list exposure in the DRM paradigm than were healthy controls (Balota et al., 1999; Budson et al., 2000). To control for response bias, we calculated the corrected false recognition rates that were obtained by subtracting the proportion of "old" responses to Dissimilar lures from the proportion of "old" responses to Similar lures. The corrected false recognition rates for Similar-1× and Similar-3× were 20.0 (SD = 16.2) and 34.7 (SD = 16.3) for AD patients and 32.2 (SD = 13.0) and 33.6 (SD = 13.0) for healthy controls, respectively. We found a significant difference in the corrected false recognition rate for Similar-1× between AD patients and healthy controls ($t(34) = 2.494$, $p < 0.05$). There was, however, no significant difference in the corrected false recognition rate for Similar-3× between AD patients and healthy controls ($t(34) = 0.227$, $p > 0.1$). This indicates that AD patients were originally less susceptible to similarity-based false recognition than were healthy controls, but stimulus repetition canceled out this effect.

4. Discussion

In the present study, we used an item-recognition memory paradigm to investigate false recognition in AD patients and healthy controls. Specifically, we focused on whether the repeated presentation of stimuli differentially affected the ability to discriminate the targets and the lures perceptually similar to the targets between these two populations. The results showed that the repeated presentation of stimuli increased the proportion of "old" responses to Same pictures in both groups and to Similar lures in the AD patients but not in control subjects. Further analysis revealed that repeated presentation of the stimuli raised a memory index for items in both groups, whereas unlike the healthy controls, repeated presentation of the stimuli did not show an improvement in the memory index for perceptual details in AD patients. The present study provides clear evidence to support the impaired recall-to-reject hypothesis in AD patients in a single-item recognition task, which excludes the factor of associative memory.

The present findings showing that false recognition was increased in an item-recognition paradigm by stimulus repetition in AD patients have provided strong support for the impaired recall-to-reject hypothesis in AD patients. As mentioned in the Introduction, Budson et al. (2000) used a modified version of the DRM task to argue that impaired item-specific recollection increases familiarity-based false recognition in AD patients. Similarly, Gallo et al. (2004) used an associative recognition task to argue that impaired recall-to-reject processes lead to an elevated level of familiarity-based false recognition in AD patients. However, the evidence for impaired recollection-based monitoring in AD patients from these studies was inconclusive because of the possible alternative explanations that could not be ruled out in these previous studies, namely, certain kinds of associative memory deficits. To avoid these possible confounding factors, we used stimuli consisting of photographs that were semantically concordant but perceptually distinct as Similar lures. We found an increased false item recognition in response to Similar lures by stimulus repetition in AD patients, but not in healthy controls. The pattern of these results is in line with the previous studies (Budson et al., 2000; Gallo et al., 2004) and is highly consistent with the impaired recall-to-reject hypothesis in AD patients.

One might think that, if the repeated presentation of the stimulus increases recollection of studied items and this increased recollection is used to more effectively reject Similar lures, then the healthy controls should show decreased "old" responses to Similar lures in the repeated condition relative to the single presentation

condition. However, our results were against this idea. The proportion of "old" responses to Similar lures remained unchanged between the single and repeated presentation conditions in the healthy controls. One possible reason is that the control subjects were also susceptible to similarity-based false recognition induced by stimulus repetition. Repetition increased the concept-based familiarity of Similar lures, which should have increased false recognition, but it also increased the ability to recall the original stimuli and thus to reduce false recognition by a recall-to-reject strategy (Kelley and Wixted, 2001). These two opposing processes canceled out on average, which indicates a lack of effect of repetition. In fact, Kelley and Wixted (2001) used a manipulation similar to Gallo et al. (2004)'s study and reported no effects of repetition in younger adults. Gallo et al. (2004) also reported no effects of repetition in their control subjects matched in age with AD patients. Budson et al. (2000) also reported a fluctuating pattern in their elderly subjects. The present findings indicate that control subjects were relatively more likely than were AD patients to use a recall-to-reject process to overcome similarity-based false recognition.

Our results also revealed a lower rate of corrected false recognition in the Similar-1× condition for AD patients relative to healthy controls. This suggests that AD patients were originally less susceptible to similarity-based false recognition than were healthy controls in the task using single-item picture memory, possibly as a result of decreased sensitivity to the semantic gist for the visually presented stimuli. Stimulus repetition, however, canceled out this effect. This pattern indicates that the repeated presentation of pictures created an increasingly robust representation of the semantic gist for presented pictures; AD patients showed elevated false recognition due to the lack of item-specific recollection, but healthy controls used recollection to counteract the gist representation. These results are highly consistent with previous works using the DRM paradigm in AD patients (Balota et al., 1999; Budson et al., 2000) and with data from amnesic patients (Schacter, Verfaellie, & Anes, 1997; Schacter et al., 1998b; Schacter, Verfaellie, & Pradere, 1996). Expanding on these previous studies, the present study has provided strong evidence that AD patients are initially less susceptible (but not after stimulus repetition) to similarity-based false recognition, regardless of the experimental paradigms used.

The precise neural dysfunctions accounting for why AD patients are impaired in the ability to use item-specific recollection to reduce false recognition are unknown. We speculate that this impairment in AD patients is associated with dysfunctions in two major areas: (1) in the hippocampus, causing recollection deficits, and/or (2) in the prefrontal cortex, causing disrupted post-retrieval processes. It is widely known that AD patients show both structural and functional abnormalities in the medial temporal lobe (Dickerson and Sperling, 2008; Frisoni, Fox, Jack, Scheltens, & Thompson, 2010). Among the subregions within the medial temporal lobe, the hippocampus has been reported to be closely linked to recollection processes (e.g., Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Mugikura et al., 2010; Vilberg & Rugg, 2007). It is also known that, even in the early stage of the disease, AD pathology might involve the prefrontal cortex, as neuropsychological and neuroimaging studies have demonstrated frontal lobe dysfunction in AD patients (Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991; Dalla Barba et al., 1999). In addition, there is considerable evidence that frontal lobe lesions may produce disruptions in the processes that check for memory errors (Janowsky, Shimamura, & Squire, 1989; Johnson, O'Connor, & Cantor, 1997). Further studies are needed to obtain data that directly elucidate the relationship between neural disruption and false recognition.

In conclusion, the results of the present study strongly support the view that AD patients are impaired in their ability to use item-specific recollection in order to avoid false recognition. One of the questions to be pursued is whether the memory deficits in AD patients observed in previous studies are caused by deficits during the retrieval phase or during the encoding phase. It remains possible that the degraded encoding of stimuli causes the subsequent deficits in the recollection of perceptual details. It is worth investigating whether experimental manipulation during encoding can alter the pattern of task performance in AD patients; on the basis of such findings we may be able to infer whether the encoding deficits are relevant to subsequent false recognition. Alternatively, a study using functional magnetic resonance imaging, which assesses neural responses during the actual performance of a task, may enable us to better assess how the brain dysfunction associated with AD gives rise to these memory impairments.

Acknowledgments

We thank Maki Suzuki for her insightful comments. We also thank the patients and their families for contributing their time to participate in this study. This work was partially supported by a Grant-in-Aid for Young Scientists (Start-up) (20800006 to N.A.), a Grant-in Aid for Scientific Research B# (21300101 to T.F.) from the Japan Society for the Promotion of Science, and a Grant-in-Aid for Scientific Research on Priority Areas—System study on higher-order brain functions—from the Ministry of Education, Culture, Sports, Science and Technology of Japan (20020004 to E.M.). This work was also partially supported by the Global COE Program (Basic & Translational Research Center for Global Brain Science, MEXT, Japan).

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Neuroanatomy of a neurobehavioral disturbance in the left anterior thalamic infarction

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Received 29 November 2010
Revised 15 February 2011
Accepted 8 March 2011
Published Online First 21 April 2011

ABSTRACT

Background and purpose Cognitive and behavioural symptoms represent primary clinical manifestations of anterior thalamic infarcts (ATIs) in the tuberothalamic artery territory. The aim of the study is to understand the pathomechanism of cognitive and behavioural disturbances in left ATI (LATI).

Methods 6 patients with isolated LATIs were investigated using neuropsychological assessments, MRI stereotactic lesion localisation and positron emission tomography.

Results The patients were characterised clinically by verbal memory impairment, language disturbances dominated by anomia and word-finding difficulty and apathy. The ventral anterior nucleus (VA) proper, magnocellular VA (VAmc), ventral lateral anterior nucleus (VLa), ventral lateral posterior nucleus (VLp) and mammillothalamic tract were involved in all patients. Compared with healthy controls, the regional cerebral blood flow was lower in the thalamus, the dorsolateral, medial and orbital frontal lobes, the anterior temporal lobe, the inferior parietal lobule and the occipital lobe of the left hemisphere.

Conclusions The authors propose that the Papez circuit disruption at the mammillothalamic tract and possibly thalamomedial temporal disconnection at the VA region is responsible for memory impairment and that the thalamo-anterior temporal disconnection is associated with language disturbance in LATI, respectively.

INTRODUCTION

Clinical observations have documented that the thalamus participates in a great variety of cognitive functions and mental activities, including memory, language, perception and emotion.[1–3] However, the precise functional attributes of the individual thalamic nuclei and fibre systems remain to be elucidated. Clinicoanatomical investigations of thalamic infarctions, in which only subsets of thalamic structures are involved, have been one of the best ways to study the functional anatomy of the human thalamus.[3] The inference of the function of individual thalamic structures on the basis of their anatomical connectivity with other brain regions has also played an important role. Here we highlight the left anterior thalamic infarction (LATI) resulting from occlusion of the left tuberothalamic artery, in which cognitive and behavioural symptoms represent primary clinical manifestations.[3] Using neuropsychological evaluations, MRI stereotactic lesion localisation[4 5] and positron emission tomography (PET), we attempted to delineate neurobehavioral and neuroanatomical profiles of LATI.

METHODS

Subjects

We recruited six right-handed patients (mean age, 76±7.4 years; two women; mean years of education, 9.2±2.9) with a subacute phase of isolated LATI. They were consecutive patients admitted to the Hyogo Institute for Aging Brain and Cognitive Disorders (HI-ABCD), a research-oriented dementia clinic, from 1993 to 2001. All of them presented to the institute with sudden onset of cognitive or behavioural problems, such as forgetfulness, loss of spontaneity and dysnomia. Duration between onset of symptoms and start of examination ranged from 1 to 4 weeks (mean, 3±1.3 weeks). Their past medical history included hypertension, diabetes mellitus and rheumatoid arthritis. The inclusion criteria were as follows: (1) sudden onset of symptoms; (2) presence of circumscribed infarction in the anterior portion of the thalamus with a lack of lesions elsewhere on MRI; (3) no severe stenosis or occlusion of the major cerebral arteries on MR angiography; (4) no history of other neurological and psychiatric diseases and (5) no history of premorbid cognitive impairment or behavioural abnormalities. The clinical diagnosis was made based on an examination by behavioural neurologists and psychiatrists and compared with MRI findings. All procedures used in this study were approved by the ethics committee of the HI-ABCD. Written informed consents were obtained from both patients and their relatives or from the control subjects.

Neuropsychology and behaviour

Neuropsychological assessments were performed within 2 weeks before and after neuroimaging investigations. The batteries and tests used in the study comprised the Mini Mental State Examination,[6] the Wechsler Adult Intelligence Scale-Revised (WAIS-R),[7] the Wechsler Memory Scale-Revised (WMS-R),[8] the Western Aphasia Battery,[9] 100-word object naming,[10] verbal fluency (animals/initial letter),[11] Raven's Coloured Progressive Matrices,[12] the Weigl's Colour-Form Sorting Test[13] and Luria's executive/motor performance tests (fist-edge-palm test, 2-1 tapping test and alternative pattern drawing).[14] These tests represent the domains of general intelligence, anterograde episodic memory, language/semantic knowledge, perceptual organisation/construction and executive function (concept formation, psychomotor speed and executive/motor control). Retrograde episodic memory and the presence and types of behavioural abnormalities were assessed based on interviews of patients and their close family members and a bedside examination. The correspondence between the cognitive

domains and the neuropsychological measures are indicated in table 1.

Stereotactic lesion localisation on MRI

Coronal three-dimensional T1-weighted SPGR images (TR, 14 ms; TE, 3 ms; flip angle, 20°; resolution, 1.5×0.86×0.86 mm) were obtained using a 1.5-T GE Signa Horizon system. The images were reconstructed into 1.0 mm isotropic transverse sections and then normalised to the Montreal Neurological Institute (MNI) T1 template using the affine transformation algorithm implemented in the SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/) software application. The lesions of each patient were traced on normalised images. The detailed localisation of the thalamic and adjacent structures involved was determined on transverse sections using an electronic version of the Schaltenbrand–Wahren (S–W) atlas.[15] The correspondence of the transverse sections between the MNI-T1 template and the S–W atlas was determined by scaling the z-axis with reference to the distance between the top of the thalamus and the AC–PC plane. In-plane two-dimensional linear coregistration was performed with reference to the intercommissural distance, interputaminal distance and contour of the thalamus.

Positron emission tomography

PET images were obtained from the six patients and six healthy subjects (75.2±9.0 years; six females) under resting conditions with their eyes closed using a Shimadzu Headtome-IV scanner. The regional cerebral blood flow (rCBF) was determined using a steady-state technique. The subjects continuously inhaled O_2 at 500 MBq/200 ml/min during a 10-minute scanning session.[16] Arterial blood samples were collected to measure the blood radioactivity concentrations. Data were collected in 128×128 matrices, and the slice interval was 6.5 mm when the z-motion mode was used.[17] The scan did not include the top of the frontal and parietal lobes and the inferior portion of the cerebellar hemispheres. Image preprocessing and statistical analyses were carried out using SPM5. The ventromedial prefrontal region was masked because of the presence of artefacts due to gas inhalation. The obtained images were reconstructed into 2 mm cubic voxels and then normalised to the SPM-PET template using affine transformation. The resultant images were smoothed with 12 mm full width at half maximum. Threshold masking was applied with a criterion of 80% of the mean global value. Proportional scaling was used to control the individual variation in the global CBF. Two-sample t-tests were used for a voxelwise group comparison between the patient and control groups. T-contrast maps were created with a height threshold of uncorrected $p<0.001$ and an extent threshold of 50 voxels (400 mm^3). As the small number of the subjects could cause underestimation of group difference in rCBF, we additionally analysed the PET data on individual subject basis using regions of interests (ROIs). Twenty-one pairs

Table 1 Results of the neuropsychological tests

Cognitive and behavioural domains	Tests		Patients 1	2	3	4	5	6	Normative data
General intelligence	MMSE (/30)		25	27	27	16*	24	22*	≥24
	WAIS-R[7]	VIQ	68*	78*	88	65*	81*	89	≥85
		PIQ	85	106	93	66*	91	91	≥85
Episodic memory	WMS-R[8]	Verbal memory index	<50*	64*	61*	<50*	50*	64*	≥85
		Visual memory index	72*	93	118	68*	114	100	≥85
		Attention/concentration index	66*	84*	94	55*	77*	97	≥85
		Delayed recall index	<50*	<50*	69*	<50*	71*	83*	≥85
	Retrograde amnesia		(−)	(−)	(−)	(−)	(−)	(−)	
Language/semantic knowledge	WAB[9]	AQ	69.2*	90.8*	86.4*	71*	83.6*	87.6*	97.7±3.0
		Spontaneous speech (/20)	13*	17*	17*	12*	16*	16*	19.7±0.6
		Auditory comprehension (/10)	7.2*	9.8	7.7*	7.2*	9*	9.5*	9.8±0.1
		Repetition (/10)	8.9*	9.6	9.9	9.2	9.9	10	9.9±0.3
		Naming (/10)	5.5*	9	8.6*	7.1*	6.9*	8.3*	9.5±0.6
		Reading (/10)	6.7*	10	8.9	4.1*	7.2*	7.7*	9.5±0.8
		Writing (/10)	6.4*	9.7	9.9	4*	9.1	8.9	9.6±1.0
	Animal fluency (/min)		4*	10	9	4*	4*	12	11.8±4.4
	Initial fluency (/min)		0*	3*	1*	1*	2*	7	6.8±3
	Picture Naming (/100)[10]		74*	97	84	66	86	89	98.2±2.3
	WAIS-R[7]	Information SS	6*	6*	10	5*	6*	8	≥7
		Vocabulary SS	5*	7	7	5*	6*	9	≥7
		Comprehension SS	2*	7	5*	2*	7	5*	≥7
		Similarities SS	4*	5*	8	4*	8	6*	≥7
Perceptual organisation/ construction	WAIS-R[7]	Picture completion SS	8	11	9	5*	8	9	≥7
		Block design SS	5*	13	9	4*	12	11	≥7
Concept formation	RCPM (/36)[12]		25	30	23	14*	32	26	26.9±5.4
	Weigl's colour-form sorting[13]		✓	✗	✓	✗	✓	✓	
Psychomotor speed	WAIS-R Digit symbol SS[7]		6*	8	9	4*	7	8	≥7
Executive/motor control	Fist-edge-palm[14]		✗	✗	✗	✓	✗	✓	
	2-1 tapping[14]		✗	✓	✓	✓	✓	✓	
	Alternative pattern drawing[14]		✓	✓	✓	✓	✓	✓	
Behaviour	Apathy		(++)	(+)	(+)	(++)	(+)	(+)	

*Score below −1 SD of the normative data.[8–12]
✓, passed; ✗, failed.
AQ, aphasia quotient; MMSE, Mini-Mental State Examination; PIQ, performance intelligence quotient; RCPM, Raven's coloured progressive matrices; SS, scaled score; VIQ, verbal intelligence quotient; WAB, Western Aphasia Battery; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised.

of 8 mm spherical ROIs of each hemisphere were determined on the mean normalised PET image of the 12 subjects using the MarsBar toolbox (http://marsbar.sourceforge.net/). Left/right asymmetry indices (calculated as (mean voxel value of left ROI)/(mean voxel value of right ROI)) of each patient were compared to 95% CIs of that obtained from the six control subjects.[18 19]

RESULTS

Neuropsychology and behaviour

The results of the neuropsychological tests and behavioural observations are summarised in table 1.

General intelligence

The verbal intelligence quotient (VIQ) of the WAIS-R was less than 85 (−1 SD of the normative mean) in four of the six patients, whereas the performance IQ was within the normal range in all patients except Patient 4.

Episodic memory

All patients showed impairments in the verbal memory index (MI) of the WMS-R (<85, −1 SD). Their verbal MI was disproportionately lower than their VIQ in the WAIS-R (verbal MI − VIQ≥10)[8]. Retrograde memory was preserved in all patients.

Language/semantic knowledge

The spontaneous speech score was impaired in all patients due to poor information content and word-finding difficulties. Semantic paraphasias were occasionally observed in some patients. Articulatory errors and phonological paraphasias were not observed. All patients excluding Patient 2 showed anomia in the naming subtest of the Western Aphasia Battery and/or in the picture naming test of 100 words. Apparent reading and writing disabilities were observed in two patients (Patients 1 and 4). All the patients were impaired (<7) in at least one of the subtests of the WAIS-R: Information, Vocabulary, Comprehension and Similarities.

Perceptual organisation/construction

Five of the six patients performed at normal levels on the Picture Completion and Block Design subtests of the WAIS-R.

Executive function (concept formation, psychomotor speed and executive/motor control)

Although all patients excluding Patient 6 were impaired in at least one of the executive function tests, no consistent tendency in the test categories showing impairment was found in the patient group.

Behaviour

Apathy was observed in all patients. Lack of spontaneity, reduced emotional response and psychomotor retardation were observed in Patients 1 and 4. In the other four patients, their apathy was milder and consisted only of lack of spontaneity. Other behavioural alterations that have been associated with frontal lobe damage, such as disinhibition, irritability and repetitive behaviours, were not observed.

Stereotactic lesion localisation

The results are shown in figure 1 and table 2. Designations of the thalamic nuclei were according to Hirai and Jones.[20] The ventral anterior proper (VA proper; also referred to as the parvocellular VA or just the VA), magnocellular ventral anterior nucleus (VAmc), ventral lateral anterior (VLa), ventral lateral posterior (VLp), reticular (R) nuclei and mammillothalamic tract (MTT)

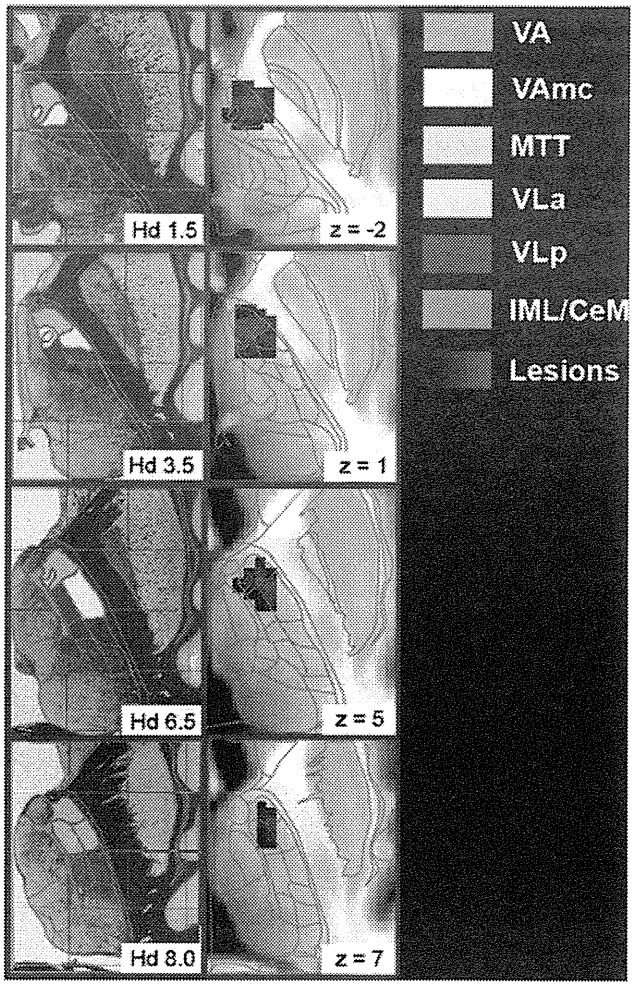


Figure 1 Transverse images from the Schaltenbrand–Wahren (S–W) atlas are shown in the left column. The structures involved in left anterior thalamic infarction are coloured. Images showing lesions (red) superimposed on the Montreal Neurological Institute (MNI) template are indicated in the right column. The voxels that overlapped in more patients are coloured in brighter red. CeM, central medial nucleus; IML, internal medullary lamina; MTT, mammillothalamic tract; VA, ventral anterior nucleus proper; VAmc, magnocellular ventral anterior nucleus; VLa, ventral lateral anterior nucleus; VLp, ventral lateral posterior nucleus.

were involved in all patients. The anterior nuclei (AN) were preserved in all patients. The mediodorsal nucleus (MD) was involved only in Patient 4. The internal medullary lamina (IML)/central medial nucleus (CeM) was affected in three patients with lesions that were located medially (Patients 2, 4 and 5). The genu of the internal capsule (ICg) was damaged at the site ventral to the thalamus in Patients 3, 4 and 5.

Positron emission tomography

A voxelwise group comparison revealed significant rCBF reductions in the anterior temporal lobe (ATL), thalamus, orbital frontal lobe (OFL) and middle frontal gyrus (MFG) of the left hemisphere in the patients with LATI compared to the control subjects (figure 2). A relative increase in rCBF was detected in the right precuneus and right lingual gyrus. An ROI analysis showed decreased left/right asymmetry index (lower rCBF in the left side compared to the right side) in the anterior cingulate gyrus, inferior temporal gyrus, inferior parietal lobule, calcarine

Table 2 The thalamic and adjacent regions affected in the patients

Thalamic regions		Patient No.						No. of
Hirai and Jones'	Hassler's	1	2	3	4	5	6	patients
VA proper	Lpo	(+)	(+)	(+)	(+)	(+)	(+)	6
VAmc	Lpo.mc	(+)	(+)	(+)	(+)	(+)	(+)	6
VLa	Zo	(+)	(+)	(+)	(+)	(+)	(+)	6
	Voa	(+)	(+)	(+)	(+)	(+)	(+)	
	Vop	(−)	(−)	(−)	(−)	(+)	(−)	
	Doe	(+)	(+)	(+)	(+)	(+)	(+)	
VLp	Voi	(+)	(+)	(+)	(+)	(+)	(+)	6
	Doi	(+)	(+)	(+)	(+)	(+)	(+)	
VM	Vom	(−)	(+)	(−)	(−)	(−)	(−)	1
MD	Mfa	(−)	(−)	(−)	(+)	(−)	(−)	1
IML/CeM	Lam	(−)	(+)	(−)	(+)	(+)	(−)	3
R		(+)	(+)	(+)	(+)	(+)	(+)	6
MTT		(+)	(+)	(+)	(+)	(+)	(+)	6
ICg		(−)	(−)	(−)	(+)	(+)	(+)	3
H		(−)	(−)	(−)	(+)	(+)	(−)	2
STN		(−)	(−)	(−)	(+)	(−)	(−)	1

The nomenclature for the thalamic nuclei is according to Hirai and Jones and Hassler. CeM, central medial nucleus; H, fields of Forel; ICg, genu of the internal capsule; IML, internal medullary lamina; MD, mediodorsal nucleus; MTT, mammillothalamic tract; R, reticular nucleus; STN, subthalamic nucleus; VA, ventral anterior nucleus; VAmc, magnocellular ventral anterior nucleus; VLa, ventral lateral anterior nucleus; VLp, ventral lateral posterior nucleus; VM, ventral medial nucleus.

gyrus and cuneus in addition to the ATL, thalamus, OFL, and MFG. Increased left/right asymmetry index was observed in the precuneus (table 3).

DISCUSSION

Clinical features of LATI

In agreement with previous reports of LATI, the symptoms of our patients were characterised primarily by memory impairment, language disturbances and apathy.[1 3 4 21] Although previous studies of acute LATI have reported a perseverative behaviour (palipsychism) and mild sensorimotor deficits,[21] we did not observe these symptoms.

The memory impairment was restricted to the anterograde domain and dominant in the verbal materials. Although the concomitant deficits in language, attention and executive function may partly explain the memory impairment observed in our patients, the dissociation between the verbal MI of the WMS-R and the VIQ of the WAIS-R suggested that our patients had deficits in the memory function itself. A hypothesis has been recently proposed that selective or predominant memory impairment of verbal materials in left temporal lobe pathology arises from concomitant deficits in semantic processing and protosemantic components of episodic memory.[22] The same perspective may be applicable to material-specific memory impairment in thalamic damage.

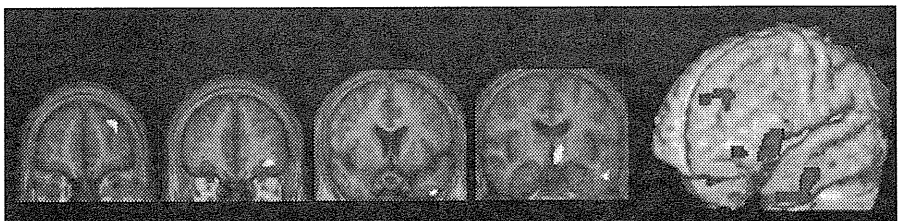
The language disturbances in our patients were characterised by word-finding difficulty and anomia. The articulation and phonological aspects were well preserved. Anomia and poor performance in the naming tests and the Information, Vocabulary, Comprehension and Similarities subtests of the WAIS-R suggested that the lexical-semantic impairment was the core deficit responsible for their language symptoms.[4] This interpretation is supported by previous reports investigating a variety of lexical-semantic deficits, including category-specific anomia, proper name anomia and degraded knowledge of object use, in patients with LATI.[5 23–25]

Cortical diaschisis in LATI

Using CBF diaschisis, we demonstrated that the connections of the thalamus with the dorsolateral, medial and orbital frontal lobes, the ATL, the inferior parietal lobule and the occipital lobe were disrupted in LATI. Compared to patients with paramedian thalamic infarction (PTI),[26] the extent of hypoperfusion regions in our patients was relatively restricted. This difference in PET findings is well correspondent with that in clinical manifestations; patients with PTI develop more severe behavioural symptoms compared with those that had anterior thalamic infarction (ATI), for example, coma, akinetic mutism and confusion.[3 26] The involvement of the intralaminar nuclei, which project broadly to the cerebral cortex,[20] and/or their projecting fibres probably causes extensive cortical dysfunction in PTI.[3 4] A previous single-case PET study of LATI reported restricted rCBF reductions in the ipsilateral amygdala and posterior cingulate cortex.[27] The disagreement between this and our studies is probably related to difference in affected thalamic structures and in neuroimaging analysis.

Neuroanatomical basis of memory impairment

The neural circuit that arises from the hippocampus via the fornix, mammillary body (MB), MTT, AN and posterior cingulate cortex and then projects back to the hippocampus is known



Contrasts	Regions	Cluster size (voxels)	Cluster-level corrected p values	T value	Voxel-level corrected p values	MNI coordinates x	y	z
LATI < Controls	Anterior temporal lobe L	223	0.103	6.58	0.465	−42	6	−40
	Thalamus L	235	0.090	5.39	0.828	−6	−12	−6
	Lateral orbital frontal lobe L	64	0.637	5.26	0.863	−36	42	−8
	Middle frontal gyrus L	84	0.514	4.71	0.964	−28	48	32
Controls < LATI	Precuneus R	104	0.409	5.34	0.844	4	−68	48
	Lingual gyrus R	56	0.691	5.04	0.912	12	−98	−14

Figure 2 Results of the voxelwise group comparison of positron emission tomography. Regions with regional cerebral blood flow (rCBF) reduction are superimposed on the mean normalised MRIs of the patients. The table indicates relative decrease and increase in rCBF in patients with left anterior thalamic infarction compared to controls. The height and extent thresholds were $p<0.001$ uncorrected and 400 mm^3, respectively. LATI, left anterior thalamic infarct.

J Neurol Neurosurg Psychiatry 2011;**82**:1195–1200. doi:10.1136/jnnp.2010.236463

Table 3 Left/right asymmetry indices obtained from the regions of interest- (ROI) based positron emission tomography analysis

	Patients						Controls (n=6)	
	1	2	3	4	5	6	95% CI	
Inferior frontal	**0.79**	1.03	0.91	**0.82**	**0.71**	0.88	0.84	1.37
Middle frontal	**0.80**	0.93	0.93	1.01	**0.76**	**0.82**	0.86	1.25
Frontal operculum	1.08	1.13	1.01	1.03	0.88	**0.85**	0.86	1.29
Lateral orbital frontal*	**0.80**	**0.92**	1.14	**0.90**	**0.69**	**0.85**	0.97	1.20
Anterior cingulate*	**0.78**	**0.87**	**0.94**	0.99	**0.80**	**0.79**	0.95	1.18
Central	*1.16*	0.97	1.04	**0.85**	**0.77**	**0.80**	0.87	1.11
Temporal pole*	**0.86**	**0.86**	**0.87**	**0.92**	**0.80**	**0.89**	0.95	1.17
Inferior temporal*	1.15	**0.92**	1.02	**0.94**	**0.93**	**0.81**	0.95	1.21
Middle temporal	1.05	0.86	0.87	1.03	*1.07*	1.02	0.85	1.05
Superior temporal	1.05	1.20	1.14	**0.77**	1.04	0.89	0.87	1.20
Medial temporal	*1.36*	1.00	*1.08*	*1.24*	0.83	0.90	0.89	1.05
Inferior parietal*	**0.84**	**0.88**	1.17	**0.89**	**0.67**	**0.87**	1.00	1.27
Posterior cingulated	0.94	1.04	1.03	1.00	*1.41*	0.93	0.86	1.10
Precuneus†	*1.17*	*1.18*	*1.17*	0.95	*1.16*	**0.84**	0.91	1.08
Cuneus*	**0.82**	**0.85**	1.12	**0.94**	**0.93**	1.07	1.05	1.25
Calcarine*	1.11	**0.79**	**0.81**	**0.87**	**0.85**	**0.82**	0.91	1.16
Lingual	1.24	1.14	0.96	0.94	1.12	0.96	0.88	1.38
Fusiform	0.95	0.98	**0.93**	1.02	0.97	0.95	0.95	1.09
Anterior striatum	1.07	*1.22*	0.90	**0.82**	0.85	0.98	0.83	1.13
Posterior striatum	1.18	1.19	1.14	0.94	**0.45**	0.94	0.92	1.21
Thalamus*	**0.66**	**0.80**	**0.86**	**0.77**	**0.57**	**0.75**	0.92	1.19

Indices lower and higher than 95% CI of the controls are shown in bold and italic, respectively.
*and † indicate ROIs in which laterality indices are lower and higher than 95% CI of the controls in four or more patients, respectively.

as the Papez or Delay–Brion circuit. This circuit has long been considered to play a central role in memory. In addition, the significance of the rhinal/parahippocampal-MD-prefrontal network has been recently recognised.[28] Because the AN and MD are spared in the majority of patients with ATI,[3 29] the disconnection of these neural networks at the intrathalamic white matter structures, namely the MTT and IML, have been considered critical in memory impairment in ATI.[5 29–31] In the present case series, the MTT was consistently involved, whereas the IML was affected only in half of the patients, suggesting the significance of Papez circuit disruption. In addition, we propose a possible role of lesions in the VA region, which is penetrated anteroposteriorly by the inferior thalamic peduncle, the bundle carrying the fibres from the rhinal/parahippocampal cortex to the MD.[20] In contrast with this view, however, our PET analysis did not detect diaschisis in the medial temporal lobe and other components of the Papez circuit. Two possible factors may be associated with this negative result: diaschisis is presumably hard to be observed in the disruption of polysynaptic connections,[26] for example, the connection between the MTT and the posterior cingulate cortex via the AN; rCBF reduction is an insensitive measure to detect medial temporal dysfunction.[32 33] This issue should be addressed using different neuroimaging modalities, such as fluorodeoxyglucose PET and diffusion tensor tractography, in future studies.

Neuroanatomical basis of language disturbance

It is noteworthy that diaschisis was observed in the ATL, which is a region that is putatively associated with the integration of lexical and semantic information.[34 35] Both LATI and left ATL damage have been linked to semantic-lexical deficits, including category-specific anomia and proper name anomia.[24 36 37] This symptomatic similarity suggests the presence of functional relationships between these two regions. Connectional anatomical studies in monkeys have shown anatomical connections between the VAmc, a thalamic structure consistently involved in ATI, and the anterior temporal neocortex.[38] We propose that thalamo-anterior temporal disconnection plays a significant role in the language disturbances observed in LATI. Some investigators have speculated that the disruption of the intralaminar nuclei-inferior thalamic peduncle-prefrontal system is critical in the language disturbances observed in LATI.[39] Although the IML was involved only in half of our patients, diaschisis in the dorsolateral prefrontal cortices was demonstrated in our PET analysis. The thalamo-dorsolateral prefrontal disconnection may also be related to the linguistic symptoms.

Behavioural symptoms and their relevance to cortical diaschisis

Apathy is the most common behavioural feature in the current and previously reported cases of LATI.[3 21] Although apathy can result from lesions in various locations,[40] it has been particularly associated with anterior cingulate damage. Consistently, rCBF reduction in the left anterior cingulated gyrus was observed in our patients. In the original formulation of the frontal-subcortical circuits,[2] disinhibited behaviour is linked to disruption of the orbitofrontal circuit. However, none of our patients developed such kind of behavioural alteration in spite of diaschisis in the OFL. Previous studies have suggested that disinhibition syndrome occurs after right-lateralised lesions.[41 42] The lack of disinhibited behaviour in our patients is presumably associated with the laterality of the lesions.

Limitations of the study

The first limitation of the study is the small sample size. Age, disease duration, subclinical neurodegenerative pathologies and individual differences in functional lateralisation among others, may have had a large effect on the clinical presentation and neuroimaging results. Clinical-PET correlation analyses were unavailable also due to the small number of subjects. Although much larger sample sizes are needed to overcome these problems, it would be quite difficult to recruit a sufficient number of subjects from a single institution due to the rarity of isolated ATI. A meta-analysis of studies that have performed detailed neuroimaging investigations would be valuable. Also, the probable selection bias on the neuropsychological and behavioural findings should be noted. Since we performed the study in a dementia department, only patients with cognitive problems mimicking dementia may have been referred to us. Lack of sensorimotor deficits and perseverative behaviours[21] and relatively long-lasting cognitive impairment may be associated with such kind of bias. Finally, as it took a long time, over 7 years, to recruit the patients, we failed to update the neuropsychological tests. Therefore, we could not incorporate new cognitive theories, such as the recollection/familiarity components of episodic memory.[43]

There are a number of methodological limitations to our neuroimaging investigations. The precision of lesion localisation on MRI is limited by image distortion due to magnetic field inhomogeneity, inaccuracy of spatial normalisation and image co-registration, difficulty in defining exact lesion boundaries and so forth. In the PET analyses, the proportional scaling probably led to underestimation of the spatial extent and strength of hypoperfusion and to spurious hyperperfusion. The ROI-based left/right asymmetry analysis is unable to detect bilateral rCBF changes.[19] Lastly, inhalation artefacts precluded the evaluation of the ventromedial frontal regions, which are reported to have dense interconnections with the thalamic structures.[20 44]

Funding This work was supported by Grants-in-Aid for dementia research from the MHLW Japan (22800).

Competing interests None.

Ethics approval This study was conducted with the approval of the Hyogo Institute for Aging Brain and Cognitive Disorders.

Provenance and peer review Not commissioned; externally peer reviewed.

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日本臨牀　69巻 増刊号10（2011年12月20日発行）別刷

認知症学 下

—その解明と治療の最新知見—

III. 臨　床　編

薬剤誘発性認知症（状態）　各論

せん妄誘発剤

水上勝義

薬剤誘発性認知症(状態) 各論

せん妄誘発剤

Drug-induced delirium

水上勝義

Key words：抗コリン作用，鎮静作用，持ち越し効果

1. せん妄とは

せん妄とは，意識障害が背景にあり，このため注意を集中，維持，転換する能力が低下し，認知に変化をきたした状態である．通常は急激に出現し，一日の中でも変動しやすい[1](表1)．経過中に錯覚，幻覚，妄想，不安，興奮，不眠など様々な精神症状がみられる．ただし，せん妄では精神症状が目立ち活動性が亢進した状態だけではなく，むしろ活動性が低下した状態もみられる．このため前者をhyperactive delirium，後者をhypoactive delirium，そして両方の特徴が混在する場合mixed deliriumと呼ぶことがある．日中は傾眠傾向で活動性が著しく低下し，夜間は不眠，不穏状態を示すこともしばしばみられる．

2. せん妄の原因

様々な身体的な原因でせん妄が生じうるが，そのうちの一つが薬剤性である．せん妄のおよそ2-3割は薬剤性と考えられている．同じ薬剤を服用しても，せん妄になる場合とならない場合がある．すなわちせん妄はしばしば幾つかの要因が組み合わさって生じ，薬剤を取り入れる患者側の要因も大きい．

表1 せん妄の診断基準(DSM-IV)(文献[1]より引用)

A. 注意の低下を伴う意識の障害
B. 認知の変化(記憶，見当識，言語の障害など)，または知覚の障害
C. 短期間の内に出現し(通常数時間から数日)，1日の内で変動する
D. 病歴，身体診察，臨床検査から，身体的原因と判断される

a. 患者側の要因

一般には，高齢，認知症疾患など脳の器質的障害がある場合，腎機能や肝機能障害のため薬剤の代謝や排泄の低下がある場合，悪性腫瘍など衰弱をきたすような身体的疾患などでは，せん妄をきたしやすい．高齢者では，代謝排泄能が低下しているうえに，体脂肪の割合が高く，ベンゾジアゼピン(BZ)系薬剤をはじめとする脂溶性の薬剤が体内に蓄積しやすく，排泄の遅延が生じる．脳の器質的障害では，血液・脳関門の損傷が起こりやすく，このため，より多くの薬剤が脳に作用しやすくなる．また低アルブミン血症があると遊離薬物濃度が上昇するため，やはりせん妄の一因となりうる．肺炎や骨折などの急性疾患では薬剤代謝酵素のcytochrome P450の活性が低下することがある[2]．また薬剤の中にはP450を抑制するものがある．P450が抑制されると，それで代謝される薬剤の血中濃

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0047-1852/11/¥60/頁/JCOPY

表2 代表的なせん妄誘発剤

1. 麻酔・鎮痛剤
2. 中枢神経系薬剤
   1) 三環系抗うつ薬
   2) 抗不安薬，睡眠薬
   3) 炭酸リチウム
   4) 抗てんかん薬
   5) その他抗コリン作用のある薬剤
3. 抗コリン剤
4. 抗パーキンソン剤
5. コルチコステロイド剤
6. ヒスタミンH1受容体阻害剤(第一世代)
7. ヒスタミンH2受容体阻害剤
8. 循環器系薬剤(ジギタリス，抗不整脈ほか)
9. 喘息治療剤(アミノフィリン，テオフィリン)
10. その他(抗がん剤，抗生剤，甲状腺剤，風邪薬ほか)

表3 抗コリン作用をもつ代表的な薬剤
(文献[3]より引用)

抗コリン剤：アトロピン，鎮痙剤(スコポラミン，ジサイクロミン)，抗潰瘍薬(プロパンテリンほか)，抗パーキンソン薬(トリヘキシフェニジル，ビペリデンほか)，過活動性膀胱治療薬，気管支拡張剤(イプラトロピウムほか)
向精神薬：三環系抗うつ薬，ベンゾジアゼピン系，フェノチアジン系
H1阻害剤(第一世代)
循環器系薬(シベンゾリン，ジソピラミド，キニジンほか)

度が上昇する．このように様々な身体的状況によってせん妄のリスクが高まる．

b. せん妄をきたしやすい薬剤

せん妄を起こしうる医薬品は多岐にわたる(表2)．特に抗コリン作用(ムスカリン受容体阻害作用)の強い薬剤や日中の覚醒度を低下させる薬剤は，せん妄をきたしやすい．またドパミン伝達系の亢進もせん妄と関連すると考えられる．以下にせん妄の原因となる代表的な薬剤について述べる．

1) 抗コリン剤

薬剤の抗コリン作用によって慢性的に認知機能障害が続き，認知症と鑑別困難な病像を呈することもあるが，比較的急性に現れると，せん妄の病像を呈する．抗コリン作用をもつ代表的な薬剤には，三環系抗うつ薬，ベンゾジアゼピン(BZ)などの向精神薬，過活動性膀胱治療薬，鎮痙薬(スコポラミン)，抗パーキンソン剤(トリヘキシフェニジル，ビペリデン)，抗ヒスタミン薬(第一世代)など多岐にわたる(表3)．単独ではそれほど抗コリン作用が大きくない薬剤でも，併用することで抗コリン作用の総和が増加し，せん妄を誘発すると考えられる[3]．

抗コリン作用が強い薬剤は高齢者にしばしば処方されている．地域に住む高齢者の23％，ナーシングホームに住む高齢者の60％が抗コリン作用をもつ薬剤を服用しており，2種類以上服用していた者も，ナーシングホーム居住者で32％，地域住民の13％に及んだ[4]．

ムスカリン受容体はサブタイプによって分布が異なり，大脳皮質や海馬に多く存在するM1やM2受容体への親和性が高いと中枢神経系への影響が大きくなる．M1受容体はシナプス前膜と後膜に存在し，シナプス後膜の阻害によりそれ以降のアセチルコリン伝達系に障害が生じるうえに，シナプス前膜のM1受容体の阻害によりアセチルコリンの放出抑制が生じるので影響が極めて大きい[5]．anticholinergic serum activity(SAA)が，抗コリン作用の指標となり，またせん妄の出現や認知機能の低下と関連すると報告されている[6]．

2) 睡眠薬および抗不安薬

BZ系薬剤は，過去に用いられていたバルビツレート系薬剤に比較して安全性が高く，現在，抗不安薬としても睡眠薬としても頻用されている．ただしBZ系睡眠薬は，抗コリン作用を有すると同時に，脂溶性薬剤のため，高齢者では蓄積されやすく，作用が延長しやすい．また高齢者ではBZ系受容体の感受性も亢進している．このため服薬直後に一過性の健忘が生じたり，せん妄を誘発することがある．特にジアゼパムやクロルジアゼポキシドなどの長時間作用型BZ薬剤は，日中の傾眠を誘発し，睡眠・覚醒リズムの障害に至りやすいため，高齢者に対して特に注意が必要である．

3) 抗パーキンソン剤

抗パーキンソン薬には，抗コリン剤(トリヘキシフェニジル，ビペリデン)のほかにも，レボドパ含有製剤，ドパミン受容体刺激剤(プラミペキソール，ロピニロール)，ドパミン遊離促進剤(アマンタジン)，モノアミン酸化酵素(MAO-B)阻害剤(セレギリン)など幾種類もあるが，いずれもせん妄の原因となりうる．この中で最も問題になるのは抗コリン剤であり，高齢者には原則使用は控えるべきである．また何種類か抗パーキンソン剤が使用されている患者にせん妄が出現した場合，まず抗コリン剤から中止する．

4) ヒスタミンH1受容体阻害剤

H1受容体阻害剤は，第一世代(クロルフェニラミン，プロメタジン，ヒドロキシジンなど)，第二世代(セチリジン，エバスチンほか)，第三世代(フェキソフェナジンほか)の3世代に大別される．第一世代薬剤は最初に開発され，受容体選択性が低く抗コリン作用も有する．また脳脊髄関門を通過しやすい．このため日中の覚醒度の低下やせん妄のリスクがある．第二世代以降のH1阻害剤は，親水性で，かつ末梢のH1受容体に対する選択性が高いことから，第一世代にみられるような副作用は軽減している[7]．

5) ヒスタミンH2受容体阻害剤

H2受容体阻害剤も，せん妄をはじめとする急性の中枢神経系の副作用が高齢者にみられることが知られている．治療開始2週間以内に出現することが多く，中止後早期に改善する．シメチジンの報告が多いが，H2阻害剤の種類による出現頻度の差はみられないとする報告もある．中枢神経系副作用の出現頻度は，地域研究や外来患者を対象とした調査では0.2％以下，入院患者を対象とした調査では2％以下の報告が多く，実際の頻度はそれほど高くはない[8]．シメチジンにはCYP450の2D6や3A4に対する阻害作用があり，これらの酵素で代謝される薬剤の代謝遅延が生じる可能性がある．

6) 鎮痛，麻酔薬

術後せん妄の頻度は10–40％程度と報告されているが，高齢者や脳器質性疾患などの患者側のリスク要因がある場合や，手術の侵襲性が大きくなるにつれ術後せん妄のリスクが高まる．ただし局所麻酔と全身麻酔で術後せん妄の頻度に差がないとする報告もある[9]．鎮痛剤のうちでは，メペリジンは，腎機能の低下によって排泄の低下をきたす．また代謝産物が抗コリン作用を有し，血液脳関門を通過することからせん妄を誘発することがある．オピオイドもせん妄との関連が報告されている．なかでもペチジンは，活性代謝産物が抗コリン作用を有し長時間作用のため，せん妄のリスクが高いとされる[10]．

7) 循環器系剤

ジゴキシンは，高齢者のように腎臓でのクリアランスが低下すると，蓄積が起きやすく，中毒症状としてせん妄が生じうる．ジソピラミドやキニジンなどの抗不整脈剤は抗コリン作用があり，高齢者に対する使用には注意が必要である．また利尿剤も電解質異常を引き起こし，その結果せん妄が生じることがある．

c. 薬剤せん妄の対応

せん妄に対しては，まず原因を検索する．身体状況の検討と同時に原因薬剤の検索は必須である．使用している薬剤のリストを確認し，せん妄の原因となった薬剤がないか検討する．最近新たに投薬された，あるいは増量された薬剤はせん妄を誘発した可能性が考えられる．一般薬(OTC医薬品)の中にも，風邪薬，睡眠薬，H2阻害薬などせん妄の原因になりうる薬剤があるため，OTCについても確認が必要である．せん妄の原因は一つとは限らない．むしろ幾つか組み合わさって現れることの方が多い．幾つかの原因が考えられる場合，一つ一つに対処する．薬剤が原因であれば，原因薬剤を中止する．急激な中止で離脱症状を起こす危険性があれば，漸減・中止する．

3. ま と め

せん妄の原因のうち，薬剤が占める割合は大きい．せん妄に対しては，薬剤性の可能性を常に念頭に置いて，早急に対応する必要がある．また薬剤せん妄を予防するために，高齢者など

せん妄のリスクが高い患者に対しては，せん妄誘発剤の使用は可能な限り控える．用いざるを得ない場合，使用量や併用薬剤数の減少に努めることが重要である．

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診断と治療〔第99巻・第5号〕別刷

2011年5月1日発行

発行所 株式会社 診断と治療社

I. 日常診療でまず使ってみたい漢方ベストチョイス15

認知症周辺症状（BPSD）―抑肝散（よくかんさん）

Key Words
○BPSD
○抑肝散
○抑肝散加陳皮半夏
○認知症

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Headline

1. 認知症の多くの患者に周辺症状（BPSD）がみられる．
2. BPSDに対してはまず非薬物的対応が行われるが，それでは改善しないBPSDに対して薬物療法が行われる．
3. BPSDの薬物療法では安全性が最も大切であり，その点で漢方治療は重要である．
4. 抑肝散（よくかんさん）は認知症全般の興奮や易刺激性に対する第一選択薬である．さらにLewy小体型認知症（DLB）の幻視やレム睡眠行動障害（RBD）に対しても有効である．

はじめに

認知症の症状には認知機能障害の他に，周辺症状あるいはbehavioral and psychological symptoms of demenia（BPSD）とよばれる症状がみられる．BPSDは幻覚，妄想，うつ，不安，興奮，睡眠障害などの精神症状や，攻撃的言動，徘徊，不潔行為，食行動異常をはじめとする行動からなる（表1）．BPSDはおよそ8割の患者に現れ，患者と介護者の心理的・身体的負担を増し，日常生活に多大な支障をきたしてしばしば在宅生活を困難にさせる．BPSDに対してはまず非薬物療法が行われる（図1）[1]．しかしながら，十分な非薬物療法を行っても改善が得られないBPSDも少なくない．そのような場合，薬物療法が併用される（図2）．これまで薬物療法においては，本来統合失調症の治療薬である抗精神病薬がしばしば用いられてきた．しかし，運動機能，認知機能，生活機能への影響が問題であった．さらに，新しく開発され副作用が軽減された非定型抗精神病薬であっても服用中の患者の死亡率が高いことが報告され，安易な抗精神病薬の使用に警鐘が鳴らされた．

BPSDに対する薬物療法で最も大切なことは安全性である．この点で漢方薬が注目されるようになった．特に本稿のテーマである抑肝散（よくかんさん）はBPSDに対する治療薬としてエビデンスが蓄積されつつある．

BPSDの病態と診断

BPSDは患者の元来の性格傾向や，患者と家族との人間関係をはじめとする環境要因から発展してくることが多い．たとえば，もともと一人で何でもこなしてきて自己に自信があるAlzheimer病（AD）の患者は，「しまったはずの場所に財布がない」と動揺し，「（普段から関係がぎくしゃくしている）嫁が盗んだに違いない」と考えるに至るようになり妄想に発展する．このため，BPSDの誘因となった心理・環境的な問題を検討し，それらに対応する非薬物的対応がBPSDの対応の基本である．しかしながら，ADをはじめとする認知症疾患では脳内の様々な神経回路や神経伝達系の障害をきたしており，この生物学的な変化もBPSDの一因と考えられている．たとえば，セロトニン伝達系は攻撃性，不安，抑うつなどと，ドパミン伝達系は幻覚，妄想，

0370-999X/11/¥100/頁/JCOPY

表1　おもなBPSD（周辺症状）

心理症状
・幻覚（幻視，幻聴，体感幻覚，幻嗅）
・妄想（もの盗られ妄想，被害妄想，嫉妬妄想，誤認妄想）
・睡眠覚醒障害（不眠，レム睡眠行動異常），
・感情面の障害（抑うつ，不安，興奮，感情失禁）
・人格面の障害（多幸，脱抑制，易怒性，アパシー，依存）

行動症状
・攻撃的言動（暴行，暴言），焦燥，叫声，拒絶，火の不始末，不潔行為，脱抑制行為，徘徊，繰り返し質問，つきまとい，独語，食行動の異常（異食，過食，拒食，盗食）

アパシーと，アセチルコリン伝達系はLewy小体型認知症（dementia with Lewy bodies; DLB）でみられる幻視との関連が推察されている．

BPSDに対しては，本人の診察はもとより家族からの病歴聴取が不可欠である．通常，診察場面と実際の生活場面では状態が大きく異なり，診察場面ではBPSDが目立たないことが多い．したがって，生活場面における障害について詳細に情報を収集することが必要である．病歴聴取の際に，時に家族の陰性感情が反映されることがあるため，できる限り客観的な情報収集を心がける．Neuropsychiatry Inventry（NPI）やBEHAVE-ADなどのBPSDに対する評価尺度を用いると収集もれが少なくなる．また，治療効果を判定するにも有用である．

抑肝散の適応とエビデンス

1．抑肝散の研究報告から

抑肝散は「保嬰撮要」に記載された方剤で，釣藤鉤，甘草，川芎，柴胡，当帰，蒼朮，茯苓の七つの生薬からなる．肝気が昂ぶり神経過敏で，もともとは小児の夜泣き，小児疳症に対して用いられた方剤である．しかし，1984年に原が認知症を含む高齢者の情緒障害に対する抑肝散の効果を報告した[2]．この報告では48例の高齢者に対して抑肝散および抑肝散の加味方を投薬し，著効32例（67%），有効11例（23%），やや有効3例，無効2例と，極めて高率の改善率を示した．特に不眠，易怒性，興奮，せん妄に有効だったという．この研究では随証治療が行われており，腹直筋の緊張のある例では抑肝散が投薬され，腹直筋にはりがなく腹部大動脈が触れる例（臍傍悸）に対しては抑肝散加陳皮半夏が投薬されている．現在の臨床研究では証が考慮されることはないが，この研究から腹症によって使い分けることの有用さが示唆される．

この報告以来，認知症のBPSDに対する抑肝散の効果が報告されるようになった．現在ではADをはじめDLB，血管性認知症（vascular dementia; VD），前頭側頭型認知症（frontotemporal dementia; FTD）など各認知症疾患のBPSDに対する効果が報告されている．

2005年Iwasakiら[3]は52例の認知症患者（AD 30例，混合型3例，VD 9例，DLB 10例）を抑肝散投与群27例，非投与群25例に無為作為に分け，4週間の治療効果を観察者ブラインドの単盲験試験で検討した．その結果，抑肝散7.5 g投与群はBPSDが改善した．特に幻覚，興奮，易刺激性，異常行動などに著明な改善効果が認められた．同時に抑肝散服用群は日常生活動作（ADL）も有意に改善した．

筆者らは，関東地区20施設が共同で抑肝散のBPSDに対する効果をクロスオーバーオープン試験で検討した（図3）[4]．この検討には106名のAD，混合型，DLBの患者がエントリーし，前半の4週間抑肝散7.5 gを服用するA群と，後半4週間抑肝散を服用するB群に無作為に分けて検討した．その結果，A群，B群ともに興奮と易刺激性に対する効果を認めた．この他，A群あるいはB群のどちらかで改善した症状は，幻覚，妄想，不安，