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Relative preservation of the recognition of positive facial expression "happiness" in Alzheimer disease

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ABSTRACT

Background: Positivity recognition bias has been reported for facial expression as well as memory and visual stimuli in aged individuals, whereas emotional facial recognition in Alzheimer disease (AD) patients is controversial, with possible involvement of confounding factors such as deficits in spatial processing of non-emotional facial features and in verbal processing to express emotions. Thus, we examined whether recognition of positive facial expressions was preserved in AD patients, by adapting a new method that eliminated the influences of these confounding factors.

Methods: Sensitivity of six basic facial expressions (happiness, sadness, surprise, anger, disgust, and fear) was evaluated in 12 outpatients with mild AD, 17 aged normal controls (ANC), and 25 young normal controls (YNC). To eliminate the factors related to non-emotional facial features, averaged faces were prepared as stimuli. To eliminate the factors related to verbal processing, the participants were required to match the images of stimulus and answer, avoiding the use of verbal labels.

Results: In recognition of happiness, there was no difference in sensitivity between YNC and ANC, and between ANC and AD patients. AD patients were less sensitive than ANC in recognition of sadness, surprise, and anger. ANC were less sensitive than YNC in recognition of surprise, anger, and disgust. Within the AD patient group, sensitivity of happiness was significantly higher than those of the other five expressions.

Conclusions: In AD patient, recognition of happiness was relatively preserved; recognition of happiness was most sensitive and was preserved against the influences of age and disease.

Key words: dementia, Alzheimer disease, emotional face recognition, positivity bias, aging, happiness, social interaction, morphing technology

Introduction

Deficits in the recognition of emotional facial expressions might lead to behavioral disturbances that often accompany Alzheimer disease (AD), and behavioral features are more distressing than cognitive deficits for caregivers of patients with AD (Donaldson *et al.*, 1998). Facial expressions are universally identified into six basic expressions: happiness, sadness, surprise, anger, disgust, and fear (Ekman *et al.*, 1971). The human face conveys non-verbal information about emotional states, the recognition of which is critical for appropriate social behavior.

In aged individuals, positivity recognition bias has been reported for facial expression (Mather and Carstensen, 2003; 2005). The positivity recognition bias was well-studied with memory; aged individuals remember a larger quantity of positive events than negative ones, and show more emotionally positive memory distortion for autobiographical information than younger adults do (Mather and Carstensen, 2005). Such positivity bias in aged individuals has been consistently reproduced in experimental settings of various recognition modalities such as emotional facial recognition and visual stimuli as well as memory (Mather and Carstensen, 2003; 2005; Kapucu *et al.*, 2008; Spaniol *et al.*, 2008). However, studies on emotional facial recognition in AD

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patients have produced various results. First, it is controversial whether facial recognition itself is declined or not; some studies reported preserved ability of emotional facial recognition (Bucks *et al.*, 2004; Luzzi *et al.*, 2007; Guaita *et al.*, 2009; Yamaguchi *et al.*, 2012), whereas others reported impairments (Spoletini *et al.*, 2008; Bediou *et al.*, 2009; Drapeau *et al.*, 2009). It is also controversial whether there were differences in the recognition of various emotions. Some studies reported no difference (Bucks *et al.*, 2004; Luzzi *et al.*, 2007), whereas others reported differences, e.g. selective impairment was reported in labeling the facial expression of sadness (Hargrave *et al*, 2002), and recognition of happy facial expressions was reported to be relatively preserved in comparison with angry facial expressions (Yamaguchi *et al.*, 2012). It was also reported that the most identified emotion was happiness among seven facial expressions (six basic expressions and boredom) in the moderate and severe stage of dementia (Guaita *et al.*, 2009).

The controversy may be partly due to confounding factors. Some studies have suggested involvement of confounding factors such as deficits in spatial processing of non-emotional facial features and in verbal processing to express emotions (Cadieux *et al.*, 1997; Burnham *et al.*, 2004). The deficits shown in the experiments could be due to the decline of the spatial recognition and/or verbal processing, which were prominent in AD. Thus, in the present study, we demonstrated characteristics of emotional face recognition in AD patients, by adapting a new method that eliminated the influences of these confounding factors to reveal whether the recognition of positive expressions is relatively preserved in AD.

Methods

Participants

The participants were 12 outpatients with mild AD in Clinical Dementia Rating scale (CDR) 1, 17 aged normal control (ANC), and 25 young normal control (YNC). Participants were limited to mild AD patients to eliminate the influence of difficulties of understandings of the rules. The exclusion criteria were: prosopagnosia, psychiatric diseases, delirium, and verbal incomprehension including aphasia. Those who had weak in eyesight were also excluded; all the participants could distinguish a 2-pixel gap (0.58 mm) on a 15″ monitor screen of Landolt ring from 70 cm away. Subjects were diagnosed based on the criteria for AD by NINCDS-ADRDA (Dubois *et al.*, 2007). Scores over 7 on the Japanese version of the Short Form of the Geriatric Depression Scale (Yesavage *et al.*, 1982) were also excluded because depressive tendencies could affect facial recognition. The Ethics Board of the Gunma University School of Health Sciences approved all procedures (No. 21-26), and written informed consent was obtained from all the participants.

Stimuli

Six hundred colored face images of six basic emotional expressions (happiness, surprise, anger, sadness, fear, and disgust) were used. To eliminate confounding factors related to individual difference in non-emotional facial features and ways to express emotions, we used standardized photos of four Japanese women (one neutral and six basic expression photos for each person) in database DB99 (Advanced Telecommunications Research Institute International, Inc. Nara, Japan); facial features and expressions of non-Japanese individuals could be confounding factors for Japanese. Then we made "averaged faces", which canceled individual differences. We prepared one neutral and six emotional expression (100% expression faces) averaged faces by morphing photos of four women. For grading the ability, we prepared photos of 1%–99% intermediate expression levels of each emotion by morphing neutral and 100% expression faces with weight. In this way, the images of 600 emotional averaged faces were prepared; e.g. 38% happy image was made by morphing the 100% happy image and the neutral image with a ratio of 38–62. Each image was framed by an oval to avoid the influence of hairstyle and clothing.

Experimental setting

The experimental setting is shown in Figure 1A (stimuli were in color in the experimental setting). One of the images of intermediate expression levels was displayed on the monitor of touch panel screen in the left, and six small faces of 100% expression were displayed on the right. To eliminate the confounding factor of verbal processing, the participants were required to answer by touching the 100% face that corresponded to the expression of intermediate face. Using the choice of faces instead of verbal labels, even those who had difficulties in verbal processing could answer the question.

The sensitivity of expression was measured using staircase method. The orders of six expressions were randomized using a computer program, and the first stimulus was 100% expression faces in each expression. In each expression respectively, if the response was correct, the level of stimuli increased in the next trial (ex. 38%–35% expression face).

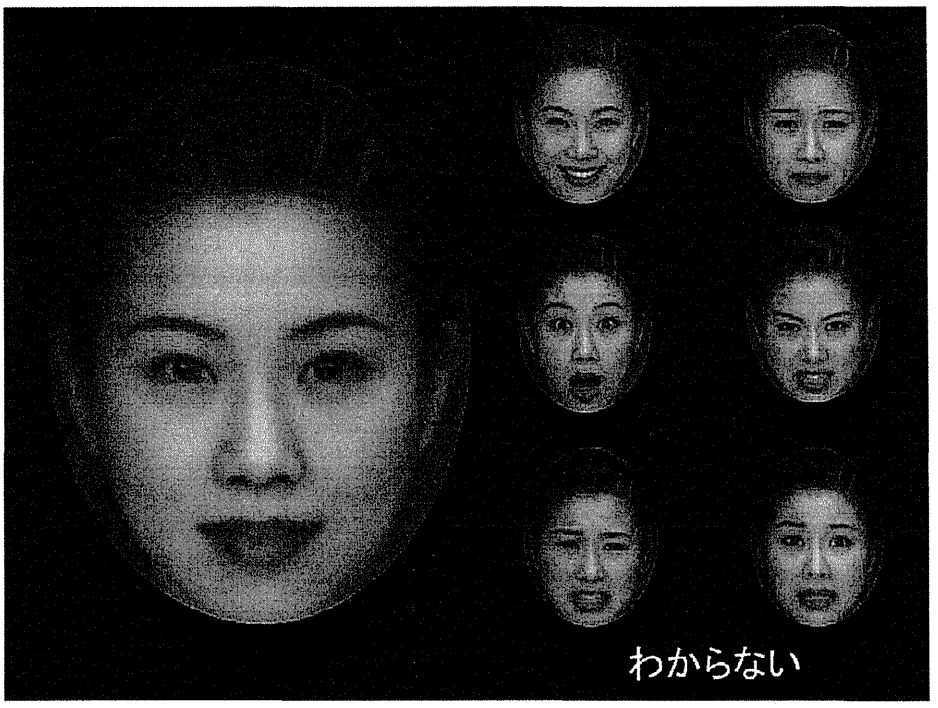

Figure 1. A stimulus shown on the monitor. On the left of the screen, 27% happy face was shown; recognition of 27% happy face corresponded to the sensitivity of 73%, which was the average sensitivity in patients with Alzheimer disease (AD). On the right, six kinds of 100% expressions were shown. The participants were required to choose and tough one of the 100% faces corresponding to the face on the left. The Japanese letters on the right bottom means to have no idea, and they could choose the option.

Alternatively if the participant made an error, the level of stimuli decreased in the subsequent trial. When the sequence was switched from ascending to descending or *vice versa*, the level was recorded as a reversal point score. The levels were changed by 15% until the first reversal point, after that, by 3%. The experiment was continued until the four reversal points were obtained. The average of the third and fourth reversal point scores was used as the sensitivity of the expression. Sensitivity was the difference calculated by subtracting expression level from 100(%); the sensitivity corresponding to 38% expression face was 62. We used the screen of a 15″ touch panel connected to a PC running C++ software based on Windows XP. Before the experimental session, a practice session was conducted. In the practice session, 100% expression images were displayed as stimuli and the participants were confirmed to be capable to match the same expression on the right, where six small faces of 100% expression were displayed as choices. The participants were also required to explain the emotion verbally to confirm that they recognized each emotion.

Statistical analysis

AD patients, ANC, and YNC were compared by using repeated-measured analysis of variance (ANOVA; 3 groups × 6 basic expressions) followed by *post hoc* testing with Bonferroni correction. According to *post hoc* analysis, significantly higher sensitivity in YNC compared with ANC was defined as age effects, and significantly higher sensitivity in ANC compared with AD patients was defined as AD effects. The data were analyzed using the Japanese version of SPSS for Windows version 19.0 (IBM Corporation, New York). Significant differences are set for two-tailed $p = 0.05$ for all analyses.

Results

The ages of the participants were 81.1±9.2 years in mild AD, 76.8±3.5 years in ANC, and 18.9±1.1 years in YNC, and there was no significant difference between age of AD patients and that of ANC by two sample *t*-test. Sensitivities of the three groups and comparisons are shown in Figure 2 and Table 1. There was a significant difference among three groups in perception of facial expressions. According to the *post hoc* analysis, both age and AD effects were observed for anger and surprise (anger: age effects $p = 0.031$, AD effects $p < 0.001$; surprise: $p < 0.001$, $p = 0.029$), whereas for happiness and fear, neither age effects nor AD effects were observed (happiness: $p = 0.138$,

Table 1. Age effects and Alzheimer disease effects

	HAPPINESS	SADNESS	SURPRISE	ANGER	DISGUST	FEAR
†YNC	86.7 ± 14.0	63.1 ± 22.9	81.1 ± 8.9	66.8 ± 15.1	55.5 ± 14.9	55.0 ± 15.3
§*YNC versus ANC*	*0.138*	*0.183*	*<0.001***	*0.031**	*<0.001***	*0.178*
††ANC	76.8 ± 16.8	48.3 ± 25.8	63.9 ± 14.3	55.0 ± 12.3	32.4 ± 19.2	43.9 ± 13.7
¶*ANC versus AD*	*1.000*	*0.048**	*0.029**	*<0.001***	*0.718*	*1.000*
AD	72.8 ± 15.8	25.3 ± 26.0	50.5 ± 18.4	23.4 ± 14.5	25.0 ± 14.6	37.3 ± 28.0

†YNC: young normal controls; ††ANC: aged normal controls; §age effects: significantly higher sensitivity of YNC in comparison with ANC; ¶AD effects: significantly higher sensitivity of ANC in comparison with AD. Both of the age and AD effects were shown by p values of intrasubject *post hoc* analysis with Bonferroni correction of 3 × 6 repeated measured ANOVA (three groups of YNC, ANC, and AD, and six expressions). *$p < 0.05$, **$p < 0.001$.

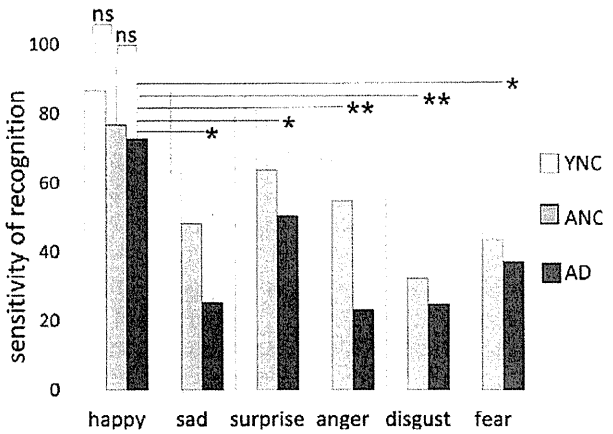

Figure 2. Results of sensitivities of the young normal controls (YNC), the aged normal controls (ANC), and the AD patients. Error bars indicate standard deviation. Regarding recognition of happy and fear faces, there was no significant difference between YNC and ANC, and ANC and AD patients. Regarding recognition of surprise and anger faces, there was significant difference between YNC and ANC, and ANC and AD patients. There was significant difference between ANC and AD in sad face recognition, and between YNC and ANC in disgust recognition. Within AD patients, sensitivity of happy face was significantly higher than that of other expressions. *$p < 0.05$, **$p < 0.001$.

$p = 1.000$; fear: $p = 0.178$, $p = 1.000$). For sadness, AD effects were observed ($p = 0.048$), whereas age effects were not ($p = 0.183$). However, for disgust, age effects were observed ($p < 0.001$), whereas AD effects were not ($p = 0.718$). Within AD patients, sensitivity of happiness was significantly higher than those of the other five expressions, and that of surprise was significantly higher than those of anger and disgust.

Discussion

This study showed that recognition of happy facial expressions was relatively preserved in AD patients. Recognition of happiness was significantly easier than recognition of five other expressions and there were no age effects or AD effects. Regarding negative expressions, age effects were observed in recognition of anger and disgust, and AD effects were observed in recognition of sadness and anger. Surprise had a neutral emotional valence and both effects were observed in surprise recognition.

The results from this study should be reliable because the task used involved a sophisticated matching task that improved on problems in previous studies to cancel confounding factors. In previous experimental settings, participants were required to match the expression of photos of different people. Thus, impairment in the matching could be a result of visuospatial dysfunctions rather than deficits in processing emotions (Ekman *et al.*, 1971). Upon misunderstanding of individual differences in facial features, the participants might fail to extract the emotional implications. The stimuli used in the present study were averaged faces with different emotional valence, where non-emotional features were shared. Thus, differences in features are directly related to emotional differences. Another merit of this matching task was to eliminate the cognitive process to convert perception to abstract verbal expression; abstract thinking and verbal recognition also decline in AD patients. The use of images of Japanese individuals for Japanese participants also eliminated irrelevant cognitive load. Social recognition, including

emotional facial expression, has sociocultural implications, and expression of facial emotions could be influenced by cultural backgrounds (Ekman *et al.*, 1987; Shioiri *et al.*, 1999).

Adding to canceling confounding factors, another advantage of this method is the precise measurement of the sensitivity by using the intermediate level of expressions. In the often used experimental settings, the participants were required to classify the photos of typical emotional faces (100% in the present study) by emotional expression. According to a meta-analysis of 17 studies on emotion recognition and aging, the average of the stimuli of one emotion was around 7. Concerning happiness recognition, the magnitude of the difference between young and aged subjects is potentially masked by a ceiling effect, with young subjects scoring 98% or better in 15 out of 17 studies (Ruffman *et al.*, 2008). Such ceiling effects could exist in the experiments comparing aged subjects and AD patients, thus more sensitive tests with subtle stimuli are desirable. In the present study, we applied 1%–99% intermediate levels of expression, which enabled precise measures of sensitivity.

After eliminating the confounding factors of deficits in spatial processing of non-emotional facial features and in verbal processing to express emotions, positivity bias in ANC was shown, in that recognition of happiness was spared in comparison with YNC. In AD patients, recognition of happiness was spared in comparison with ANC. Hargrave *et al.* (2002) reported that AD patients showed selective impairment in labeling facial expressions of sadness compared with ANC. The results were not identical, as there were differences in the methods used to eliminate the confounding factors of facial features of different people. Hargrave *et al.* (2002) tried to remove the factors by analysis. The experimental setting involved matching the emotion displayed on the reference face with one of six simultaneously presented alternatives, and all seven photographs were faces of different people. A multivariate analysis of covariance (MANCOVA) model was adapted using each subject's score on the facial identity matching task as a covariate. The advantage of the present study is eliminating the confounding factors at the experimental phase.

The mechanism of positivity recognition bias in aged individuals and AD patients remains unproven. Positivity bias in aged individuals was explained by lifetime perspective motivational changes; as the time perspective is reduced, current emotional goals associated with well-being become more important (Carstensen *et al.*, 1999). Consequently, aged individuals would tend to allocate more cognitive resources to improve emotion regulation, and their information processing was characterized by a positivity bias (Mather and Carstensen, 2005; Mather and Knight, 2005; Brassen *et al.*, 2011). Within this framework, positivity bias in facial emotional recognition could be explained by shifts in attention allocation for positive stimuli (Mather and Carstensen, 2005; Goeleven *et al.*, 2010).

Concerning such allocation of cognitive resources to emotion regulation, capacities of cognitive resources should be considered. Mather and Knight reported that aged individuals with superior cognitive abilities were more likely to exhibit positivity bias (Mather and Knight, 2005). In line with the report, the positivity bias should be reduced in AD patients with cognitive decline. However, the experiment was conducted on memory, and if the allocation occurred only in the remembering phase, and not the memorizing phase, the explanation could not be applied to facial recognition. Goeleven *et al.* (2010) suggested that increased age is associated with reduced allocation of resources to negative stimuli, and the explanation could also be true in AD patients.

The present study showed decreases of negative emotion recognition and relatively preserved positive recognition. Our results are in line with the conclusions based on the meta-analysis of Murphy and Issacowitz, which revealed an age-related decrease of negativity preference as compared to an increased positivity preference (Murphy and Isaacowitz, 2008). The above explanations are still hypotheses, and specifying the interaction between cognitive decline and emotion processing would be a valuable topic for future research.

Regarding study limitations, it is possible that recognizing happy facial expressions was easier, as this was the only positive emotion in the study. The differentiation of the four negative expressions, sadness, anger, disgust, and fear, was more difficult. Thus, the results should be confirmed in an experimental setting using stimuli with three facial expressions: happiness, a negative emotion, and a neutral expression.

This study showed that recognition of happy facial expressions was relatively preserved in AD patients; the results could be generalized to other ethnicity because emotional facial recognition is basically universal. These experimental results may be useful if they are implemented in a way to improve the daily life of AD patients. Caregivers should take advantage of cues from happy facial expressions to provide beneficial care.

Conflict of interest

None.

Description of authors' roles

Y. Maki designed the study, collected and analyzed the data, and wrote the paper. H. Yoshida designed the study and did the computer programming for the task. T. Yamaguchi collected and analyzed the data. H. Yamaguchi supervised the study and wrote the paper.

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原著

リバスチグミン貼付薬（イクセロン® パッチ）の実践的投与経験

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要　旨

【目的】アルツハイマー型認知症へのリバスチグミン貼付薬（イクセロン® パッチ）投与の後方視研究を行った．【方法】対象はもの忘れ外来の44例（79.8±6.7歳）で，評価はMMSE他を行った．【結果】1）経緯と有害事象：44例中16例が4～20週で投与中止となった．その理由は皮膚症状が11例と多くを占めた．継続例は28例で，47.87±27.0週間，16.2±3.5 mgを投与し，うち21例が18 mgで継続投与であった．2）効果：メマンチン併用5例を除き，MMSEを前後比較できた20例で，投与前18.0±6.6点から26.1±19.9週間後に20.2±6.2点と有意に改善した（p=0.022）．3）有効5例を個別に紹介した．【まとめ】リバスチグミン貼付剤は認知機能維持・改善効果が優れているが，皮膚症状対策が必要である．

Key Words：リバスチグミン，アルツハイマー型認知症，皮膚症状

1．はじめに

アルツハイマー型認知症（Alzheimer-type dementia；AD）治療薬であるアセチルコリンエステラーゼ阻害薬（acetylcholinesterase inhibitor；AChEI）はドネペジルに限られていたが，2011年にガランタミンとリバスチグミンが本邦で使えるようになった．リバスチグミン内服薬は海外で使われたが消化器系の副作用が多いため，貼付剤が開発され（Winblad et al.；2007），本邦では貼付薬が発売された．

リバスチグミンには，AChEに加えてブチリルコリンエステラーゼ（butyrylcholinesterase；BuChE）も阻害する作用がある．AD脳でのACh分解の主役は，初期にはAChEであるが，進行とともにAChEが減り，グリア細胞に由来するBuChEが増える（Ballard, 2002）．したがって，リバスチグミンは高度のADでも効果を発揮することが期待される薬剤であり，米国で実施された高度ADを対象とした大規模臨床試験で高用量製剤（本邦では認可されていない27 mg貼付薬）の有効性が示され（Farlow et al., 2013），高度ADに適応拡大となった．

発売前の国内臨床試験では，859例を対象として18 mgの貼付薬を24週間，二重盲検で投与した結果，

Rivastigmine transdermal patch (Exelon™) in clinical practice
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ADAS-Jcogでの認知機能低下抑制効果が示され（Nakamura et al., 2011），さらに，その後の経過観察で，生活機能としてIADLやコミュニケーション能力の維持効果が示されている（中村ら，2012b）．

今回，ADの49例に投与した経験をまとめた．これは研究プロトコルにしたがって実施した前向き研究ではなく，一臨床医の後ろ向き研究であり，データは不完全であるが，筆者の経験が，一人ひとりの患者に向き合う診療に役立つと思い執筆した．

2. 対象と方法

2医療機関（一般病院と診療所）のもの忘れ外来で，2011年8月～2013年4月までにリバスチグミン貼付薬（全例イクセロン®パッチ）を投与したADの49例のうち，3か月以内にかかりつけ医などへの転医や診療中断で経過を追えなかった5例を除く44例，79.8±6.7歳（平均±標準偏差）を分析の対象とし，後方視的に検討した．ADの44例中8例ではMRIで虚血性大脳白質病変や基底核のラクナ梗塞を認めた．重症度は，軽度認知症（CDR 1）32例，中等度認知症（CDR 2）9例，重度認知症（CDR 3であるが，MMSEは8～11点で歩行可能なレベル）3例であった．ADの診断基準はNINCDS-ADRDA criteria（Dubois et al., 2007）を用いた．

AChEI治療歴無し30例，他のAChEIからの切り替え14例（ドネペジルから11例，ガランタミンから3例）であった．

投与量は4週ごとに4.5 mg増量して18 mg（10 cm^2）で維持を原則としたが，有害事象が見られた場合は，介護家族や本人と相談して減量または中止とした．

併用薬については，メマンチン10 mg/日が2例，20 mg/日が3例，抑肝散2.5 g/日が4例，5.0 g/日が1例で，抗精神病薬は併用していない．これらの併用薬はリバスチグミン貼付薬使用前から継続使用しており，評価期間中に用量の変更はなかった．

Mini-mental state examination（MMSE；Folstein et al., 1975）を，投与開始前と3か月以上経過後に評価した．一部の症例（症例呈示）では，認知症の行動・心理症状（Behavioral and psychological symptoms of dementia；BPSD）の指標としてdementia behavior disturbance（DBD）スケール（溝口ら，1993）やNeuropsychiatric Inventory（NPI；博野ら，1997），介護負担の指標としてZarit-8（荒井ら，2003）を用いた．

投与前後の比較には，Wilcoxon符号順位検定を用いた．年齢の群間比較はt検定を用いた．

臨床データの利用については，事前に本人や家族より了解を得た．なお，本研究は群馬大学医学部疫学倫理委員会の承認を得ている．

3. 結　果

3.1. 投与の経緯と有害事象

44例中28例（80.7±7.3歳）が継続投与，16例（78.9±6.1歳）が投与中止となった（Table 1）．両群の年齢に有意差はなかった（p=0.40）．

Table 1. Relation between dose at discontinuation and reason

Dose	4.5 mg	9 mg	13.5 mg	18 mg	Total
Discontinuation	5	3	3	5	16
Reason					
Skin irritation	2	2	2	5	11
Hyperactivity/irritability	2	1	0	0	3
Request of oral medicine	1	0	0	0	1
Cognitive decline*	0	0	1	0	1

*Switched form donepezil

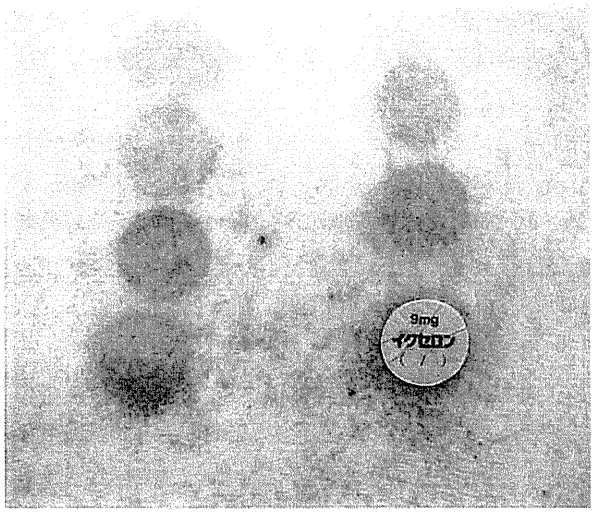

Fig. 1. Example of skin irritation, causing discontinuation at 9 mg.
Caregiver everyday changed the place downward with changing right and left side for 1 week. Intense inflammation continued for 3 days after removing the patch, even though the subjects used skin moisture cream.

中止群の投与期間は9.9±5.7週（4〜20週）で，中止時の用量は11.3±5.7 mgであった．この16例中6例は投与開始3か月の時点では継続例であったが，その後の継続中に中止となったので，3か月経過時点での中止は10/44（23%）である．中止の理由は皮膚症状（発赤と掻痒など）が11例（投与開始49例中の22%；解析44例中の25%）と，中止16例の2/3を占めた（Fig. 1）．9 mg以上となってから中止した11例では9例が皮膚症状で，用量が増えると皮膚症状が問題となった．残り2例のうち1例は過活動・易怒性，1例は切り替えにより認知機能が低下しドネペジルへの復帰を家族が希望した．一方4.5 gmgで中止した5例の理由は，皮膚症状が2例で，過活動・易怒性が2例，内服を希望が1例であった．胃腸障害による中止例はなかった．

継続できた28例では，47.8±27.0週間と約1年間にわたって，16.2±3.1 mgを投与した．このうち22例が18 mgで継続投与できた．減量投与は，9 mgの5例と13.5 mgの1例の合計6例（継続28例中の21%）で，嘔気・嘔吐などの胃腸障害が減量理由であった．減量により胃腸障害が消失して継続でき，中止には至らなかった．

3.2. 評価結果

認知機能に影響を及ぼすことが推測されるメマンチンの併用5例は除き，投与開始3か月以降に認知機能を事後評価できた20例で認知機能の評価を前後比較した．継続期間26.1±19.9週間，投与量16.2±3.1 mg/日の時点で事後評価を行うと，MMSEは投与前18.0±6.6点から，投与後20.2±6.2点と有意に改善した（p=0.022；Wilcoxon符号順位検定）（Table 2）．

この20例を，AChEI治療歴無し例と切り替え例に分けると，治療歴無し14例ではMMSEが18.1±6.8点から20.1±6.1点へと上昇したが，統計学的な有意差がみられなかった（p=0.114）．ドネペジルなどからの切り替え6例でも17.7±6.8点から20.2±7.1点と上昇したが，有意ではなかった（p=0.084）（Table 3）．

このほか，介護家族の声として，生活意欲の向上が多く聞かれた．

3.3. 有効例

MMSEが6点以上上昇した4例と，易怒性があっても投与できBPSDが軽減した1例を示す．

症例1：70代後半の女性．もの忘れで始まり徐々に進行し，初診時MMSE 22点だった．ADと診断し，

Table 2. Change of MMSE score

	Pre	Post	P value#
All (n=20)	18.0±6.6	20.2±6.2	0.022*
AChEI untreated (n=14)	18.1±6.8	20.1±6.1	0.114
AChEI switched (n=6)	17.7±6.8	20.2±7.1	0.084

Wilcoxon signed-rank test ; * <0.05

ガランタミン8 mg/日で開始したが，4日で嘔吐が出現し，4 mg朝のみに減量しても易怒性が出て中止した．1か月の休薬後にリバスチグミン貼付薬を開始した（開始時MMSE 21点）．3か月後の13.5 mgで嘔気が出現し，9 mgに減量したが，エソメプラゾールを併用して18 mgに増量可能で，18 mgを継続した．開始から1年6か月後にMMSE 27点（+6点）と改善した．畑に行ったり草むしりなどが日課で自宅にて過ごし，デイサービスには通っていない．リバスチグミン貼付薬では易怒性が出現しなかった．

症例2：70代前半の女性．もの忘れが出現してから4年経過し，初診時MMSE 8点だが，農家で1人暮らしのため，受診が遅れたAD例である．デイサービスなどの利用なく，娘が通って介護をしている．治療前は，もの盗られ妄想などのBPSDが高度でNPI 29点だった．1人暮らしで内服管理ができないため，リバスチグミン貼付薬を娘が毎日貼ることで開始した．抑肝散2.5/夕を併用し，順調に18 mgまで増量すると，4か月後にはMMSE 16点（+8点）まで改善した．介護保険を申請し，デイサービスを週3回利用するようになったことも好影響している．その後投与開始から1年が経過して（18 mg継続），MMSEは11点（+3点），NPIは5点（−24点）まで改善し，娘の支援で穏やかに独居を続けている．

症例3：80代後半の女性．8か月前からもの忘れが多くなった．脳梗塞の既往歴はあるが，運動麻痺はない．MMSE 14点，DBD 18点で，MRIにて大脳基底核のラクナ梗塞を認めた．リバスチグミン貼付薬を開始し，順調に18 mgに増量して7か月の時点では，自分から日にちを確認する，洗濯機のボタンを押すなど，生活意欲が向上し，ウロウロすることもなくなった．開始10か月後にはMMSE 20点（+6点）となった．開始前は落ち着きがなかったが，1年後には色鉛筆を使って1時間集中して描くことが可能となり，素晴らしい色使いを示した（Fig. 2）．当初は家族が施設入所を希望して受診したが，デイサービスを週2回使い，1年8か月後（18 mg）も在宅生活を継続できている．

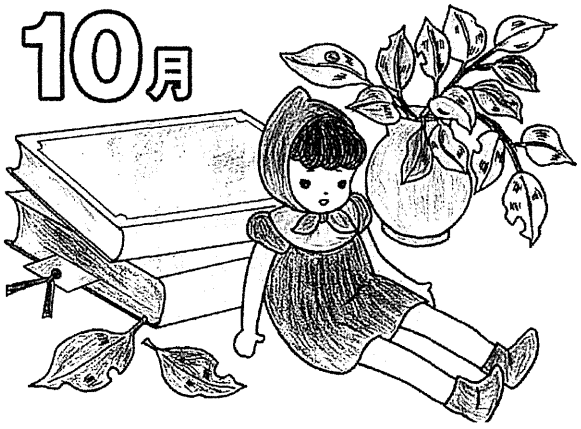

Fig. 2. Case 3 colored this picture. She became to be able to concentrate on coloring for 1 hour after treated with rivastigmine transdermal patch for 1 year, although she could not use color pencils before the treatment.

症例4：80代後半の男性．2年前からもの忘れがあり，置き忘れが多発し，同じことを何度も尋ねる，道に迷うなどの症状が加わり受診した．MMSE 24と得点は高かったが，視空間認知機能が低下しており，ADと診断した．リバスチグミン貼付薬を開始し，13か月後（18 mg継続）にMMSE 30点（+6点）に上昇し，生活意欲も向上し，日々の生活を楽しんでいる．改善要因として，会長を務める会社に毎日通うという日課を持っていた．

症例5：70代後半の男性．20年前と4年前に脳梗塞の既往があるが，運動麻痺はない．最近もの忘れが目立つようになり，易怒性もあり受診した．初診時，MMSE 21点，HDS-R 17点，ADAS-Jcog 14.4点，NPI 18点（興奮，無為無関心，脱抑制，易刺激性），Zarit-8 7点であった．MRIでは大脳基底核のラクナ梗塞と虚血性大脳白質病変を認めたが，大きな梗塞巣はなかった．リバスチグミン貼付薬を開始3か月後（13.5 mg），MMSE 23点（+2点），Zarit-8 4点（−3点）と改善した．5か月後（18 mg）にはNPI 12点（−6点；興奮，脱抑制，易刺激性の項目が消失）と改善した．易怒性があってもAChEIを使うことができ，認知機能向上とともにBPSDや介護負担が軽減した例である．

4. 考 察

今回，認知機能再評価まで平均26週間の投与でMMSEの有意な改善がみられた．本剤の国内臨床試験（24週投与）では，認知機能の低下抑制効果が示されたのみで，改善は示されなかった．発売後に国内で発表された論文では，安間＆安間（2012）が18 mg継続投与57例で，MMSEが使用前19.2±5.2点から使用後22.0±5.0点と有意に上昇した（$p<0.001$）と，報告している．上田ら（2013）の94例では，HDS-Rが使用前16.2±4.8点から使用後17.8±5.7点へと上昇したが，有意差はなかった．さらに，上田ら（2013）は20例で使用前後の脳血流SPECT所見を比較して，前頭葉，側頭葉，頭頂葉，さらには視床や脳幹と広い範囲で脳血流が増えたと報告している．そして，前頭葉の血流改善が自覚・他覚症状の改善に関連していたという．

AChEI治療歴無し例と切り替え例に分けると，両群ともに認知テストスコアの平均点が，有意ではないが上昇した．上田ら（2013）は，切り替え例でも治療歴無し例と同様に有効だと報告している．他のAChEI使用例で効果がみられない場合は，本剤に切り替えてみるのも一つの方法であろう．

本剤はADの進行とともに増加するBuChEの阻害作用も有するので，高度ADでも有効性が期待されることから，やや重度に進行した3例（投与前MMSE 8〜11点）も対象に含めた．このうちの2例では投与後評価でMMSEが8→17点，11→14点と上昇した．高度ADの716例をランダム化した米国での臨床試験（Farlow et al., 2013）により，認知機能と生活機能への有効性が示され，米国では2013年6月に高度ADにも適応が拡大された（日本より高用量の27 mg製剤であるが）．

本剤の第一の特徴は，貼付薬という剤形にある．このため，貼っている間は血中濃度がほぼ一定に保たれ，嘔吐・嘔気などの胃腸障害発現頻度が少ない（Winblad et al., 2007）．さらに，剥がすとその効果が速やかに消える（半減期は約3時間）．このメリットは副作用出現時にある．嘔吐・嘔気などの胃腸障害が出ても，剥がすことによって速やかに消失する．生じる可能性のある副作用を事前に伝え，さらに副作用と思われる症状が出たらすぐに剥がすように本人・介護者に伝えておくことが，継続投与に有用であった．今回，胃腸障害が出現した場合は9 mgや13.5 mgに減量することで継続が可能となり，胃腸障害による中止が一例もなかったことは特筆できる．本剤は，4.5 mgで治療開始4週間後の段階で，本人・家族介護者から，「元気になった」「意欲が出た」「同じことの繰り返しが減った」などの効果が指摘されることが多く，「効いているので減量してでも続けたい」という家族の声が多かった．

カナダで1,204例を対象とした研究では，18か月後も認知機能や生活機能が維持され，さらに，内服薬から切り替えた症例の介護者の88%が，経口薬よりも貼付剤の方が好ましいと答えている（Gauthier et al., 2013）．その理由として，使いやすさ（56%）や本人の好み（43%）などをあげている．今回の研究でも，「服薬を確認できて良い」などという介護者の声が聞かれた．このほか，誤嚥性肺炎で内服困難例に貼付剤が有効だという報告もある（工藤ら，2012）．

この貼付薬であるが故に，皮膚症状によって11例（22%）の脱落例が出た．安間＆安間（2012）の94例中では皮膚症状による中止が5例（5%）あった．上田ら（2013）の94例中では，局所皮膚発赤17例（18%），そう痒15例（16%）であったが，これらによる中止率は2%であった．谷内（2012）の22例中では2例（9%）が皮膚症状で中止している．発売前の国内臨床試験（24週）では，貼付部位の発赤が39.4%，掻痒が34.8%でみられているが（Nakamura, 2011），皮膚症状で中止に至ったのは8%であった（ノバルティスファーマ，2012）．海外では，ヨーロッパで行ったWinbladら（2007）の皮膚症状での中止2%や，米国で行ったCummingsら（2012）の貼付部位の紅斑5.7%，掻痒3.9%（中止%は記載無し）と，皮膚症状発現率や中止率が低い報告がある一方，カナダでの18か月投与の研究では約1割（掻痒4%，紅斑2.9%，貼付部位紅斑1.6%，貼付部位掻痒0.7%などの記載）が皮膚症状

で中止しており（Gauthier et al., 2013），また韓国でも皮膚症状で11%が中止という報告がある（Han et al., 2011）．

筆者らはQOLの面から発赤や掻痒を重く捉えて投与中止したので，皮膚症状による高い中止率となった．安間＆安間（2012）は，ステロイドホルモン剤を貼付前使用すると皮膚症状を低減できるとしており（中村はローションタイプを奨めている；中村，2012a），そのような処置で脱落例を減らしていると推測される．しかし，行き過ぎた医療のパターナリズムは控えねばならない．

皮膚症状による脱落例を減らすためにはスキンケアが重要であり，保湿剤（ヒルドイド®）の使用も推奨されるが（中村，2012a），一方で，接着成分の見直しという根本的な改善も望まれる．

AChEIで易怒性が出現することを，筆者は訴えてきた．筆者の外来はBPSDによる紹介患者が多いので，ドネペジル投与例の約1割に易怒性が見られ，減量で軽快することを報告した（山口ら，2010）．今回のリバスチグミン投与では，4.5 mgで2例，13.5 mgで1例に過活動・易怒性が見られて中止した．このような場合，メマンチンを使うと落ち着き，その後に再開することも可能である．筆者は，抗精神病薬を追加してAChEIを継続することは好ましくないと考えている．一方，他剤で易怒性がみられた症例でも，リバスチグミン貼付剤で易怒性が生じなかった例（症例1）や，易怒性があっても使えた例（症例5）を示した．リバスチグミン貼付薬は，AChEIの中では易怒性が比較的生じにくい薬剤と思われる．

本剤は18 mgが維持用量になっているが，少量から有効な例や副作用により増量できない場合があり，添付文書に「適宜減」が加わることが望まれる．本来，医師には処方裁量権があるが，減量投与のレセプトが切られる可能性があることから，院外薬局からは減量投与をしないで欲しいと苦情が寄せられる．患者の状態によっては，「適宜減」が可能となるような添付文書上の柔軟性が期待される．

認知症は経過の長い疾患である．4週ごとにゆっくりと増量しながらその人の適量を見つけ，また経過と共にその量を適宜見なおしていくという実践臨床の姿勢（ガイドラインを基本に，一人ひとりの患者の症状に合わせた医療）が必要であろう．メマンチンについても，20 mgでは過量で，10 mgが適量のケースが相当あることを指摘した（山口ら，2012）．添付文書と診断だけを元にした機械的な処方ではなく，患者・介護者の声に耳を傾けることが，その薬剤の真価を発揮させると考える．

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Rivastigmine transdermal patch (Exelon™) in clinical practice.

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Purpose : Practical clinical application of rivastigmine transdermal patch for Alzheimer-type dementia.

Participants : 44 outpatients, aged 79.8±6.7 y, of memory clinic.

Medication : Dose of rivastigmine transdermal patch (Exelon™) was increased up to 18 mg (10 cm^2 ; 9 mg/day), if adverse effect was not appeared.

Evaluation : Cognitive function was evaluated by Mini-mental state examination (MMSE).

Results : In 44 subjects, 16 discontinued at 4 to 20 weeks by adverse events : 11 with skin irritation, 3 with mental irritability and 2 others. Remaining 28 subjects continued the medication, and MMSE score was significantly improved ($n=20, p=0.022$, Wilcoxon) from 18.0±6.6 to 20.2±6.2. We described clinical courses of 5 subjects, who showed marked improvement.

Conclusion : Treatment with the rivastigmine transdermal patch has significant benefit to maintain/improve cognitive function. However, high-frequency adverse events of skin irritation should be prevented.

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原著

老健における認知症短期集中リハビリテーション：脳活性化リハビリテーション5原則に基づく介入効果

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要　旨

【目的】介護老人保健施設（老健）において認知症短期集中リハビリテーション（リハ）の有効性を示す．【方法】対象は122名の入所者．脳活性化リハ5原則（快・会話・役割・褒める・成功体験）に基づく認知症短期集中リハを個別で週3回，3か月間実施し，前後評価を行った．【結果】HDS-Rが14.7±6.5→16.5±7.6（$p<0.001$）と，MMSEが17.5±5.6→18.9±5.8（$p<0.001$）と有意に向上した．行動・心理症状はDBD 10.8±10.3→9.4±9.3へと，意欲はVitality Index 6.9±1.8→7.4±1.9と，抑うつはGDS5 2.6±1.4→2.0±1.4と，いずれの指標も有意に（$p<0.001$）改善した．HDS-R低値（14点以下）群とHDS-R高値群に分けても，ほぼ同様な結果だった．【結論】老健での認知症短期集中リハは，認知機能や意欲の向上，行動・心理症状と抑うつの低減に有効なことを多数例で示した．

Key Words：介護老人保健施設，認知症，リハビリテーション，行動・心理症状

1．はじめに

平成18年より介護老人保健施設（老健）における認知症リハビリテーション（リハ）として，「認知症短期集中リハビリテーション実施加算」が算定可能となった．この算定には，1）精神科医師もしくは神経内科医師または認知症に対するリハの研修を受けた医師の指示のもと，2）入所から3か月以内の対象者に，週3回，1回20分以上の個別リハを，3）理学療法士・作業療法士・言語聴覚士が実施することで算定できる．当初は，改訂長谷川式簡易知能評価スケール（HDS-R；加藤ら，1991）またはMini-Mental State Examination（MMSE；Folstein et al., 1975）が15～25点までの軽度～中等度認知症が対象とされていたが，平成21年4月の介護報酬改定に伴い対象範囲が重度認知症にも拡大し，点数が5～25点の範囲でサービスが提供できるようになった．また，加算も1回60単位（600円）から240

Intensive rehabilitation for dementia in a Geriatric Health Services Facility (Roken): Effect of intervention with 5 principles of Brain-activating rehabilitation

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単位（2,400円）へと大幅に増え，老健での認知症短期集中リハへの期待が高まった．

老健での認知症短期集中リハの有効性を示す研究はいくつかあるものの（衛本ら，2007；長谷川ら，2011；長友ら，2011；遠山ら，2011；鳥谷部ら，2011），対象者が数名と少数であり，多数例で統計学的に実証した研究報告は少ない．長友らの研究（長友ら，2011）で，51例の対象者に認知症短期集中リハを回想法・学習・運動療法を中心に実施したところHDS-Rの得点が有意に改善したと報告しているだけである．このほか，公益社団法人全国老人保健施設協会が平成18, 19, 20年度に実施した調査研究事業で認知症短期集中リハの有用性を示しているが，その成果が論文化されていない．そこで，今回122例を対象として効果を検証したので報告する．

2. 対象・方法

2.1. 対象

対象は平成23年1月～平成24年9月までの老健（陽光苑；定員100名）入所者のうち，入所して3か月以内でHDS-RまたはMMSEが5～25点という認知症短期集中リハ実施加算組み入れ基準に該当した者122名とした．脱落者はなく，リハ介入前後の評価を122名で終えた．内訳は男性33名　女性89名．平均年齢は，82.3±9.3歳（平均±標準偏差）であった．

2.2. 方法

週3回，1回20分以上の個別リハを入所から3か月間実施した．介入メンバーは理学療法士2名，作業療法士3名，言語聴覚士2名である．

リハプログラムは，脳活性化リハ5原則に則った．脳活性化リハとは，認知症者が役割を演じながら楽しく人と交わることで，生きがいを感じ，不安を解消して前向きに生きるようになることを目指すリハの原則である（山口ら，2010；Yamaguchi et al., 2010）．その5原則とは：

1）**快**：セラピストも認知症者も共に“快”で，共に笑顔でリハを行う．笑顔で楽しく過ごせる場面設定や雰囲気作りがセラピストに求められる．

2）**コミュニケーション**：親密の情を表したコミュニケーションは不安や喪失感を感じている認知症者に安心感を与える．

3）**褒める**：認知症者の生活意欲が高まるよう“褒める”．褒められることは報酬であり，生活意欲や学習意欲を高める．さらには傷ついた自尊心の回復にも繋がる．セラピストは，褒めようという意識を常に持って，些細なことでも見つけて褒める．

4）**役割**：たとえ認知症になっても「社会（他者）の役に立ちたい」と本人は思っている．リハセッションではセラピストと患者という主従関係になりがちだが，患者が主役で活動する，セラピストがそれを支えるというスタンスが重要である．たとえ簡単な作業であっても役割を持つことが，認知症者の不安を和らげ，尊厳を高める．それをセラピストが感謝する・褒める．

5）**失敗を防ぐ支援**：“できること”と“できないこと”を見極め，なるべく本人の残存能力を引き出しながら，最低限の援助でうまくできるようにして成功体験に結びつける．

事前評価に基づいて，対象者に適した技法を現実見当識練習，回想法，語想起練習，記憶練習，学習，アクティビティなどの中から2～3種類選択して個別に実施した．画一的な介入ではなく，対象者個々の好みに応じて技法を選択することで楽しい介入とした．

評価指標として，認知機能はHDS-RとMMSE（どちらも30点満点で，得点が高いほど認知機能が高い），BPSDはDementia Behavior Disturbance Scale（DBD；28項目5段階，112点満点で高いほど行動障害が強い；溝口ら，1993），意欲はVitality Index（VI；5項目3段階，10点満点で高いほど意欲が高い；Toba et al., 2002），抑うつはGeriatric Depression Scale 5項目短縮版（GDS5；5項目の有無，5点満点で高いほど抑うつ傾向が強い；Hoyl et al., 1999；町田ら，2002）を使用した（Table 1）．介入前後の評価は同一評価者が実施した．

統計はWilcoxon符号順位和検定で前後比較を行った．全122例での解析に加えて，介入前

Table 1. Effects of rehabilitation

a All 122 subjects

	Scale	Before intervention	After intervention	*P* value
Cognitive function	HDS-R	14.7±6.48	16.5±7.63	$p<0.001$
	MMSE	17.5±5.56	18.9±5.81	$p<0.001$
BPSD	DBD	10.8±10.3	9.38±9.31	$p<0.001$
Vitality	VI	6.89±1.81	7.43±1.90	$p<0.001$
Depression	GDS5	2.55±1.38	2.04±1.38	$p<0.001$

b Low HDS-R (14 or less) group, 58 subjects

	Scale	Before intervention	After intervention	*P* value
Cognitive function	HDS-R	8.83±3.00	10.4±4.61	$p=0.005$
	MMSE	13.1±3.57	14.8±4.56	$p<0.001$
BPSD	DBD	16.5±11.7	14.1±10.8	$p<0.001$
Vitality	VI	6.31±1.77	7.07±2.03	$p<0.001$
Depression	GDS5	2.38±1.36	1.88±1.35	$p=0.005$

c High HDS-R (15 or more) group, 64 subjects

	Scale	Before intervention	After intervention	*P* value
Cognitive function	HDS-R	20.1±3.35	22.1±5.16	$p<0.001$
	MMSE	21.5±3.74	22.6±4.04	$p=0.006$
BPSD	DBD	5.55±4.70	5.13±4.71	$p=0.09$
Vitality	VI	7.42±1.70	7.75±1.72	$p=0.02$
Depression	GDS5	2.70±1.39	2.19±1.39	$p=0.003$

Any scales showed significant improvement by comparison before and after the intensive rehabilitation for dementia with 5 principles of Brain-activating rehabilitation (mean±S.D.; Wilcoxon single-rank test).

HDS-R が 14 点以下の低値群 58 例と 15 点以上の高値群 64 例に分けた解析も行った.

また, ① HDS-R と MMSE は前後の得点差が±2 点の範囲を維持, −3 点以下を悪化, +3 点以上を改善とし, ② DBD は得点差が±1 点を維持, −2 点以下を悪化, +2 点以上を改善とし, ③ VI と GDS5 は得点差が±0 点を維持, −1 点以下を悪化, +1 点以上を改善とした分析も行った.

本研究は通常のリハ業務の成果を後方視的に検討したものであり, 新規入所者で認知症短期集中リハ実施加算組み入れ基準該当者をすべて対象としたもので, 群分けなど対象者に不利益になるような事項を含んでいない. 脳活性化リハ 5 原則に基づく介入（快・会話・褒める・役割・成功体験）は群馬大学疫学倫理委員会の承認（21-26）を得て実施した.

3. 結　果

全 122 例で介入期間（入所から 3 か月間）の前後で評価結果を比較した（Table 1a）. 認知機能では, HDS-Rは介入前 14.7 ±6.48 点（平均±標準偏差）から介入後 16.5±7.63 点と有意に改善した ($p<0.001$). MMSE も介入前 17.5±5.56 点から介入後 18.9±5.81 点と有意に改善した ($p<0.001$). BPSD 指標の DBD は介入前 10.8±10.3 点から介入後 9.38±9.31 点と有意に改善した ($p<0.001$). 意欲

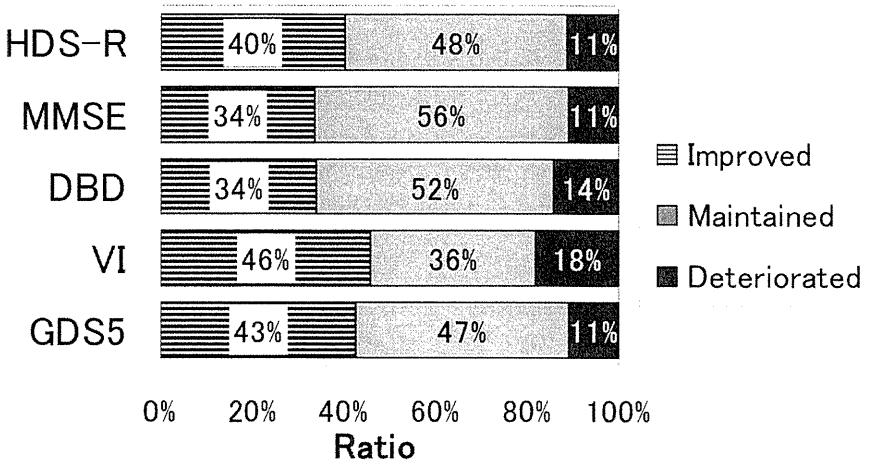

Fig. 1. Ratio of subjects in improved, maintained and deteriorated groups, which were divided by the score of each scale.
Ratio of the improved group was much higher than that of deteriorated group in any scales, showing the effects of intensive rehabilitation for dementia in Roken.
HDS-R: Hasegawa dementia scale-revised; MMSE: Mini-mental state examination; DBD: Dementia disturbance scale; VI: Vitality index; GDS5: Geriatric depression scale 5 item-version

を示すVIは介入前6.89±1.81点から介入後7.43±1.90点と有意に改善した（$p<0.001$）．抑うつ指標のGDS5は，介入前2.55±1.38から介入後2.04±1.38と点数が有意に低下した（$p<0.001$）．このように評価項目の全てで有意な改善効果が認められた．

介入前HDS-R得点で対象者を2群に分けると，HDS-R低値（14点以下）群58例ではすべての項目が有意に改善していた(Table 1b)．HDS-R高値(15点以上）群64例では，DBDを除く全ての項目が有意に改善した（Table 1c)．高値群でDBDが有意に改善しなかったので，この群内で介入前DBDが10点以上の14例に絞って検討すると，DBDは12.8±2.75点から11.3±3.79点と有意（$p<0.02$）に改善していた．

全対象者を項目ごとに改善・維持・悪化の3群に分けるとFig. 1のようになる．すべての指標で34～46%が改善，11～18%が悪化で，改善が悪化の2～3倍と大きく上回った．

4. 考　察

今回の研究で，3か月間継続した関わりを持つ集中的な個別アプローチである認知症短期集中リハは，認知機能だけでなく，意欲の向上，抑うつやBPSDの改善にも効果があることを示した．さらに，対象者をHDS-R 15点以上の高値群と14点以下の低値群に分けて検討すると，低値群では全ての項目で有意な改善がみられた．平成21年4月の介護報酬改定で，それまでのMMSEまたはHDS-Rで15～25点だった対象範囲が5～25点の範囲に拡大されたことを踏まえて，今回HDS-R 14点以下群でも有効性を示すことができ，対象範囲の拡大を支持する結果であった．

高値群ではDBDで有意な改善がみられなかったが，HDS-R高値群は元々DBDの得点平均が5.55点でHDS-R低値群16.5点の1/3程度と低く（BPSDが目立たないケースが多い），また，DBDが10点以上の14例に限れば有意な改善が認められたことから，HDS-R高値群全体ではフロア効果によりDBDの有意な改善が示せなかったものと推測され