Emotional Status in Patients with Parkinson's Disease

巴金森病人之情緒功能：長期追蹤研究(II)

第二年成果報告

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摘要

巴金森病是一種常見中樞神經系統的退化疾病。運動障礙、認知功能缺損、以及情緒功能失調，特別憂鬱問題是主要的症狀。但是文獻上所呈現這類患者罹患憂鬱與焦慮問題的盛行率，卻是不大一致。本研究計劃以三年的時間，利用追蹤方式來探討這個爭議未決的問題。

完成第二年研究計劃，總共收集到 192 位成年受試參與本研究，其中包括 127 位巴金森患者和 65 位正常受試。依照侯-葉氏(Hoehn-Yahr,1967)運動障礙評量表 127 患者中，58 位屬於第一級輕度運動障礙、52 位第二級輕中度動障礙、以及 18 位第三級中度運動障礙.。每一位受試都分別接受一組認知功能之神經心理測驗，以及一組情緒功能之測量。受試之主要照顧者同時也接受一組情緒功能之測量。完成第一年追蹤研究之受試者總共 53 人；其中 21 人屬於第一級輕度運動障礙、17 位第二級輕中度動障礙、9 位第三級中度運動障礙，以及正常受試者 6 位。

初步資料分析之結果顯示巴金森病患呈現情緒功能失調的問題。主要包括了憂鬱、焦慮、身心不適、強迫性行爲等症狀。大約 40%的巴金森患有憂鬱的問題；第一級輕度運動障礙患者有 43%患有這種情緒症狀、第二級輕中度動障礙患者有 30%、第三級中度運動障礙患者有 50%。這三組巴金森病患中約有 55%罹患失智症狀群，不過只有 40%的這些失智患者同時出現憂鬱症狀。完成第一年追蹤研究之患者中，約有 32%呈現憂鬱問題。第一級輕度運動障礙患者有 24%、第二級輕中度動障礙患者有 35%、第三級中度運動障礙患者有 44%這種情緒症狀。憂鬱症狀程度達到重憂鬱症(major depressive disorder)約有 15%；其中第一級輕度運動障礙患者約 15%、第二級輕中度動障礙患者 18%、第三級中度運動障礙患者 11%出現該疾患。完成第一年追蹤研究之患者中約有 64%罹患失智症狀群。

關鍵詞:情緒狀態、巴金森病、單氨類化學物質失調

ABSTRACT

Parkinson's disease (PD) is a prevailing degenerative disease of central nervous system. Motor symptoms, cognitive impairments including dementia, and emotional disturbances, especially depression are the cardinal features of the disease. The prevalence rate of depression and anxiety in the parkinsonian patients has a great variation. The present 3-year follow-up study, thus, is designed to examine emotional function in these patients.

In this second-year study, we have already included a total of 192 adult participants, 127 patients with idiopathic PD and 65 normal controls. On the basis of the motor staging of Hoehn and Yahr (1967), Group 1 consisted of 58 patients with the staging I, Group 2 included 52 patients with the staging II, and Group 3 were composed of 18 patients with the staging III. Each subject received a series of non-emotional neuropsychological test battery, and emotional status measures. The significant informant of each subject also received a series of emotional function measures. Currently, 53 patients have already completed the first-year follow-up. Among these, 21 of them were rated as the staging I in terms of their motor disabilities; 17 the staging II; and 9 the staging III, as well as 6 normal counterparts.

The preliminary results revealed that emotional disturbances, including depression, anxiety, somatic, and obsessive-compulsive symptoms, were evident in our patients with PD. About 40% of our patients manifested depression symptom. .43% of patients with staging I, 30% with staging II, and 50% with staging III were evident of this symptom. About 55% of our patients suffered from the syndrome of dementia based on the demented diagnostic criteria of the DSM-IV. However, only 40% of these demented patients were also evident of depression problem. Among 47 patients who have already received one-year follow-up, about 32% of these patients were evident of depression. About 24% patients with staging I, 35% with staging II, and 44.% with staging III manifested the symptom. About 15% suffered from Major Depressive Disorder in which 15%, 18%, and 11% with the motor staging I-III respectively had this disorder. Approximately, 64% of these 47 patients manifested dementia.

Keywords: Emotional Status, Parkinson's Disease, Monoaminergic Imbalance

INTRODUCTION

Parkinson's disease (PD) is a common disorder of central nervous system. The main motor features of the syndrome of parkinsonism, chiefly due to PD, consist of tremor, muscle rigidity, bradykinesia, and postural instability (Adam, Victor, & Ropper, 1997). A variety of cognitive impairments, such as verbal and visual memory problems (Levin, 1989), visuospatial deficits (Boller et al., 1984; Levin, 1989), executive dysfunction (e.g., Kuzis et al., 1995), language difficulties (e.g., Bayles, 1990), and dementia (Mayeux, 1990) have been noted in the patients. Additionally, the cardinal psychiatric features include affective disorders and psychosis (White & Cummings, 1997).

Clinical and economic implications of emotional disturbances in the patients with brain lesions are multifold (e.g., Spencer, Tompkins & Schultz, 1997). First, the patients with emotional problems undertake more negative thinking and stress negative results (Ingram, Kendall, Smith, Donnell & Roanan, 1987). Subsequently, Diverse cognitive function changes in these patients might be exaggerated though cognitive deficits tend to co-occur with emotional disturbances (Seibert & Ellis, 1991; Speedie et al., 1990). Secondly, emotional changes, such as depression can be an essential obstacle to treatment, and eventually these cause elevated use of health care services, longer hospital stays, and greater morbidity and mortality from medical illness or suicide (Reynolds, 1992). Finally, the quality of life of the patients and their caregivers might be greatly changed by these emotional sequelae (Spencer et al., 1997). Therefore, in order to provide the patients with the supreme opportunity for treatment profits, a great care for their emotional disturbances is merited.

Mood disorders have generally been considered to be the most common psychiatric disturbance with estimates ranging from 20% to 90% in the patients with PD (Mayeux et al., 1986). Depression, mainly major depression and dysthymic disorder, has often been reported in this patient population (Mayeux et al., 1986; Ring et al., 1994). It is also suggested to be the most common emotional problem that co-occurs in PD patients with dementia (Mayeux et al., 1986) though the exact co-morbid rate has been equivocal. A body of literature indicates no remarkable relationship between depression and physical illness and duration of illness (Brown & Jahanashi, 1995; Starkstein et al., 1992; Troster et al., 1995). Accordingly, it is too simplistic to attribute depression to a reactive feature, particularly early in the disease (White & Cummings, 1997).

In fact, a body of literature favors the view of neurobiological mechanism to account for the issue as follows. First, since degeneration of serotonergic and noradrenergic projections occurs alongside degeneration of dopaminergic neurons in

the patients, this emotional disturbance has generally been speculated to be in an association with an extensive monoaminergic dysfunction (Beatty, 1995; Conn, 1995; Fibigier, 1984; Mayeux, 1990). Secondly, recent studies revealed that depression in the patients with PD was associated with significant hypometabolic rate in the head of the caudate and the orbitofrontal cortex (Mayberg et al., 1990), and with bilateral reductions in regional cerebral blood flow in anteromedial frontal and cingulate cortex (Ring et al., 1994).

Review of the literature indicates that the prevalence rate of depression in the parkinsonian patients has a great variation, ranging from 4% to 70% with an average of around 40% (Cummings, 1992). This considerable variation is mainly attributable to methodological discrepancy, such as the divergent source patient populations, and various ways of depression diagnosis (e.g., based on the DSM system, semi-structured interview, or psychometric measures) (Sano, Marder & Dooneief, 1996). The investigators (Hoen & Yahr, 1967; Sano et al., 1989) reported about 51% of depression in PD based on clinic/hospital-based studies, and about 32% based on population-based investigations. Taken these data together, it implicates that at least about 50% of the patients with PD do not suffer from depression. As mentioned above, depression has been thought to be associated with a widespread monoaminergic dysfunction, and degeneration of serotonic and noradrenergic projections occurs alongside degeneration of dopaminergic neurons in the patients with PD (Beatty, 1995; Conn, 1995; Fibigier, 1984; Mayeux, 1990). Accordingly, it is expected that the patients with PD but without depression will be evident of depression gradually along with the neural degenerative processes. This issue, however, has been lacking in systematic investigation.

Anxiety has been generally thought to have a co-morbidity of depression in primary psychiatric patients (Davison & Neale, 1998). It has also been reported in the patients with PD (Schiffer, Kurlan, Rubin, & Boer, 1988). Most of the patients with PD who suffered from anxiety occurred in the early course of PD, in younger individuals, and after diagnosis of the disease (Iruela, Ibanez-Rojo, Palanca, & Caballero, 1992; Stein, Heuser, Juncos & Uhde, 1990). The prevalence rate of this emotional problem in the patients with PD has been reported to be around 20% to 30% (Stein et al., 1990). A disturbance in dopamine and norepinephrine concentration in the locus ceruleus has been connected with anxiety in the patients with PD (Iruela et al., 1992). Since the literature is scanty, the speculation of whether anxiety will be progressively evident in company with the evolution of the disease in the parkinsonian patients who do not have this disturbance initially merits further investigation.

Otherwise emotional disturbances, such as mania, hypomania, and psychosis characterized by paranoid delusions and hallucinations have also reported in the

patients with PD. These problems, however, are rare and most of them were associated with the patient's taking antiparkinosnian medications (Celesia & Barr, 1970; Factor & Brown, 1992; Goodwin, 1971; Jouvent et al., 1983; Lang et al., 1982).

A prospective longitudinal study of emotional function changes, particularly for depression, in the patients with PD is limited. Using such a research design with one-year follow-up, Starkstein and his colleagues (1990, 1992) have investigated depression in the patients with PD. The results revealed that both depressed and non-depressed patients had a significant deterioration of cognitive function (the former was remarkably more severe than the latter), and about 18 % (10 out of the 55) of the non-depressed patients with PD were progressively evident of depression a year later. The findings seem to partially support the hypothesis of depression associated with a widespread monoaminergic imbalance in the patients with PD (Fibigier, 1984; Mayeux, 1990). Because these results were only based on a one-year follow-up, the hypothesis, however, deserves further investigation.

The report of emotional disturbances, particularly depression, in the patients with PD in Taiwan is meager. In order to explore the aforementioned issues (i.e., the prevalence of depression and otherwise emotional disturbances, and the hypothesis of monoaminergic imbalance and its relation to depression and anxiety), and to document the literature in Taiwan, we design this three-year longitudinal study. In our study, 2 groups of participants, 1 cohort of parkinsonian patients and 1 group of normal controls will be included. The goal of the first-year study is to complete the initial and part of 1-year follow-up evaluation of the emotional status and cognitive function. The objective of the second-year study is to complete 1-year follow-up and part of 2-year follow-up evaluation of emotional status and cognitive function; and the third-year is to complete 2-year and part of 3-year follow-up evaluation of emotional status and cognitive function.

The specific aims of the study, thus, are to examine the following questions: 1) Is there an impairment of emotional status in the patients with PD? 2) If so, does the deficit only involve depression or also include otherwise emotional function evaluated? 3) If depression symptoms do occur in the patients, are they persistent in nature and can thus these patients be diagnosed as Major Depressive or Dysthymic Disorder? 4) If anxiety symptoms do occur in the patients, are they persistent in nature and then can these patients be classified as Generalized Anxiety Disorder? 5) If depression does occur, is it significantly associated with dementia? 6) If depression or anxiety does not occur in the patients with PD at first, will it be evident in company with the progression of the disease?

METHOD

Participants. A total of 192 adult participants, including three groups of patients with idiopathic PD with varying degree of motor disabilities and one normal control group, participated in the 1st- and 2nd-year study. Groups were matched for age and educational level (Table1). However, the VIQs, derived from the WAIS-R, of Groups 2 and 3 were significantly different from Groups 1 and 4. 47 patients have already received one-year follow-up (Table 2). The VIQ of Gp1 was significantly higher than that of Gp2. The diagnosis of PD was based on the Parkinson's Disease Society Brain Bank in London (PDSBB) guidelines (Fahn & Elton, 1987), and the patients with severe motor symptoms (staging 5) according to the criteria derived from Hoehn and Yahr (1967) were excluded in the study. All of the patients were also free of any other CNS, and psychiatric history.

All participants were right-handed in which hand dominance was ascertained by the history that the participant has always used his/her right hand preferentially for doing skillful activities, such as writing and holding chopsticks.

Tests and Procedure. After giving informed consent, each participant received a series of neuropsychological tests. These tests included following cognitive tests: the Temporal Orientation Test (Benton, Hamsher, Varney & Spreen, 1983), the Orientation to Personal Information and Place (Hamsher, 1983), the Object Naming Test (Spreen & Benton, 1969), the Semantic Association of Verbal Fluency (Hua, 1987), the Token Test (Benton & Hamsher, 1978), the verbal subtests of the WAIS-R (Wechsler, 1981), the Judgment of Line Orientation (Benton et al., 1983), the Facial Recognition Test (Benton et al., 1983), the Word Sequence Learning (Hua, 1987), the Benton Visual Retention Test (Benton,1974), the Wisconsin Card Sorting (Nelson, 1974), and the Trails Making A and B (Reitan & Wolfson, 1993). The battery also included the following emotional status measures: Symptom Checklist-90-R (Derogatis, 1977), Beck Depression Inventory (Beck,1987), and a semi-structured Standard Neurobehavioral Interview Inventory (Hamsher, 1983). Evaluations were administered in an examining room between 11AM and 2 PM to minimize any possible effects of diurnal mood variation on interview response, as suggested by Starkstein and his colleagues (1992). All these measures are Chinese versions.

In order to obtain reliable and valid ratings of the patient's emotional status, we asked the significant informants, particularly family caregivers of the patient, to rate the patient's emotional function. All of the significant informants of the patients were free of emotional disturbances, dementia, and psychiatric history. Each participant received the above evaluation at around 1 week after the diagnosis of PD, and at 12,

24, and 36 (if possible) months following the first evaluation.

RESULTS

Parametric and non-parametric statistical procedures, one-way ANOVA, ANCOVA with the covariate of VIQ, and Kruskall-Wallis one-way ANOVA, were used to analyze the test score or scale rating differences between the patients and normal controls. Post-hoc pairwise comparison procedures, Scheffe's and Nemenyi's contrasts, were subsequently employed if either overall F and H tests reached a statistically significant level. On the non-emotional status measures, performance of the patients with the motor staging I was not significantly different from that of the normal controls on the 1st evaluation and one-year follow-up. However, the patients with the motor stagings II and III performed poorly on memory, visuoconstructive praxis, visual perception of faces, language, and frontal lobe function measures compared to their normal counterparts (Tables 2-5) on these two studies. With respect to semantic memory, the mean recall and recognition scores of Gps 2 and 3 on the Recent Life Events test were significantly lower than those of the normal controls and Gp 1. The mean differences of recall and recognition scores of Gp 2 on the Remote Life Events test were remarkably lower than those of the normal controls. On the Word Sequence Learning test, both Gps 2 and 3 performed poorer than Gp1 and the normal control. Furthermore, more error scores were evident in these patient Gps on the Benton Visual Test.

On the visuconstructive praxis task, Three-Dimensional Block Constructional-Model test, the performance of Gp3 was significantly poorer than their patient and normal counterparts. In respect to core linguistic function task, performance of Gps 2 and 3 on the Token test was significantly inferior to that of the normal controls. For the frontal lobe function tasks, the performance of Gp3 on the Wisconsin Card Sorting, Trail Making Tests A and B, was significantly poorer than that of their normal and patient counterparts

On the emotional status measures (Table 6), the patients' score on the Beck Depression Inventory was significantly higher than that of their normal counterparts. The patients' rating scores on Somatic, Obsessive-Compulsive, Depressed Mood, and Anxiety Symptoms subscales on the SCL-90-R were remarkably higher than their normal counterparts. On the Somatic Symptom subscale, the differences of rating scores between both Gps 1, 2 amd 3, and their normal counterparts were statistically significant ($p<.05$). Only the differences of rating scores between Gp 1 and the normal controls on the Obsessive-Compulsive ($p<.05$), while the differences between

Gps 1 and 2, and normal controls on the Depressed Mood ($p<.05$), and Anxiety ($p<.05$) subscales reached a statistically significant level.

Concerning the ratings of the patients' and normal controls' significant informants on the subjects' emotional status with the Beck Depression Inventory and the 4 subscales of SCL-90-R, the scores of the patients' significant informants were also significantly higher than those of the normal controls (Table 7). The ratings between the patients and their significant informants on both of the emotional scales were consistent, with the exception of the subscales of Obsessive-Compulsive symptom and Depressed Mood of the SCL-90-R in which the rating score of the patients' the significant informants was significantly higher than that of the patients.

The examiner's ratings of the four group subjects' emotional status based on the items 9, 13, 15, 17, and 21 (which are associated with depression), and items 4 and 25 (which are related to anxiety) of the Neurobehavioral Rating Scale Interview are indicated in Table 8. The results revealed that on the depressed mood ratings, the mean score of Gps 1, 2 and 3 was significantly higher than that of their normal counterparts. However, the mean score of Gps 1 and 2 on the items related to anxiety was remarkably higher than that of the normal controls.

We used a preliminary cut-off point score of 12 or more, that is, one standard deviation above the mean score of the normal controls on the Beck Depression Inventory, to determine whether the patient had depressed mood. On the basis of this cut-off point score, we classified about 40% (50 out of 127) of our patients evident of depression symptom. Among these depressed patients, about 43% (25 out of 58) patients were rated as the motor staging I, about 30% (16 out of 52) the staging II, and 50% (9 out of 18) the staging III.

On the basis of the dementia criteria of the DSM-IV, about 55% (70 out of 127) of our patients were included in this diagnostic category. Among these demented patients, about 45% (26 out of 58) were those with the motor staging I, 65% (34 out of 52) the staging II, and 56% (10 out of 18) the staging III.

Among these demented patients, about 40% (28 out of 77) of them were also depressed. These included 21% (12 out of 58) of the patients with the motor staging I, 21% (11 out of 52) the staging II, and 30% (5 out of 18) the staging III.

For the 47 patients completed one-year follow-up, about 32% (15 out of 47) were evident of depression symptoms. These included about 24% (5 out of 21) patients with the staging I, 35% (6 out of 17) the staging II, and 44% (4 out of 9) the staging III. About 15% (7 out of 47) patients manifested Major Depressive Disorder including about 15% (3 out of 21) of the patients with the staging I, 18% (3 out of 17) the staging II, and 11% (1 out of 9).

For these 47 patients, about 64% (30 out of 47) were evident of dementia. There

were about 43% (9 out of 21) patients with the staging I, 82% (14 out of 17) the staging II, and 78% (7 out of 9) the staging III. For these 30 demented patients, about 33% (10 out of 30) of them also manifested depression problem, and there were about 5% (1 out of 21) of the patients with the staging I; about 30% (5 out of 17) with the staging II, 44% (4 out of 9) with the staging III.

DISCUSSION

Is there an impairment of emotional status in the patients with PD? On the basis of our preliminary results, our patients did have emotional problems. We found that about 40% of our patients with PD were evident of depressed mood. In the literature, depression has often been observed in parkinsonian patients (Mayeux et al., 1986; Ring et al., 1994). The prevalence rate of depression in the patient population was around 40% in average ranging from 4% to 70% (Cummings, 1992). Our results indicating the evidence of depression problem in the parkinsonian patients did corroborate the prior findings. Furthermore, 32-40% of our parkinsonian patients (including one-year follow-up), having this emotional function seemed to be not only compatible with the prevalence rate reported in western literature (Cummings, 1992), but also with the recent observations (Liu et al., 1997) based on a sample of Taiwanese patients with idiopathic PD. Furthermore, our results of about 15% our patients having major depressive disorder based on the current available one-year follow-up also seemed to be consistent with the prior findings (e.g., Cummings, 1992; Liu et al., 1997).

Is depressed mood associated with degree of motor disabilities in our patients with PD? The answer seemed to be negative. Liu and his colleagues (1997) noted that most of their depressed patients had nothing to do with their motor disabilities in terms of motor symptom staging (mainly, I and II) of Hoehn and Yahr (1967). Likewise, our patients included the motor stagings I-III, and we did also find that for patients with motor stagings I and II, the proportions of those patients with depression symptom did not seem remarkably different. However, the proportion of our patients who had moderate motor severity (stage III) manifested depression symptom was only higher than that of patients with staging II. On the basis of the findings of both studies, we would suggest that depression problem evident in patients with idiopathic PD might not have a remarkable association with their motor disabilities. In light of scanty literature on this issue, our tentative claim awaits further investigation.

If so, does the deficit only involve depression or also include otherwise emotional function evaluated? The answer appeared to be partially positive. In addition to depression evident in our patients with PD, otherwise emotional

disturbances, including somatic, obsessive-compulsive, and anxiety symptoms were slightly to mildly also manifest, particularly for patients with staging III. Among them, somatic symptom was noted in the patients regardless of the ratings of the patients per se, or of the corresponding significant informants.

If depression does occur, is it significantly associated with dementia? The answer might not be true. In the literature, prevalence rate of dementia in patients with PD has been controversial, ranging from 2% to 93%, and the variation probably attributable to different definitions of dementia and population investigated (e.g., Dubois, Boller, Pillon, & Agid, 1991). In the recent reports, Chui (1989), Mayeux and his co-workers (1988), and Rajput (1992) found that the prevalence rate in the demented patients with PD was in the range from 10% to 40%. On the basis of the dementia criteria of the DSM-IV, around 55% of our patients had the syndrome. It appeared that the frequency of our demented patients was consistent with researchers' observations (e.g., Dubois et al., 1991) while it was higher than that of others' (e.g., Mayeux and his co-workers' (1988) findings. These inconsistent results await further investigation. In addition, the present results revealed that dementia did not seem to be positively associated with the degree of motor disabilities in our patients with PD. Our results further corroborated these previous findings (e,g., Sagar, 1999).

The investigators (Mayeux et al., 1981) claimed that there was a remarkable relationship between depression and dementia in the patients with PD. However, only about 40% of our demented patients with PD were also evident of depression symptom. In light of the present results, we only could partially substantiate Mayeux and his colleagues' observations. Methodological differences, such as using varying dementia and depression measures, and diverse rating sources (i.e., including or not including the significant informants of the patients and the examiner) to determine whether the patient had dementia and depression mood might account for the contradictory findings. All of our patients received a series of neurocognitive test battery. On the basis of demented diagnostic criteria, confirmed by neuropsychological test results, of the DSM-IV, we classified our dementia patients. The prior study merely used a screening test, MMSE, to determine whether the patient was evident of dementia. The difference definition of dementia, thus, might partially account for these inconsistent finding.

Self-awareness is one of the frontal lobe functions (Stuss & Alexander, 2000), and the neuropathological involvement of frontal-striatal loop is generally evident in patients with PD (e.g., Lichter & Cummings, 2001). Accordingly, these patients' subjective complaints of emotional disturbances, such as depressed mood on the conventional inventories (e.g., Beck Depression Inventory) or interview scales (Hamilton Depression Scale) might not be valid and reliable because of their poor

self-awareness functioning. In the present study, we determined whether the patient manifested depressed mood based on multiple data sources, including the patient's self-report, his/her significant informant's description, and the examiner's clinical observations, rather than the patient's self-report only used in the prior studies. Thus, it appeared that our results might be more justifiable than those previous ones, and the contradictory findings might also be partially attributable to this methodological variation.

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Table1-1. Demographic Data and VIQ Score of Subject Groups (1st year evaluation)

	Gp1 (n=58)			Gp2 (n=52)			Gp3 (n=18)			Gp4 (n=65)			F/H(ANOVA)	p
	M	(SD)	Range	M	(SD)	Range	M	(SD)	Range	M	(SD)	Range		
Age(years)	58.90[bc]	12.08	37-78	64.55	11.50	32-85	69.17	10.28	44-81	61.82	9.39	46-86	5.02	<.05
Edu.(Yrs)	10.91	3.98	2-18	9.74	4.64	2-20	10.06	4.52	3-20	11.35	4.17	3-16	1.43	>.05
VIQ	97.21	13.83		92.18	16.17		85.83	10.30		103.63	13.91		10.09	<.05
Gender(M/F)		33/25			36/16			13/5			33/32			

WAIS-R: Wechsler Adult Intelligence Scale-Revised; H: Kruskal-Wallis one way ANOVA

Table1-2. Demographic Data and VIQ Score of Subject Groups (1st year follow-up)

	Gp1 (n=21)			Gp2 (n=17)			Gp3 (n=9)			Gp4 (n=6)			F/H(ANOVA)	p
	M	(SD)	Range	M	(SD)	Range	M	(SD)	Range	M	(SD)	Range		
Age(years)	61.33	12.5	37-78	68.94	9.44	45-85	72.56a	3.50	46-81	67.33	5.09	68-79	3.40	<.05
Edu.(Yrs)	11.43	3.75	4-16	9.06	4.89	2-16	9.78	3.73	6-16	11.00	4.10	6-16	1.10	>.05
VIQ	103.24	15.41		87.06[b]	11.90		93.78	15.88		101.17	13.57		4.37	<.05
Gender(M/F)		14/7			10/7			9/0			2/4			

WAIS-R: Wechsler Adult Intelligence Scale-Revised; H: Kruskal-Wallis one way ANOVA

Table 2-1. Learning and Memory Test Performance of Subject Groups (1st year evaluation)

	Gp1		Gp2		Gp3		Gp4		F/H(ACNOVA)*	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Orientation										
TO	0.25	0.77	0.27	0.87	0.28[ab]	3.69	0.34	1.46	2.93	<.05
OPIP	13.95	14.70	11.73	0.79	11.89	0.47	11.91	0.34	0.91	>.05
Remote Memory Test	45.18	4.29	42.17	7.46	43.00	4.64	47.38[b]	2.70	10.07	<.05
Remote Memory Test(Recognition)	47.71	2.70	45.88	4.93	46.67	3.41	49.17[b]	1.81	6.45	<.05
Recent Memory Test	35.18[bc]	4.30	30.71	7.41	28.83	7.87	37.18	3.23	5.63	<.05
Recent Memory Test(Recognition)	38.67[bc]	1.96	35.81	5.34	34.83	6.99	39.48[bc]	1.64	5.66	<.05
Verbal learning and memory										
WSL										
Correct	46.79	9.60	37.72[a]	13.64	37.93	8.62	49.00[b]	8.00	7.69	<.05
Position	35.61	14.73	24.12[a]	15.84	17.60[a]	10.80	35.34[c]	13.81	6.94	<.05
Recall	2.52	1.78	1.80	1.86	2.00	1.77	2.85	1.69	1.69	>.05
Cue	3.82	1.89	2.76	2.18	2.40	2.26	4.05[c]	1.66	3.03	<.05
Recognition	26.88	3.92	24.81	5.03	25.33	5.07	27.26	3.56	1.90	>.05
BVRT										
Correct	6.18	1.82	5.02	2.01	5.28	3.06	6.33	1.52	2.32	>.05
Error	5.78[bc]	3.47	8.52	4.12	9.44	3.18	5.08[bc]	2.43	7.62	<.05

TO: Temporal Orientation; OPIP: Orientation to Personal Information and Place; WSL: Word Sequence Learning-Revised; BVRT: Benton Visual Retention Test; a: significant pairwise contrast between Gp1 and otherwise Gps; b: significant pairwise contrast between Gp2 and otherwise Gps; c: significant pairwise contrast between Gp3 and otherwise Gps

*VIQ as covariate

Table 2-2. Learning and Memory Test Performance of Subject Groups (1st year follow-up)

	Gp1		Gp2		Gp3		Gp4		F/H(ANCOVA)	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Orientation										
TO	0.19	0.40	1.82	4.46	1.78	3.27	0.17	0.41	0.71	>.05
OPIP	12.00	0.00	11.41	1.18	11.78	0.67	11.83	0.41	0.96	>.05
Remote Memory Test	34.43	3.53	28.65	6.41	28.89	8.52	35.33	5.47	1.65	>.05
Remote Memory Test (Recognition)	37.29	2.35	33.06	4.97	33.67	6.58	38.00	1.79	1.11	>.05
Recent Memory Test	45.19	3.22	41.18	7.37	39.11	8.28	45.17	4.79	1.76	>.05
Recent Memory Test (Recognition)	47.14	3.14	44.18	5.57	46.22	13.57	50.00	0.00	2.25	>.05
Verbal learning and memory										
WSL										
Correct	50.53	7.57	32.00	14.67	34.33	11.15	53.33	5.47	11.25	>.05
Position	38.74	16.15	19.25	12.59	20.83	17.88	45.83	7.78	7.34	>.05
Recall	3.37	1.34	1.92	2.02	0.50	0.84	2.33	2.73	4.65	>.05
Cue	4.63	1.01	2.92	1.78	3.00	1.41	3.33	2.07	4.22	>.05
Recognition	27.47	3.13	22.08	8.30	24.60	4.62	27.33	1.97	2.90	>.05
BVRT										
Correct	6.33	1.20	4.35	1.87	5.38	2.45	5.50	1.05	4.48	>.05
Error	9.05	15.74	9.82	4.53	8.50	5.37	6.33	1.51	0.16	>.05

TO: Temporal Orientation; OPIP: Orientation to Personal Information and Place; WSL: Word Sequence Learning-Revised; BVRT: Benton Visual Retention Test

Table 3-1. Visual Perception Test Performance of Subject Groups(1st year evaluation)

	Gp1		Gp2		Gp3		Gp4		F/H(ANCOVA)	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
JLO	19.48	5.57	17.84	5.13	17.41	5.23	21.23	4.25	1.33	>.05
3-DBC										
Correct	28.44	2.03	28.44	1.56	26.75[ab]	3.44	28.88[c]	0.52	4.88	<.05
FRT	40.05	5.05	38.17	5.54	36.56	5.49	41.44	4.61	2.29	>.05

JLO: Judgement of Line Orientation; 3-DBC: Block Construction-Model; FRT: Facial Recognition Test

Table 3-2. Visual Perception Test Performance of Subject Groups (1st year follow-up)

	Gp1		Gp2		Gp3		Gp4		F/H(ANCOVA)	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
JLO	19.24	5.59	14.93	4.54	21.14	5.46	20.33	5.79	1.93	>.05
3-DBC										
Correct	29.00	0.00	27.65	2.76	27.13	3.48	27.67	2.80	1.15	>.05
FRT	37.05	3.85	35.63	5.68	34.88	2.53	41.67	4.08	2.82	>.05

JLO: Judgement of Line Orientation; 3-DBC: Block Construction-Model; FRT: Facial Recognition Test

Table 4-1. Core Linguistic Test Performance of Subject Groups(1st year evaluation)

	Gp1		Gp2		Gp3		Gp4		F/H(ANCOVA)	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
TT	41.23	2.21	39.27[a]	3.94	38.22	4.28	42.08[bc]	1.61	5.54	<.05
VN	53.96	5.01	53.35	4.53	52.56	5.12	55.82	4.83	0.39	>.05

TT: Token Test; VN: Visual Naming

Table 4-2. Core Linguistic Test Performance of Subject Groups (1st year follow-up)

	Gp1		Gp2		Gp3		Gp4		F/H(ANCOVA)	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
TT	40.90	1.97	36.53	10.28	37.89	3.66	40.67	1.97	0.53	>.05
VN	55.05	3.72	50.94	5.20	52.22	7.38	53.33	4.68	0.19	>.05

TT: Token Test; VN: Visual Naming

Table 5-1. Frontal Lobe Function Test Performance of Subject Groups(1st year evaluation)

	Gp1		Gp2		Gp3		Gp4		F/H(ANCOVA)	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
WCST-M										
No. of complete categories	4.06	2.06	3.52	1.95	2.27	1.44	4.88[c]	1.99	4.57	<.05
No. of preservative errors	5.81	6.27	7.21	6.56	11.40	9.63	5.60	7.59	1.55	>.05
No. of non-preservative errors	10.15	5.54	11.19	5.58	11.53	5.24	7.12[b]	4.67	3.98	<.05
No. of unique errors	1.13	1.81	2.13	2.57	0.93[b]	1.79	1.20	1.71	2.82	<.05
Trail Making A (sec.)	58.87	25.85	100.38	69.71	156.56[a]	191.39	49.71[c]	22.74	6.86	<.05
Trail Making B (sec.)	194.52	160.18	216.36	148.69	418.27[ab]	260.66	115.57[c]	61.50	9.13	<.05
VF	34.25	7.31	33.54	10.00	31.94	8.61	38.12	7.30	2.54	>.05
Similarity (WAIS-R)	8.16	2.90	7.60	2.92	6.78	2.82	9.80	3.37	1.07	>.05
Digit Span(forward-backward	3.13	1.32	2.85	1.43	2.94	1.51	3.03	1.33	0.71	>.05

WCST-M: Wisconsin Card Sorting Test-Modified; VF: Semantic Association of Verbal Fluency

Table 5-2. Frontal Lobe Function Test Performance of Subject Groups (1st year follow-up)

	Gp1		Gp2		Gp3		Gp4		F/H(ANCOVA)	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
WCST-M										
No. of complete categories	4.25	1.77	3.63	2.62	4.17	1.33	6.67	0.52	4.42	<.05
No. of preservative errors	4.40	3.56	7.63	6.65	5.33	6.62	2.33	2.42	1.27	>.05
No. of non-preservative errors	9.75	4.48	9.75	5.34	10.50	4.85	3.67	2.34	3.89	<.05
% of preservative errors	2.70	4.99	2.13	1.55	1.33	1.37	0.00	0.00	0.93	>.05
Trail Making A (sec.)	61.33	29.23	116.20	74.24	112.25	33.74	46.67	21.21	3.85	<.05
Trail Making B (sec.)	160.17	93.11	219.60	106.48	289.00	109.42	172.80	92.61	1.77	>.05
VF	31.29	8.19	30.82	11.29	23.78	10.65	38.67	9.46	2.61	>.05
Similarity (WAIS-R)	9.57	2.42	6.88	1.90	9.22	3.80	10.83	3.60	2.19	>.05
Digit Span(forward-backward	2.76	1.45	3.29	0.85	3.00	1.50	3.60	1.52	0.98	>.05

WCST-M: Wisconsin Card Sorting Test-Modified; VF: Semantic Association of Verbal Fluency

Table 6-1. Emotional Status Measure Performance of Subject Groups(1st year evaluation)

	Gp1		Gp2		Gp3		Gp4		F/H(ANCOVA)	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
BDI	9.93	7.46	10.38	8.28	15.71	11.35	5.51 [abc]	6.49	7.07	<.05
SCL-90-R										
Somatization	0.72	0.47	0.66	0.41	0.83	0.66	0.37 [abc]	0.33	24.07	<.05
Obsessive-compulsive	0.70	0.47	0.62	0.43	0.54	0.38	0.44 [a]	0.38	11.59	<.05
Depression	0.63	0.49	0.62	0.46	0.70	0.57	0.38 [ab]	0.37	14.38	<.05
Anxiety	0.58	0.43	0.47	0.40	0.36	0.32	0.20 [abc]	0.25	38.46	<.05

BDI: Beck Depression Inventory; SCL-90R: Symptom Checklist-90-R

Table 6-2. Emotional Status Measure Performance of Subject Groups (1st year follow-up)

	Gp1		Gp2		Gp3		Gp4		F/H(ANCOVA)	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
BDI	7.70	6.91	8.32	7.11	11.88	4.64	4.33	8.73	1.52	>.05
SCL-90-R										
Somatization	0.50	0.33	0.75	0.36	0.93	0.63	0.58	0.65	8.22	<.05
Obsessive-compulsive	0.55	0.43	0.54	0.40	0.59	0.25	0.60	0.70	0.57	>.05
Depression	0.48	0.36	0.61	0.47	0.81	0.45	0.54	0.64	3.96	>.05
Anxiety	0.42	0.35	0.36	0.42	0.49	0.29	0.35	0.51	0.69	>.05

BDI: Beck Depression Inventory; SCL-90R: Symptom Checklist-90-R

Table 7-1. Emotional Status Measure Performance of Significant Informant Groups(1st year evaluation)

	Gp1		Gp2		Gp3		Gp4		F/H(ANCOVA)	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
BDI	6.88	4.84	11.08[a]	7.39	15.21[a]	7.50	3.24[abc]	3.87	25.39	<.05
SCL-90-R										
Somatization	0.61	0.43	0.81	0.51	1.20[a]	0.68	0.27[abc]	0.33	45.83	<.05
Obsessive-compulsive	0.46	0.45	0.70[a]	0.46	1.09[a]	0.83	0.28[bc]	0.35	34.20	<.05
Depression	0.51	0.38	0.81	0.51	1.15[a]	0.66	0.27[bc]	0.37	44.72	<.05
Anxiety	0.43	0.42	0.53	0.43	1.07	0.92	0.17[abc]	0.28	36.50	<.05

Table 7-2. Emotional Status Measure Performance of Significant Informant Groups (1st year follow-up)

	Gp1		Gp2		Gp3		Gp4		F/H(ANCOVA)	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
BDI_F	5.35	4.60	11.18	10.39	13.29	5.38	0.17	0.41	5.47	<.05
SCL-90-R										
Somatization	0.44	0.44	0.83	0.54	1.38	0.63	0.17	0.00	12.82	<.05
Obsessive-compulsive	0.42	0.32	0.72	0.50	1.09	0.66	0.40	0.00	6.38	>.05
Depression	0.48	0.36	0.80	0.53	1.07	0.76	0.38	0.00	5.24	>.05
Anxiety	0.32	0.23	0.53	0.41	0.89	0.62	0.10	0.00	10.21	<.05

Table 8-1. The Examiner's Rating Scores on the Emotional Status Interview Scales(1st year evaluation)

	Gp1		Gp2		Gp3		Gp4		F/H(ANCOVA)	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Depression	0.30 [bc]	0.39	0.51 [c]	0.55	1.01	0.82	0.05 [abc]	0.18	50.55	<.05
Anxiety	0.57	0.69	0.44	0.68	0.11 [ab]	0.21	0.12 [ab]	0.41	26.46	<.05

Table 8-2. The Examiner's Rating Scores on the Emotional Status Interview Scales (1st year follow-up)

	Gp1		Gp2		Gp3		Gp4		F/H(ANCOVA)	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Depression	1.43	2.80	5.06	8.56	2.75	6.02	0.00	0.00	34.23	<.05
Anxiety	0.67	1.46	3.63	8.15	1.38	3.89	0.00	0.00	28.67	<.05