# Depression and Quality of Life in Stroke:

# A Magnetic Resonance Imaging Study

**LU, Jinyan**

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ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 - 1346

# DECLARATION OF ORIGINALITY

The work contained in this thesis is original research carried out by the author in the Department of Psychiatry, Faculty of Medicine, the Chinese University of Hong Kong. No part of the thesis has been submitted to other universities or institutions for the purpose of being awarded a degree or diploma.

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# PUBLICATIONS AND PRESENTATIONS

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2. WK Tang, YK Chen, **JY Lu**, CCW Chu, VCT Mok, GS Ungvari, KS Wong. White Matter Hyperintensities in Poststroke Depression: a Case-Control Study. *Journal of Neurology, Neurosurgery, and Psychiatry* 2010 Dec; 81(12):1312-5.
3. Tang WK, **Lu JY**, Chen YK, Chu WC, Mok V, Ungvari GS, Wong KS. Association of frontal subcortical circuits infarcts in poststroke depression: a magnetic resonance imaging study of 591 Chinese patients with ischemic stroke. *J Geriatr Psychiatry Neurol.* 2011 Mar; 24(1): 44-9. Epub 2010 Dec 31.
4. Tang WK, Chen YK, **Lu JY**, Ahuja AT, Chu WC, Mok VC, Ungvari GS, Xiang YT, Wong KS.Cerebral microbleeds and quality of life in acute ischemic stroke. *Neurol Sci.* 2011 Jun;32(3):449-54. Epub 2011 Apr 9.

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5. WK Tang, YK Chen, **JY Lu**, VCT Mok, YT Xiang, GS Ungvari, AT Ahuja, KS Wong. Microbleeds and post-stroke emotional lability. *Journal of Neurology, Neurosurgery, and Psychiatry* 2009; 80:1082-86.

6. WK Tang, **JY Lu**, HJ Liang, TT Chan, VCT Mok, Ungvari GS, KS Wong. Is insomnia associated with suicidality in stroke? *Archives of Physical Medicine and Rehabilitation (in press)*
7. An FR, Xiang YT, **Lu JY**, Lai KY, Ungvari GS. Falls in a psychiatric institution in Beijing, China. *Perspect Psychiatr Care*. 2009 Jul; 45(3): 183-90.
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    Is fatigue associated with short-term health-related quality of life in stroke? *Arch Phys Med Rehabil* 2010 Oct; 91(10): 1511-1515.
12. Yang-Kun Chen, **Jin-Yan Lu**, DML Chan, M Au Yeung, Vincent CT Mok, Ka Sing Wong, Gabor S Ungvari, Wai Kwong Tang. Anxiety disorders in Chinese patients with Parkinson's disease. *International Journal of Psychiatry in Medicine* 2010;40(1):97-107.
13. Yangkun Chen, **Jinyan Lu**, Ka Sing Wong, Vincent CT Mok, Gabor S Ungvari, Wai Kwong Tang. Health-related quality of life in the family caregivers of stroke survivors. *International Journal of Rehabilitation Research*.2010 Sep; 33(3): 232-237
14. Yang-Kun Chen, **Jin-Yan Lu**, Vincent CT Mok, GS Ungvari, Winnie CW Chu, Ka Sing Wong, Wai Kwong Tang. Clinical and radiological correlates of insomnia symptoms in ischemic stroke patients. *International Journal of Geriatric Psychiatry* 2011 May;26(5):451-7

## Presentations in academic conferences

## Oral presentations

1. **JY Lu**, Tang WK, Chen YK, Mok V, Chu WC, Ungvari GS, Ahuja AT, Wong KS. Acute basal ganglia infarcts in poststroke fatigue: an MRI study. CUHK-Mayo Clinic-Asia Cardiovascular Summit, Hong Kong, March 2011
2. Y Chen, **JY Lu**, VCT Mok, KS Wong, WK Tang. Vascular Cognitive impairment in Chinese Ischemic Stroke patients. Fourth International Symposium on Healthy Aging, Hong Kong, March 2009 (p. 55).
3. Y Chen, **JY Lu**, VCT Mok, AT Ahuja, KS Wong, WK Tang. Correlates of fatigue after acute ischemic stroke in Chinese population. CUHK Mayo Clinic-Asia Cardiovascular Summit, Hong Kong, 18-19 April 2009.
4. Y Chen, **JY Lu**, VCT Mok, KS Wong, WK Tang. Vascular Cognitive impairment in Chinese Ischemic Stroke patients. CUHK Mayo Clinic-Asia Cardiovascular Summit, Hong Kong, 18-19 April 2009.

## Poster presentations

1. **Lu JY**, Chen Y, Tang NLS, Wong LKS, Lam WWM, Mok VCT, Tang WK. A pilot study on the 5-Hydroxytryptamine 1A receptor gene polymorphism in post-stroke fatigue. CUHK Mayo Clinic-Asia Cardiovascular Summit, Hong Kong, 18-19 April 2009.
2. **Lu JY**, Chen YK, Ungvari GS, Mok Vincent CT, Ahuja AT; Chu WCW, Wong KS, Tang WK. Acute basal ganglia infarcts in poststroke fatigue: an MRI study. The seventh Asia Pacific Multidisciplinary Meeting for Nervous System Diseases. Hong Kong, January 2010.
3. Y Chen, **JY Lu**, VCT Mok, KS Wong, WK Tang. Vascular Cognitive impairment in Chinese Ischemic Stroke patients. Fourth International Symposium on Healthy Aging, Hong Kong, March 2009 (p. 55).

4. YK Chen, V Mok, KS Wong, GS Ungvari, **JY Lu**, WK Tang. Anxiety disorders in Chinese patients with Parkinson's disease. Movement Disorder Society (MDS) 13th International Congress of Parkinson's disease and Movement Disorders, Paris, 8 June 2009. *Movement Disorders* 2009; 24 (suppl 1).
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6. Chen YK, **Lu JY**, Xiong YY, Mok Vincent CT, Ahuja AT, Chu WCW, Wong KS, Tang WK. Cognitive impairment in Chinese stroke patients: a one-year follow-up study. The seventh Asia Pacific Multidisciplinary Meeting for Nervous System Diseases. Hong Kong, January 2010.
7. YK Chen, **JY Lu,** L Shi, DF Wang, WCW Chu, VCT Mok, KS Wong, WK Tang. Atrophy of left dorsalateral prefrontal cortex contributes to verbal fluency impairment in elderly stroke women. XXVII CINP Congress. Hong Kong, June, 2010.

## LIST OF ABBREVIATIONS

| | |
|---|---|
| **ANCOVA** | Analysis of Co-variance |
| **ASU** | Acute Stroke Unit |
| **CMBs** | Cerebral Microbleeds |
| **CT** | Computed Tomography |
| **DSM** | Diagnostic Statistical Manual for Mental Disorder |
| **DSMIV** | Diagnostic and Statistical Manual, Fourth Edition |
| **GDS** | Geriatric Depression Scale |
| **HAD** | Hospital Anxiety and Depression Scale |
| **HT** | Hypertension |
| **MLES** | Modified Life Event Scale |
| **MMSE** | Mini-mental State Examination |
| **MRI** | Magnetic Resonance Imaging |
| **NIHSS** | National Institute of Health Stroke Scale |
| **PSD** | Poststroke Depression |
| **PWH** | Prince of Wales Hospital |
| **QOL** | Quality of Life |
| **SPSS16.0** | Statistical Package for the Social Sciences, version 16.0 |
| **WHO** | World Health Organization |
| **WMLs** | White Matter Lesions |

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## ABSTRACT

Abstract of thesis entitled

*Depression and Quality of Life in Chinese Stroke patients:*

*A Magnetic Resonance Imaging Study*

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Poststroke behavioral consequences are common in stroke survivors, often leading to poor prognosis. Up-to-date data on and imaging analyses of poststroke behavioral consequence remain limited in Chinese populations.

Cerebral microbleeds (CMBs) are common in stroke survivors, although their clinical significance in the development of psychiatric conditions following stroke remains unknown. This study examines the association between post-stroke depression (PSD) symptom severity and CMBs. Amongst the 4088 patients with acute ischemic stroke who had been admitted to the acute stroke unit of a university-affiliated regional hospital in Hong Kong, between December 2004 and May 2009, 994 patients were recruited. A psychiatrist administered the Structural Clinical Interview for DSM-IV to all 994 patients and made a diagnosis of PSD three months after the index stroke. PSD symptom severity was assessed with the 15-item Geriatric Depression Scale (GDS). Seventy-eight patients were found to have PSD. The presence and location of CMBs were evaluated with magnetic resonance imaging (MRI). Seventy-eight patients (7.8%) had PSD. CMBs were identified in 20 PSD patients. Relative to the no-CMB group, the mean GDS score of patients with lobar CMBs was significantly higher (12.6+2.6 versus 10.4+2.5, p=.01 after adjusting for age, sex, global cognitive functions, neurological deficits and white matter hyperintensities). The results suggest that lobar CMBs may contribute to PSD symptom severity. The importance of CMBs in the pathogenesis of other psychiatric disorders in stroke survivors and other patient populations warrants further investigation.

Poststroke depression (PSD) is the most common form of poststroke psychiatric morbidity. Despite extensive research on poststroke depression (PSD), the role of white matter hyperintensities (WMHs) in its pathogenesis remains uncertain. To address this gap, a cohort of 994 patients with acute ischemic stroke admitted to the acute stroke unit of a university-affiliated

regional hospital in Hong Kong was recruited. A psychiatrist administered the Structural Clinical Interview for DSM-IV to all patients and made a diagnosis of PSD 3 months after the index stroke. Seventy-eight (7.8%) patients had PSD; 78 stroke patients matched according to age and sex but without PSD served as a control group. The severity and location of WMHs were evaluated with magnetic resonance imaging (MRI). In comparison with the non-PSD group, patients in the PSD group were more likely to have severe deep WMHs (12.8% vs. 1.3%; p=0.009). Severe deep WMHs remained an independent predictor of PSD in the multivariate analysis, with an odds ratio of 13.8 (p=0.016). The results suggest that WMHs may play a role in the development of PSD.

Despite extensive research into poststroke depression (PSD), the role played by lesion location in the pathogenesis of PSD remains uncertain. The aim of this study was to estimate the magnetic resonance imaging (MRI) correlates of PSD in Chinese patients with first or recurrent stroke. A total of 591 patients with acute ischemic stroke admitted to the acute stroke unit of a university-affiliated regional hospital in Hong Kong were recruited. A psychiatrist assessed all the patients 3 months after the stroke. The psychiatrist used the Structured Clinical Interview for Diagnostic and Statistical Manual, fourth edition (DSM-IV) to confirm whether the patients met the criteria of a depressive disorder. In addition, a host of demographic, clinical, and radiological variables were examined. A total of 475 and 116 patients had first and recurrent strokes, respectively. In all, 75 (12.7%) patients received a diagnosis of PSD. In univariate analysis of the MRI findings, the presence of infarcts in the frontal subcortical circuits ([FSC], 66.7% vs 53.3%) was significantly associated with PSD (P = .03) compared to the patients without PSD. The FSC infarct-PSD association remained significant (odds ratio = 2.6) in subsequent logistic regression

analysis after adjusting for gender, history of depression, neurological impairment, level of social support, and major life events.

No data have been published on the impact of CMBs on the HRQoL of stroke patients, and hence their effect on HRQoL in stroke remains unknown. This study evaluated the impact of cerebral microbleeds (CMBs) on the health-related quality of life (HRQoL) in 458 Chinese patients with first or recurrent acute ischemic stroke. HRQoL was assessed with the Short Form-36 (SF-36). Univariate analysis showed the presence of lobar CMBs to be negatively correlated with patients' physical functioning (PF; $p < 0.01$), social function (SF; $p < 0.01$), and role-emotional (RE; $p < 0.05$) scores. Subsequent linear regression analysis revealed lobar CMBs to be independently associated with the PF and SF scores ($p < 0.05$). The study's findings suggest that CMBs have a significant impact on the HRQoL of stroke survivors.

This thesis investigates the clinical and imaging characterization of depression and quality of life in Chinese stroke patients. The conclusions of the studies reported herein can be summarized as follows. (1) The lobar CMBs may contribute to PSD symptom severity; (2) WMHs may play a role in the development of PSD; (3) FSC infarcts are independent predictors of PSD; and (4). The CMBs have a significant impact on the HRQoL of stroke survivors.

## 摘 要

腦卒中後行為障礙在腦卒中存活者中十分常見，是導致預後不良的因素。到目前為止，在中國人群中，具有神經影像學分析的腦卒中後行為障礙的研究仍然十分有限。本研究旨在探討中國腦卒中患者卒中後行為的臨床與影像學特徵。

抑鬱是腦卒中後最常見的精神障礙。大腦微出血在中風後常見，但目前尚無研究探討在大腦微出血制與卒中後抑鬱的關系。我們納入了994缺血性腦卒中患者進行抑鬱的評估，並測量MRI中大腦微出血的分佈和數目。結果顯示，78例（7.8%）患者有抑鬱障礙。大腦微出血組的抑鬱分數明顯高於無大腦微出血者 （12+2.6 vs 10.4+2.5, p=0.01），顯示丘腦微出血是腦卒中後抑鬱障礙的危險因素。

在腦卒中後抑鬱的研究中，亦尚無研究探討在大腦白質病變與卒中後抑鬱的關系。我們納入了994例缺血性腦卒中患者進行抑鬱的評估，並測量MRI中大腦白質高信號的分佈和數目。結果顯示，78例（7.8%）患者有抑鬱障礙。抑鬱障礙組的大腦白質病變的比例明顯高於無抑鬱組（ 12.8% vs 1.3%, p=0.009），顯示大腦白質病變可能與腦卒中後抑鬱障礙的發生有關。

為了研究腦卒中後抑鬱與病發位置的關係，我們納入了591例缺血性腦卒中患者進行抑鬱評估和MRI的測量，75例（12.7%）患者有抑鬱障礙。抑鬱患者額葉梗死的比例明顯高於無抑鬱患者（66.7% vs 53.3%，p=0.03)。Logistic 回歸顯示，額葉梗死是腦卒中後抑鬱障礙的獨立危險因素（OR=2.6)。研究結果提示了額葉梗死可能與腦卒中後抑鬱障礙的發生有關，額葉梗死對卒中後精神障礙的影響有待進一步研究。

最後，我們研究了在腦卒中患者中，大腦微出血是否影響到患者的生存品質。我們分析了458例腦卒中患者的MRI，使用SF-36來評估患者的生存品

質，Linear回歸顯示：大腦微出血是生存品質低分的危險因素，提示了大腦微出血可能會嚴重影響到腦卒中患者的生存品質。

本研究探討了中國人群中腦卒中行為障礙的臨床與影像學特徵。本研究的結論為：（1）丘腦微出血與腦卒中後抑鬱障礙的發生有關；（2）大腦白質病變與腦卒中後抑鬱障礙的發生有關；（3）額葉病變可能對卒中後抑鬱有影響；（4）大腦微出血可能會嚴重影響到腦卒中患者的生存品質。

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# CHAPTER 1 INTRODUCTION AND LITERATURE REVIEW

## 1. Defining the Problem

### 1.1. An overview of stroke

The World Health Organization (WHO) defines stroke as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting for 24 hours or more or leading to death, with no apparent cause other than vascular origin" (WHO, 1988). Stroke is the third commonest cause of death in most countries of the world and the second leading cause in developing countries (R. Bonita, S. Mendis, *et al*, 2004; L.R Caplan 2000), and the first leading cause in China (Prc Ministry of Public Health, 2008) in both urban and rural areas. In 2005, there were 5.7 million fatal strokes worldwide, and more than 1.4 million of these occurred in China (K. Strong, C. Mathers & R. Bonita, 2007). The overall incidence rate of stroke is around 2.0 to 2.5 per thousand populations, and the total prevalence rate is around 5 per thousand populations (Wolfe Cd, 2000). The global stroke death toll is expected to reach 7.8 million in 25 years' time if the current trend continues (K. Strong, C. Mathers & R. Bonita, 2007). Annual stroke mortalities in Hong Kong consistently number above 3,000 (Ng Pw, 2007).

Among developing countries, China has the largest population (with one-fifth of the world's population). Chronic diseases now account for an estimated 80% of deaths and 70% of disability-adjusted life-years lost in China. The major causes of death in China are vascular disease, cancer, and chronic respiratory disease. Unlike in western countries, cerebrovascular

disease predominates; the number of patients who die from stroke is more than three times that from coronary heart disease (M. Liu, B. Wu, *et al*, 2007). In the past 20 years, China has experienced a rapid economic development. Over time, the proportion of elderly people in the population will likely increase, life expectancies will lengthen, and, as in some other developing countries, the influence of a westernized lifestyle might shift disease patterns towards a profile more similar to that seen in more developed regions, so the numbers of stroke would rise (M. Liu, B. Wu, W. Z. Wang, *et al*, 2007).

The overall risk of recurrent stroke after first-ever ischaemic stroke is about 2% at one week, 4% at one month, 12% at one year, and 30% at 5 years in western countries (S. Macmahon & A. Rodgers, 1996). More recent studies showed the true risk of stroke after TIA or minor stroke is up to 10% at one week and 20% at one month (P. M. Rothwell, 2005). Few data are available for accurate stroke recurrence rates in China.

Previous study reported the annual age-adjusted incidence of stroke was 76.1-150 per100, 000 which was conducted in three large cities in mainland China from 1991-2000 (B. Jiang, W. Z. Wang, *et al*, 2006). It is thus estimated that 1.5-2 million new strokes occur in China every year. In hong kong, statistics from the Hospital Authority show that annual stroke admissions to public hospitals have surged to 20,000 (Ng Pw, 2007). Stroke patients take up nearly half of all of the government nursing home places in Hong Kong (J. Woo, R. Kay, *et al*, 1992). With the aging of the population across China, society can no longer afford to ignore stroke.

Stroke has an enormous adverse impact on patients, their families, and society as a whole, and is the leading cause of long-term disability (R. Bonita, R. Beaglehole & K. Asplund, 1994). One year after a stroke, 65% of surviors are functionally independent. The majorities of stroke survivors lives in the community, and frequently use long-term professional care (C. D. Wolfe, K.

Tilling & A. G. Rudd, 2000). The partners of stroke patients perceive most of the caregiving burden in terms of feeling of heavy responsibility, constant worries, restraints social life (W. J. Scholte Op Reimer, R. J. De Haan, *et al*, 1998). A study conducted in Hong Kong showed that more than 50% of stroke patients were unable to live independently one year after the index stroke (R. S. Lo, J. O. Cheng, *et al*, 2008). Stroke often precludes patients from returning to work or regaining their role within the family. It also represents a great burden to the family, especially if the patient is dependent on a family member as his or her caregiver. Both the stroke survivor's and the caregiver's quality of life is adversely affected (W. J. Scholte Op Reimer, R. J. De Haan, P. T. Rijnders, *et al*, 1998).

A few studies reported the proportion of different types of stroke in China. Early studies showed that cerebral infarction acounted for 48.6–51.0% of total strokes, and intracerebral haemorrhage for 44.0–44.7%, subrachnoid haemorrhage for 2.0–3.9%, and undetermined type for 2.8–3.0% (Xm Cheng and Sc Li Et Al. Cc Wang, 1985; S. C. Li, B. S. Schoenberg, *et al*, 1985; M. Liu, B. Wu, W. Z. Wang, *et al*, 2007). Since in these studies few patients had CT or MRI scanning, the results might not be reliable. The development of neuroimaging techniques, especially magnetic resonance imaging (MRI), and angiography techniques has greatly helped clinicians to identify the accurate location of infarctions and has shed light on the mechanisms of stroke. In recents studies, the propotion of stroke types varied from 43.7-78.9% cerebral infarction to 18.8-47.6% intracerebral haemorrhage (B. Jiang, W. Z. Wang, H. Chen, *et al*, 2006; L. F. Zhang, J. Yang, *et al*, 2003). Of the stroke subtypes among the Chinese, most are ischemic stroke (X. Liu, G. Xu, *et al*, 2006), for which hypertension, diabetes mellitus, hyperlipidemia, smoking, and heart disease are the common risk factors. Measures aimed at the primary prevention of stroke, which focus on controlling the risk factors, have successfully reduced the

incidence of stroke in a number of large clinical trials (R. E. Gilbert, G. Jerums & M. E. Cooper, 1996; S. Macmahon & A. Rodgers, 1996) and secondary prevention measures, e.g., antiplatelet therapy and statin treatment, have successfully reduced its recurrence. Advances in the treatment of acute-phase stroke, e.g., antiplatelet therapy thrombolysis using a recombinant tissue-type plasminogen activator (r-TPA) within three to half and four hours, and the therapy employed in a stroke unit, have also led to reduced mortality in the acute phase of stroke and to reduced disability (S. Macmahon & A. Rodgers, 1996).

Results of a randomized trial suggest that treatment with tissue plasminogen activator (tPA) given 3 to 4.5 hours after symptom onset can still provide "modest but significant" improvement in clinical outcomes after an acute ischemic stroke vs placebo. The trial, the third European Cooperative Acute Stroke Study (ECASS 3), showed that although symptomatic intracerebral hemorrhage was higher in treated patients, the rate was not higher than reported previously in patients treated within the currently approved 3-hour window and was not associated with increased mortality rates.

However, chronic complications following stroke, such as behavioral consequences, which is also important in rehabilitation, have received less attention from clinicians. Aside from their strong association with stroke severity, these complications can also occur in independent stroke survivors.

## 1.2. Poststroke Depression

### 1.2.1. Historical Background

In the early 1900s, leading psychiatrists began to acknowledge important clinical association between manic-depressive insanity and cerebrovascular disease. In the eight edition of his textbook, Kraepelin (1921) wrote "the diagnosis of states of depression may, apart from the distinctions discussed, offer difficulties especially when the possibility of atherosclerosis has to be taken into consideration. It may, at a time, be an accompanying phenomenon of manic depressive insanity but at another time may itself engender states of depression." Similarly, it was stated by Bleuler (1911/1950) that depression following stroke could become chronic, and observed that, "melancholic moods lasting for months and sometimes longer appear frequently."

Post (1962) commented that the association between brain ischemia and the first episode of depressive disorder in the elderly was so common that it suggested that the causes of atherosclerotic disease and depression may be "etiologically linked." Hurwitz (1963) commented that the discouragement and frustration that is caused by disability could themselves impede recovery from stroke.

Steffens DC (K. R. Krishnan, W. D. Taylor, *et al*, 2004)proposed that the diagnostic criteria for vascular depression should have two key elements: 1) presence of major depression and 2) presence of "sufficient" cerebrovascular disease on neuroimaging. Steffens suggested that the presence of any of the following may be regarded as sufficient cerebrovascular disease: a score of 2 or more on periventricular white matter hyperintensity, deep white matter hyperintensity or subcortical gray matter. Krishnan et al. (2004) proposed that the term subcortical ischemic vascular depression as a subtype of vascular depression and found that lassitude and a history of hypertension were also positively associated with the diagnosis; a family history of mental illness and loss of libido were negatively associated with the diagnosis.

## 1.2. 2. Impact of Poststroke Depression on Stroke Survivors

Depression is common among stroke patients, with its prevalence estimated to be between 7.8% and 60% (W. W. Eaton, M. Badawi & B. Melton, 1995). This wide range in PSD estimates is due to differences in research methods and samples. Longitudinal studies have suggested the prevalence of PSD increases within two to three years after stroke (Astrom et al., 1993), but data on PSD in Chinese populations are limited. Tang et al. (2005) investigated 189 consecutive Chinese patients from an acute hospital and found 16.4% of them to experience some type of depression (DSM-IV criteria) at three months after the index stroke. PSD is associated with the impaired recovery of cognitive function (M. Astrom, R. Adolfsson & K. Asplund, 1993; R. G. Robinson, P. L. Bolduc & T. R. Price, 1987) and the activities of daily living (T. Pohjasvaara, A. Leppavuori, *et al*, 1998). Patients with diagnoses of major or minor depression after stroke are 3.4 times more likely to die within 10 years of a stroke than are non-depressed patients (P. L. Morris, R. G. Robinson, *et al*, 1993).

Most recent studies that have examined the prevalence or other aspects of PSD have employed structured interviews and operationalized diagnostic criteria. Categories of depressive disorders that are commonly applied to patients with stroke include major depressive episode [hereafter referred to as major depression (MD)] dysthymia, and adjustment disorder with depressed mood (ADDM). In the majority of studies, the diagnosis of depression is made according to the Diagnostic and Statistical Manual of Mental Disorders Third Edition Revised (DSM-III-R; American Psychiatric Association 1987) or the DSM-IV criteria. In some recent studies, minor depression, which is a research category in the DSM-IV, has also been also diagnosed. Minor depression represents a less severe form of depression, and is defined by at

least two but less than five symptoms of major depression, which include either depressed mood or loss of interest as the core symptoms. In earlier studies, the DSM-III or DSM-III-R criteria for dysthymia were used to define minor depression, and the duration criterion of at least 2 years was ignored (R. G. Robinson, P. L. Bolduc & T. R. Price, 1987).

PSD may increase the long term mortality following a stroke. Morris et al. (P. L. Morris, R. G. Robinson, P. Andrzejewski, *et al*, 1993) conducted a 10-year follow up of 103 patients. The subjects were assessed for PSD approximately 2 weeks after stroke, and mortality was determined for 91 of them 10 years later. Patients with a diagnosis of PSD at initial assessment were 3.4 times more likely to die during the follow-up period than the nondepressed patients, and this relationship was independent of other measured risk factors such as age, gender, social class, type of stroke, lesion location, and level of social functioning. In a recent attempt to replicate the aforementioned findings, House et al. (A. House, P. Knapp, *et al*, 2001) found that it was the severity of mood symptoms as measured by the General Health Questionnaire (GHQ; Goldberg 1972) at 1-month poststroke, rather than the DSM-III-defined major depression, that significantly correlated with the mortality 24 months after the index stroke.

It is important to identify those at risk of PSD. Its risk factors have been found to include functional and cognitive impairment, a previous history of depression and stroke, being female, an older age, hypercortisolism, and poor social support (Terroni et al., 2003). Many studies have attempted to find the neuroanatomic correlates of PSD. Despite extensive research, however, the role of infarct location in PSD pathogenesis remains uncertain (Astrom et al., 1993; Herrmann et al., 1995; Vataja et al., 2004). In meta-analysis of 34 primary studies (Carson et al., 2000), no association was found between lesion location and PSD. Differences in depression measurement, study design, and presentation of the results may have contributed to the heterogeneity of the

findings (Sanjit et al., 2004), although some studies have suggested that lesions involving the structures of the frontal-subcortical circuits (FSC) (Vataja et al., 2004; Tang et al., 2005; Hama et al., 2007) may be more likely to produce PSD. Evidence obtained using the Xenon inhalation method also indicates that regional cerebral hypoperfusion may be a possible mechanism (Yamaguchi et al., 1992).

PSD treatment has been examined in several placebo-controlled, randomized clinical trials with nortriptyline, citalopram, and sertraline and shown their efficacy (J. R. Lipsey, W. C. Spencer, *et al*, 1986) The progression of recovery following stroke can be altered by treating depression, and such treatment has also been shown to improve recovery in activities of daily living and cognitive impairment and to decrease mortality (A. J. Carson, S. Machale, *et al*, 2000).

## 1.3. The health related quality of life in stroke

Stroke is known to affect heavily health related quality of life (HRQoL) with special regard to physical and psychosocial factors.

Quality of Life (QoL) assessment has been an important part of the evaluation of stroke patients and their treatment for more than 30 years. QoL is difficult to define and no universal definition of this term exists. However, there is a general agreement that QoL is a multi–dimensional construct that consists of at least three broad domains: physical, mental and social. Researchers and physicians have often used the health–related quality of life concept in the field of medicine, which specifically focuses on the impact of an illness and/or the treatment on the patients' perception, of their status of health, and, on subjective well–being or satisfaction with life. (K. Jaracz & W. Kozubski, 2003)

The impact of stroke on health related quality of life may be disastrous; stroke can affect multiple domains of life. To assess these consequences several instruments have been developed. Most of them are questionnaires based on a patient's subjective self–report or self–evaluation. Some of these tools provide information about perceived health status, for example: physical and mental functions, ability to perform everyday activities/roles or the limitation in performing these activities/roles. The other scales capture an assessment of well–being or positive/negative evaluation of particular life domains or satisfaction with life (or specific life domains). There are also questionnaires which produce both information about perceived health status and subjective evaluation (1990).

# CHAPTER 2 OBJECTIVES AND RECRUITMENT OF THE STUDY PARTICIPANTS

## 2.1. Objectives

1) To examine the role of cerebral microbleeds (CMBs) in PSD. We hypothesized that CMBs play a role in the development of PSD.

2) To explore the effect of White matter hyperintensities (WMHs) in PSD. We hypothesized that WMHs play a role in the development of PSD.

3) To examine if Frontal Subcortical Circuits (FSC) infarcts are independent predictors of PSD. We hypothesized the FSC infarcts does.

4) To study if CMBs have a significant impact on the HRQoL of stroke survivors. We hypothesized the CMBs play a role in effecting the HRQoL.

## 2.2. Participants:

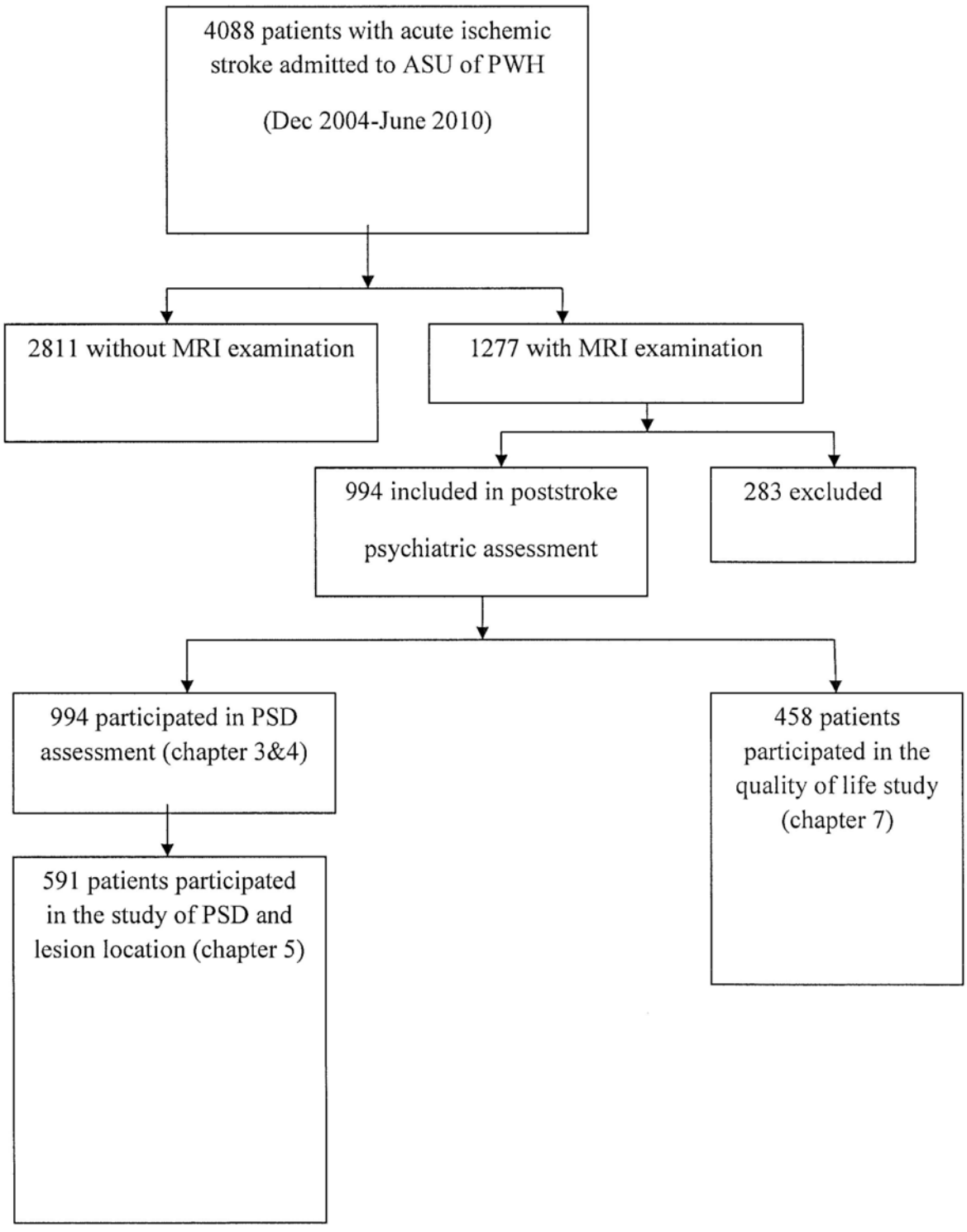
The study participants were all recruited from the Acute Stroke Unit (ASU) of the Prince of Wales Hospital (PWH), a university-affiliated general hospital serving a population of 800,000 in Hong Kong. All had been admitted to the ASU because of acute first-ever or recurrent ischemic stroke. They were screened for participation in a psychiatric (or cognitive) interview at three months after stroke.

Patients were invited to participate in the psychiatric (or cognitive) interview if they (1) were aged $\geq$ 40 years; (2) had acute first or recurrent ischemic stroke; (3) were of Chinese descent and fluent in the Cantonese dialect; and (4) were willing and able to give informed consent. Patients

were excluded if they (1) had a central nervous system disease other than stroke; (2) did not have an MRI scan; (3) had significant aphasia or dysarthria (a National Institutes of Health Stroke Scale [NIHSS] best language score ≥2 or dysarthria score ≥ 2) to the extent of precluding meaningful communication; (4) had a recurrent stroke within three months of the index stroke; (5) were too fragile or had had prolonged hospitalization; or (6) had a severe co-morbid disease (e.g., malignant tumors, schizophrenia, decompensatory chronic heart failure, or chronic respiratory failure).

Flow charts illustrating the recruitment periods and sample numbers of the various studies reported herein are presented in Figures 2-1.

**Figure 2-1 Flow chart of participant recruitment for poststroke behavioral consequence study**



# CHAPTER 3 CEREBRAL MICROBLEEDS AND SYMPTOM SEVERITY OF POST-STROKE DEPRESSION

## 3.1. Background

Cerebral microbleeds (CMBs) are focal deposits of hemosiderin that indicate prior micro-haemorrhages. Microbleeds (MBs) are related to cerebral amyloid angiopathy, hypertension and atherosclerosis (M. W. Vernooij, A. Van Der Lugt, *et al*, 2008).

MBs are common in ischemic stroke (D. J. Werring, L. J. Coward, *et al*, 2005) and are associated with advanced small artery disease of the brain (H. Kato, M. Izumiyama, *et al*, 2002). Recent evidence suggests that they may be an important factor in the development of emotional lability in stroke (W. K. Tang, Y. K. Chen, *et al*, 2009). The significance of MBs in the development of other psychiatric conditions following stroke remains unknown.

Depression is the most common and serious affective disorder following stroke, although the neuroanatomical model of post-stroke depression (PSD), a depressive illness in patients with well-established cerebrovascular disease, remains unclear. There is no compelling evidence to suggest a close relationship between lesion location and PSD (A. J. Carson, S. Machale, K. Allen, *et al*, 2000). It has recently been suggested, however, that chronic vascular burden may be important in PSDpathogenesis (M. Santos, E. Kovari, *et al*, 2009).

White matter hyperintensities (WMHs) have been shown to be associated with late-life depression (L. L. Herrmann, M. Le Masurier & K. P. Ebmeier, 2008) and possibly to affect its

symptom severity (S. Komaki, H. Nagayama, *et al*, 2008). WMHs are conceptualised as an indicator of vascular damage to brain structures and, as such, contribute to the development of vascular depression (J. R. Sneed, D. Rindskopf, *et al*, 2008). CMBs are also indicators of underlying vascular damage; hence, it is surprising that, hitherto, no study has examined the relationship between CMBs and depression in stroke and other patient populations. In order to fill this gap, this study was conducted to determine the relationship between CMBs and PSD symptom severity in stroke survivors diagnosed with depression.

## 3.2. Methods

### 3.2.1. Subjects

Amongst the 4088 patients with acute ischemic stroke who had been admitted to the acute stroke unit of a university-affiliated regional hospital in Hong Kong, between December 2004 and May 2009, 994 patients first-ever or recurrent acute ischemic stroke were recruited. Inclusion criteria were: 1. Chinese ethnicity; 2. Cantonese as the primary language; 3. age 18 or above; 4. well-documented (clinical presentation and a CT brain scan) first or recurrent acute stroke within the seven days prior to admission; 5. MRI scan; and 6. ability and willingness to give consent. Exclusion criteria were 1. transient ischemic attack (brief episode of neurological dysfunction caused by focal brain or retinal ischemia with clinical symptoms typically lasting less than one hour and without evidence of acute brain infarction ), cerebral haemorrhage,

subdural haematoma or subarachnoid haemorrhage; 2. history of a central nervous system (CNS) disease such as tumour, trauma, hydrocephalus, Parkinson's disease, etc.; and 3. history of depression before the index stroke.

The study protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All the participants signed a consent form.

### 3.2.2. Collection of demographic and clinical data

A research nurse blind to the psychiatrist's diagnoses collected the demographic and clinical data (age, sex and educational level, history of hypertension, diabetes, and previous stroke) and assessed stroke severity using the National Institute of Health Stroke Scale (NIHSS; Brott et al.,1989) within two days of admission.

### 3.2.3. Assessment of PSD symptom severity

Three months after index stroke onset, a psychiatrist, who was blind to the subjects' radiological data, administered the Chinese version of the Structured Clinical Interview for DSM-IV (I.W.K. Kam, 2000) at a research clinic. Diagnosis of major and minor depression was made according to the DSM-IV criteria. The timing of the assessment was chosen to avoid the period of transient emotional adjustment to the disability caused by the stroke (W. K. Tang, S. S. Chan, *et al*, 2005). Symptom severity was assessed with the validated Chinese version of the 15-item Geriatric Depression Scale (P. P. Lim, L. L. Ng, *et al*, 2000). Personal history and family history of psychiatric illness were recorded. The level of functional impairment, social support

and exposure to recent life events were assessed with the Barthel Index (F. I. Mahoney & D. W. Barthel, 1965), the Instrumental Activities of Daily Living (M. P. Lawton & E. M. Brody, 1969), the Lubben Social Network Scale (J.E Lubben, 1988) and the Modified Life Event Scale (H. F. Chiu, L. C. Lam, *et al*, 1998; E. S. Paykel, B. A. Prusoff & E. H. Uhlenhuth, 1971) , respectively.

### 3.2.4. Radiological examination

MRI with diffusion-weighted imaging (DWI) and conventional sequences, including a gradient echo (blood productsensitive) sequence, was performed on each participant with a 1.5-T system (Sonata, Siemens Medical, Erlangen, Germany) within seven days of admission. DWI spin echo EPI (TR/TE/excitation=180/122/4, matrix= 128×128, FOV=230 mm, slice thickness/gap=5 mm/1 mm, EPI factor=90, acquisition time=55 s) with three orthogonally applied gradients was usedwith b values of 1000 and 500. Axial gradient echo images were acquired as the second sequence with imaging parameters of TR/TE/excitation=350/ 30/2, a flip angle of 30°, slice thickness/gap5 mm/0.5 mm, FOV=230 mm, matrix=256×256, and acquisition time= 5 min, 4 s. Axial SE T1 (TR/TE/excitation=425/14/2, FOV= 230 mm, slice thickness/gap=5 mm/0.5 mm, matrix= 256×256, and acquisition time=4 min, 28 s) and TSE T2 (TR/TE/excitation=2500/120/1, turbo factor of 15, FOV= 230 mm, slice thickness/gap=5 mm/0.5 mm, matrix= 256×256, and acquisition time=1 min, 39 s) images were also acquired.

A neurologist (YKC) blind to the psychiatric diagnoses assessed the MRIs using the following criteria:

[1] CMBs were defined as small (2–10 mm) hypointense lesions on the T2*-weighted gradient echo sequence, with symmetric basal ganglia calcification and flow void artefacts of the

pial blood vessels excluded (M. Dichgans, M. Holtmannspotter, *et al*, 2002). Lesions located within a region of infarctions were not considered to be MBs. Based on their location, CMBs were divided into lobar (cortex and subcortical white matter), deep (basal ganglia, internal and external capsules, and thalamus) and posterior fossa (brain stem and cerebellum) groups (M. Dichgans, M. Holtmannspotter, J. Herzog, *et al*, 2002). The number of MBs in each location was recorded. The intra-rater agreement on CMBs measurements was good (W. K. Tang, Y. K. Chen, J. Y. Lu, *et al*, 2009).

[2] WMHs were defined as ill-defined hyperintensities ≥5 mm on the T2 images. The WMH severity was assessed using the age-related white matter changes (ARWMC) scale (L. O. Wahlund, F. Barkhof, *et al*, 2001) on both sides of the frontal, parietal–occipital, temporal, basal ganglia and infratentorial regions. The ARWMC score was the sum of the scores for both sides of all regions.

[3] Brain infarcts, the total area of acute infarcts on the DWI, were measured with manual outlines. Acute infarcts were defined as areas of restricted water diffusion on the DWIs with b values of 1000. Total volume was calculated by multiplying the total area by the sum of the slice thickness and gap. Intra-rater reliability tests on 20 participants indicated good agreement; infarct volume: intra-rater kappa=0.96; number of infarcts: intra-rater kappa=0.94.

### 3.2.5. Statistical analysis

The demographic and clinical variables (age, sex, and NIHSS and GDS scores) and radiological characteristics of the any-CMB and no-CMB groups were compared using the $\chi 2$ test, Fisher's exact test and Mann–Whitney U test. The GDS scores were then adjusted for age,

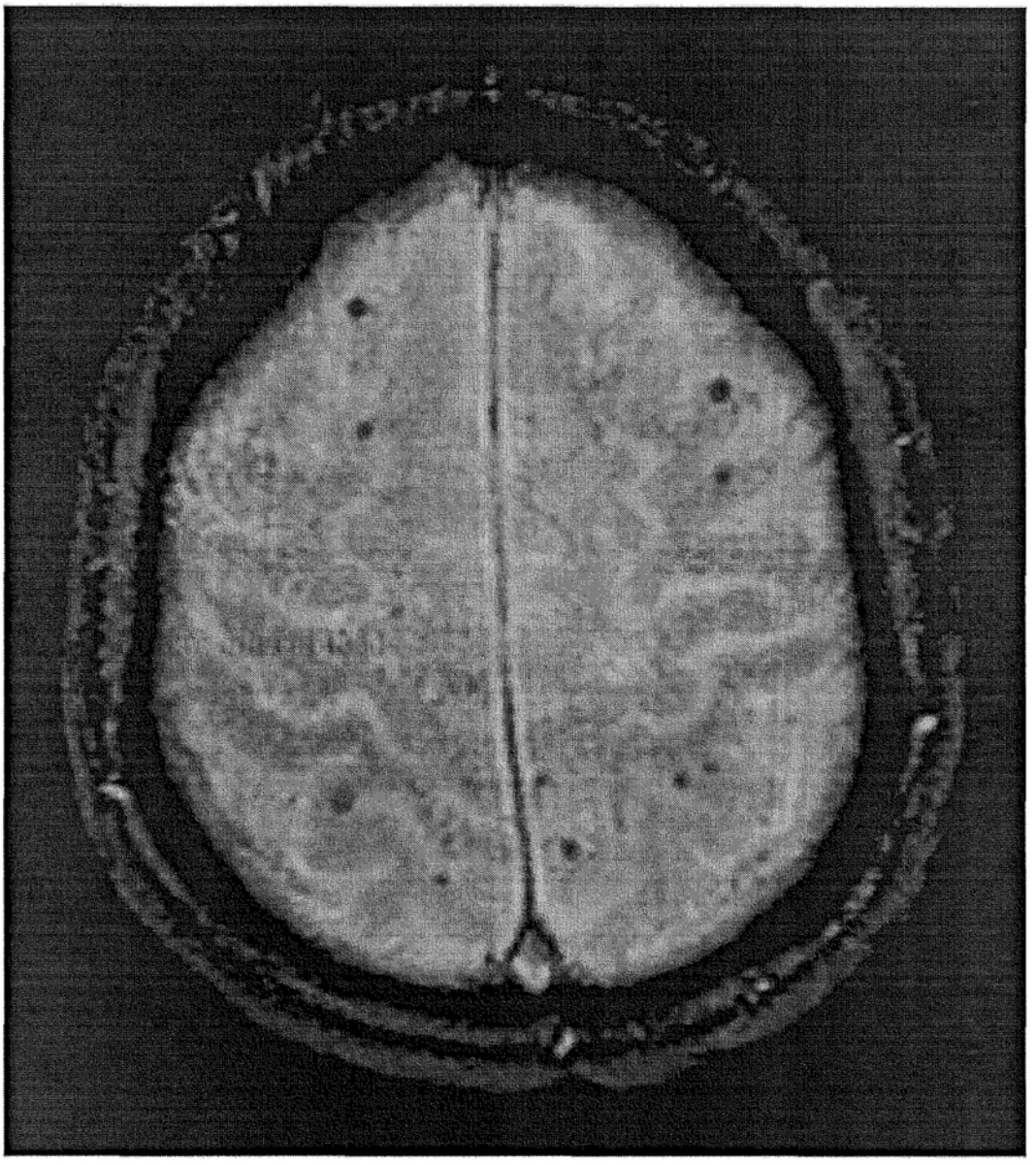
sex and NIHSS, and the ARWMC scores by analysis of covariance. To explore the effect of CMB location, the foregoing analysis was repeated for the no-CMB and lobar, deep and posterior fossa CMB groups. All statistical tests were performed using SPSS for Windows (Release 14.0; SPSS Inc., Chicago, IL, USA). The significance level was set at 0.05.

## 3.3. Results

Of the 994 patients examined, 78 (7.8%; 36 men, and 42 women) who had PSD (34 with major depression and were refered to the Psychiatry department for treatment and 44 with minor depression) were enrolled in the study. The mean age and the NIHSS and GDS scores were 66.8±11.2 years, 5.2± 3.5 and 10.9±2.6, respectively. The mean number and volume of acute infarcts were 1.1±1.4 and 2.7±5.4 mm3, respectively. The ARWMC scores ranged from 0 to 24, with an average of 6.9±6.4. CMBs were identified in 20 (25.6%) patients; 5 had pure lobar CMBs [Fig. 3-1], 3 had lobar and deep CMBs, 1 had lobar and posterior fossa CMBs; 5 had pure deep and 2 had pure posterior fossa CMBs. Four patients had CMBs in all three regions. In the lobar CMBs group, 46.2% had parietal lobe CMBs, 46.2% had temporal lobe CMBs, 46.2% had basal ganglia CMBs, 30.8% had frontal lobe CMBs, 30.8% had thalamus CMBs and 23.1% had occipital lobe CMBs. Compared with the no-CMB group, the any-CMB, lobar and deep CMB groups had significantly higher ARWMC scores. The NIHSS score was also higher in the deep CMB group [Table 3-1]. The unadjusted GDS scores in the any-CMB and lobar and posterior fossa CMB groups were significantly higher than those in the no-CMB group. The GDS scores of the lobar CMB group, adjusted for age, sex, LSNS, NIHSS, MMSE, prior stroke and ARWMC score, remained significantly higher than those of the no-CMB group (12.9±2.6 versus

10.5±2.5, p=0.003) [Table 3-1]. The correlation between the number of MBs and the GDS scores in the 20 patients with CMBs was 0.263 (p=0.262).

**Fig 3-1 Lobar microbleeds**



## Table 3-1 Group comparisons

| | No CMBs | Any CMBs | | Lobar CMBs | | Deep CMBs | | Posterior fossa CMBs | |
|---|---|---|---|---|---|---|---|---|---|
| N | 58 | 20 | | 13 | | 12 | | 7 | |
| | Mean±SD | Mean±SD | $p^a$ | Mean±SD | $p^a$ | Mean±SD | $p^a$ | Mean±SD | $p^a$ |
| Age | 66.4±11.3 | 68.0±11.3 | .571[b] | 68.5±12.3[a] | .559[b] | 72.9±9.0 | .064[b] | 63.9±11.6 | .582[b] |
| Female | 33(56.9%) | 9(45.0%) | .357[c] | 8(61.5%)[b] | .759[c] | 5(41.7%) | .335[c] | 1(14.3%) | .047[c] |
| NIHSS | 4.7±3.3 | 6.5±4.0 | .100 | 7.2±4.7 | .090 | 7.9±4.1 | .011 | 5.3±4.5[c] | .870 |
| Hypertension | 35(60.3%) | 14(70.0%) | .441 | 9(69.2%) | .754 | 10(83.3%) | .130 | 6(85.7%) | 0.246 |
| Diabetes | 22(37.9%) | 9(45.0%) | .577 | 6(46.2%) | .583 | 7(58.3%) | .192 | 2(28.6%) | 1.000 |
| Prior stroke | 10(17.2%) | 6(30.0%) | .223 | 3(23.1%) | .694 | 5(41.7%) | .061 | 1(14.3%) | 1.000 |
| Past psychiatric illness | 5(8.6%) | 1(5.0%) | 1.000 | 1(7.7%) | 1.000 | 1(8.3%) | 1.000 | 1(14.3%) | .510 |
| Family history of psychiatric illness | 4(6.9%) | 0(0.0%) | 1.000 | 0(0.0%) | 1.000 | 0(0.0%) | 1.000 | 0(0.0%) | 1.000 |
| LSNS | 26.2±6.9 | 25.3±10.1 | 0.717b | 28.2±10.5 | .512b | 25.8±9.9 | .853b | 20.3±9.3 | .043b |
| MLES | 2.5±1.5 | 2.2±1.2 | .354 | 2.1±1.2 | .444 | 2.3±1.4 | .598 | 2.6±1.4 | .906 |
| BI | 18.6±2.4 | 18.5±2.4 | .288 | 18.2±2.8 | .200 | 18.1±3.0 | .271 | 19.0±0.8 | .720 |
| IADL | 3.8±4.9 | 4.7±5.6 | .595 | 5.1±5.9 | 0.485 | 5.3±5.7 | .307 | 2.0±1.9 | .447 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| MMSE | 25.5±3.5 | 24.4±3.5 | .192 | 24.3±4.1 | .306 | 22.8±2.7 | .010 | 25.1±4.2 | .865 |
| No. of acute infarcts | 1.0±1.3 | 1.2±1.7 | 1.000 | 0.9±0.8[c] | .923 | 1.6±2.0[c] | .472 | 0.7±1.1 | .493 |
| Volume of acute infarcts, $mm^3$ | 3.0±5.9 | 1.9±3.9 | .491 | 2.7±4.6[c] | .982 | 2.0±3.6[c] | .893 | 0.4±0.6 | .171 |
| No. of lacunar infarcts | 1.3±1.8 | 1.6±1.5 | .818 | 1.6±1.3 | .510 | 2.2±1.7 | .141 | 1.1±1.3 | .460 |
| ARWMC score | 6.1±5.9 | 9.3±7.1 | .033 | 9.0±6.2 | .042 | 12.3±7.6 | .002 | 10.3±8. | .172 |
| GDS | 10.5±2.6 | 12.0±2.5 | .382 | 12.8±2.1 | .010 | 11.4±2.4 | .253 | 12.9±2.4 | .031 |
| GDS adjusted | 10.5±2.5 | 11.8±2.5‡ | .084[e] | 12.9±2.6 | .003[e] | 11.2±2.4 | .441[e] | 12.1±2.4 | .207[e] |

ARWMC=Age-related White Matter Changes Scale, BI=Barthel Index, CMBs=cerebral microbleeds, GDS= Geriatric Depression Scale, IADL=Instrumental Activities of Daily Living, LSNS=Lubben Social Network Scale, MLES=Modified Life Event Scale, MMSE=Mini-Mental State Examination, NIHSS=National Institute of Health Stroke Scale, SD=standard deviation

[a] In comparison to the no CMBs group by means of Mann-Whitney U test unless otherwise specified.

[b] In comparison to the no CMBs group by means of t-test.

[c] In comparison to the no CMBs group by means of Chi-square U test.

[d] In comparison to the no CMBs group by means of Fisher's exact test.

[e] Analysis of covariance adjusting for age, sex, LSNS, NIHSS, MMSE, prior stroke, and ARWMC score

## 3.4. Discussion

To the best of our knowledge, this is the first study to report an association between CMBs and the symptom severity of depression in stroke survivors. The results suggest that lobar CMBs are associated with more severe depression symptoms in patients with well-established cerebrovascular disease. Histopathological studies have revealed that MBs are not only circumscribed haemosiderin deposits, but also affect the surrounding gliosis and cause frank necrosis or infarction, which suggests their clinical importance (A. Tanaka, Y. Ueno, *et al*, 1999).

Our finding that only lobar CMBs are associated with greater depression symptom severity suggests that, in addition to signifying underlying vascular pathology, CMBs may also directly affect depressive symptoms. The importance of CMB location has been reported in other post-stroke pathologies, namely, thalamic CMBs in post-stroke emotional lability (W. K. Tang, Y. K. Chen, J. Y. Lu, *et al*, 2009) and frontal and basal ganglia CMBs in executive dysfunction (D. J. Werring, D. W. Frazer, *et al*, 2004). Lobar regions consist of the cerebral cortex and subcortical white matter. Studies of adult (K. Zou, X. Huang, *et al*, 2008) and late-life depression (K. Nobuhara, G. Okugawa, *et al*, 2006) have revealed that alterations of the integrity of white matter in the frontal lobe are related to the severity of depression. It is suggested that these white matter abnormalities and the resulting dysfunctions of the frontosubcortical circuits may lead to a variety of symptoms that are common in depressed patients (S. Tekin & J. L. Cummings, 2002). It is possible that CMBs in the lobar region increase severity of PSD via a similar mechanism.

The study's first limitation is its small sample size, which reduces its statistical power. Second, stroke severity in this sample was mild, and PSD assessment was made only once, at the three-month follow-up. Third, patients with more severe stroke, those who died before the three-month

follow-up and those who became depressed later were excluded, as were those unable to give their consent due to dementia or aphasia. These selection biases may limit the generalisability of the findings. Fourth, MRI examination was performed only in the acute phase of stroke and new CMBs might have appeared duration the three months period between the MRI examination and the assessment of depression and contribute to the development of PSD (S. B. Jeon, S. U. Kwon, *et al*, 2009). Fifth, severity of depression was measured using the GDS. Besides being a screening instrument, the Fig. 1. Lobar microbleeds. GDS has been commonly used to measure depressive symptoms in studies on stroke survivors (F. J. Carod-Artal, L. Ferreira Coral, *et al*, 2009; B. T. Mast, 2004; W. K. Tang, Y. K. Chen, *et al*, 2010) and neuroimaging studies on geriatric depression (M. Lamar, R. A. Charlton, *et al*, 2010; J. T. O'brien, M. J. Firbank, *et al*, 2006; A. Teodorczuk, Firbank, M.J., Pantoni, L., Poggesi, A., Erkinjuntti, T., Wallin, A., Wahlund, L.O., Scheltens, P., Waldemar, G., Schrotter, G., Ferro, J.M., Chabriat, H., Bazner, H., Visser, M., Inzitari, D., O'brien, J.T., Ladis Group, 2010). More importantly, the GDS has also been used tomeasure symptoms severity in elderly patientswith depressive disorders (P. Allard, L. Gram, *et al*, 2004; R. T. Loving, D. F. Kripke, *et al*, 2005; J. Raskin, J. Y. Xu & D. K. Kajdasz, 2008; E. Savaskan, S. E. Muller, *et al*, 2008; T. N. Wise, C. G. Wiltse, *et al*, 2007). Our sample had a mean age well above 60 years， hence we believe that the GDS is a valid measure of symptoms severity of depression in our sample and in linewith the PSD and geriatric depression literature.

## 3.5. Conclusion

In conclusion, the results of this study suggest that lobar CMBs are associated with greater PSD symptom severity. Further investigations are needed to clarify whether CMBs have any impact on the clinical presentation, treatment response and outcome of depression or other psychiatric conditions in stroke survivors and those with other neuropsychiatric disorders.

# CHAPTER 4 WHITE MATTER HYPERINTENSITIES IN POSTSTROKE DEPRESSION: A CASE –CONTROL STUDY

## 4.1. Background

White matter hyperintensities (WMHs) are areas of increased signal intensity that become apparent, particularly on T2 weighted magnetic resonance imaging (MRI) (L. L. Herrmann, M. Le Masurier & K. P. Ebmeier, 2008). WMHs are thought to reflect underlying cerebrovascular disease. Neuropathological studies show that WMH characterize arteriosclerosis, ischaemia, incomplete infarction and infarction with necrosis (A. J. Thomas, J. T. O'brien, *et al*, 2002).

WMHs are common in ischemic stroke (D. Leys, E. Englund, *et al*, 1999), and are associated with small artery disease of the brain and they could also predict dependency, death, recurrent stroke and poststroke dementia(B. Kissela, C. J. Lindsell, *et al*, 2009; D. Leys, E. Englund, T. Del Ser, *et al*, 1999; N. K. Oksala, A. Oksala, *et al*, 2009).

Depression is the most common and serious emotional disorder following stroke. Depression is associated with excess disability, cognitive impairment, and mortality (E. M. Whyte & B. H. Mulsant, 2002). The neuroanatomical model of poststroke depression (PSD), a depressive illness in patients with well established cerebrovascular disease, remains unclear. There is no strong evidence for the hypothesis of a close relationship between lesion location and PSD(A. J. Carson, S. Machale, K. Allen, *et al*, 2000). It has been recently suggested that chronic vascular burden may be an important factor in the development of PSD(M. Santos, E. Kovari, G. Gold, *et al*, 2009).

WMHs have been shown to be associated with late life depression,1 possibly affecting its long term course (A. Heiden, J. Kettenbach, *et al*, 2005) and treatment response (J. Janssen, H. E.

Hulshoff Pol, *et al*, 2007). White matter changes are conceptualised as a sign of vascular damage to brain structures and as such they contribute to the development of vascular depression(J. R. Sneed, D. Rindskopf, D. C. Steffens, *et al*, 2008). Hence it is surprising that no study has found any association between WMHs and PSD (G. M. Nys, M. J. Van Zandvoort, *et al*, 2005; R. Vataja, A. Leppavuori, *et al*, 2004; R. Vataja, T. Pohjasvaara, *et al*, 2001).

The aim of this case-control study was to re-examine the relationship between WMHs and PSD in stroke survivors.

## 4.2. Methods

### 4.2.1. Participants

Altogether 4088 patients with first-ever or recurrent acute ischemic stroke were admitted to the Acute Stroke Unit of the Prince of Wales Hospital between December 2004 and May 2009. Prince of Wales Hospital is a university-affiliated general hospital serving a population of 800,000 in Hong Kong. Of the 4088 patients, 1700 received an MRI examination and a convenient sample of 994 (58.5%) patients were recruited. The inclusion criteria for the study were: 1. Chinese ethnicity; 2. Cantonese as the primary language; 3. age 18 or above; 4. well-documented (clinical presentation and CT scan or MRI of the brain) first or recurrent acute stroke occurring within 7 days before admission; and 5. ability and willingness to give consent. The exclusion criteria included 1. transient ischemic attack, cerebral haemorrhage, subdural heamatoma or subarachnoid haemorrhage; 2. history of a CNS disease such as tumour, trauma,

hydrocephalus, Parkinson's disease, etc; 3. history of depression or substance abuse/dependence before the index stroke.; 4. aphasia, which was defined as a score of 2 or more in the best language item of the National Institute of Health Stroke Scale (NIHSS)(T. Brott, H. P. Adams, Jr., *et al*, 1989) .and 4. And dementia, which was defined as a Mini-Mental State Examination (MMSE) (Boey Kw. Chi I, 1994) score less than 17.

All 994 patients were screened for PSD by a psychiatrist [WKT]. Seventy-eight (7.8%) patients had PSD. A control group (n=78), matched in terms of age and sex, was selected from the same cohort of stroke patients who did not present with PSD. The recruitment of both the PSD and control groups was conducted simultaneously. The study protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All participants signed a written consent form.

### 4.2.2. Collection of demographic and clinical data

A research nurse, who was blind to the psychiatrist's diagnoses, collected the demographic data (age, sex and education level in terms of school years) and assessed the stroke severity using the NIHSS within 2 days of admission. A research assistant assessed all of the participants with the MMSE and the Lubben Social Network Scale(J.E Lubben, 1988) 3 months after the onset of the index stroke. The LSNS is a composite social network scale that was specifically designed for use in the elderly. It measures the level of social support patients receive and also their social interaction with relatives and friends. The LSNS has been translated into Chinese and validated in Hong Kong elderly.

### 4.2.3. Assessment of PSD

Three months after the onset of the index stroke, a qualified psychiatrist (WKT), who was blind to the subjects' radiological data, administered the Chinese version of the Structured Clinical Interview for DSM-IV (SCID-DSM-IV)(American Psychiatric Association., 1994; I.W.K. Kam, 2000) at a research clinic. The timing of the assessment was chosen to avoid the period of transient emotional adjustment to the disability that was caused by the stroke(W. K. Tang, S. S. Chan, H. F. Chiu, *et al*, 2005).

### 4.2.4. MRI examination

MRI with diffusion-weighted imaging and sequence of proton density, was performed on each participant with a 1.5-T system (Sonata, Siemens Medical, Erlangen, Germany) within 7 days of admission.

DWI spin echo EPI (TR/TE/excitation=180/122/4, matrix=128 x 128, FOV=230mm, slice thickness/gap=5mm/1mm, EPI factor=90, acquisition time=55 seconds) with three orthogonally applied gradients was used with a b value of 1000 and 500. Axial gradient echo images were acquired as the second sequence with imaging parameters of TR/TE/excitation=350/30/2, flip angle of 30 degrees, slice thickness/gap=5mm/0.5mm, FOV=230mm, matrix 256 x 256, and acquisition time=5 minutes 4 seconds. Axial SE T1 (TR/TE/excitation=425/14/2, FOV=230mm, slice thickness/gap=5 mm/0.5mm, matrix=256 x 256, and acquisition time=4 minutes 28 seconds) and TSE T2 (TR/TE/excitation=2500/120/1, turbo factor of 15, FOV=230mm, slice

thickness/gap=5 mm/0.5mm, matrix of 256 x256, and acquisition time=1 minute 39 seconds) images were also acquired.

A neurologist (YKC), who was blind to the psychiatric diagnoses, assessed the MRIs, which included the following:

(1) WMHs. The severity of WMHs was graded using the 4-point scale developed by Fazekas et al (F. Fazekas, J. B. Chawluk, *et al*, 1987; M. J. Firbank, J. T. O'brien, *et al*, 2005). Periventricular WMHs (PVWMHs) and deep white matter hyperintensities (DWMHs) were scored on axial protondensity images. The inter-rater agreement was good for both the PVWMH (weighted kappa: 0.82) and DWMH ratings (weighted kappa: 0.88). The intrarater weighted kappa was 0.87–0.93 (PVWMHs: 0.87; DWMHs: 0.93).

(2) Brain infarcts. Acute infarcts affecting the frontal, temporal, parietal and occipital lobes, subcortical deep white matter (including the centrum semiovale, coronal radiate and internal capsule), basal ganglia, thalamus, brainstem and cerebellum were recorded (V. C. Mok, A. Wong, *et al*, 2004) Multiple infarcts or infarct(s) involving more than one location were counted in all locations they occurred. The total area of acute infarcts on DWI was measured with manual outlines with restricted water diffusion identified on diffusion weighted images with b values of 1000. The total volume was calculated by multiplying the total area by the sum of the slice thickness and the gap. Intra-rater reliability tests were performed on 20 participants, the kappa for the volume and number of infarcts were 0.96 and 0.94, respectively.

### 4.2.5. Statistical analysis

All statistical tests were performed by SPSS for Windows (Release 14.0; SPSS Inc., Chicago, IL, USA). Demographic and clinical variables (age, sex, education level, and NIHSS and MMSE scores) and radiological characteristics of the PSD subjects were compared with those of the matched controls using the $\chi 2$ test, Fisher's exact test, Student's t-test, and the Mann-Whitney U test, as appropriate. Risk factors with a value of $P<0.10$ were then analyzed by multivariate logistic regression analysis using a forward stepwise selection strategy. If the correlations between any of these putative risk factors were >/=0.50, then additional models were examined to rule out co-linearity. In the analysis, the odds ratio of any independent risk factor was interpreted as the risk of subsequent PSD when all other risk factors were held constant. The level of significance was set at 0.05.

## 4.3. Results

Patient who were excluded from the study were older ($73.9\pm12.0$ vs. $66.0\pm11.7$; $p<0.001$) were more likely to be female (52.8% vs. 39.3%; $p<0.001$) and had a higher NIHSS score ($10.1\pm9.3$ vs. $4.5\pm3.4$; $p<0.001$).

Of the 994 patients screened, 78 (7.8%) had PSD, 39 of them had major depression and 39 had minor depression. Three patients in the PSD group received antidepressant at the time of assessment, whereas no patient in the control group received antidepressant treatment. The demographic and MRI characteristics and stroke-related data stratified by PSD status are shown in Tables 4-1 and 4-2. The PSD and control groups did not differ in terms of age, sex, severity of stroke (NIHSS score), and previous stroke. The PSD group had a lower level of social support

(LSNS score). There was a trend that the PSD group had a lower frequency of hypertension and hyperlipidemia and a lower level of education, cognitive function (MMSE score) [Table 1].

The proportion of patients with severe DWMHs (Fazekas score = 3) was significantly higher in the PSD group (12.8% vs 1.3%, $p = 0.009$). Frontal lobe acute infarcts were also more frequent in the PSD group (10.3% vs 1.3%, $p = 0.034$) [Table 4-1].

MMSE score and education were correlated ($r=0.641$, $p<0.01$). The following variables were entered into the regression model: LSNS, MMSE, presence of frontal lobe acute infarcts and severe DWMHs. Severe DWMHs and acute frontal infarcts were significant independent predictors of PSD with an odds ratio of 13.8 and 9.4, respectively [Table 4-2].

**Table 4-1 Demographic characteristics, psychosocial risk factors, stroke severity and radiological characteristics by PSD status**

| Variables | PSD | | p |
|---|---|---|---|
| | Yes (n = 78) | No (n = 78) | |
| Age (years)[a] | 66.8 ± 11.2 | 66.9 ± 11.3 | 0.989 |
| Female sex (n, %)[b] | 42, 53.0 | 42,53.0 | 1.000 |
| Education (years)[a] | 4.3 ± 4.3 | 5.7 ± 4.8 | 0.058 |
| Previous stroke[b] (n, %) | 16 (20.5) | 11 (14.1) | 0.290 |
| Hypertension[b] (n,%) | 49(62.8) | 59(75.6) | 0.083 |
| Hyperlipidemia[b] (n,%) | 40(51.3) | 51(65.4) | 0.074 |
| smoking history[b] (n,%) | 34(43.6) | 27(34.6) | 0.251 |
| MMSE [c] score | 25.2 ± 3.5 | 26.1 ± 3.1 | 0.068 |
| NIHSS total [c] score | 5.2 ± 3.5 | 4.5 ± 3.6 | 0.143 |
| LSNS [c] score | 26.0 ± 7.8 | 31.2 ± 8.3 | <0.001 |
| Fazekas DWMH score (n, %)[b] | | | |
| 0 – 2 | 68 (87.2) | 77 (98.8) | 0.009 |

| | | | |
|---|---|---|---|
| 3 | 10 (12.8) | 1 (1.3) | |
| Fazekas PVH score (n, %)[b] | | | |
| 0 – 2 | 73 (93.6) | 73 (93.6) | 1.000 |
| 3 | 5 (6.4) | 5 (6.4) | |
| Number of acute infarcts[c] | 1.1 ± 1.4 | 1.5 ± 2.5 | 0.957 |
| Volume of acute infarcts (ml)[c] | 2.7 ± 5.4 | 2.6 ± 7.3 | 0.946 |
| Number of lacunar infarcts [c] | 1.4 ± 1.7 | 1.6 ± 2.4 | 0.932 |
| Acute infarcts (n, %) in: | | | |
| Frontal lobe[d] | 8 (10.3) | 1 (1.3) | 0.034 |
| Parietal lobe[d] | 2 (2.6) | 6 (5.4) | 0.442 |
| Temporal lobe[d] | 2 (2.6) | 1 (1.3) | 1.000 |
| Occipital lobe[d] | 4 (5.1) | 0 (0.0) | 0.120 |
| Basal ganglia[b] | 12 (15.4) | 15 (19.2) | 0.676 |
| Thalamus[b] | 13 (16.7) | 7 (9.0) | 0.548 |
| Subcortical white matter[b] | 12 (15.4) | 9 (11.5) | 0.821 |
| Brainstem[b] | 11 (14.1) | 9 (11.5) | 1.000 |
| Cerebellum[d] | 2 (2.6) | 3 (3.8) | 1.000 |

| | | | |
|---|---|---|---|
| Laterality of acute hemispheric infarcts | | | |
| left hemisphere (n,%)[b] | 20 (25.7) | 16 (20.5) | 0.447 |
| right hemisphere (n,%)[b] | 15 (19.2) | 17 (21.8) | 0.692 |

MMSE=Mini-Mental State Examination; NIHSS=National Institute of Health Stroke Scale; LSNS=Lubben Social Network Scale; DWMH=Deep white matter hyperintensities; PVH=Periventricular hyperintensities

[a] mean ± standard deviation, t test; [b] chi-square test; [c] mean ± standard deviation , Mann-Whitney U test; [d] Fisher's exact test.

## Table 4-2 Multivariate logistic model of the clinical determinants of PSD

| Variables | OR (95% CI) | p Value * |
|---|---|---|
| Severe DWMH | 13.790 (1.644 to 115.654) | 0.016 |
| Acute frontal infarct | 9.409 (1.130 to 78.371) | 0.038 |
| LSNS score | 0.923 (0.884 to 0.964) | <0.001 |
| MMSE score | 0.965 (0.866 to 1.076) | 0.522 |
| r square | | 0.242 |

*Logistic regression.

DWMH, deep white matter hyperintensities; LSNS, Lubben Social Network Scale;

PSD, post-stroke depression; PVH, periventricular hyperintensities.

## 4.4. Discussion

To the best of our knowledge, this is the first study to report an association between WMHs and PSD. The results suggest that WMHs are important in the development of depression in patients with well established cerebrovascular disease.

Vataja et al. (R. Vataja, T. Pohjasvaara, A. Leppavuori, *et al*, 2001) evaluated the MRI correlates of PSD in 275 stroke patients. They found that brain infarct but not WMHs were correlated with PSD. Compared to the subjects of the present study, Vataja et al.'s sample had more infarcts (mean number of infarcts=3), as well as larger infarcts (mean volume=34 ml). The association between WMHs and depression has been reported in elderly with previous stroke (M. J. Firbank, J. T. O'brien, S. Pakrasi, *et al*, 2005). One possible explanation for the above observations is that WMHs play a major role only in the development of depression in patients with no, little or small brain infarcts, whereas the impact of larger brain infarcts supersede that of WMHs in the pathogenesis of PSD.

A large number of cross sectional studies have found a higher rate and severity of WMHs in individuals with geriatric depression compared with healthy elderly controls and especially in individuals with late onset illness(L. L. Herrmann, M. Le Masurier & K. P. Ebmeier, 2008). For example, Taylor et al (Macfall Jr Taylor Wd, Payne Me, Et Al., 2005). examined white matter lesion volumes on brain MRI between 253 depressed and 146 control subjects and found that depressed subjects had greater white matter lesion volumes (mean 7.2 ml) than the control subjects (mean 4.8 ml). Similarly, Heiden et al. (A. Heiden, J. Kettenbach, P. Fischer, *et al*, 2005) examined the prognostic value of WMHs in geriatric depression in a 5-year follow up study and

revealed that subjects with more severe WMHs had more depressive symptoms at follow up and had more severe courses of depression. Finally, a recent 4-year prospective study of a community sample of 1658 elderly subjects showed that increase in WMH load at baseline predicted higher risk of developing depression during follow up (O. Godin, C. Dufouil, *et al*, 2008). In the present study of PSD, WMHs was found to be associated with the development of depression, a finding in line with the findings of structural imaging in geriatric depression in general.

In this study, only severe WMHs were associated with PSD. O'Brien (J. O'brien, D. Ames, *et al*, 1998) also reported that severe, but not mild or moderate WMHs predict poor outcome in late life depression. It was hypothesized that severe WMHs may represent pathological brain changes whereas mild and moderate WMHs may indicate normal, age-related changes.

Only DWMHs but not PVHs were associated with PSD in this study, which is in line with a recent report suggesting that DWMHs, but not PVHs were associated with depressive symptoms in older subjects (M. S. Krishnan, J. T. O'brien, *et al*, 2006). Other authors also observed a relationship between DWMHs and depression (J. C. De Groot, F. E. De Leeuw, *et al*, 2000; R. D. Nebes, I. J. Vora, *et al*, 2001; Desmond P O'brien J, Ames D, Et Al, 1996). It is suggested that DWMHs is the result of vascular ischemic damage, whereas PVHs are not (A. J. Thomas, J. T. O'brien, S. Davis, *et al*, 2002).

The main limitation of this study is the relatively low frequency of PSD resulting in a relatively small number of affected patients, which reduced the statistical power of the study. Furthermore, the severity of strokes was mild in the sample and the assessment of PSD was made only once, at the 3-month follow-up. Patients who died before the 3-month follow up were not included in the study. In addition, patients who could not give consent due to dementia or

aphasia-associated left side infarcts were also excluded; excluded patients were more likely to be female, they were older and had more severe stroke. Since cognitive impairment (M. L. Hackett & C. S. Anderson, 2005), left side lesions (S. Hama, H. Yamashita, *et al*, 2007), female sex (American Psychiatric Association., 1994), younger age (S. L. Barker-Collo, 2007), and neurological deficits (M. L. Hackett & C. S. Anderson, 2005) are all associated with PSD, this selection bias may limit the generalisability of our findings. Furthermore, the reported findings may not apply to late onset form of PSD. Finally, additional vascular lesions might have appeared duration the three months period between the MRI examination and the assessment of depression. These new lesions may include new ischemic infarct (recurrent stroke) (H. Ay, L. Gungor, *et al*) or silent lacunar infarcts (A. Boon, J. Lodder, *et al*, 1994) or progression of WMHs (P. Maillard, F. Crivello, *et al*, 2009). These unmeasured vascular burdens may also contribute to the development of PSD (M. Santos, G. Gold, *et al*, 2009).

In conclusion, the results of this study suggest that WMHs may contribute to the development of PSD. Further work is needed to clarify if WMHs impact on PSD patients' clinical presentation, treatment response and outcome.

# CHAPTER 5 ASSOCIATION OF FRONTAL SUBCORTICAL CIRCUITS INFARCTS IN POSTSTROKE DEPRESSION: A MAGNETIC RESONANCE IMAGING STUDY OF 591 CHINESE PATIENTS WITH ISCHEMIC STROKE

## 5.1. Introduction

The frontal subcortical neuronal loops control emotions and behaviour (J. L. Cummings, 1993). It has been hypothesised that lesions that disrupt the frontal subcortical circuits (FSC) may precipitate depression (G. S. Alexopoulos, B. S. Meyers, *et al*, 1997). Several studies have linked depression with magnetic resonance imaging (MRI)-identified lesions in the frontal deep white matter (A. J. Thomas, J. T. O'brien, S. Davis, *et al*, 2002), basal ganglia and other subcortical grey nuclei (B. S. Greenwald, E. Kramer-Ginsberg, *et al*, 1998; T. Iidaka, T. Nakajima, *et al*, 1996). Frontal and basal ganglia lesions have also been reported as risk factors for poststroke depression (PSD) by computed tomography (CT) studies (P. L. Morris, R. G. Robinson, *et al*, 1996; A. Singh, S. E. Black, *et al*, 2000). The findings of an MRI spectroscopy study suggested that PSD is accompanied by metabolic changes in the frontal lobe (L. Glodzik-Sobanska, A. Slowik, *et al*, 2006).

Despite extensive research into PSD, the role played by infarct location in its pathogenesis remains uncertain (I. Aben, J. Lodder, *et al*, 2006; M. Astrom, R. Adolfsson & K. Asplund, 1993; A. J. Carson, S. Machale, K. Allen, *et al*, 2000; M. Herrmann, C. Bartels, *et al*, 1995; G. M. Nys,

M. J. Van Zandvoort, H. B. Van Der Worp, *et al*, 2005; R. Vataja, T. Pohjasvaara, A. Leppavuori, *et al*, 2001). A meta-analysis (A. J. Carson, S. Machale, K. Allen, *et al*, 2000) found no association between lesion location and PSD. It is possible that the strength of the association between such location and the risk of PSD depends on the time elapsed since the stroke and subject selection (S. K. Bhogal, R. Teasell, *et al*, 2004). Many early studies employed CT rather than MRI, thus resulting in poorer spatial resolution and less sensitive lesion detection. In addition, the localisation of infarcts in most studies has been rather crude, e.g., the anterior-posterior axis, as measured by the distance from the anterior pole (R. G. Robinson & B. Szetela, 1981).

Only a few studies have examined the MRI correlates of PSD. Bokura et al., (H. Bokura, S. Kobayashi, *et al*, 1994) for example, reported PSD to be associated with periventricular hyperintensity around the anterior horn in a sample of 159 Japanese stroke survivors. Kim and Choi-Kwon (J. S. Kim & S. Choi-Kwon, 2000) examined 148 Korean outpatients with single, unilateral stroke and found PSD to be associated with anterior cortical lesions.

The role played by FSC infarcts in PSD remains uncertain. Vataja et al. (R. Vataja, A. Leppavuori, T. Pohjasvaara, *et al*, 2004; R. Vataja, T. Pohjasvaara, A. Leppavuori, *et al*, 2001) conducted the first large-scale MRI study of PSD involving 275 hospital-based ischemic stroke survivors and found such depression to be associated with a larger number and volume of infarcts affecting the FSC. However, they failed to consider important non-radiological factors, namely, history of depression (P. Appelros & M. Viitanen, 2004), level of social support (W. K. Tang, S. S. Chan, H. F. Chiu, *et al*, 2005) and life events (W. K. Tang, S. S. Chan, H. F. Chiu, *et al*, 2005). A recent review of lesion location and PSD concluded that a multifactorial approach should be adopted in the study of PSD, with concurrent psychosocial variables taken into

account (S. K. Bhogal, R. Teasell, N. Foley, *et al*, 2004).

In the current study reported herein, we set out to examine whether infarcts that involve the FSC are associated with PSD in Chinese stroke survivors after controlling for important putative psychosocial risk factors.

## 5.2. Methods

### 5.2.1. Participants

Study participants were recruited from patients admitted with first-ever or recurrent stroke to the Acute Stroke Unit (ASU) of the Prince of Wales Hospital (PWH) from December 2004 to June 2007. The PWH is a university-affiliated general hospital serving a population of 800,000 in Hong Kong. The inclusion criteria for the study were: 1. Chinese ethnicity; 2. aged 18 or above; 3. well-documented (clinical presentation and CT scan of the brain) first or recurrent acute ischemic stroke occurring within the seven days prior to admission; 4. MRI examination; 5. Cantonese as the primary language; and 6. ability to give consent. The exclusion criteria included 1. transient ischemic attack, cerebral haemorrhage, subdural haematoma or subarachnoid haemorrhage; 2. history of a CNS disease such as tumour, trauma, hydrocephalus, Parkinson's disease, etc.; 3. severe cognitive impairment defined by a Mini-Mental State Examination (MMSE) (Lee Hcb Chiu Hfk, Chung D., 1994) score of less than 17; 4. aphasia; 5. recurrent

stroke during the three-month follow-up period; 6. prolonged (> 3 months) hospitalisation; and 7. physical frailty.

The study protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All participants signed written consent forms.

### 5.2.2. Collection of demographic and clinical data

A research nurse who was blind to the psychiatrist's diagnoses collected the demographic data (age, sex and educational level in terms of school years) and assessed stroke severity using the National Institute of Health Stroke Scale (NIHSS) within two days of admission. A research assistant assessed all of the participants with the MMSE, Lubben Social Network Scale (LSNS) (J.E Lubben, 1988) and Modified Life Event Scale (MLES) (E. S. Paykel, B. A. Prusoff & E. H. Uhlenhuth, 1971) three months after the onset of the index stroke. The LSNS is a composite social network scale that was specifically designed for use in the elderly. It measures the level of social support that patients receive and their degree of social interaction with relatives and friends. The LSNS has been translated into Chinese and validated in a Hong Kong elderly cohort (Boey Kw. Chi I, 1994). The MLES assesses whether an individual has experienced any of 18 major life events, such as the death of a spouse or divorce, in the past six months. Participants' reports on their depression history were complemented by scrutiny of their medical records.

### 5.2.3. Assessment of PSD

Three months after the onset of the index stroke, a qualified psychiatrist (WKT) who was blind to the subjects' radiological data administered the Chinese version of the Structured Clinical Interview for DSM-IV (SCID-DSM-IV) (I.W.K. Kam, 2000) at a research clinic. Assessment timing was chosen to avoid the period of transient emotional adjustment to the disability caused by the stroke (W. K. Tang, S. S. Chan, H. F. Chiu, *et al*, 2005). Consistent with the DSM-IV (American Psychiatric Association., 1994), depressive disorders were categorised as major depression, minor depression or dysthymia.

### 5.2.4. Radiological examination

Nearly all (99.8%) of the MRIs were obtained within one week of the stroke. MRI was performed with a 1.5-T system (Sonata, Siemens Medical, Erlangen, Germany) within seven days of admission. Diffusion weighted imaging (DWI) (TR/TE/excitation = 180/122/4, matrix = 128 x 128, FOV = 230mm, slice thickness/gap = 5 mm/1 mm, EPI factor = 90, acquisition time = 55 seconds) with three orthogonally applied gradients was employed, with b values of 1000 and 500. The other sequences performed included axial gradient echo (GE) images (TR/TE/excitation = 350/30/2, flip angle = 30°, slice thickness/gap = 5 mm/0.5 mm, FOV = 230 mm, matrix = 256 x 256, time of acquisition = 5 minutes 4 seconds); axial SE T1 (TR/TE/excitation = 425/14/2, FOV = 230 mm, slice thickness/gap = 5 mm/0.5 mm, matrix = 256 x 256, time of acquisition = 4 minutes 28 seconds); TSE T2 (TR/TE/excitation = 2500/120/1, turbo factor = 15, FOV = 230 mm, slice thickness/gap = 5 mm/0.5 mm, matrix = 256 x 256, time of acquisition = 1 minute 39 seconds); and axial Flair images (TR/TE/TI/excitation =

9000/117/2500/2, turbo factor = 31, FOV = 230 mm, slice thickness/gap = 5 mm/1 mm, matrix = 256 x 256, time of acquisition = 3 minutes 20 seconds).

A neurologist (YKC) who was blind to the psychiatric diagnoses assessed the MRIs. The number and size of acute or old infarcts affecting different structures of the FSC, including the frontal lobe, frontal subcortical white matter, striatum, globus pallidus, substantia nigra and thalamus (Lichter Jl David G, Cummings, 2001), were evaluated. The total area of acute or subacute infarcts on the DWI was measured with manual outlines of all areas with restricted water diffusion identified on the diffusion weighted images with b values of 1000. The total volume was calculated by multiplying the total area by the sum of the slice thickness and gap. Intra-rater reliability tests were performed on 20 participants, with a good degree of agreement found (volume of acute infarcts: kappa = 0.96; number of infarcts: kappa = 0.94).

### 5.2.5. Statistical analysis

Demographic and clinical characteristics of the patients who developed PSD were compared with those who did have PSD using Chi square, Mann-Whitney U test and Student t tests. The frequency of PSD was calculated in the whole cohort of patients. The normality of data distribution was examined with the Kolmogorov-Smirnov test. To investigate the clinical determinants of PSD, chi-square and Student t-tests were first performed to identify possible risk factors, namely, age, sex, level of education, previous history of depression and/or stroke, and NIHSS, MLES and LSNS scores. A Mann-Whitney U test was administered for the MMSE and NIHSS scores, as they were not normally distributed. Risk factors with a value of $P < 0.10$ were

then analysed via multivariate logistic regression using a forward stepwise selection strategy. If the correlations between any of these putative risk factors were >/= 0.50, then additional models were examined to rule out collinearity. In the analysis, the odds ratio of any independent risk factor was interpreted as the risk of subsequent PSD when all other risk factors were held constant. All statistical tests were performed with SPSS for Windows (Release 11.0; SPSS Inc., Chicago, IL, USA). The level of significance was set at 0.05.

## 5.3. Results

Over the 30 months of the study, of the 874 patients with acute stroke who had been admitted to the PWH and received an MRI examination, 863 (98.7%) were still alive three months after the index stroke. Of the 591 (68.5%) patients who participated in the study, 475 and 116 had first and recurrent strokes, respectively. The reasons for exclusion included an MMSE score of < 17 (n = 87, 31.6%), refusal to participate (n = 38, 14.0%), concurrent neurological disease (n = 44, 16.0%), lost to follow-up (n = 30, 11.0%), aphasia (n = 27, 9.8%), physical frailty (n = 19, 6.9%), recurrent stroke before the three-month follow-up (n = 14, 5.1%), prolonged (> 3 months) hospitalisation (n = 8, 2.9%) and lack of fluency in Cantonese (n = 5, 1.8%). The excluded patients (n = 272) were older (70.6 $\pm$ 12.0 versus 66.0 11.8, p < .001), more likely to be female (45.1% versus 39.1%, p < .001) and had higher NIHSS scores (7.4 $\pm$ 5.4 versus 4.5 $\pm$ 3.4, p < .001).

The demographic and clinical characteristics of the final sample (n = 591) are presented in Table 5-1. Psychiatric assessment took place 14.3 $\pm$ 1.9 weeks after the index stroke. Seventeen

(2.9%) patients had a history of depressive illness prior to the index stroke. 75 (12.7%) had a diagnosis of PSD that included major depression (6.6%, n = 39), minor depression (4.2%, n = 25) or dysthymia (1.9%, n = 11). Only two were receiving antidepressant treatment at the time of the psychiatric interview.

As noted, the patients were divided into PSD (n = 75) and non-depressed (n=516) groups. The demographic characteristics, psychosocial risk factors, stroke severity and MRI findings stratified by PSD status are shown in Tables 1 and 2. Univariate analyses revealed PSD to be significantly associated with the female sex, a lower level of education, a history of depression, lower LSNS and MMSE scores, and higher MLES and NIHSS scores (Table 5-1). In terms of the MRI findings, the presence of FSC infarcts (acute or old) was found to be significantly associated with PSD (Table 5-2). There was no difference in regional FSC infarcts between the two groups, and the correlations between all of the foregoing variables were less than 0.50. FSC infarcts, female sex, history of depression, level of education, and NIHSS, LSNS, and MLES scores were entered into the multivariate logistic regression analysis, which identified FSC infarcts as one of the independent radiological risk factors for PSD (Table 5-3). The regression model was repeated after excluding patients with dysthymia (Table 5-4) and previous stroke (Table 5-5), and FSC infarcts remained an independent risk factor for PSD.

**Table 5-1. Demographic characteristics, psychosocial risk factors and stroke severity by PSD status**

| Variables | All patients (n = 591) | PSD (n = 75) | No PSD (n = 516) | *P* |
|---|---|---|---|---|
| Age (years)[a] | 66.0 ± 11.8 | 66.0 ± 8.7 | 65.8 ± 11.8 | 0.512 |
| Female sex (n, %)[b] | 231, 39.1 | 42, 56.0 | 189, 36.8 | 0.001 |
| Education (years)[a] | 5.4 ± 4.0 | 3.9 ± 4.7 | 5.6 ± 4.3 | 0.008 |
| History of depression[b] (n, %) | 17 (2.9) | 11 (14.7) | 6 (1.2) | <0.001 |
| Previous stroke[b] (n, %) | 116 (19.6) | 12 (16.0) | 104 (20.2) | 0.442 |
| MMSE [a, c] score | 25.3 ± 3.4 | 24.8 ± 3.7 | 26.1 ± 3.2 | 0.004 |
| NIHSS total [a, c] score | 4.5 ± 3.4 | 5.4 ± 3.5 | 4.4 ± 3.4 | 0.017 |
| MLES [a, c] score | 1.8 ±0.9 | 2.2 ± 1.1 | 1.7 ± 0.8 | <0.001 |
| LSNS [a, c] score | 29.8 ± 8.2 | 25.4 ± 8.5 | 30.4 ± 7.9 | <0.001 |

[a] mean ± standard deviation, t test

[b] Chi-square test

[c] Mann-Whitney U test

MMSE, Mini-Mental State Examination; NIHSS, National Institute of Health Stroke Scale; MLES, Modified Life Event Scale; LSNS, Lubben Social Network Scale

**Table 5-2. Radiological characteristics of the whole sample by PSD status**

| Variables | PSD | | *P* |
|---|---|---|---|
| | Yes (n=75) | No (n=516) | |
| FSC infarcts | | | |
| Presence of all infarcts (n, %)[a] | 50 (66.7) | 275 (53.3) | 0.030 |
| Number all of infarcts [b] | 1.2 ± 1.2 | 1.1 ± 1.5 | 0.194 |
| Volume of acute infarcts (ml)[b] | 1.2 ± 3.4 | 0.7 ± 2.9 | 0.308 |
| Presence of all infarcts in the structures of FSC (n, %) | | | |
| Frontal lobe[a] | 9 (12.0) | 44 (8.5) | 0.216 |
| Fronto-subcortical white matter[a] | 13 (20.3) | 73 (16.0) | 0.390 |
| Striatum[a] | 21 (32.8) | 129 (28.4) | 0.461 |
| Globus pallidus[a] | 4 (6.2) | 16 (3.5) | 0.292 |
| Substantia nigra[c] | 2 (3.1) | 6 (1.3) | 0.258 |
| Thalamus[a] | 6 (9.4) | 44 (9.7) | 0.940 |
| Presence of all infarcts in (n, %) | | | |

| | | | |
|---|---|---|---|
| Temporal lobe[c] | 1 (1.3) | 30 (5.8) | 0.160 |
| Parietal-occipital lobe[c] | 4 (6.3) | 66 (13.0) | 0.156 |
| Posterior subcortical white matter[c] | 3 (4.0) | 45 (8.7) | 0.162 |
| Infratentorial region[a] | 13 (17.3) | 91 (17.6) | 0.949 |

FSC=Frontal subcortical circuits; PSD=poststroke depression

[a]Chi-square test

[b]mean ± standard deviation, Mann-Whitney U test

[c]Fisher's exact test

**Table 5-3. Multivariate logistic model of the clinical determinants of PSD**

| Variables | Odds ratio (95% C.I.) | $P$[a] |
|---|---|---|
| FSC infarcts | 2.630 (1.401 – 4.937) | 0.003 |
| Female sex | 2.781 (1.533 – 5.048) | 0.001 |
| History of depression | 9.897 (2.690 – 36.409) | 0.001 |
| NIHSS score | 1.061(0.976–1.153) | 0.164 |
| LSNS score | 0.927(0.896–0.959) | <0.001 |
| MLES score | 1.783(1.333–2.385) | <0.001 |
| Years of education | 0.978(0.918–1.042) | 0.485 |
| R square | | 0.232 |

[a]Logistic regression

FSC=Frontal subcortical circuits; PSD=poststroke depression; LSNS=Lubben Social Network Scale; MLES=Modified Life Events Scale; NIHSS=National Institute of Health Stroke Scale

**Table 5-4. Multivariate logistic model of the clinical determinants of poststroke depression (Patients with dysthymia are excluded from the analysis)**

| Variables | Odds ratio (95% C.I.) | $P$ [a] |
|---|---|---|
| FSC infarcts | 2.568 (1.300 – 5.074) | 0.007 |
| Female sex | 2.195 (1.185 – 4.065) | 0.012 |
| History of depression | 19.577 (5.461 –70.180) | <0.001 |
| NIHSS score | 1.097 (1.012–1.188) | 0.025 |
| LSNS score | 0.914 (0.882–0.948) | <0.001 |
| MLES score | 2.114 (1.552–2.879) | <0.001 |
| Years of education | 0.929 (0.858–1.006) | 0.072 |
| R square | | 0.298 |

[a]Logistic regression

FSC=Frontal subcortical circuits; LSNS=Lubben Social Network Scale; MLES=Modified Life Events Scale; NIHSS=National Institute of Health Stroke Scale

**Table 5-5. Multivariate logistic model of the clinical determinants of poststroke depression (Patients with previous stroke are excluded from the analysis)**

| Variables | Odds ratio (95% C.I.) | $P$ [a] |
|---|---|---|
| FSC infarct | 2.423 (1.137 –5.163) | 0.022 |
| Female sex | 1.882 (0.933 –3.799) | 0.077 |
| History of depression | 10.839 (2.436–48.229) | 0.002 |
| LSNS score | 0.909 (0.872–0.949) | <0.001 |
| MLES score | 2.328 (1.669–3.246) | <0.001 |
| NIHSS score | 1.098 (1.000–1.205) | 0.049 |
| Years of education | 0.954 (0.875–1.040) | 0.282 |
| R square | | 0.274 |

[a]Logistic regression

FSC=Frontal subcortical circuits; LSNS=Lubben Social Network Scale; MLES= Modified Life Events Scale; NIHSS=National Institute of Health Stroke Scale

## 5.4. Discussion

This study provides further support for the hypothesis that FSC infarcts are predictors of PSD (R. Vataja, A. Leppavuori, T. Pohjasvaara, *et al*, 2004; R. Vataja, T. Pohjasvaara, A. Leppavuori, *et al*, 2001). In addition, the sample in thus study constituted a large consecutive cohort, and the radiological findings were examined against the background of a wide range of known clinical and psychosocial PSD risk factors.

The vascular depression hypothesis postulates that cerebrovascular diseases can predispose older adults to depressive syndrome or precipitate such a syndrome (G. S. Alexopoulos, B. S. Meyers, R. C. Young, *et al*, 1997) (S. Hama, H. Yamashita, M. Shigenobu, *et al*, 2007). According to this hypothesis, there is a relationship between the neuroanatomic localisation of lesions and PSD. The review carried out by Carson et al. (A. J. Carson, S. Machale, K. Allen, *et al*, 2000) failed to examine the role played by FSC infarcts, and only the left/right or anterior/posterior locations of lesions were considered to be determinants of PSD risk. Vataja et al. (R. Vataja, T. Pohjasvaara, A. Leppavuori, *et al*, 2001) evaluated the MRI correlates of PSD in a group of 275 stroke patients on the basis of the vascular depression concept (G. S. Alexopoulos, B. S. Meyers, R. C. Young, *et al*, 1997), and found the number and volume of FSC infarcts, particularly those affecting the basal ganglia and internal capsule, to be correlated with PSD. In our study, in contrast, neither the number nor the volume of FSC infarcts, nor regional FSC infarcts, was found to be a significant correlate of PSD. The discrepancy may be because the mean number (1.6 versus 1.1) and, particularly, mean volume (1.2 versus 78.8 ml) of FSC

infarcts in the PSD patients in our sample were much smaller than those reported by Vataja et al. (R. Vataja, T. Pohjasvaara, A. Leppavuori, *et al*, 2001) It appears that lesions in different structures of the FSC may produce diverse patterns of mood symptoms. Hama et al. (S. Hama, H. Yamashita, M. Shigenobu, *et al*, 2007) examined the role of frontal and basal ganglia infarcts in 243 stroke patients and found that the affective component of PSD was associated with frontal infarcts, whereas the apathetic component was related to basal ganglia infarcts. In line with the literature (S. K. Bhogal, R. Teasell, N. Foley, *et al*, 2004; A. J. Carson, S. Machale, K. Allen, *et al*, 2000), we found no difference between subjects with and without PSD with respect to the presence of infarcts in the temporal, parietal-occipital and infratentorial regions.

In our study, both a history of depression and the female sex were found to be powerful determinants of PSD. This finding is in line with a systematic review of PSD risk factors, which found previous depression and the female sex to be associated with PSD in five and ten published studies, respectively (M. L. Hackett & C. S. Anderson, 2005).

Our findings suggest that PSD is a complex disorder and that both psychosocial factors and acute vascular events contribute to its development. Only a few studies on PSD have considered lesion location and psychosocial risk factors simultaneously (M. L. Hackett & C. S. Anderson, 2005). Astrom et al. (M. Astrom, R. Adolfsson & K. Asplund, 1993) showed that both living alone and anterior brain lesions predict PSD, and Tang et al. (W. K. Tang, S. S. Chan, H. F. Chiu, *et al*, 2005) found both life events and infarcts in the anterior cerebral artery territory to be independent risk factors for such depression.

The main limitation of this study is the relatively low frequency of PSD in the sample, which reduces the statistical power of our findings. Furthermore, stroke was mild in our sample, and PSD was assessed only once – at the three-month follow-up. As patients who had aphasia or

more severe stroke and those who died before the three-month follow-up were excluded from the study, the sample was biased to an unknown degree. The exclusion of most of the patients with severe stroke may have resulted in the sample's lower PSD frequency, as severe stroke is a known PSD risk factor (M. L. Hackett & C. S. Anderson, 2005). Finally, we did not measure pre-existing lesions, such as white matter lesions or lacunar infarcts, although they may be predisposing factors for PSD (M. Santos, E. Kovari, G. Gold, *et al*, 2009). It was recently suggested that lacunar infarcts within the thalamus, basal ganglia and deep white matter may also contribute to the development of PSD (M. Santos, G. Gold, E. Kovari, *et al*, 2009).

In conclusion, the results of this study suggest that FSC infarcts are an important predictor of PSD. Further work is needed to clarify whether such infarcts have any impact on the clinical presentation, treatment responses and prognosis of PSD. In addition, a comprehensive biopsychosocial model covering infarct location, premorbid factors such as a history of depression, and post-stroke stressors such as neurological deficit and social support levels may constitute a fruitful approach to the research and clinical management of stroke survivors at risk of PSD.

# CHAPTER 6 CEREBRAL MICROBLEEDS AND QUALITY OF LIFE IN ACUTE ISCHEMIC STROKE

## 6.1. Introduction

Cerebral microbleeds (CMBs) are primarily a radiological construct (small MRI signal voids) indicative of specific underlying microscopic pathological changes, i.e., perivascular collections of hemosiderin deposits that indicate prior micro-hemorrhages (S. M. Greenberg, M. W. Vernooij, *et al*, 2009). Histopathological analyses of CMBs generally reveal two types of vascular pathological changes: hypertensive vasculopathy and cerebral amyloid angiopathy. The distribution of CMBs is different in these two disorders: lobar CMBs are associated with cerebral amyloid angiopathy, whereas deep CMBs are associated with hypertensive vasculopathy (S. M. Greenberg, M. W. Vernooij, C. Cordonnier, *et al*, 2009; K. A. Knudsen, J. Rosand, *et al*, 2001).

The prevailing view is that microbleeds are clinically silent (H. Kato, M. Izumiyama, K. Izumiyama, *et al*, 2002). However, recent histopathological data have revealed that CMBs are not only circumscribed hemosiderin deposits, but also affect the surrounding gliosis and cause frank necrosis or microinfarctions, which suggests that they may be of clinical importance (A. Tanaka, Y. Ueno, Y. Nakayama, *et al*, 1999). Recent evidence also suggests that CMBs may be an important factor in cognitive impairments in subcortical vascular dementia (S. W. Seo, B. Hwa Lee, *et al*, 2007), where they are associated with cognitive dysfunction, particularly executive dysfunction (D. J. Werring, D. W. Frazer, L. J. Coward, *et al*, 2004). CMBs are common in ischemic stroke (D. J. Werring, L. J. Coward, N. A. Losseff, *et al*, 2005), and they

may predict the recurrence of stroke (H. Naka, E. Nomura, *et al*, 2006) and the emergence of emotional lability (W. K. Tang, Y. K. Chen, J. Y. Lu, *et al*, 2009). These microbleeds are also associated with factors that may affect health-related quality of life (HRQoL) in stroke, including advanced small artery disease of the brain (H. Kato, M. Izumiyama, K. Izumiyama, *et al*, 2002), leukoaraiosis (T. Gao, Y. Wang & Z. Zhang, 2008), and recurrent stroke.

Patients with stroke have been shown to have poor HRQoL (M. L. Kauhanen, J. T. Korpelainen, *et al*, 2000). The correlates of poor HRQoL one month to three years after stroke include an older age (T. Gao, Y. Wang & Z. Zhang, 2008; M. L. Kauhanen, J. T. Korpelainen, P. Hiltunen, *et al*, 2000), the female sex (L. J. Gray, N. Sprigg, *et al*, 2007), being single or widowed (P. Kim, S. Warren, *et al*, 1999), a lack of social support (E. B. Lynch, Z. Butt, *et al*, 2008), a high degree of neurological deficit (E. J. Jonkman, A. W. De Weerd & N. L. Vrijens, 1998), cognitive impairment (M. D. Patel, C. Mckevitt, *et al*, 2007), and depression (G. Robinson-Smith, M. V. Johnston & J. Allen, 2000).

Data on the impact of infarcts and other radiological findings on HRQoL are limited, although large lesion volumes (S. K. Schiemanck, M. W. Post, *et al*, 2005) have been found to predict poor HRQoL following stroke (Y. S. Moon, S. J. Kim, *et al*, 2004). To date, only one study has examined the role that acute infarct location and white matter lesions (WMLs) play in HRQoL, with no correlation found between either lesion location or WMLs and HRQoL (Y. S. Moon, S. J. Kim, H. C. Kim, *et al*, 2004).

To the best of our knowledge, no data have been published on the impact of CMBs on the HRQoL of stroke patients, and hence their effect on HRQoL in stroke remains unknown. This study set out to examine whether the presence or location of CMBs contributes to HRQoL in acute ischemic stroke survivors.

## 6.2. Methods

### 6.2.1. Participants

Of the 2,337 patients admitted with first-ever or recurrent stroke to the Acute Stroke Unit (ASU) of the Prince of Wales Hospital (PWH) – a university-affiliated general hospital serving a population of 800,000 in Hong Kong – from December 2004 to May 2007, 874 received an MRI examination. Due to limited access to an MRI machine, MRI is generally reserved for stroke patients with stable neurological conditions. Compared to patients who did not receive an MRI examination, those who did had a lower mean age (67.8 + 12.1 versus 74.5 + 12.0; $p < 0.001$) and less severe stroke, as reflected by a lower National Institutes of Health Stroke Scale (NIHSS) score (5.6 + 4.6 versus 10.6 + 9.8, $p < 0.001$), and were more likely to be men (58.8% versus 46.6%; $p < 0.001$). Four hundred and fifty-eight (52.2%) patients who had received an MRI were recruited for the study. The inclusion criteria were: 1. Chinese ethnicity; 2. aged 18 or above; 3. well-documented (clinical presentation and CT scan of the brain) first or recurrent acute stroke occurring within the seven days prior to admission; 4. Cantonese dialect as the primary language; and 5. ability and willingness to give consent. The exclusion criteria included 1. transient ischemic attack, cerebral hemorrhage, subdural hematoma, or subarachnoid hemorrhage; 2. history of a central nervous system (CNS) disease other than stroke, such as tumor, trauma, hydrocephalus, or Parkinson's disease; 3. severe cognitive impairment, as defined by a Mini-Mental State Examination (MMSE) (M. F. Folstein, S. E. Folstein & P. R. Mchugh, 1975) score

of less than 19; 4. aphasia; and 5. medical conditions that would preclude follow-up three months after the index stroke, such as recurrent stroke, prolonged hospitalization (> 3 months), and physical frailty.

The study protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All participants signed a consent form.

### 6.2.2. Collection of demographic and clinical data

A research nurse collected subjects' demographic data (age, sex, and educational level in terms of school years) and assessed their stroke severity using the NIHSS (T. Brott, H. P. Adams, Jr., C. P. Olinger, *et al*, 1989).

### 6.2.3. Assessment of HRQoL

Three months after the onset of the index stroke, a trained research assistant, who was blind to the subjects' radiological data, assessed all participants in a research clinic with the Chinese (Hong Kong) version of the Short Form-36 (SF-36) (C. L. Lam, B. Gandek, *et al*, 1998), a valid and reliable instrument for measuring HRQoL in stroke (C. Anderson, S. Laubscher & R. Burns, 1996). The SF-36 focuses on subjective perceptions of health. It contains eight subscales that cover general health (GH), mental health (MH), role limitations due to emotional problems (RE), role limitations due to physical problems (RP), social functions (SF), vitality (VT), bodily pain

(BP), and physical functioning (PF). The subscale scores range from 0 to 100, with higher values representing better functions. The SF-36 has two composite scores: the physical component (PCS) and mental component (MCS) summary scores.

The research assistant also administered the 15-item version of the Geriatric Depression Scale (GDS) (P. P. Lim, L. L. Ng, P. C. Chiam, *et al*, 2000), the MMSE, and the Lubben Social Network Scale (LSNS) (Lubben Je, 1998) to assess participants' depressive symptoms, cognitive functioning, and degree of social support, respectively. The GDS and MMSE scores range from 0 to 15 and 0 to 30, respectively. A higher GDS score indicates more severe depressive symptoms, whereas a lower MMSE score represents poorer global cognitive functioning. The LSNS is a composite social network scale that was specifically designed for use in the elderly (Boey Kw. Chi I, 1994). It measures the level of social support that patients receive and their degree of social interaction with relatives and friends. The maximum score is 50, with a higher score indicating better social support.

### 6.2.4. Radiological examination

MRI was performed with a 1.5-T system (Sonata, Siemens Medical, Erlangen, Germany) within seven days of admission. Diffusion weighted imaging (DWI) (TR/TE/excitation = 180/122/4, matrix = 128 x 128, field of view (FOV) = 230 mm, slice thickness/gap = 5 mm/1 mm, echo planar imaging (EPI) factor = 90, acquisition time = 55 seconds) with three orthogonally applied gradients (b values of 1000, 500, and 0) was used. Other sequences included axial gradient echo (GRE) (TR/TE/excitation = 350/30/2, flip angle of 30 degrees, slice thickness/gap = 5 mm/0.5 mm, FOV = 230 mm, matrix = 256 x 256, time of acquisition = 5

minutes, 4 seconds), axial spin echo (SE) T1-weighted (TR/TE/excitation = 425/14/2, FOV = 230 mm, slice thickness/gap = 5 mm/0.5 mm, matrix = 256 x 256, time of acquisition = 4 minutes, 28 seconds), turbo spin echo (TSE), proton density (PD), T2-weighted (TR/TE/excitation = 2500/13-120/1, turbo factor = 5-15, FOV = 230 mm, slice thickness/gap = 5 mm/0.5 mm, matrix = 256 x 256, time of acquisition = 3 minutes, 30 seconds), and axial flair (fluid attenuated inversion recovery) (TR/TE/TI/excitation = 9000/117/2500/2, turbo factor = 31, FOV = 230 mm, slice thickness/gap = 5 mm/1 mm, matrix = 256 x 256, time of acquisition = 3 minutes, 20 seconds) sequences.

A neurologist (YKC), who was blind to the results of the other assessments, evaluated the MRIs for the following.

(1) Brain infarcts. Lesions approaching the signal characteristics of cerebrospinal fluid on the T1-weighted images and measuring over 3 mm in diameter were regarded as brain infarcts (H. Jokinen, H. Kalska, *et al*, 2006). Both the number and size of infarcts were measured. The total area of acute infarcts was measured with manual outlines of all areas with restricted water diffusion that were identified on the DWI with b values of 1000. Their total volume was calculated by multiplying the total area by the sum of the slice thickness and gap. Inter- and intra-rater reliability tests were performed on 20 participants, with good agreement found (volume of acute infarcts: inter-rater kappa = 0.93, intra-rater kappa = 0.96; number of infarcts: inter-rater kappa = 0.89, intra-rater kappa = 0.94).

(2) CMBs. CMBs were defined as small (2-10 mm) hypointense lesions on the T2*-weighted GRE sequence, but symmetric basal ganglia calcification and flow void artifacts of the pial blood vessels were excluded (M. Dichgans, M. Holtmannspotter, J. Herzog, *et al*, 2002). The CMB locations were divided into lobar (cortex and sub-cortical white matter), deep (caudate, lentiform,

thalamus, internal, and external capsule), and posterior fossa (brainstem and cerebellum) groups (C. Cordonnier, G. M. Potter, *et al*, 2009). The number of CMBs in each region was also recorded. Intra-rater reliability tests of the CMB measurements were performed on 30 participants, with good agreement found (presence of CMBs: intra-rater kappa = 0.85; number of CMBs: intra-rater intra-class correlation [ICC] = 0.95).

(3) WMLs. The extent of WMLs was graded using a modified version of Fazekas' scale (M. J. Firbank, J. T. O'brien, S. Pakrasi, *et al*, 2005), which scores deep and subcortical WMLs as mild, moderate, or severe (H. Baezner, C. Blahak, *et al*, 2008). The WMLs were scored on the basis of the PD images. The inter- and intra-rater weighted kappas for the WMLs were 0.85 and 0.90, respectively.

### 6.2.5. Statistical analysis

Descriptive data are presented as proportions or means, as appropriate. The correlation between the participants' clinical (age, sex, education, NIHSS, MMSE, and GDS scores) and radiological (number and volume of infarcts, presence of CMBs, and severity of WMLs) characteristics and the SF-36 domain and summary scores were examined using Spearman's correlation, except for the correlations between age and the SF-36 scores, which were examined with Pearson's correlation because not all of the other variables were normally distributed. Both the unadjusted and Bonferroni-adjusted p values were computed. Variables with an unadjusted $p < 0.05$ in these analyses were entered into different multivariate stepwise linear regression models to determine the partial correlations of the predictors of the SF-36 domain and summary

scores. All statistical tests were performed using SPSS for Windows (Release 14.0; SPSS Inc., Chicago, IL, USA).

## 6.3. Results

The study sample (n = 458) had the following characteristics: 74.5% were married, and their mean age and educational level were 66.2 ± 11.9 and 5.2 ± 4.5 years, respectively; 99.8% of the MRIs were obtained within one week of the stroke. The mean number and volume of acute infarcts were 1.1 ± 1.7 and 3.0 ± 9.3 ml, respectively. CMBs were found in 111 (24.2%) participants, and the mean number of CMBs was 5.6 ± 8.7. A significant correlation was found between the volume of acute infarcts and the presence of CMBs (rho = 0.269, $p < 0.001$).

The psychiatric, social, and HRQoL assessments took place 14.6 + 2.0 weeks after the index stroke. The mean MMSE, GDS, LSNS, and NIHSS scores were 25.9 ± 3.3, 5.0 ±3.7, 30.4 ± 8.0, and 4.7 ± 3.4, respectively. The PF, RP, BP, GH, VT, SF, RE, and MH subscale scores were 71.6 ± 27.9, 58.1 ± 41.4, 77.5 ± 24.6, 49.8 ± 20.6, 64.6 ± 21.3, 89.9 ± 15.6, 80.0 ± 35.0, and 73.5 ± 19.4, respectively.

Univariate analyses revealed that the female sex, education, neurological deficits (NIHSS), depressive symptoms (GDS), and cognitive function (MMSE) were correlated with all eight subscale and two summary scores (PCS and MCS; Table 6-1). The presence of lobar CMBs was negatively correlated with the PF, SF, RE, and PCS scores. After Bonferroni adjustment, the correlation between lobar CMBs and PF remained significant, whereas those between lobar CMBs and SF and RE became borderline and nonsignificant, respectively. Deep CMBs were

also negatively correlated with the SF and RE scores, whereas posterior fossa CMBs were negatively correlated with the RP score. The severity of WMLs was correlated with four of the SF-36 subscale scores and the PCS score, whereas the number of old infarcts was correlated with the PF and RP scores of the SF-36 (Table 6-2).

Linear regression analysis was performed for the PF, SF, RE, RP, PCS, and MCS scores (Table 6-3), and the presence of lobar CMBs was found to be independently associated with the PF and SF scores ($p < 0.05$).

## Table 6-1 statistically significant correlations between demographic and clinical characteristics and quality of life

| | PF | RP | BP | GH | VT | SF | RE | MH | PCS | MCS |
|---|---|---|---|---|---|---|---|---|---|---|
| Age | -0.365[c§] | -0.187[c§] | | | | | | | -0.229[c§] | |
| Female sex | -0.153[b§] | -0.170[b§] | -0.167[b§] | -0.160[b] | -0.171[c§] | -0.213[c§] | -0.168[b§] | -0.154[b§] | -0.204[c§] | -0.181[c§] |
| Education | 0.242[c§] | 0.143[b§] | 0.146[b§] | 0.147[b§] | 0.104[a] | 0.123[b] | 0.095[a] | 0.125[b‖] | 0.222[c§] | 0.122[b] |
| Married | 0.144[b§] | 0.126[b‖] | 0.118[a] | | | | 0.107[a] | | 0.150[b§] | 0.103a[a] |
| Recurrent stroke | -0.142[b§] | -0.097[a] | | | | -0.101[a] | -0.097[a] | | -0.132[b] | -0.096[a] |
| GDS | -0.347[c§] | -0.372[c§] | -0.385[‡§] | -0.430[c§] | -0.550[c§] | -0.427[c§] | -0.522[c§] | -0.562[c§] | -0.478[c§] | -0.676[c§] |
| MMSE | 0.385[c§] | 0.318[c§] | 0.201[c§] | 0.193[c§] | 0.144[b§] | 0.125[b‖] | 0.150[b§] | 0.124[b] | 0.386[c§] | 0.149[b§] |
| NIHSS | -0.296[c§] | -0.254[c§] | -0.125[b‖] | -0.147[b§] | -0.105[a] | -0.120[a] | -0.173[c§] | -0.121[*] | -0.293[c§] | -0.153[b] |

[a] P<0.05; [b] P<0.01; [c] P<0.001

[‖]Boderline significance after Bonferroni adjustment; [§]significant after Bonferroni adjustment

PF=Physical Functioning; RP=Role-Physical; BP=Bodily Pain, GH=General Health; VT=Vitality; SF =Social Functioning; RE=Role-Emotional; MH=Mental Health; PCS =Physical Component Summary Score; MCS=Mental Component Summary Score; NIHSS=National Institute of Health Stroke Scale; MMSE=Mini-Mental State Examination; GDS=Geriatric Depression Scale.

## Table 6-2 Satistically significant correlations between radiological characteristics and quality of life

| | PF | RP | BP | GH | VT | SF | RE | MH | PCS | MCS |
|---|---|---|---|---|---|---|---|---|---|---|
| Presence of CMBs | | | | | | | | | -0.107[a] | |
| Lobar CMBs | -0.141[b§] | | | | | 0.148[b‖] | 0.093[a] | | -0.115[a] | |
| Deep CMBs | | | | | | 0.107[a] | 0.097[a] | | | |
| Posterior fossa CMBs | | 0.100[a] | | | | | | | | |
| Severity of WMLs | -0.194[b§] | -0.163[b§] | | | | 0.121[a‖] | 0.099[a] | | -0.150[b‖] | |
| Number of acute infarcts | | | | | | | | | | |
| Volume of acute infarcts | | | | | | | | | | |
| Number of old infarcts | -0.112[a] | -0.158[b] | | | | | | | | |

[a] $P<0.05$; [b] $P<0.01$

‖Boderline significance after Bonferroni adjustment; §significant after Bonferroni adjustment

PF=Physical Functioning; RP=Role-Physical; BP=Bodily Pain, GH=General Health; VT=Vitality; SF=Social Functioning; RE=Role-Emotional; MH=Mental Health; PCS =Physical Component Summary Score; MCS=Mental Component Summary Score; CMBs=Cerebral microbleeds; WMLs=White matter lesions

**Table 6-3 Partial correlations from linear regression analysis of quality of life (dependent variable) and demographic, clinical and radiological variables**

| | PF | SF | RP | RE | PCS | MCS |
|---|---|---|---|---|---|---|
| Age | -0.150[b] | | | | | |
| Female sex | | -0.147[c] | | -0.089[a] | -0.094[a] | -0.122[a] |
| GDS | -0.201[c] | -0.420[c] | -0.331[c] | -0.572[c] | -0.402[c] | -0.647[c] |
| MMSE | 0.253[c] | | 0.208[c] | | 0.262[c] | |
| NIHSS | -0.157[c] | | -0.134[b] | | -0.142[b] | |
| Lobar CMBs | -0.084[a] | -0.087[a] | | | | |
| Severity of WMLs | | -0.089[a] | | | | |
| Number of old infarcts | | | -0.088[a] | | | |

[a] $P<0.05$; [b] $P<0.01$; [c] $P<0.001$

PF=Physical Functioning; RP=Role-Physical; SF=Social Functioning; RE=Role-Emotional; PCS=Physical Component Summary Score; MCS=Mental Component Summary Score; NIHSS=National Institute of Health Stroke Scale; MMSE=Mini-Mental State Examination; GDS=Geriatric Depression Scale; CMBs=Cerebral microbleeds; WMLs=White matter lesions

## 6.4. Discussion

To the best of our knowledge, this study was the first to examine the impact of CMBs on the HRQoL of stroke patients. The results show that lobar CMBs are correlated with HRQoL in stroke survivors. The study sample comprised a large cohort of stroke patients, and the radiological findings were examined against the background of several clinical and psychosocial correlates of HRQoL.

In addition to being a marker of underlying vascular disease, CMBs may also have a direct effect on neurological function, cognition, psychiatric morbidity, and disability, thereby resulting in poorer HRQoL. A higher number of baseline CMBs was associated with greater risk of cognitive impairment, functional dependence, and death in a three-year prospective study of patients with lobar hemorrhages (S. M. Greenberg, J. A. Eng, *et al*, 2004). CMBs have also been associated with executive function impairment in patients with ischemic stroke (D. J. Werring, D. W. Frazer, L. J. Coward, *et al*, 2004). Finally, CMBs are known to be an independent correlate of emotional liability in stroke (W. K. Tang, Y. K. Chen, J. Y. Lu, *et al*, 2009).

If CMBs do have a direct effect on HRQoL, then their location would be expected to play a part. Indeed, our findings suggest that only lobar, not deep or posterior fossa, CMBs are independent correlates of HRQoL. This finding also suggests that the CMBs associated with cerebral amyloid angiopathy, which has a lobar distribution, may have a greater impact on HRQoL in stroke. The importance of CMB location has been reported previously in studies of the effects of frontal lobe and basal ganglia CMBs on executive function (D. J. Werring, D. W.

Frazer, L. J. Coward, *et al*, 2004) and thalamic CMBs on emotional liability (W. K. Tang, Y. K. Chen, J. Y. Lu, *et al*, 2009).

The current study has several limitations. The assessment of PSD was made only once, at the three-month follow-up. Hence, the causality of the relationship between the MRI findings and long-term HRQoL remains unknown. Moreover, patients who did not receive an MRI examination and those with more severe stroke resulting in prolonged hospitalization and physical frailty were excluded. Another limitation is that the SF-36 is a generic scale, and some investigators have questioned its validity in stroke (J. C. Hobart, L. S. Williams, *et al*, 2002). Stroke-specific measures, such as the Stroke-Specific Quality of Life Scale, may have produced more valid information and should be used in future studies. Finally, the CMBs were measured in GRE with a slice thickness of 5 mm, which is less sensitive than thin-section susceptibility-weighted imaging (R. N. Nandigam, A. Viswanathan, *et al*, 2009).

In summary, the results of this study suggest that lobar CMBs have an impact on the HRQoL of stroke survivors. The importance of CMBs to other short- and long-term outcome measures in stroke warrants further investigation.

# CHAPTER 7 CONCLUSION

## 7.1. Summary of New Findings

The results suggest that WMHs and FSC infarcts may contribute to the development of PSD. In addition, lobar CMBs may affect the PSD symptom severity. Finally, our findings suggest that CMBs have a significant impact on the HRQoL of stroke survivors.

## 7.2. Strength and Limitations of the Studies

The strengths of the studies that are presented in this thesis are as follows. First, the sample sizes in the studies were reasonably large. Second, they are all prospective studies with a well-defined sampling frame that involved consecutively admitted Chinese stroke survivors from a well-defined catchment area. Third, the inter-rater reliability (Kappa=0.933) between two psychiatrists in the diagnosis of PSD was measured, which thereby diminished the possibility of idiosyncratic diagnostic practices that would have seriously biased the results. Forth, psychosical predictors of PSD, such as the level of social support and life events, were measured.

The limitations of the studies that are presented in this thesis should be acknowledged. The severity of strokes was mild in the sample and the assessment of PSD was made only once at the 3-month follow-up. Patients who died before the 3-month follow-up were not included in the study. Second, the relatively low frequency of PSD resulting in a relatively small number of

affected patients, which reduced the statistical power of the study. Third, MRI examination was performed only in the acute phase of stroke and new CMBs/ MBs might have appeared duration the three months period between the MRI examination and the assessment and contribute to the development of PSD.

## 7.3. Future research directions

Further longitudinal studies could provide valuable information on the incidence, natural course, and prognostic impact of depression in stroke. Prevention and treatment studies are also important. In addition, an in-depth examination of brain physiology through advanced imaging techniques or a neuroendocrine paradigm could provide further insight into the pathogenesis of these conditions.

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# APPENDIX

## I. DSM-IV criteria for diagnosis of depression

DSM IV Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do note include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.(1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood

(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

(3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.

(4) insomnia or hypersomnia nearly every day

(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

(6) fatigue or loss of energy nearly every day

(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either

by subjective account or as observed by others)

(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

DSM IV Major Depressive Episode:

More than two symptoms include one core symptom.

## II. Mini-mental state examination Chinese version

### 簡易智能狀態測驗

### Mini-Mental Status Examination (MMSE)

Name: _____ Study ID: _____ Date: 西元_____年____月_____ _____ _____日

Chart No.: _____ Handness: _____ Examination: _____ _____ _____ _____

| 錯誤 | 正確 | 不明 | | |
|---|---|---|---|---|
| 0 | 1 | 9 | 1) | 今年是那一年？ |
| 0 | 1 | 9 | 2) | 現在是什麼季節？ |
| 0 | 1 | 9 | 3) | 今天是幾號？ |
| 0 | 1 | 9 | 4) | 今天是禮拜幾？ |
| 0 | 1 | 9 | 5) | 現在是那一個月份？ |
| 0 | 1 | 9 | 6) | 我們現在是在那一個縣、市？ |
| 0 | 1 | 9 | 7) | 這棟樓房/建築是做什麼用的？用途是什麼？ |
| 0 | 1 | 9 | 8) | 這間醫院（診所）的名稱？ |
| 0 | 1 | 9 | 9) | 現在我們是在幾樓？ |
| 0 | 1 | 9 | 10) | 這裡是哪一科？ |
| 0 | 1 | 9 | 11) | 樹木『牡丹』 請重複這三個名稱，按第一次複述結果計分， |
| 0 | 1 | 9 | | 剪刀『汽車』 最多只能重複練習三次；練習次數：_____ |
| 0 | 1 | 9 | | 火車『石頭』 |

□ 12) 請從 100 開始連續減 7，一直減 7 直到我說停為止。

93_____; 86_____; 79_____; 72_____; 65_____;

0 1 9 13) 樹木（三分鐘以後）

0 1 9 14) 剪刀

0 1 9 15) 火車

0 1 9 16) （拿出手錶）這是什麼？_____

0 1 9 17) （拿出鉛筆）這是什麼？_____

0 1 9 18) "知足天地寬『心安菜根香』"

0 1 9 19) "請閉上眼睛"

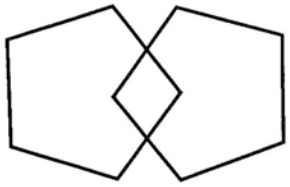
0 1 9 20) 請用左/右手（非利手）拿這張紙

0 1 9 把它折成對半

0 1 9 然後置於大腿上面

0 1 9 21) 請在紙上寫一句語意完整的句子。（含主詞動詞且語意完整的句子）

0 1 9 22) 這裡有一個圖形，請在旁邊畫出一個相同的圖形。



總分

□□ （圈選 9 的部分不予計入，並說明無法施測之原因）

## III. Geriatric Depression Scale Chinese version

# 老年抑鬱量表（GDS）

選擇最切合您一周來的感受的答案，在每題後[ ]內答“是”或“否”。

您的姓名（ ）性別（ ）出生日期（ ）職業(　)、文化程度（ ）。

1. [ ]　你對生活基本上滿意嗎？

2. [ ]　你是否已放棄了許多活動與興趣？

3. [ ]　你是否覺得生活空虛？

4. [ ]　你是否感到厭倦？

5. [ ]　你是否大部分時間精力充沛？

6. [ ]　你是否害怕會有不幸的事落到你頭上？

7. [ ]　你是否大部分時間感到幸福？

8. [ ]　你是否常感到孤立無援？

9. [ ]　你是否願意呆在家裡而不願去做些新鮮事？

10. [ ]　你是否覺得記憶力比以前差？

11. [ ]　你覺得現在活著很愜意嗎？

12. [ ]　你是否覺得像現在這樣活著毫無意義？

13. [ ]　你覺得生活充滿活力嗎？

14. [ ]　你是否覺得你的處境已毫無希望？

15. [ ]　你是否覺得大多數人比你強得多？

## IV. The NIH Stroke Scale (NIHSS) International

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

| Instruction | Scale Definition | Score |
|---|---|---|
| 1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation. | : Not alert; but arousable by minor stimulation to obey, answer, or respond.<br>Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped).<br>Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic. | |
| 1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak | 0 = Answers both questions correctly.<br>1= Answers one question correctly.<br>2 = Answers neither question correctly. | |

| | | |
|---|---|---|
| because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues. | | |
| 1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored. | 0 = Performs both tasks correctly.<br>1 = Performs one task correctly.<br>2 = Performs neither task correctly. | |
| 2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be | 0 = Normal.<br>1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present.<br>2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver. | |

| | | |
|---|---|---|
| scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy. | | |
| 3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a | 0 = No visual loss.<br>1 = Partial hemianopia.<br>2 = Complete hemianopia.<br>3 = Bilateral hemianopia (blind including cortical blindness). | |

| | | |
|---|---|---|
| clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11. | | |
| 4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible. | 0 = Normal symmetrical movements.<br>1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling).<br>2 = Partial paralysis (total or near-total paralysis of lower face).<br>3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face). | |
| 5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the | No drift; limb holds 90 (or 45) degrees for full 10 seconds.<br>1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.<br>2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.<br>3 = No effort against gravity; limb falls.<br>4 = No movement.<br>UN = Amputation or joint fusion, explain: | |

| | | |
|---|---|---|
| voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. | 5a. Left Arm<br>5b. Right Arm | |
| 6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. | 1 = Drift; leg falls by the end of the 5-second period but does not hit bed.<br>2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity.<br>3 = No effort against gravity; leg falls to bed immediately.<br>4 = No movement.<br>UN = Amputation or joint fusion, explain:<br>_____<br>6a. Left Leg<br>6b. Right Leg | |
| 7. Limb Ataxia: This item is aimed at finding | 0 = Absent.<br>1 = Present in one limb. | |

| | | |
|---|---|---|
| evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position. | 2 = Present in two limbs.<br>UN = Amputation or joint fusion, explain:<br>_____ | |
| 8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or | 0 = Normal; no sensory loss.<br>1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched.<br>2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg. | |

| | | |
|---|---|---|
| total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item. | | |
| 9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The | 0 = No aphasia; normal.<br>1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response.<br>2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response.<br>3 = Mute, global aphasia; no usable speech or auditory comprehension. | |

| | | |
|---|---|---|
| intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands. | | |
| 10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested. | 0 = Normal.<br>1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty.<br>2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.<br>UN = Intubated or other physical barrier, explain:_____ | |
| 11. Extinction and Inattention (formerly Neglect): Sufficient | 0 = No abnormality.<br>1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral | |

| | | |
|---|---|---|
| information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable. | simultaneous stimulation in one of the sensory modalities.<br>2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space. | |

## V. The Short Form (36) Health Survey Chinese Version

1、總體來講，您的健康狀況是：
①非常好　②很好　③好　④一般　⑤差
2、跟 1 年以前比您覺得自己的健康狀況是：
①比 1 年前好多了　②比 1 年前好一些　③跟 1 年前差不多　④比 1 年前差一些　⑤比 1 年前差多了
（權重或得分依次為 1，2，3，4 和 5）
健康和日常活動
3、以下這些問題都和日常活動有關。請您想一想，您的健康狀況是否限制了這些活動？如果有限制，程度如何？
（1）重體力活動。如跑步舉重、參加劇烈運動等：
①限制很大　②有些限制　③毫無限制
（權重或得分依次為 1，2，3；下同）注意：如果採用漢化版本，則得分為 1，2，3，4，則得分轉換時做相應的改變。
（2）適度的活動。如移動一張桌子、掃地、打太極拳、做簡單體操等：
①限制很大　②有些限制　③毫無限制
（3）手提日用品。如買菜、購物等：
①限制很大　②有些限制　③毫無限制
（4）上幾層樓梯：
①限制很大　②有些限制　③毫無限制
（5）上一層樓梯：
①限制很大　②有些限制　③毫無限制
（6）彎腰、屈膝、下蹲：
①限制很大　②有些限制　③毫無限制
（7）步行 1500 米以上的路程：
①限制很大　②有些限制　③毫無限制
（8）步行 1000 米的路程：
①限制很大　②有些限制　③毫無限制
（9）步行 100 米的路程：
①限制很大　②有些限制　③毫無限制
（10）自己洗澡、穿衣：
①限制很大　②有些限制　③毫無限制
4、在過去 4 個星期裡，您的工作和日常活動有無因為身體健康的原因而出現以下這些問題？

（1）減少了工作或其他活動時間：
①是　②不是
（權重或得分依次為 1，2；下同）
（2）本來想要做的事情只能完成一部分：
①是　②不是
（3）想要幹的工作或活動種類受到限制：
①是　②不是
（4）完成工作或其他活動困難增多（比如需要額外的努力）：
①是　②不是
5、在過去 4 個星期裡，您的工作和日常活動有無因為情緒的原因（如壓抑或憂慮）而出現以下這些問題？
（1）減少了工作或活動時間：
①是　②不是
（權重或得分依次為 1，2；下同）
（2）本來想要做的事情只能完成一部分：
①是　②不是
（3）幹事情不如平時仔細：
①是　②不是
6、在過去 4 個星期裡，您的健康或情緒不好在多大程度上影響了您與家人、朋友、鄰居或集體的正常社會交往？
①完全沒有影響　②有一點影響　③中等影響　④影響很大　⑤影響非常大
（權重或得分依次為 5，4，3，2，1）
7、在過去 4 個星期裡，您有身體疼痛嗎？
①完全沒有疼痛　②有一點疼痛　③中等疼痛　④嚴重疼痛　⑤很嚴重疼痛
（權重或得分依次為 6，5.4，4.2，3.1，2.2，1）
8、在過去 4 個星期裡，您的身體疼痛影響了您的工作和家務嗎？
①完全沒有影響　②有一點影響　③中等影響　④影響很大　⑤影響非常大
（如果 7 無 8 無，權重或得分依次為 6，4.75，3.5，2.25，1.0；如果為 7 有 8 無，則為 5，4，3，2，1）
您的感覺
9、以下這些問題是關於過去 1 個月裡您自己的感覺，對每一條問題所說的事情，您的情況是什麼樣的？
（1）您覺得生活充實：
①所有的時間　②大部分時間　③比較多時間　④一部分時間　⑤小部分時間　⑥沒有這種感覺
（權重或得分依次為 6，5，4，3，2，1）

（2）您是一個敏感的人：

①所有的時間　②大部分時間　③比較多時間　④一部分時間　⑤小部分時間　⑥沒有這種感覺

（權重或得分依次為 1，2，3，4，5，6）

（3）您的情緒非常不好，什麼事都不能使您高興起來：

①所有的時間　②大部分時間　③比較多時間　④一部分時間　⑤小部分時間　⑥沒有這種感覺

（權重或得分依次為 1，2，3，4，5，6）

（4）您的心理很平靜：

①所有的時間　②大部分時間　③比較多時間　④一部分時間　⑤小部分時間　⑥沒有這種感覺

（權重或得分依次為 6，5，4，3，2，1）

（5）您做事精力充沛：

①所有的時間　②大部分時間　③比較多時間　④一部分時間　⑤小部分時間　⑥沒有這種感覺

（權重或得分依次為 6，5，4，3，2，1）

（6）您的情緒低落：

①所有的時間　②大部分時間　③比較多時間　④一部分時間　⑤小部分時間　⑥沒有這種感覺

（權重或得分依次為 1，2，3，4，5，6）

（7）您覺得筋疲力盡：

①所有的時間　②大部分時間　③比較多時間　④一部分時間　⑤小部分時間　⑥沒有這種感覺

（權重或得分依次為 1，2，3，4，5，6）

（8）您是個快樂的人：

①所有的時間　②大部分時間　③比較多時間　④一部分時間　⑤小部分時間　⑥沒有這種感覺

（權重或得分依次為 6，5，4，3，2，1）

（9）您感覺厭煩：

①所有的時間　②大部分時間　③比較多時間　④一部分時間　⑤小部分時間　⑥沒有這種感覺

（權重或得分依次為 1，2，3，4，5，6）

10、不健康影響了您的社會活動（如走親訪友）：

①所有的時間　②大部分時間　③比較多時間　④一部分時間　⑤小部分時間　⑥沒有這種感覺

（權重或得分依次為 1，2，3，4，5）

總體健康情況

11、請看下列每一條問題，哪一種答案最符合您的情況？

（1）我好象比別人容易生病：

①絕對正確　②大部分正確　③不能肯定　④大部分錯誤　⑤絕對錯誤`

（權重或得分依次為 1，2，3，4，5）

（2）我跟周圍人一樣健康：

①絕對正確　②大部分正確　③不能肯定　④大部分錯誤　⑤絕對錯誤

（權重或得分依次為 5，4，3，2，1）

（3）我認為我的健康狀況在變壞：

①絕對正確　②大部分正確　③不能肯定　④大部分錯誤　⑤絕對錯誤

（權重或得分依次為 1，2，3，4，5）

（4）我的健康狀況非常好：

①絕對正確　②大部分正確　③不能肯定　④大部分錯誤　⑤絕對錯誤

（權重或得分依次為 5，4，3，2，1）

## VI. The Lubben Social Network Scale Chinese Version

陸斌社會網路量表

1，你至少一个月内见过或联络过多少家人和亲戚？

0. 没有任何人
1. 一个
2. 二个
3. 三个至四个
4. 五个至八个
5. 九个或以上

2，最常与你联络的那位家人或亲戚，请问多久与他联络一次？

0. 少過一個月一次
1. 一個月一次
2. 一個月數次
3. 一個星期一次
4. 一個星期數次
5. 每一天

3，有多少家人和亲戚你觉得与他们亲近？即是你有多少家人和亲戚你觉得能与他们谈自己的心事或向他们求帮助？

0. 没有任何人

1. 一个

2. 二个

3. 三个至四个

4. 五个至八个

5. 九个或以上

4. 你有多少好朋友？即是你有多少好朋友能畅所欲言自己的心事或向他们求帮助？

0. 沒有任何人
1. 一個
2. 二個
3. 三個至四個
4. 五個至八個
5. 九個或以上

5. 有多少好朋友你最少一个月见面或联络一次？

0. 沒有任何人

1. 一個

2. 二個

3. 三個至四個

4. 五個至八個

5. 九個或以上

6. 请告诉我你与那一位跟你接触最多的朋友见面或联络的次数？

0. 沒有任何人

1. 一個

2. 二個

3. 三個至四個

4. 五個至八個

5. 九個或以上

7. 当你有重要的事情要决定，有没有人和你商量？

5. 每次都有
4. 經常有
3. 時常有
2. 有時有
1. 很少
0. 沒有

8. 当你认识的人有重要的事要决定时，他们有没有跟你商量？

5. 每次都有
4. 經常有
3. 時常有
2. 有時有
1. 很少
0. 沒有

9. 是否有人依赖你为他们做些事，如买东西、煮饭、修理东西、清洁、看小孩？

5. 每次都有
4. 經常有
3. 時常有
2. 有時有
1. 很少
0. 沒有

10. 你独居或与他人同住 （注意：他们包括亲戚或妯娌）

5. 與配偶同住
4. 與家人或親戚同住
1. 與其他沒有關係的人同住 （譬如傭人）
0. 獨居

## VII. Hosopital Anxiety and Depression Scale Chinese Version

### 醫院焦慮抑鬱量表 (HAD)

醫生都認識到情緒在多種疾病中扮演重要的角色，因此，如果你的醫生了解你的感受，他便能更加全面地幫助你。這份問卷的設計就是為了幫助你的醫生去了解你的感受，請閱讀下列每題，並圈出最接近你過去一星期的情緒狀況。

請不要花太多時間考慮你的答案，你對問題的立刻反應，往往比反覆思量來得更準確。

1. 我感到神經緊張：
   - A. 大部份時候感到 3
   - B. 很多時候感到 2
   - C. 有時候、間中感到 1
   - D. 完全不感到 0

2. 我有一種驚恐，好像有些可怕的事情會發生：
   - A. 很肯定有，而且相當厲害 3
   - B. 有，但不太厲害 2
   - C. 有少許，但不令我擔心 1
   - D. 完全沒有 0

3. 煩惱的念頭在我腦海中浮現：
   - A. 絕大部份時候 3
   - B. 很多時候 2
   - C. 有時候，但不太常 1
   - D. 只是間中 0

4. 我能安坐並感到鬆弛：
   - A. 肯定能夠 0
   - B. 通常能夠 1
   - C. 不時常能夠 2
   - D. 完全不能 3

5. 我有一種忐忑不安的驚恐（十五、十六的感覺）：
   A. 完全沒有 0
   B. 間中有 1
   C. 相當多時候有 2
   D. 很常有 3

6. 我感到不能安靜，像要不停地走動：
   A. 很強烈 3
   B. 相當強烈 2
   C. 不太強烈 1
   D. 完全沒有 0

7. 我突然感到驚惶失措：
   A. 非常多時候 3
   B. 相當多時候 2
   C. 不太多時候 1
   D. 完全沒有 0

Total score: _____

## VIII. Magnetic resonance imaging data form

Study ID: _____

| | | ACUTE | | | | OLD | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Left | | Right | | Left | | Right | |
| | | No. | Vol. | No. | Vol. | No. | Vol. | No. | Vol. |
| **Brain Regions:** | 1. Frontal Lobe | | | | | | | | |
| | *a. Prefrontal Cortex* | | | | | | | | |
| | *b. Orbitofrontal prefrontal* | | | | | | | | |
| | *c. Dorsolateral prefrontal* | | | | | | | | |
| | *d. Anterior cingulated gyrus* | | | | | | | | |
| | 2. Temporal Lobe | | | | | | | | |
| | 3. Parietal Lobe | | | | | | | | |
| | 4. Occipital Lobe | | | | | | | | |
| | 5. Brainstem | | | | | | | | |
| | *a. Medulla* | | | | | | | | |
| | *b. Pons* | | | | | | | | |
| | *c. Midbrain* | | | | | | | | |
| | 6. Cerebellum | | | | | | | | |
| | 7. Thalamus | | | | | | | | |
| | 8. Caudate | | | | | | | | |
| | 9. Lentiform nucleus | | | | | | | | |
| | *a. Putamen* | | | | | | | | |

| | | ACUTE | | | | OLD | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Left | | Right | | Left | | Right | |
| | | No. | Vol. | No. | Vol. | No. | Vol. | No. | Vol. |
| | *b. Globus pallidus* | | | | | | | | |
| | 10. Internal capsule | | | | | | | | |
| | *a. Anterior internal capsules* | | | | | | | | |
| | *b. Posterior internal capsules* | | | | | | | | |
| | *c. Genu of internal capsule* | | | | | | | | |
| | 11. Anterior corona radiata | | | | | | | | |
| | 12. Posterior corona radiata | | | | | | | | |
| | 13. Corpus callosum | | | | | | | | |
| | 14. Others: | | | | | | | | |
| | **Total:** | | | | | | | | |