

Neuropsychiatric Disorders Following Vascular Brain Injury

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Abstract

Several neuropsychiatric disorders such as mood, anxiety and psychotic disorders occur following cerebrovascular lesions. Post-stroke depression is the most common of these disorders and, along with post-stroke anxiety, has been shown to inhibit physical and cognitive recovery. Antidepressants have been shown to effectively treat post-stroke depression and to have a positive impact on rehabilitation efforts in patients suffering from this disorder. Much less is known about the potential impact of psychiatric conditions on recovery after stroke. Controlled trials will be able to adequately determine the effectiveness of treatment for these disorders.

Key Words: Stroke, neuropsychiatric disorders, review.

Introduction

DESPITE A STEADY DECLINE in the incidence of strokes over the last 50 years, due to improvement in the treatment of diseases such as hypertension, diabetes mellitus and hypercholesterolemia, this disorder continues to represent a major health problem. Stroke is the second leading cause of death worldwide. According to estimates of the American Stroke Association, about 750,000 strokes occur annually in the U.S. and, as a result of improvement in the acute management of this disorder, there are about 4.5 million stroke survivors in the U.S. (1). Neuropsychiatric disorders related to stroke are prevalent (Table 1; 2–15). This article will address a number of these disorders and their impact on recovery from stroke.

Post-stroke Depression

Depression is the most frequently occurring psychiatric disorder after stroke. It has been consistently associated with poor cognitive status (16) and functional outcome (17, 18) in stroke sur-

vivors. Despite its prevalence, it has been reported that general practitioners underdiagnose post-stroke depression (PSD) in up to 80% of cases (19). This is thought to be due to lack of awareness of this disorder.

Diagnosis

Despite adopting a non-etiological view to define most psychiatric syndromes, the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, 4th edition (DSM-IV-TR) (Table 2) contemplates for PSD a diagnosis of “mood disorder due to stroke with depressive features.” However, since this concept lacks the syndromic specificity of affective disorders, PSD has been mostly defined, for research purposes, as either major or minor depression according to the Research Diagnostic Criteria (20).

The DSM-IV-TR symptom criteria for PSD involve signs or symptoms frequently observed in stroke patients who are not depressed, such as hypomimia, motor or speech retardation, apathy, insomnia or decrease in appetite (21). Thus, there is a lack of consensus among different research groups on the most appropriate method for diagnosing PSD when cognitive or neurovegetative symptoms result from physical illness (22, 23). While some researchers advocate the use of an inclusive approach in which depressive diagnostic symptoms are counted regardless of whether they may be related to physical illness (24), others favor an etiologic approach. Using the etiologic approach, a symptom is counted only if the diagnostician feels that it is not the result of physical ill-

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TABLE 1
Prevalence of Post-Stroke Neuropsychiatric Disorders

Syndrome/Investigator	Setting	N	Prevalence
Depression			
Burvill et al. (2)	Community	294	23%
House et al. (3)	Community	89	23%
Eastwood et al. (4)	Rehabilitation unit	87	50%
Morris et al. (5)	Rehabilitation unit	99	35%
Astrom et al. (6)	Acute hospitalization	80	25%
Anxiety Disorder			
Leppavuori et al. (7)	3–4 months post-stroke	277	20.6%
Castillo et al. (8)	Acute hospitalization	309	27%
Mania			
Starkstein et al. (9)	Acute hospitalization	700	3 cases
Dunne et al. (10)	Acute hospitalization	661	3 cases
Anosognosia			
Stone et al. (11)	Acute hospitalization	69 right side stroke 102 left side stroke	28% 5%
Pathological Affect			
Piamarta et al. (12)	Acute hospitalization	33	48.5%
Calvert et al. (13)	Acute hospitalization	448	21.5%
Apathy without Depression			
Starkstein et al. (14)	Acute hospitalization	80	11%
Brodsky et al. (15)	3–6 months post-stroke	167	26.7%

TABLE 2
DSM-IV-TR Criteria for 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 not 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.

ness (25). Thus, there is a need to determine what symptom clusters have diagnostic validity in PSD.

To examine the phenomenology of post-stroke depression, Gainotti et al. (26) developed a scale to compare patients with PSD to patients admitted to a psychiatric unit with a diagnosis of primary major depression (i.e. not due to a general medical cause). PSD patients exhibited higher scores in the following items of this scale: catastrophic reactions, hyperemotionalism, and diurnal mood variation. Moreover, among 142 stroke patients, Fedoroff et al. (27) found that at 2-year follow-up, depressed patients exhibited a significant higher frequency of all the assessed vegetative and psychologic symptoms, except for guilt and self-deprecation.

Prevalence

The prevalence of PSD has been examined by numerous systematic reviews (28, 29). Different factors, including the setting (in-hospital vs. community surveys) and time frame (acute post-stroke period vs. several months after the stroke) of epidemiological studies, contribute to the reported differences in the prevalence rates of PSD. Other factors that complicate the diagnostic accuracy are methodological limitations such as the lack of standardized criteria for diagnosing PSD (30–32) and the difficulty in assessing the presence of mood disorders in patients who might exhibit post-stroke residual cognitive and language impairments.

A systematic review by Robinson (33) reported that the mean frequency of major depression among stroke patients in acute and rehabilitation hospitals was 19.3% while the mean prevalence of major depression among stroke patients studied in community settings was 14.1%. Consistent with these findings, a review of prevalence studies by White and Mulsant (29) demonstrated a greater occurrence of PSD in hospitalized patients compared to patients in the community, reflecting a reciprocal relationship between depression and post-stroke-persistent physical disability. This review also found that the prevalence of major depression was higher when patients were studied soon after their stroke.

Clinical Course

Results from several longitudinal studies that examined the duration of PSD suggest that PSD can extend up to 3 years from the acute phase of the stroke (34). In a longitudinal study, Morris et al. (5) found that the mean duration of post-stroke major depression was 39 ± 31.8 weeks, whereas the mean duration of minor depression was only

12.2 ± 18.2 weeks. Another longitudinal study by Astrom et al. (6) followed 80 PSD patients for a 3-year period and found that 30% of patients with in-hospital major depression remained depressed at 1-year follow-up. Of them, 25% remained depressed at 2-year follow-up while at 3-year follow-up 20% were still depressed.

A longitudinal study of acute stroke patients by Burvill et al. (35) reported that at 24 months follow-up, patients who had in-hospital minor depression had a significantly higher frequency of depression (major or minor) compared to patients with in-hospital major depression. These results suggested that while major post-stroke depression has a natural course of less than 1 year, minor depression is often more persistent.

Premorbid Risk Factors

Little is known about the risk factors for developing depression after stroke. Knowledge of these factors would allow clinicians to initiate, during the acute post-stroke period, measures to better target prevention and treatment of PSD.

In a prospective study that examined the contributions of neurobiological, functional and psychosocial factors to PSD by Astrom et al. (36), a population-based cohort of 80 patients with acute stroke was assessed for a period of 3 years for the presence of depression, functional ability and social network. Left anterior brain lesion, dysphasia and living alone were found to be the most important predictors of immediate major depression after stroke. While at 3 months post-stroke the most important predictor for depression was dependence in activities of daily living, at 3 years post-stroke, generalized cerebral atrophy was the most important predictor. There is a need for further research to elucidate this correlation between cerebral atrophy and function. Specifically, there is a need to correlate focal versus generalized atrophy with the underlying pathology and outcome. A more recent study by Morrison et al. (37) that also assessed stroke patients repeatedly for a 3-year period, reported that earlier levels of functional deficit and anxiety are significant predictors of depression at follow-up. A study by Spalletta et al. (38) reported that predictors of cognitive function and depression severity are different in subjects with different laterality of lesion. These authors showed that PSD is associated with cognitive impairment only in patients with left-brain lesions.

A systematic review by Hackett and colleagues (28) found that most studies consistently associated physical disability, stroke severity and cognitive impairment with depression. However, this re-

view also demonstrated that major limitations such as variable selection and poor statistical methodology present in these studies still prevent the identification of patients who are most at risk of developing PSD.

Anatomical Correlates

Many investigators have attempted to find a correlation between lesion location and PSD in order to delineate an organic hypothesis for the emergence of depression in a subpopulation of stroke patients. The earliest and most prevalent pathophysiological hypothesis of increased risk of PSD linked this disorder with left-sided anterior brain lesions (39, 40). However, the significance of stroke lesion location for the consequent appearance of depression has been disputed by several authors (41, 42).

A recent meta-analytical study by Narushima et al. (43) aimed at reappraising the original localization hypothesis found, at 6 months follow-up, a moderately strong inverse correlation between the severity of depressive symptoms and the distance of the anterior border of the left hemisphere lesion from the frontal pole. These authors also hypothesize that the correlation between the proximity of the lesion to the frontal pole and the severity of depressive symptoms may be due to anterior lesions interrupting ascending noradrenergic and serotonergic fibers closer to their origin from the brainstem causing greater depletion of these neurotransmitters than more posterior lesions.

Relationship with Cognitive and Social Impairment

Dementia is frequently observed after stroke (44–46). As many as one third of stroke survivors assessed during hospitalization were found to meet criteria for dementia at a four-year follow-up assessment (47). Additionally, cognitive performance has been reported to be more prevalent in stroke patients with concurrent major depressive episodes compared to non-depressed stroke patients (48–50), especially after left hemisphere lesions (49). Studies are needed to further delineate the temporal relationship between conditions predisposing to dementia and post-stroke cognitive function.

However, the association between depression and cognitive impairment in stroke was found to decline with time. House et al. failed to show significance at 1-year (51) and 2-year follow-ups (52). Furthermore, during the course of a recent double-blind treatment trial with nortriptyline by

Kimura et al. (53), patients whose mood disorders remitted exhibited significantly greater recovery in cognitive function compared to patients whose mood disorders did not remit.

Relationship with Functional Impairment and Recovery

Patients affected by stroke manifest a high prevalence of sensory-motor impairment (54, 55). Approximately 80% of patients with acute stroke present with focal weakness or paralysis. The relationship between PSD and functional impairment is complex. The measurement of physical impairment involves an evaluation of motor and sensory functions and of deficits in the performance of activities of daily living (ADL) (18). In a large population of PSD patients, a significant correlation was found between the severity of depressive symptoms and the severity of impairment in ADL (e.g., patients' ability of dress and feed themselves, walk, read and maintain sphincter control) (56). However, a recent study by Nannetti et al. (57) of 117 acute stroke patients selected in an intensive rehabilitation unit failed to show a negative impact of PSD on functional recovery.

Although most stroke patients experience some natural recovery of their neurologic function and ability to perform ADL, at 3 and 6 month follow-ups, patients with depression after stroke were significantly more impaired in their ADL than patients without depression. Moreover, in-hospital ADL impairment was found to correlate with severity of depression (18), suggesting that depression influences ADL recovery.

Chemerinski et al. (58) examined the effect of remission of PSD on ADL recovery. Patients with PSD were selected and randomly assigned to either active treatment with the antidepressant nortriptyline or with placebo. Patients whose depressive disorders remitted during the medication trial had significantly greater recovery in ADL functions, compared with patients whose depression failed to remit.

Treatment

Despite multiple reports on the negative impact of depression on functional post-stroke recovery and prognosis, many patients with PSD do not receive adequate treatment. Physician reluctance to prescribe antidepressants to post-stroke patients may include the belief that depression is an understandable and expectable emotional reaction to the physical impairment of stroke as well as the fear of the potential side effects of psychotropic medications in this mostly elderly patient population.

In the earliest double-blind, placebo-controlled study that examined the efficacy of antidepressant medication in PSD, patients given nortriptyline showed a significantly greater improvement in various measures of depressive symptoms (i.e., the Ham-D, the Zung Self-Rating Depression Scale, and the profile of depressive symptoms assessed by the Present State Exam) than placebo-treated subjects (59). This study also reported that patients who received active treatment for 6 weeks had significantly lower depression scores than patients who were treated for 4 weeks, suggesting that longer duration of treatment may improve outcome. In later studies, agents such as trazodone (60) and selective serotonin reuptake inhibitors (SSRIs) [i.e., citalopram (61), sertraline (62), fluoxetine (63)] have also shown to be effective treatments for PSD. For example, PSD patients daily treated with 20 mg of fluoxetine showed a higher reduction of Montgomery-Asberg Depression Scores (MADRS) compared to placebo-treated patients (63). In contrast, a study by Robinson et al. (64) failed to show significant differences between PSD patients treated with fluoxetine vs. those treated with placebo.

Besides antidepressant medication, other treatment modalities such as methylphenidate (65), electroconvulsive therapy (66) and repetitive transcranial magnetic stimulation (67) have also been shown to be effective in PSD

Post-stroke Anxiety Disorder

Diagnosis and Prevalence

The DSM-IV-TR criteria for primary generalized anxiety disorder (GAD) include the presence of a sustained worrying state associated with at least three anxiety symptoms, including restlessness, decreased energy, concentration difficulties, irritability, muscle tension, and sleep disturbance, for a period of at least 6 months. The DSM-IV-TR characterizes post-stroke generalized anxiety disorder as "anxiety disorder due to stroke, with generalized anxiety."

As with PSD, differences in selection of patient populations, diagnostic criteria, and time elapsed since stroke account for the variability in reported prevalence rates of post-stroke anxiety disorders by different studies. For example, Lepavuo et al. (68) found, in a study of 277 patients studied at 3–4 months after ischemic stroke, that the frequency of GAD was 20.6%, while a study by Castillo et al. (8) reported that the mean prevalence of GAD in a group of 309 patients hospitalized with an acute stroke was 27%. Moreover,

these authors also reported that 75% of those patients who met DSM-III-R criteria for GAD (except for the 6-month duration) also met criteria for major or minor depression, suggesting that post-stroke anxiety disorder and PSD are comorbid conditions.

Anatomical Correlates

A study by Castillo et al. (69) reported that left-hemisphere strokes were associated with comorbid anxiety/depression disorders while right-hemisphere strokes were correlated with pure anxiety disorders. Similar findings were found in a longitudinal study by Astrom (6). In this study, patients with post-stroke GAD also exhibited, at a 3-year follow-up assessment, generalized cerebral cortical and subcortical atrophy. The author hypothesized that this atrophy might play a role in the pervasive nature of post-stroke anxiety though aging, preexisting Alzheimer's disease, chronic decreased cerebral blood flow; comorbid conditions would also need to be considered and ruled out.

Treatment

Since the treatment of post-stroke anxiety disorder has never been systematically studied, at the present time results from studies of patients with anxiety without brain lesions are the only available source of information for the treatment of this disorder.

Benzodiazepine medication is the most commonly employed treatment for anxiety. However, in this mostly elderly population long-acting benzodiazepines can be associated with significant side effects. Due to their more tolerable side effect profile, buspirone and SSRIs might constitute an alternative treatment option (69).

Post-stroke Mania

The concept of secondary mania refers to the occurrence of manic symptoms resulting from neurological, metabolic or toxic disorders (70). Patients with secondary mania showed similar frequencies of insomnia, elation, pressured speech, flight of ideas, and grandiosity when compared to patients suffering from a primary mood disorder (71, 72). While PSD has been the focus of considerable research, because of its relatively rare occurrence, post-stroke mania has rarely been studied (73). In a series of 700 consecutive stroke patients, Starkstein et al. (9) identified only 3 cases of post-stroke mania. Similarly, among 661 stroke patients, Dunne et al. (10) only identified 3 cases with this disorder. Moreover, no patients were found to suffer from post-stroke mania in two large

community studies that examined the prevalence of neuropsychiatric disorders after stroke, the Oxfordshire Community Stroke Project (3) and the Perth Community Stroke Study (35).

Clinical, demographic and prognostic features have been difficult to identify in post-stroke mania due to its low prevalence. However, family history of mood disorder was found to be correlated with this disorder (74). Furthermore, Cummings and Mendez (75) reported a significant correlation of post-stroke mania with right hemispheric lesions leading to dysfunction of the ventral limbic circuit involving the orbitofrontal and basotemporal cortex as well as the caudate and dorsomedial thalamic nucleus. The authors hypothesized that, in contrast with PSD, post-stroke mania may be rare because dysfunction in more than one area (i.e., limbic lesion and subcortical atrophy) of the right hemisphere is required for its production.

Lithium has been the most commonly used treatment for secondary mania. However, since the results published in the literature involve only individual case reports and open label treatment studies, there is no clear evidence currently regarding the most effective treatment for post-stroke mania.

Other Post-stroke Neuropsychiatric Disorders

Besides the post-stroke psychiatric disorders described above, other conditions such as catastrophic reaction, anosognosia, pseudobulbar affect, psychosis, and abulia can also be observed in stroke patients.

Catastrophic Reaction

“Catastrophic reaction” is a term created by Goldstein in 1939 (76) to describe a series of symptoms including aggressiveness, anxiety, tearfulness and renouncement occurring in patients with brain insults who are unable to cope with their physical or cognitive impairments. These emotional outbursts are believed to be short lived and related to trigger stressors such as performing a cognitive task during a neuropsychological assessment.

Results from a study by Gainotti (77, 78) suggested that in stroke patients, catastrophic reaction (CR) is associated with left hemisphere brain damage. This author also hypothesized that many patients who exhibit tearfulness and depression triggered by the stress of psychiatric examinations are usually diagnosed as having PSD; however, rather than having a prolonged depressive disorder, they may be having a brief CR.

Starkstein et al. (79) developed a CR scale to examine the frequency of this disorder and its rela-

tionship with depression. In this study the frequency of major depression was reported to be significantly greater in stroke patients with CR. Moreover, these patients also had significantly higher Hamilton anxiety scale scores and greater impairment in activities of daily living than patients without CR. However, patients with CR did not show significantly more cognitive impairment than those without this disorder.

Anosognosia

Anosognosia is a term coined by Babinski (80) to describe patients with cerebral lesions who ignore their hemiplegia. Currently, this term is used also to characterize patients with lack of awareness of other deficits (e.g., amnesia and visual loss) resulting from any brain disorder (81).

A meta-analysis by Pia et al. (82) found that the probability of developing anosognosia is highest when the stroke lesion involves both parietal and frontal structures. Moreover, in a study of patients with stroke, those who exhibited anosognosia showed significantly higher rates of hemineglect, disturbances in prosody and deficits in recognizing facial emotions (83).

Pathological Affect

Pseudobulbar affect describes uncontrollable episodes of laughing and crying induced by corticobulbar or corticopontine lesions resulting from bilateral strokes. Since it was later recognized that in most cases these symptoms were not associated with bilateral upper motor neuron lesions, the term pseudobulbar affect was replaced with the more general term pathological affect. Thus, pathological affect is an affective disinhibition syndrome characterized by uncontrollable episodes of laughter or crying that are discordant or disproportionate to the situation at hand (84). Besides strokes, this disorder has been frequently reported in demyelinating diseases (85), and amyotrophic lateral sclerosis (86). The reported prevalence rates of this disorder following strokes vary from 11–52% (86).

In a study by Robinson et al. (88) of 28 patients with either acute or chronic stroke, patients treated with nortriptyline for 4–6 weeks showed significantly greater improvement in pathological affect as measured by the Pathological Laughter and Crying Scale (PLACS) when compared with placebo-treated controls. Moreover, in another double-blind drug trial using a crossover design, Andersen et al. (89) reported that patients treated with citalopram responded to treatment, with a reduction in the number of crying episodes by at least 50%.

Post-stroke Psychosis

Psychotic symptoms (i.e., delusions and hallucinations) are rarely observed after stroke. A 9-year follow-up longitudinal study of stroke patients only found five patients who exhibited psychotic symptoms. Moreover, since all of these patients had right frontoparietal lesions and, when compared to stroke patients without psychosis, showed higher frequency of subcortical atrophy (90), the authors hypothesized that these structural findings are risk factors for developing psychosis after stroke.

Levin and Finklestein (91) found, in 8 patients without earlier psychiatric disorder, delayed psychotic symptoms (i.e., delusions, hallucinations) up to 11 years after right temporoparietooccipital stroke. Seven of these patients had clinical seizures in close temporal relationship to the psychosis, and a significant improvement of psychotic symptoms was observed after administration of antiepileptic drugs, but nonconvulsive status was not ruled out in any of these cases.

Post-stroke Apathy

The apathy syndrome is a simultaneous decrease in the behavioral, cognitive and emotional concomitants of goal-directed behavior due to loss of motivation, clinically evidenced by symptoms such as flat affect as well as decreased interest and poor effort in everyday activities (92).

In a study of 80 acute stroke patients by Starkstein et al. (14) apathy alone was exhibited by 11% of patients while another 11% displayed both apathy and depression. However, a study by Brodaty et al. (15) found that the rate of apathy in a cohort of 167 patients assessed at 3–6 months post-stroke was 26.7%. The variability in the methods used to assess apathy might explain the profound differences in the reported rates of this disorder after strokes (15).

A significant inconsistency also exists with respect to the association between apathy and stroke lesion location, with reports of left (93), right (77) and bilateral (94) cerebral dysfunctions.

Multiple factors such as advanced age, deficits in ADL (14), lower global cognitive function (14, 95), poor verbal fluency (94, 95), reduced attention and speed of information processing (15) have been reported to be correlated with apathy after stroke.

Conclusion

This review has examined a few of the numerous neuropsychiatric disorders that may occur

after stroke. Depression and anxiety, the two most common of these disorders, have been shown to be associated with particular lesion locations and to adversely affect the physical recovery from cerebrovascular lesions. On the other hand, depression has been shown to respond to treatment with antidepressant medication. Since the effective treatment of post-stroke neuropsychiatric disorders have the potential for improving the outcome and quality of life of stroke survivors, additional studies are needed to elucidate the course, mechanism, and effective treatment of these disorders.

References

1. American Heart Association. 2001 Heart and stroke statistical update. Dallas Meeting. 2000.
2. Burvill PW, Johnson GA, Jamrozik KD, et al. Prevalence of depression after stroke: the Perth Community Stroke Study. *Br J Psychiatry* 1995; 166(3):320–327.
3. House A, Dennis M, Mogridge L, et al. Mood disorders in the year after stroke. *Br J Psychiatry* 1991; 158: 83–92.
4. Eastwood MR, Rifat SL, Nobbs H, Ruderman J. Mood disorder following cerebrovascular accident. *Br J Psychiatry* 1989; 154:195–200.
5. Morris PLP, Robinson RG, Raphael B. Prevalence and outcome of poststroke depression in hospitalized patients. *Int J Psychiatr Med* 1990; 20:327–342.
6. Astrom M, Adolfsson R, Asplund K. Major depression in stroke patients: a 3-year longitudinal study. *Stroke* 1993; 24:976–982.
7. Leppavuori A, Pohjasvaara T, Vataja R, et al. Generalized anxiety disorders three to four months after ischemic stroke. *Cerebrovasc Dis* 2003; 16(3):257–264.
8. Castillo CS, Starkstein SE, Fedoroff P, et al. Generalized anxiety disorder following stroke. *J Nerv Ment Dis* 1993; 181:100–106.
9. Starkstein SE, Boston J, Robinson RG. Mechanisms of mania after brain injury: 12 case reports and review of the literature. *J Nerv Ment Dis* 1988; 176:87–100.
10. Dunne JW, Leedman PJ, Edis RH. Inobvious stroke: a cause of delirium and dementia. *Aust N Z J Med* 1986; 16(6):771–778.
11. Stone SP, Halligan PW, Greenwood RJ. The incidence of neglect phenomena and related disorders in patients with an acute right or left hemisphere stroke. *Age Ageing* 1993; 22(1):46–52.
12. Piamarta F, Iurlaro S, Isella V, et al. Unconventional affective symptoms and executive functions after stroke in the elderly. *Arch Gerontol Geriatr Suppl* 2004; (9):315–323.
13. Calvert T, Knapp P, House A. Psychological associations with emotionalism after stroke. *J Neurol Neurosurg Psychiatry*. 1998; 65(6):928–929.
14. Starkstein SE, Fedoroff JP, Rice TR, et al. Apathy following cerebrovascular lesions. *Stroke* 1993; 24:1625–1630.
15. Brodaty H, Sachdev PS, Withall A, et al. Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke—the Sydney Stroke Study. *Psychol Med* 2005; 35(12):1707–1716.
16. Kauhanen M, Korpelainen JT, Brusin E, et al. Post stroke depression correlates with cognitive impairment and neurological deficits. *Stroke* 1999; 30:1875–1880.

17. Kotila M, Waltimo O, Niemi ML, et al. The profile of recovery from stroke in factors influencing outcome. *Stroke* 1984; 15:1039–1044.
18. Chemerinski E, Robinson RG. The Neuropsychiatry of stroke. *Psychosomatics* 2000; 41:5–14.
19. Shubert DS, Burns R, Paras W, et al. Increase of medical hospital length of stay by depression in stroke and amputation patients: a pilot study. *Psychother Psychosom* 1992; 57:61–66.
20. Spitzer RL, Endicott J, Robins E. Research Diagnostic Criteria (RDC) for a group of functional disorders. New York: Biometrics Research Division, New York Psychiatric Institute, NY; 1975.
21. Aben I, Verhey F, Honig A, et al. Research into the specificity of depression after stroke: a review on an unresolved issue. *Prog Neuropsychopharmacol Biol Psychiatry* 2001; 25(4):671–689.
22. House A. Mood disorders after stroke: a review of the evidence. *Int J Ger Psychiatry* 1987; 2:211–221.
23. Paradiso S, Robinson RG. Minor depression after stroke: an initial validation of the DSM-IV construct. *Am J Geriatr Psychiatry* 1999; 7:244–251.
24. Rifkin A, Reardon G, Siris S, et al. Trimipramine therapy after stroke: a double-blind trial. *Arch Neurol* 1986; 46:4–8.
25. Rapp SR, Vrana S. Substituting nonsomatic for somatic symptoms in the diagnosis of depression in elderly male medical patients. *Am J Psychiatry* 1989; 146:1191–1197.
26. Gainotti G, Azzoni A, Marra C. Frequency, phenomenology and anatomical-correlates of major post-stroke depression. *Br J Psychiatry* 1999; 175:163–167.
27. Fedoroff JP, Starkstein SE, Parikh RM, et al. Are depressive symptoms non-specific in patients with acute stroke? *Am J Psychiatry* 1991; 148:1172–1176.
28. Hackett ML, Yapa C, Parag V, Anderson CS. Frequency of depression after stroke: a systematic review of observational studies. *Stroke* 2005; 36:1330–1340.
29. Whyte E, Mulsant BH. Post stroke depression: epidemiology, pathophysiology, and biological treatment. *Biol Psychiatry* 2002; 52:253–264.
30. Andersen G, Vestergaard K, Riis JO, Lauritzen L. Incidence of post-stroke depression during the first year in a large unselected stroke population determined using a valid standardized rating scale. *Acta Psychiatr Scand* 1994; 90:190–195.
31. Finklestein S, Benowitz LI, Baldessarini RJ, et al. Mood, vegetative disturbance, and dexamethasone suppression test after stroke. *Ann Neurol* 1982; 12:463–468.
32. Robinson RG, Price TR. Post-stroke depressive disorders: a follow up study of 103 outpatients. *Stroke* 1982; 13:635–641.
33. Robinson RG. Poststroke depression: prevalence, diagnosis, treatment, and disease progression. *Biol Psychiatry* 2003; 54(3):376–387.
34. Berg A, Palomaki H, Lehtihalmes P, et al. Post stroke depression. an 18-month follow-up. *Stroke* 2003; 34:138–143.
35. Burvill PW, Johnson GA, Jamrozik KD, et al. Risk factors for post-stroke depression. *Int J Geriatr Psychiatr* 1997; 12:219–226.
36. Astrom M, Olsson T, Asplund K. Different linkage of depression to hypercortisolism early versus late after stroke: a 3-year longitudinal study. *Stroke* 1993; 24:52–57.
37. Morrison V, Pollard B, Johnston M. Anxiety and depression 3 years following stroke: demographic, clinical, and psychological predictors. *J Psychosomatic Res* 2005; 59:209–213.
38. Spalletta G, Guida G, DeAngelis D, Caltagirone C. Predictors of cognitive level and depression severity are different in patients with left and right hemispheric stroke within the first year of illness. *J Neurol* 2002; 249(11):1541–1551.
39. Robinson RG, Kubos KL, Starr LB, et al. Mood changes in stroke patients: relationship to lesion location. *Compr Psychiatry* 1983; 24:555–566.
40. Starkstein SE, Robinson RG, Price TR. Comparison of cortical and subcortical lesions in the production of poststroke mood disorders. *Brain* 1987; 110:1045–1059.
41. Carson AJ, MacHale S, Allen K, et al. Depression after stroke and lesion location: a systematic review. *Lancet* 2000; 356:122–126.
42. Singh A, Herrmann N, Black SE. The importance of lesion location in poststroke depression: a critical review. *Can J Psychiatry* 1998; 43:921–927.
43. Narushima K, Kosier JT, Robinson RG. A reappraisal of post-stroke depression, intra- and inter-hemispheric lesion location using meta-analysis. *J Neuropsychiatry Clin Neurosci* 2003; 15:422–430.
44. Verdelho A, Henon H, Lebert F, et al. Depressive symptoms after stroke and relationship with dementia. A three-year follow-up study. *Neurology* 2004; 62:905–911.
45. Tatemichi TK, Foulkes MA, Mohr JP, et al. Dementia in stroke survivors in the stroke data bank cohort. Prevalence, incidence, risk factors, and computed tomographic findings. *Stroke* 1990; 21:858–866.
46. Henon H, Durieu I, Guerouaou D, et al. Preexisting dementia in stroke patients. Baseline frequency, associated factors, and outcome. *Stroke* 1997; 28:2429–2436.
47. Tatemichi TK, Paik M, Bagiella E, et al. Risk of dementia after stroke in a hospitalized cohort: results of a longitudinal study. *Neurology* 1994; 44:1885–1891.
48. Robinson RG, Wilson KB, Kaplan E, et al. Depression influences intellectual impairment in stroke patients. *Br J Psychiatry* 1986; 148:541–547.
49. Bolla-Wilson K, Robinson RG, Starkstein SE, et al. Lateralization of dementia of depression in stroke patients. *Am J Psychiatry* 1989; 146:627–634.
50. Andersen G, Vestergaard K, Riis JO, et al. Dementia of depression or depression of dementia in stroke? *Acta Psychiatr Scand* 1996; 94:272–278.
51. House A, Dennis M, Warlow C, et al. The relationship between intellectual impairment and mood disorder in the first year after stroke. *Psychol Med* 1990; 20:805–814.
52. Downhill JE, Robinson RG. Longitudinal assessment of depression and cognitive impairment following stroke. *J Nerv Ment Dis* 1994; 182:425–431.
53. Kimura M, Robinson RG, Kosier JT. Treatment of cognitive impairment after poststroke depression. A double-blind treatment trial. *Stroke* 2000; 31:1482–1486.
54. Anderson E, Anderson TP, Kottke FJ. Stroke rehabilitation: maintenance of achieved gains. *Arch Phys Med Rehabil* 1997; 58:345–352.
55. Everson SA, Roberts RE, Goldberg DE, Kaplan GA. Depressive symptoms and increased risk of stroke mortality over a 29-year period. *Arch Intern Med* 1998; 158:1133–1138.
56. Robinson RG, Starr LB, Kubos KL, et al. A two-year longitudinal study of post-stroke mood disorders: findings during the initial evaluation. *Stroke* 1983; 14:736–744.
57. Nannetti L, Paci M, Pasquini J, et al. Motor and functional recovery in patients with post-stroke depression. *Disabil Rehabil* 2005; 18:170–175.
58. Chemerinski E, Robinson RG, Arndt S, Kosier JT. The effect of remission of poststroke depression on activities of daily living in a double-blind randomized treatment study. *J Nerv Ment Dis* 2001; 189:421–425.
59. Lipsey JR, Robinson RG, Pearlson GD, et al. Nortriptyline treatment of post-stroke depression: a double-blind study. *Lancet* 1984; 1(8372):297–300.

60. Redding JJ, Orto LA, Winter SW, et al. Antidepressant therapy after stroke: a double-blind trial. *Arch Neurol* 1986;43: 763–765.
61. Andersen G, Vestergaard K, Lauritzen L. Effective treatment of poststroke depression with the selective serotonin reuptake inhibitor citalopram. *Stroke* 1994; 25(6):1099–1104.
62. Murray V, von Arbin M, Bartfai A, et al. Double-blind comparison of sertraline and placebo in stroke patients with minor depression and less severe major depression. *J Clin Psychiatry* 2005; 66 (6):708–716.
63. Wiart L, Petit H, Joseph PA, et al. Fluoxetine in early poststroke depression: a double-blind placebo-controlled study. *Stroke* 2000; 31:1829–1832.
64. Robinson RG, Schultz SK, Castillo C, et al. Nortriptyline versus fluoxetine in the treatment of depression and in short term recovery after stroke: a placebo controlled double-blind study. *Am J Psychiatry* 2000; 157:351–359.
65. Grade C, Redford B, Chrostowski J. Methylphenidate in early post stroke recovery: a double-blind, placebo-controlled study. *Arch Phys Med Rehabil* 1998; 79:1047–1050.
66. Murray GB, Shea V, Conn DR. Electroconvulsive therapy for post-stroke depression. *J Clin Psychiatry* 1987; 47:358–360.
67. Jorge RE, Robinson RG, Tateno A, et al. Repetitive transcranial magnetic stimulation as treatment of poststroke depression: a preliminary study. *Biol Psychiatry* 2004; 55:398–405.
68. Leppavuori A, Pohjasvaara T, Vataja R, et al. Generalized anxiety disorders three to four months after ischemic stroke. *Cerebrovasc Dis* 2003; 16:257–264.
69. Castillo CS, Schultz SK, Robinson RG. Clinical correlates of early-onset and late-onset poststroke generalized anxiety. *Am J Psychiatry* 1995; 152:1174–1179.
70. Krauthammer C, Klerman G. Secondary Mania. Manic syndromes associated with antecedent physical illness or drugs. *Arch Gen Psychiatry* 1978; 35:1333–1339.
71. Starkstein SE, Pearlson GD, Boston J, Robinson RG. Mania after brain injury. A controlled study of causative factors. *Arch Neurol* 1987 ; 44(10):1069–1073.
72. Jorge RE, Robinson RG, Starkstein SE, et al. Secondary mania following traumatic brain injury. *Am J Psychiatry* 1993; 150:916–921.
73. Fenn D, George K. Post-stroke mania late in life involving the left hemisphere. *Aust N Z J Psychiatry* 1999; 33(4):598–600.
74. Robinson RG, Boston JD, Starkstein SE, Price TR. Comparison of mania with depression following brain injury: casual factors. *Am J Psychiatry* 1988; 145:172–178.
75. Cummings JL, Mendez MF. Secondary mania with focal cerebrovascular lesions. *Am J Psychiatry* 1984; 141:1084–1087.
76. Goldstein K. *The organism: a holistic approach to biology derived from pathological data in man*. New York: Zone Books; 1995.
77. Gainotti G. Emotional behavior and hemispheric side of the lesion. *Cortex* 1972; 8:41–55.
78. Gainotti G. Disorders of emotions and affect in patients with unilateral brain damage. In: Boller F, Grafman J, editors. *Handbook of neuropsychology*. Amsterdam: Elsevier; 1989; pp. 345–361.
79. Starkstein SE, Fedoroff JP, Price TR, et al. Catastrophic reaction after cerebrovascular lesions: frequency, correlates, and validation of a scale. *J Neurol Neurosurg Psychiatry* 1993; 5:189–194.
80. Babinski J. Contribution à l'étude des troubles mentaux dans l'hémiplégie organique cérébrale (anosognosie) [French]. *Rev Neurol* 1914; 27:845–848.
81. Breier JI, Adair JC, Gold M, et al. Dissociation of anosognosia for hemiplegia and aphasia during left-hemisphere anesthesia. *Neurology* 1995; 45:65–67.
82. Pia L, Neppi-Modona M, Ricci R, Berti A. The anatomy of anosognosia for hemiplegia: a meta-analysis. *Cortex* 2004; 40:367–377.
83. Starkstein SE, Fedoroff JP, Price TR, et al. Anosognosia in patients with cerebrovascular lesions: a study of causative factors. *Stroke* 1992; 23:1446–1453.
84. Okuda DT, Chyung A, Chin C, Waubant E. Acute pathological laughter. *Mov Disord* 2005; 20:1389–1390.
85. Feinstein A, O'Connor P, Gray T, Feinstein K. Pathological laughter and crying in multiple sclerosis: a preliminary report suggesting a role of the prefrontal cortex. *Mult Scler* 1999; 5:69–73.
86. Borasio GD, Miller RG. Clinical characteristics and management of ALS. *Semin Neurol* 2001; 21:155–166.
87. Schiffer R, Pope LE. Review of pseudobulbar affect including a novel and potential therapy. *J Neuropsychiatry Clin Neurosci* 2005; 17:447–454.
88. Robinson RG, Parikh RM, Lipsey JR, et al. Pathological laughing and crying following stroke: validation of a measurement scale and double-blind treatment study. *Am J Psychiatry* 1993; 150:286–293.
89. Andersen G, Vestergaard K, Riis JO, et al. Citalopram for post-stroke pathological crying. *Lancet* 1993; 342:837–839.
90. Rabins PV, Starkstein SE, Robinson RG. Risk factors for developing atypical (schizophreniform) psychosis following stroke. *J Neuropsychiatry Clin Neurosci* 1991; 3:6–9.
91. Levin DN, Finklestein S. Delayed psychosis after right temporoparietal stroke or trauma: relation to epilepsy. *Neurology* 1982; 32:267–273.
92. Marin RS. In: Dickstein LJ, Riba MB, Olham JM, editors. *Review of psychiatry*. Vol. 15. Washington, (DC): American Psychiatric Press; 1996. pp. 205–242.
93. Robinson RG, Starkstein SE. Current research in affective disorders following stroke. *J Neuropsych Clin Neurosci* 1990; 2:1–14.
94. Okada K, Kabayashi S, Yamagata S, et al. Poststroke apathy and regional cerebral blood flow. *Stroke* 1997; 28:2437–2441.
95. Yamagata S, Yamaguchi S, Kobayashi S. Impaired novelty processing in apathy after subcortical stroke. *Stroke* 2004; 35:1935–1940.