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The neuroanatomical model of post-stroke depression: Towards a change of focus?

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Abstract

One third of all stroke survivors develop post-stroke depression (PSD). Depressive symptoms adversely affect rehabilitation and significantly increase risk of death in the post-stroke period. One of the theoretical views on the determinants of PSD focuses on psychosocial factors like disability and social support. Others emphasize biologic mechanisms such as disruption of biogenic amine neurotransmission and release of proinflammatory cytokines. The “lesion location” perspective attempts to establish a relationship between localization of stroke and occurrence of depression, but empirical results remain contradictory. These divergences are partly related to the fact that neuroimaging methods, unlike neuropathology, are not able to assess precisely the full extent of stroke-affected areas and do not specify the different types of vascular lesions. We provide here an overview of the known phenomenological profile and current pathogenic hypotheses of PSD and present neuropathological data challenging the classic “single-stroke”-based neuroanatomical model of PSD. We suggest that vascular burden due to the chronic accumulation of small macrovascular and microvascular lesions may be a crucial determinant of the development and evolution of PSD.

Keywords

Cerebral ischemia; Location; Macroinfarcts; Microvascular; Mood; Neuropathology

1. Introduction

More than a hundred years ago, Meyer [1] postulated that depression may be the consequence of the combined effect of brain injury, affecting mainly the left frontal lobe as well as other lobar convexities, and psychosocial vulnerability such as past psychiatric history. Although the association of depression with stroke has been recognized clinically for several decades, only in the past 25 years systematic studies on this subject have been conducted (for review see [2]). According to the World Health Organization [3], stroke is the most common severe neurological disorder and the third leading cause of mortality

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among adults, with 15 million people worldwide suffering stroke annually. A recent review reported a markedly stable frequency of depressive symptoms in 33% of *all* stroke survivors at *any time* during the follow-up [4]. In addition, stroke survivors have more than six fold higher risk of developing clinically overt depression even two or more years after index stroke compared to age-matched controls [5]. Depression is significantly more likely after stroke than other illnesses with comparable disability and adversely affects both short-term recovery and long-term rehabilitation [6]. Moreover, death risk is three-fold higher over the next decade in depressed stroke survivors compared to those without depression [7].

The possibility that the risk of depression after stroke is related to lesion location was developed in the mid-seventies at John Hopkins University and originated the concept of *post-stroke depression (PSD)* [8]. The first animal data in this field showed an association between the laterality of brain damage after middle cerebral artery occlusion and both brain catecholamine concentration and behavioral patterns in rats suggesting that the ischemic damage may induce depression via the disruption of biogenic amine pathways [9]. Later on, the first associations between the localization of stroke and occurrence of depression were reported by the same group in humans [10]. Several subsequent studies suggested a link between PSD and macrovascular lesions in various brain regions such as the left frontal lobe, bilateral prefrontal cortex, left anterior and right occipital cortex (for review see [11]). Despite these research efforts, the relationships between vascular lesions and the occurrence of depression remain a matter of debate [12–14]. Equally intriguing are the recent contradictory results on the location of brain lesions in PSD [8,11,15,16]. Methodological issues such as differences in sampling, assessment interval from stroke and type of lesions considered have been evoked to explain the discrepant results. After providing a brief overview of the clinical, epidemiological and treatment issues related to PSD, the present review focuses on the pathogenetic models of this condition and critically discusses its neuroanatomical substrates with particular reference to the contribution of neuropathological data in this field.

2. Clinical and epidemiological characteristics of PSD

The peak prevalence of major depression occurs 3–6 months after the stroke with a range of 9–34% during this time-frame [17]. The greatest increase in the prevalence of PSD is observed between the initial and 1-month repeated assessments despite an overall decrease of disability [18]. However, the risk appears to remain high even 1–3 years after stroke so that if one considers all depressive episodes occurring both in the acute and later post-stroke periods, PSD prevalence would be even higher reaching 25% to 79% [17]. Thus far, no precise data are available regarding the impact of PSD on community healthcare resources but it is thought that PSD patients are more often in institutional care, are more frequent users of health services and show poorer functional recovery compared to non-depressed stroke survivors [19]. Only physical disability, stroke severity and cognitive impairment have been consistently identified as risk factors for PSD [20]. The depression-stroke Italian multicenter study added female gender and previous cerebrovascular or depressive episodes as significant risk factors for this condition [16]. More rarely cited psychosocial risk factors include positive family history of anxiety or mood disorder, high trait neuroticism on the Eysenck inventory, older age, bereavement, sleep disturbance, poor social support and recent adverse life events [21].

Not surprisingly, a consensual definition of PSD is difficult to achieve [22]. Typically, DSM-IV diagnostic criteria classify PSD within the group of “mood disorders due to stroke, with depressive features” or “with major depressive-like episode” (DSM-IV, American Psychiatric Association, 1994). Whyte and Mulsant [17] defined PSD as “depression occurring in the context of a clinically apparent stroke (as opposed to silent vascular

disease)" emphasizing the sequential nature of the two temporally related events – stroke followed by depression – although an etiopathogenetic relationship is not assumed. The clinical patterns of PSD remain quite vague. Paradiso et al. indicated that early-onset PSD is characterized by anxiety, loss of libido and feelings of guilt, whereas later-onset PSD is more frequently associated with diurnal variation of mood and social isolation [23]. In an attempt to delineate PSD from major depression, Gainotti et al. proposed that catastrophic reactions, hyperemotionality and diurnal mood variation are more consistently associated with PSD, suicidal thoughts and anhedonia being more frequent in endogenous depression [24]. However, catastrophic reactions and altered emotional regulation have been described in several neurological conditions with or without depression raising doubts about the specificity of this cluster for defining PSD [2].

The course of PSD seems to be dependent on the timing of onset. Early onset depressive episodes tend to have a shorter course with more probable spontaneous remission in comparison to later-onset depressive episodes. Astrom et al. showed that, at 1 year, 60% of the patients with early depression (0 to 3 months) had recovered and that those who had not recovered at this follow-up had a high risk of developing chronic depression [25]. The results of Andersen et al. confirmed this notion showing that stroke survivors who experience onset of depression seven weeks or later after their stroke have a lower rate of spontaneous recovery [26]. There may be different biological or psychological processes working in acute PSD in comparison to subacute or chronic mood disorder. Early PSD may represent a transient reaction to the stroke with remission based on neural regeneration or biochemical mechanisms (changes in receptor regulation, rate of transmitter or enzyme synthesis). In contrast, late PSD may reflect neuropathological changes secondary to the stroke with a delayed but enduring impact on mood [27].

3. Pharmacotherapy in PSD

Several placebo-controlled, randomized double-blind studies support the efficacy of antidepressant medication in PSD. Citalopram [28], nortriptyline [29], and fluoxetine [30] were all reported to be significantly more efficacious than placebo in the treatment of depressive symptoms after stroke. The two latter agents also improved activities of daily living [31] and reduced mortality [32]. Similarly, sertraline showed to be superior to placebo in preventing the occurrence of PSD [33]. Besides its direct effect on depressive symptoms, antidepressant treatment in PSD may also exert outcome-improving effects on the brain in at least two ways [34]. An action on monoaminergic nuclei modulating cortico-striato-pallido-thalamo-cortical (CSPTC) pathways is one of the options. Five CSPTC pathways referred to as the oculomotor, dorsolateral prefrontal, lateral orbital frontal and anterior cingulated pathways form closed loops, which originate from the prefrontal cortex and project to the globus pallidus, substantia nigra and thalamus [35]. The last three pathways are involved in both executive functions and affective regulation. Their functionality is thought to be closely modulated by the activity of monoaminergic nuclei (namely, raphe, locus coeruleus and ventral tegmental area) which are preferential sites of action of antidepressant medication [36]. Alternatively, antidepressants may promote the secretion of neurotrophins favoring brain recovery. One of these neurotrophins, brain-derived neurotrophic factor (BDNF), and its receptor trkB, are increased by antidepressant treatment and it has been shown that BDNF-dependent signaling, affecting intracellular signal transduction and synaptic connectivity, is required for antidepressants to induce mood recovery [37]. One should, however, keep in mind that the positive impact of antidepressants in PSD is not generally accepted. For instance, a recent systematic review of pharmacological treatments in PSD was unable to find any strong evidence on the effectiveness of pharmacotherapy in either producing a remission or preventing the onset of depression after stroke [38].

4. Impact of biological and psychosocial factors on PSD pathogenesis

Research into the pathogenesis of PSD is characterized by the striking opposition between two theoretical models: that of the psychosocial vulnerability and that of the biological determinism. This polarity of thought may have impeded the development of a comprehensive approach to PSD prevention and treatment. In this section we will attempt to explore both the relative impact and conceptual limits of each hypothesis.

4.1. Psychosocial vulnerability

The notion that depression in stroke patients involves the psychosocial response to disability and loss has been present from the pioneer reports on emotional disorders following stroke. Considering the brain as “the most cherished organ of humanity”, Fisher considered depression an understandable reaction to cerebrovascular disease [39]. The relationship between PSD and disability is complex since bidirectional causality has been sustained. Disability after stroke may trigger PSD which in turn led to reduced functional outcome [19,29,40]. Astrom et al. showed that several psychosocial factors play a role in the development of both early and late-onset PSD [25]. The absence of family support is a strong determinant of acute depressive reactions following stroke. Dependence for the activities of daily living (ADL) is not associated with acute depressive reactions but it becomes the most important predictor of depression after the first three months. This observation may support the notion that functional impairment does not determine the onset of depression but rather interacts with it to limit the results of long-term rehabilitation. One year post-stroke, the persistence of few social contacts is the main psychosocial factor associated with PSD. In the same line, during the 3 years following stroke depressed patients have a marked paucity of social contacts compared to non-depressed patients. Although these data point to the influence of psychosocial determinants in the development of PSD, one should acknowledge that the distinction between dependent and independent variables is quite ambiguous in this context (i.e. reduced social contacts can be a cause as well as a result of depression).

4.2. Biological determinism

The biogenic amine and cytokine hypotheses represent the two main theories surrounding a biological origin of PSD [41]. Robinson and Bloom postulated that ischemic lesions may interrupt the biogenic amine-containing axons ascending from the brainstem to the cerebral cortex leading to a decreased production of serotonin (5HT) and norepinephrine (NE) in limbic structures of frontal and temporal lobes as well as basal ganglia [42]. The deficit of biogenic amines in these areas or the failure to up-regulate 5HT receptors after stroke may trigger PSD [43]. Supporting this hypothesis, significantly lower CSF concentrations of the serotonin metabolite 5-hydroxy-indoleacetic acid were measured in PSD patients compared to non-depressed stroke survivors [44]. Equally in line are the recent PET-scan findings of Moller et al. [45] on $5HT_{1A}$ receptor availability after stroke suggesting that changes of serotonin neurotransmission may occur in the early phase of stroke and be modulated by treatment with serotonin reuptake inhibitors (SSRI). In another study [46], growth hormone (GH) response to desipramine was significantly blunted in PSD patients compared to non-depressed post-stroke patients, suggesting diminished α_2 adrenoreceptor function as a possible marker of PSD.

Alternatively, the proinflammatory cytokines IL-1, tumor necrosis factor α (TNF-α), IL-6, IL-8 and IL-18 that are involved in the initiation and amplification of the inflammatory response to acute cerebral ischemia may also have depressiogenic properties. In fact, the participation of proinflammatory cytokines in the etiology of depression has been explored by several authors [47,48]. Interleukine-1β (IL-1β) and TNF-α can induce a depressive-like

behavior in mice resembling the somatic syndrome of depression in humans. It is known that autoimmune disorders and HIV, primarily affecting the immunological system, are associated with depression. Additionally, increased brain levels of IL-1β, TNF-α, IL-6 have been found in patients suffering from mood disorders [49]. Cytokine activation may induce depressive symptoms by increasing the activity of the hypothalamus-pituitary-adrenal (HPA) axis and altering biogenic amine neurotransmission in several hypothalamic nuclei as well as limbic sites. Some cytokines are also known to up-regulate the tryptophane-catabolizing enzyme indoleamine 2,3-deoxygenase (IDO) leading to decreased synthesis of 5HT. Although attractive, this hypothesis shows two main conceptual weaknesses. First, no relationship was established between the level of proinflammatory cytokine induction and PSD in humans. Most importantly, molecular cascades after stroke also include a marked induction of anti-inflammatory cytokines which may counterbalance the depressiogenic effect of proinflammatory cytokines [50,51].

5. Lesion location in PSD: the contribution of structural neuroimaging

After the pioneering work of Robinson and Szetela [52] who reported a significant inverse correlation between the severity of PSD and distance of the anterior border of the lesion from the frontal pole, several MRI studies attempted to explore the neuroanatomical background of PSD leading to conflicting data. A first observation in this field concerns the predominance of left hemisphere lesions in patients with PSD [10]. This right–left difference was present both for cortical and subcortical lesions and seems to be more robust for left anterior lesions [53]. More recent publications confirmed these findings suggesting the existence of a significant relationship between PSD severity and proximity to the left frontal pole (for review see [11]). However, the association between left anterior lesion location and PSD is far from being consensual. Whereas Robinson's pooling results [54] suggested that left anterior cerebral lesions were associated with significantly higher depression scores than left posterior lesions (the site of the lesion explaining 50% of the variance), two systematic reviews by Singh et al. [55] and Carson et al. [8] did not support this association. The lack of uniformity in definition and measurement of depression as well as sampling differences (i.e., in-patient versus community-based series) may partly explain these discrepancies. However, the conflicting conclusions of different studies may be mostly attributed to the highly variable assessment interval from the acute post-stroke period to the chronic stroke phase [55]. In fact, it is conceivable that lesion location is a key determinant of PSD immediately after stroke (namely by affecting biogenic amines and 5HT receptor function), while in late-onset PSD failure to adapt to the consequences of stroke can be more important (through impairments such as social isolation or visual perceptual decline and changes in arousal and attention related to right hemisphere stroke). In this context, Shimoda and Robinson [56] reported that, during the acute post-stroke period, PSD in inpatients was associated with left anterior lesions. By 3–6 months post-stroke, the proximity of the lesion to the frontal pole in both hemispheres rather than the hemispheric location influences the occurrence of PSD. At this period, depression was also related to the impairment in daily living activities and social functioning. At 1–2 years follow-ups, the occurrence of depression among the patients with left hemisphere stroke was mostly determined by the severity of ADL impairment. At this time period, depression in patients with right hemisphere damage was associated with lesion volume and proximity to the occipital pole.

Undoubtedly, another parameter to consider is the strategic location of ischemic damage. However, data in this field are scarce and contradictory probably reflecting the fact that unlike neuropathology, most neuroimaging methods did not assess precisely the total extent of the affected area. MRI-documented infarcts in hippocampus, basal ganglia and frontal areas have been classically associated with PSD [57–59]. Hama et al. found that the severity of *affective* depression was associated with left frontal lobe damage whereas *apathetic*

depression was mostly related to basal ganglia damage [60]. In another study, the mean frequency of infarcts in the genu of the internal capsule on the left side and bilateral pallidum as well as the mean volume of infarcts in the right occipital lobe were independent determinants of PSD [61].

6. Neuropathological substrates of PSD

Although difficult to perform, neuropathological analyses may be of great value in order to assess the validity of the neuroanatomical model of PSD. Unlike structural imaging, they allow for evaluating both the extent of vascular burden and different types of vascular lesions in the human brain. In fact, as for vascular cognitive impairment, one could suspect that not all vascular lesions had a deleterious impact on mood. In addition, they provide reliable estimates of the number of small vascular lesions not easily identified by MRI. We recently performed the only available neuropathological study of 95 consecutive autopsy cases of patients with stroke [62]. Among them, there were 21 patients (9 men and 12 women) who developed PSD (mean age: 78.7±8.0 for men and 80.6±9.2 for women) and 74 (30 men and 44 women) patients without PSD (mean age: 83.5±7.2 for men and 86.5±5.4 for women). Clinical diagnosis of stroke was based on the presence of focal neurological deficits of acute onset and supportive neuroimaging. Subjects with stroke were included only if the diagnosis could be confirmed pathologically by the presence of cortical macroinfarcts and if post-stroke survival was at least one month. Cases presenting with first-onset depression more than 2 years after a stroke were excluded (4 cases). The clinical diagnosis of depression was established prospectively using the DSM-IV criteria for major and minor depression on the basis of the psychiatric examination performed by a specialist in geriatric psychiatry. Lifetime history of depression was also established on the basis of this interview. The diagnosis was confirmed in all cases after review of the medical records by the same trained psychiatrist blind to the neuropathological findings. Both hemispheres were cut into 1 cm thick coronal slices and examined for macroscopic vascular lesions including brain infracts, cerebral hemorrhage or lacunar infarcts. Microscopic infarcts were identified and dated on two adjacent sections of each level with hematoxylin–eosin and cresyl violet stains. All cases with concurrent neuropathological evidence of Alzheimer's disease (Braak stages IV, V, and VI or dementia with Lewy bodies were excluded. Macroscopic brain infracts, multiple lacunar infracts and substantial microvascular pathology confined to one brain region were classified as focal ischemic pathology, whereas multiple vascular lesions involving more than one cortical area were classified as multifocal ischemic pathology. Our findings showed no relationship between the development of focal and multifocal vascular pathology in a specific brain area and PSD in elderly patients without lifetime history of depression. Among demographic variables, only younger age at death was significantly related to PSD further confirming that depression after stroke is also a predisposing factor for earlier death. Although these first neuropathological data could be interpreted as an indirect support of the psychosocial model of PSD, several methodological limitations should be taken into account. First, as is the case for all neuropathological studies, autopsy-related biases cannot be excluded. Second, due to the limited number of cases with PSD, the power of the present study does not permit to identify mild size effects. Most importantly, this qualitative assessment mainly focused on macrovascular pathology and did not include a detailed assessment of the brain microvascular burden.

7. Conclusions

Considering the discrepancies of neuroimaging studies about the link between lesion location and PSD occurrence and our negative data in autopsy series, one could argue that psychological rather than neurological factors are the main determinants of PSD. Such statement may, however, be erroneous or at least premature. Paralleling the debate on the

origin of PSD, the possible role of small macrovascular and microvascular lesions in triggering depressive episodes has received further support in the late 90s when several groups described a possible deleterious effect of MRI hyperintensities on affective regulation. MRI hyperintensities referred to as leucoencephalopathy, leucoaraïosis and subcortical encephalomalacia have been described both in depression and Alzheimer's disease [63] but also in normal brain aging [64]. They correspond to small vascular or microvascular pathologic changes such as demyelination, cortical microinfarcts and lacunae [65]. Usually associated with an increased vulnerability to cognitive impairment and dementia [13,66], they gained significance in the pathogenesis of depression after the introduction of the "vascular depression hypothesis" by Alexopoulos et al. [57]. Based on the comorbidity of depressive syndromes with cerebrovascular lesions and cardiovascular risk factors these authors postulated the existence of small macrovascular and microvascular lesions affecting brain circuits responsible for mood control. Simultaneously, Krishnan et al. described the clinical profile of vascular depression based on MRI observation of punctate hyperintensities of the subcortical gray matter, deep white matter and periventricular regions corresponding to vascularlesions [67]. Patients classified as having vascular depression on MRI ratings were more likely to be elderly, nonpsychotic and to have a late-onset depressive disorder. As concisely stated by Newberg et al. [68] "Overall, the concept of vascular depression emphasizes the *etiopathophysiologic relationship* between cerebrovascular lesions and depression while the concept of PSD emphasizes the *temporal relationship* between the two". In terms of etiopathogenesis, a progressive change of focus from macroinfarcts to small vascular lesions has been already introduced by the concept of "vascular cognitive impairment" in another highly debated field, that of the pathological basis of vascular dementia. Our recent work in this field clearly demonstrates that some microvascular lesions such as cortical microinfarcts, periventricular demyelination and thalamic and basal ganglia lacunae may have an unexpected negative impact on cognitive functions (for review see [69]). In a recently published article, Brodaty et al. proposed the same change of focus for PSD stating that "depression after stroke may be related to cumulative vascular brain pathology rather than side and severity of single stroke" [70]. In this perspective, patients with chronic vascular burden could develop a PSD with a lower rate of spontaneous recovery and higher risk of chronic depression compared to an early PSD episode with spontaneous remission more probably associated with the location of macrovascular stroke lesion. Further neuropathological studies in large and clinically well characterized series are urgently needed to obtain a definite answer about the pertinence of the neuroanatomical model of PSD.

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References

1. Meyer A. The anatomical facts and clinical varieties of traumatic insanity. Am J Insanity. 1904; 60:373–442.
2. Robinson RG. Poststroke depression: prevalence, diagnosis, treatment, and disease progression. Biol Psychiatry. 2003; 54:376–87. [PubMed: 12893112]
3. WHO. Stroke – 1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. Stroke. 1989; 20:1407–31. [PubMed: 2799873]
4. Hackett ML, Yapa C, Parag V, Anderson CS. Frequency of depression after stroke: a systematic review of observational studies. Stroke. 2005; 36:1330–40. [PubMed: 15879342]

5. Whyte EM, Mulsant BH, Vanderbilt J, Dodge HH, Ganguli M. Depression after stroke: a prospective epidemiological study. J Am Geriatr Soc. 2004; 52:774–8. [PubMed: 15086660]
6. Burvill PW, Johnson GA, Jamrozik KD, Anderson CS, Stewart-Wynne EG, Chakera TM. Prevalence of depression after stroke: the Perth Community Stroke Study. Br J Psychiatry. 1995; 166:320–7. [PubMed: 7788123]
7. 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; 25 (158):1133–8. [PubMed: 9605786]
8. Carson AJ, MacHale S, Allen K, Lawrie SM, Dennis M, House A, et al. Depression after stroke and lesion location: a systematic review. Lancet. 2000; 356:122–6. [PubMed: 10963248]
9. Robinson RG, Shoemaker WJ, Schlumpf M, Valk T, Bloom FE. Effect of experimental cerebral infarction in rat brain on catecholamines and behaviour. Nature. 1975; 22 (255):332–4. [PubMed: 1128692]
10. Robinson RG, Kubos KL, Starr LB, Rao K, Price TR. Mood changes in stroke patients: relationship to lesion location. Compr Psychiatry. 1983; 24:555–66. [PubMed: 6653097]
11. Provinciali L, Coccia M. Post-stroke and vascular depression: a critical review. Neurol Sci. 2002; 22:417–28. [PubMed: 11976972]
12. Reeves RR, Rose ES. Depression and vascular disease: conceptual issues, relationships and clinical implications. Vasc Dis Prev. 2006; 3:193–203.
13. Taylor WD, Steffens DC, Krishnan KR. Psychiatric disease in the twenty-first century: the case for subcortical ischemic depression. Biol Psychiatry. 2006; 60:1299–303. [PubMed: 17014829]
14. Thuile J, Even C, Guelfi JD. Validity of vascular depression as a specific diagnostic: a review. Encephale. 2007; 33:39–48. [PubMed: 17457293]
15. Bhogal SK, Teasell R, Foley N, Speechley M. Lesion location and poststroke depression: systematic review of the methodological limitations in the literature. Stroke. 2004; 35:794–802. [PubMed: 14963278]
16. Paolucci S, Gandolfo C, Provinciali L, Torta R, Toso V. The Italian multicenter observational study on post-stroke depression (DESTRO). J Neurol. 2006; 253:556–62. [PubMed: 16767539]
17. Whyte EM, Mulsant BH. Post stroke depression: epidemiology, pathophysiology, and biological treatment. Biol Psychiatry. 2002; 52:253–64. [PubMed: 12182931]
18. Townend BS, Whyte S, Desborough T, Crimmins D, Markus R, Levi C, et al. Longitudinal prevalence and determinants of early mood disorder post-stroke. J Clin Neurosci. 2007; 14:429–34. [PubMed: 17336529]
19. Kotila M, Numminen H, Waltimo O, Kaste M. Post-stroke depression and functional recovery in a population-based stroke register. The Finnstroke study. Eur J Neurol. 1999; 6:309–12. [PubMed: 10210911]
20. Hackett ML, Anderson CS. Predictors of depression after stroke: a systematic review of observational studies. Stroke. 2005; 36:2296–301. [PubMed: 16179565]
21. Oldehinkel AJ, Ormel J, Brilman EI, van den Berg MD. Psychosocial and vascular risk factors of depression in later life. J Affect Disord. 2003; 74:237–46. [PubMed: 12738042]
22. Aben I, Verhey F, Honig A, Lodder J, Lousberg R, Maes M. Research into the specificity of depression after stroke: a review on an unresolved issue. Prog Neuropsychopharmacol Biol Psychiatry. 2001; 25:671–89. [PubMed: 11383972]
23. Paradiso S, Ohkubo T, Robinson RG. Vegetative and psychological symptoms associated with depressed mood over the first two years after stroke. Int J Psychiatry Med. 1997; 27:137–57. [PubMed: 9565720]
24. Gainotti G, Azzoni A, Marra C. Frequency, phenomenology and anatomical–clinical correlates of major post-stroke depression. Br J Psychiatry. 1999; 175:163–7. [PubMed: 10627800]
25. Astrom M, Adolfsson R, Asplund K. Major depression in stroke patients. A 3-year longitudinal study. Stroke. 1993; 24:976–82. [PubMed: 8322398]
26. Andersen G, Vestergaard K, Ingemann-Nielsen M, Lauritzen L. Risk factors for post-stroke depression. Acta Psychiatr Scand. 1995; 92:193–8. [PubMed: 7484197]

27. Robinson RG, Bolduc PL, Price TR. Two-year longitudinal study of poststroke mood disorders: diagnosis and outcome at one and two years. Stroke. 1987; 18:837–43. [PubMed: 3629640]
28. Andersen G, Vestergaard K, Lauritzen L. Effective treatment of poststroke depression with the selective serotonin reuptake inhibitor citalopram. Stroke. 1994; 25:1099–104. [PubMed: 8202964]
29. Parikh RM, Robinson RG, Lipsey JR, Starkstein SE, Fedoroff JP, Price TR. The impact of poststroke depression on recovery in activities of daily living over a 2-year follow-up. Arch Neurol. 1990; 47:785–9. [PubMed: 2357159]
30. Wiart L, Petit H, Joseph PA, Mazaux JM, Barat M. Fluoxetine in early poststroke depression: a double-blind placebo-controlled study. Stroke. 2000; 31:1829–32. [PubMed: 10926942]
31. Narushima K, Robinson RG. The effect of early versus late antidepressant treatment on physical impairment associated with poststroke depression: is there a time-related therapeutic window? J Nerv Ment Dis. 2003; 191:645–52. [PubMed: 14555866]
32. Jorge RE, Robinson RG, Arndt S, Starkstein S. Mortality and poststroke depression: a placebo-controlled trial of antidepressants. Am J Psychiatry. 2003; 160:1823–9. [PubMed: 14514497]
33. Rasmussen A, Lunde M, Poulsen DL, Sorensen K, Qvitzau S, Bech P. A double-blind, placebo-controlled study of sertraline in the prevention of depression in stroke patients. Psychosomatics. 2003; 44:216–21. [PubMed: 12724503]
34. Narushima K, Paradiso S, Moser DJ, Jorge R, Robinson RG. Effect of antidepressant therapy on executive function after stroke. Br J Psychiatry. 2007; 190:260–5. [PubMed: 17329748]
35. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci. 1986; 9:357–81. [PubMed: 3085570]
36. Alexopoulos GS, Meyers BS, Young RC, Kalayam B, Kakuma T, Gabrielle M, et al. Executive dysfunction and long-term outcomes of geriatric depression. Arch Gen Psychiatry. 2000; 57:285–90. [PubMed: 10711915]
37. Saarelainen T, Hendolin P, Lucas G, Koponen E, Sairanen M, MacDonald E, et al. Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. J Neurosci. 2003; 23:349–57. [PubMed: 12514234]
38. Hackett ML, Anderson CS, House AO. Management of depression after stroke: a systematic review of pharmacological therapies. Stroke. 2005; 36:1098–103. [PubMed: 15802637]
39. Fisher SH. Psychiatric considerations of cerebral vascular disease. Am J Cardiol. 1961; 7:379–85. [PubMed: 13700002]
40. Paolucci S, Antonucci G, Pratesi L, Traballesi M, Grasso MG, Lubich S. Poststroke depression and its role in rehabilitation of inpatients. Arch Phys Med Rehabil. 1999; 80:985–90. [PubMed: 10488996]
41. Spalletta G, Bossu P, Ciaramella A, Bria P, Caltagirone C, Robinson RG. The etiology of poststroke depression: a review of the literature and a new hypothesis involving inflammatory cytokines. Mol Psychiatry. 2006; 11:984–91. [PubMed: 16894392]
42. Robinson RG, Bloom FE. Pharmacological treatment following experimental cerebral infarction: implications for understanding psychological symptoms of human stroke. Biol Psychiatry. 1977; 12:669–80. [PubMed: 588647]
43. Mayberg HS, Robinson RG, Wong DF, Parikh R, Bolduc P, Starkstein SE, et al. PET imaging of cortical S2 serotonin receptors after stroke: lateralized changes and relationship to depression. Am J Psychiatry. 1988; 145:937–43. [PubMed: 3394877]
44. Bryer JB, Starkstein SE, Votypka V, Parikh RM, Price TR, Robinson RG. Reduction of CSF monoamine metabolites in poststroke depression: a preliminary report. J Neuropsychiatry Clin Neurosci. 1992; 4:440–2. [PubMed: 1384852]
45. Moller M, Andersen G, Gjedde A. Serotonin 5HT1A receptor availability and pathological crying after stroke. Acta Neurol Scand. 2007; 116:83–90. [PubMed: 17661792]
46. Barry S, Dinan TG. Alpha-2 adrenergic receptor function in post-stroke depression. Psychol Med. 1990; 20:305–9. [PubMed: 2162547]
47. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 2006; 27:24–31. [PubMed: 16316783]
48. Schiepers OJ, Wichers MC, Maes M. Cytokines and major depression. Prog Neuropsychopharmacol Biol Psychiatry. 2005; 29:201–17. [PubMed: 15694227]

49. Levine J, Barak Y, Chengappa KN, Rapoport A, Rebey M, Barak V. Cerebrospinal cytokine levels in patients with acute depression. Neuropsychobiology. 1999; 40:171–6. [PubMed: 10559698]
50. Perini F, Morra M, Alecci M, Galloni E, Marchi M, Toso V. Temporal profile of serum anti-inflammatory and pro-inflammatory interleukins in acute ischemic stroke patients. Neurol Sci. 2001; 22:289–96. [PubMed: 11808851]
51. Vila N, Castillo J, Davalos A, Esteve A, Planas AM, Chamorro A. Levels of anti-inflammatory cytokines and neurological worsening in acute ischemic stroke. Stroke. 2003; 34:671–5. [PubMed: 12624290]
52. Robinson RG, Szetela B. Mood change following left hemispheric brain injury. Ann Neurol. 1981; 9:447–53. [PubMed: 7271239]
53. Starkstein SE, Robinson RG, Price TR. Comparison of cortical and subcortical lesions in the production of poststroke mood disorders. Brain. 1987; 110:1045–59. [PubMed: 3651794]
54. Robinson RG. Post-stroke mood disorders. Hosp Pract. 1986; 21(4):83–9.
55. Singh A, Herrmann N, Black SE. The importance of lesion location in poststroke depression: a critical review. Can J Psychiatry. 1998; 43:921–7. [PubMed: 9825164]
56. Shimoda K, Robinson RG. The relationship between poststroke depression and lesion location in long-term follow-up. Biol Psychiatry. 1999; 45:187–92. [PubMed: 9951566]
57. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. Arch Gen Psychiatry. 1997; 54:915–22. [PubMed: 9337771]
58. Bielau H, Trubner K, Krell D, Agelink MW, Bernstein HG, Stauch R, et al. Volume deficits of subcortical nuclei in mood disorders A postmortem study. Eur Arch Psychiatry Clin Neurosci. 2005; 255:401–12. [PubMed: 16080015]
59. Frodl T, Meisenzahl EM, Zetzsche T, Hohne T, Banac S, Schorr C, et al. Hippocampal and amygdala changes in patients with major depressive disorder and healthy controls during a 1-year follow-up. J Clin Psychiatry. 2004; 65:492–9. [PubMed: 15119911]
60. Hama S, Yamashita H, Shigenobu M, Watanabe A, Kurisu K, Yamawaki S, et al. Post-stroke affective or apathetic depression and lesion location: left frontal lobe and bilateral basal ganglia. Eur Arch Psychiatry Clin Neurosci. 2007; 257:149–52. [PubMed: 17131217]
61. Vataja R, Leppavuori A, Pohjasvaara T, Mantyla R, Aronen HJ, Salonen O, et al. Poststroke depression and lesion location revisited. J Neuropsychiatry Clin Neurosci. 2004; 16:156–62. [PubMed: 15260366]
62. Bozikas VP, Gold G, Kovari E, Herrmann F, Karavatos A, Giannakopoulos P, et al. Pathological correlates of poststroke depression in elderly patients. Am J Geriatr Psychiatry. 2005; 13:166–9. [PubMed: 15703326]
63. O'Brien JT, Ames D. White matter lesions in depression and Alzheimer's disease. Br J Psychiatry. 1996; 169:671.
64. Guttmann CR, Jolesz FA, Kikinis R, Killiany RJ, Moss MB, Sandor T, et al. White matter changes with normal aging. Neurology. 1998; 50:972–8. [PubMed: 9566381]
65. Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F, et al. Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology. 1993; 43:1683–9. [PubMed: 8414012]
66. Kovari E, Gold G, Herrmann FR, Canuto A, Hof PR, Michel JP, et al. Cortical microinfarcts and demyelination significantly affect cognition in brain aging. Stroke. 2004; 35:410–4. [PubMed: 14707236]
67. Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. Am J Psychiatry. 1997; 154:497–501. [PubMed: 9090336]
68. Newberg AR, Davydow DS, Lee HB. Cerebrovascular disease basis of depression: post-stroke depression and vascular depression. Int Rev Psychiatry. 2006; 18:433–41. [PubMed: 17085362]
69. Gold G, Giannakopoulos P, Herrmann FR, Bouras C, Kovari E. Identification of Alzheimer and vascular lesion thresholds for mixed dementia. Brain. 2007; 130:2830–6. [PubMed: 17878206]
70. Brodaty H, Withall A, Altendorf A, Sachdev PS. Rates of depression at 3 and 15 months poststroke and their relationship with cognitive decline: the Sydney Stroke Study. Am J Geriatr Psychiatry. 2007; 15:477–86. [PubMed: 17545448]