Neuropsychiatric sequelae of stroke

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Abstract | Stroke survivors are often affected by psychological distress and neuropsychiatric disturbances. About one-third of stroke survivors experience depression, anxiety or apathy, which are the most common neuropsychiatric sequelae of stroke. Neuropsychiatric sequelae are disabling, and can have a negative influence on recovery, reduce quality of life and lead to exhaustion of the caregiver. Despite the availability of screening instruments and effective treatments, neuropsychiatric disturbances attributed to stroke are currently underdiagnosed and undertreated. Stroke severity, stroke-related disabilities, cerebral small vessel disease, previous psychiatric disease, poor coping strategies and unfavourable psychosocial environment influence the presence and severity of the psychiatric sequelae of stroke. Although consistent associations between psychiatric disturbances and specific stroke locations have yet to be confirmed, functional MRI studies are beginning to unveil the anatomical networks that are disrupted in stroke-associated psychiatric disorders. Evidence regarding biochemical and genetic biomarkers for stroke-associated psychiatric disorders is still limited, and better understanding of the biological determinants and pathophysiology of these disorders is needed. Investigation into the management of these conditions must be continued, and should include pilot studies to assess the benefits of innovative behavioural interventions and large-scale cooperative randomized controlled pharmacological trials of drugs that are safe to use in patients with stroke.

Stroke is a major cause of death and disability worldwide[1]. In developed countries, the acute treatment of stroke has improved substantially in the past two decades with the implementation of stroke units and the use of thrombolysis and/or thrombectomy. As a consequence, the mortality associated with acute stroke has decreased and the proportion of survivors with mild to moderate disability has increased[2]. Traditionally, research into the functional impairments following stroke and care of stroke sequelae has focused on motor and sensory deficits, language disorders, visuospatial neglect, and impairment of daily living. However, long term follow-up of stroke survivors by multidisciplinary teams shows that a substantial proportion of these individuals are also affected by psychological distress and numerous psychiatric disorders[3]. These disabling psychiatric outcomes markedly reduce the quality of life after stroke; they are a major source of burden, stress and exhaustion for the caregiver, and often precipitate institutionalization of the patient.

The psychiatric complications of stroke are underrecognized and undertreated, despite growing evidence for the beneficial effects of available pharmacological and behavioural interventions. Health-care professionals are becoming more aware of the prevalence and relevance of neuropsychiatric disorders in patients with stroke. Unfortunately, physicians, nurses and physiotherapists rarely receive formal training in the screening and management of emotional and behavioural disorders.

This Review provides medical practitioners, including neurologists, psychiatrists, neurosurgeons, emergency and internal medicine physicians, family physicians, nurses and rehabilitation specialists, with an update on the acute and long-term psychiatric consequences of stroke, with an emphasis on the clinical aspects, biological and psychosocial determinants, and management of stroke-related psychiatric symptoms. We focus on disorders that are the most common, that are preventable and treatable (such as mood and anxiety disorders), and/or for which scientific advances have accumulated in recent years (for example, post-traumatic stress disorder and personality changes) (TABLE 1). Stroke-associated acute psychiatric disorders (delirium, acute stress disorders, acute psychosis, hallucinations and delusions) and chronic neurocognitive disorders (vascular cognitive impairment and dementia) will not be covered here. Disorders with predominantly somatic manifestations (disorders of sleep, eating and sexual function) are also not included because of the confounding effect of other comorbidities with similar symptoms that are common in elderly stroke survivors. Finally, fatigue, pain and disorders that affect the

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Key points

- Neuropsychiatric sequelae of stroke are often disabling, have a negative effect on stroke recovery, and decrease quality of life
- Neuropsychiatric disorders after stroke are relatively common: one-third of stroke survivors experience depression, anxiety or apathy; recovery from these disorders is only moderate, and the risk of recurrence is high
- Some of these disorders are treatable; for example, antidepressants reduce the number and severity of depressive symptoms and episodes and decrease anxiety scores in patients with stroke
- Research into the pathophysiology of stroke-associated neuropsychiatric disturbances would greatly benefit from improved study design, including incorporation of control groups in functional imaging studies and specification of working hypotheses
- Pilot studies on the effects of behavioural interventions and large-scale randomized trials of drugs that are safe to use in patients with stroke would improve the management of neuropsychiatric sequelae of stroke

control of expression of emotions will not be covered in this Review, because they are not included as psychiatric disorders in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[4]. The reader is referred to other excellent reviews[3,5] and books[6] on the neuropsychiatric manifestations of cerebrovascular diseases that are not covered here.

Depressive disorders

Clinical and diagnostic features

After an unexpected and dramatic stressor event, such as stroke, transient feelings of sadness are a nonpathological reaction. However, some patients with stroke develop a prominent and persistent depressed mood and/or diminished interest or pleasure in activities that used to be enjoyable (anhedonia)[4,7] (TABLE 1). These two criteria — depressed mood and anhedonia — define depressive disorder due to stroke[4]. Other symptoms, such as loss of energy, decreased concentration, psychomotor retardation and decreased appetite and insomnia, are also frequent. Suicidal thoughts and guilt can also occur after stroke, but are less common[8,9] (TABLE 1). Of note, some of the symptoms, in particular somatic complaints, might be directly caused by stroke-induced lesions or stroke complications, and can confound the diagnosis of depression.

Depressive disorders after stroke are subdivided into three categories. First, major depressive-like episodes are defined as presentation with five or more of the following symptoms for more than 2 weeks: depressed mood, anhedonia, weight loss or decrease in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, loss of energy, worthlessness or guilt, difficulty concentrating, and suicidal ideation. Second, if patients present with some of the above symptoms but do not meet the criteria of a major depressive episode, they are considered to have depressive features. Last, mixed features are described as symptoms of mania in addition to symptoms of depression[4,10].

The diagnosis of depression (and of psychiatric disturbances in general) requires the clinical judgement and expertise of a qualified physician, and the use of validated questionnaires[11] and accepted diagnostic criteria[4,12]. Depression scales are often used to screen patients and to quantify the severity of depressive symptoms. In most of the recent studies, stroke-related depression was evaluated with several scales, including the Montgomery and Åsberg Depression Rating Scale (MADRS)[13], the Hamilton Depression Rating Scale (HDRS)[14], the Hospital Anxiety and Depression Scale (HADS)[15], the Beck Depression Inventory (BDI)[16], and the Mini International Neuropsychiatric Interview (M.I.N.I.)[11] — a structured interview instrument that is widely used for psychiatric diagnosis.

Clinician-administered structured clinical interviews and screening scales for depression showed acceptable to excellent results for all validation measures when used to screen for psychiatric disorders in patients with stroke. No significant differences in performance were observed between the screening scales, with the exception of the Distress Thermometer, which was less accurate than the other scales[17].

Prevalence

Depressive disorders, which are considered to be distinct from bipolar and bipolar-related disorders in the DSM-5 classification[4], are much more common than bipolar disorders in patients who have experienced stroke[18,19]. In a systematic review of 61 observational studies, the prevalence of depression at any time between 1 year and 5 years after stroke was estimated at 31%, although the figures at 1 year and 5 years were lower (25% and 23%, respectively)[20]. Another meta-analysis of 50 studies reported a similar figure (29% early after stroke)[21]; however, in this study, the prevalence of depression remained stable up to 10 years after stroke, a finding also supported by the analysis of the South London Stroke Registry, which followed patients up for several years[21,22]. Of note, patients who have experienced a transient ischaemic attack (TIA) show a comparable risk of depression to stroke survivors[23–26].

The variation in the prevalence of depression between studies stems from several factors, including the setting of the study (depression is least common in community-dwelling patients, intermediate in patients undergoing rehabilitation, and highest in outpatients)[10], the type of stroke (ischaemic versus haemorrhagic), the amount of time elapsed since the stroke, and the types of stroke-related deficits (for example, severe aphasia or anosognosia)[10]. The different diagnostic criteria and the various methods used to diagnose depression are another major source of variation[27,28]. In most studies, the diagnosis of depression depends on the score on a given scale. As stressed above, these scales are more appropriate for screening for depression and to grade the severity of depressive symptoms than for validating the diagnosis of depression.

Predictors

The major predictors of stroke-induced depressive disorder are prestroke depression, anxiety and cognitive impairment associated with stroke, and the severity of the neurological deficit and physical disability following stroke[21,29].

Table 1 | **Neuropsychiatric disturbances after stroke**

Disorder	Prevalence in stroke survivors (%)	Main clinical characteristics	Screening tools	Treatment options
Depression	31	• Depressed mood • Anhedonia • Loss of energy • Decreased concentration • Psychomotor retardation • Decreased appetite • Insomnia • Suicidal thoughts • Guilt	• Montgomery and Åsberg Depression Rating Scale (MADRS) • Hamilton Depression Rating Scale (HDRS) • HADS • Beck Depression Inventory (BDI)	• Antidepressants (SSRIs) • Psychotherapy
Anxiety	18	• Anxiety or worry • Restlessness • Decreased energy • Poor concentration • Irritation • Nervous tension • Insomnia	HADS	• Antidepressants (SSRIs) • Benzodiazepines • Buspirone • Pregabalin • Psychotherapy • Lifestyle modifications
PTSD	10–25	• Unpleasant and uncontrollable re-experiences of stroke • Intrusion symptoms (memories, dreams or flashbacks about stroke) • Persistent avoidance of stimuli associated with the stroke • Stroke-related negative alterations in cognition, mood, arousal and reactivity	• Impact of Events Scale — Revised • Interview	• Exposure psychotherapy • Learning coping skills
Aggressive personality change	15–57	• Feelings of anger • Aggressive reactions and behaviour • Hostility	• Personality scales and questionnaires • Neuropsychiatric Inventory	• SSRIs (fluoxetine) • Neuroleptics (haloperidol or atypical neuroleptics) • Antiepileptic drugs or beta blockers
Apathetic personality change	36	• Low motivation • Reduced initiative • Loss of self-activation • Emotional indifference	• Personality scales and questionnaires • Apathy Evaluation Scale • Apathy Scale • Neuropsychiatric Inventory	• Dopaminergic agents • Buproprion • Noradrenergic antidepressants • Nefiracetam • Cholinergic agents • Stimulants

HADS, Hospital Anxiety and Depression Scale; PTSD, post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitor.

Traditionally, stroke-induced depressive disorder, especially in the first months after stroke, has been associated with lesions in the left hemisphere, particularly in the cortical or subcortical left anterior pole[30]. However, systematic reviews have shown that neither the anterior–posterior nor the right–left hemispherical localization of the lesions is relevant to the occurrence of stroke-induced depression[31,32]. According to current understanding, factors associated with increased risk of depression after stroke include large lesion volume[33], silent infarcts[34], and subcortical small vessel disease (characterized by lacunes, white matter lesions[35,36] and microbleeds[37–40]), presumably because they interfere with frontal subcortical circuits and ascending monoaminergic and serotonergic pathways, which are essential components of the motivational circuit.

Besides the severity of the neurological impairment and of stroke-associated disability, the personality of the patient, the subjective experience of the stroke by the patient, and the patient's coping strategies[41,42], lifestyle and lack of social support and networks also contribute to the risk of depression[43,44] (FIG. 1).

Clinical course and outcome

According to the South of London Stroke Registry, most episodes of stroke-associated depression begin within 1 year after stroke[21]. In patients who are depressed a few months after stroke, the depression recovery rate at 1 year after stroke is moderate (15–57%)[21]. Among patients with stroke-associated depression, the frequency of recurrent episodes of depression increases gradually from 38% at 2 years after stroke to 100% at years 14–15 (REF. 22). These figures illustrate the dynamic pattern of depression after stroke: depression affects a large subset of stroke survivors, and the risk of recurrent depressive episodes is high.

Stroke-associated depressive disorder increases mortality (HR = 1.27–1.41) up to 5 years after stroke[45]; the excess mortality is particularly notable in patients younger than 65 years and is not better explained by other medical factors, or by comorbidities, smoking, alcohol use, social support or compliance with medication[45]. Stroke-induced depression also has a negative effect on functional outcomes[29] and quality of life (mostly in the emotional and social domains), and

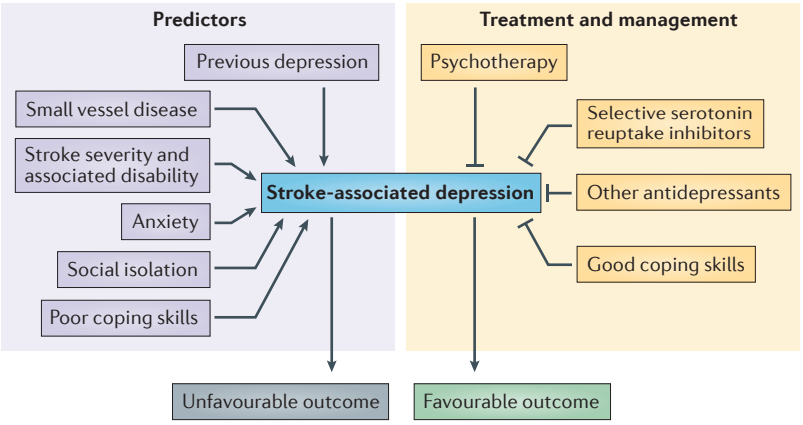

Figure 1 | **Major psychosocial and cerebrovascular predictors of stroke-associated depression.** Anxiety and poor coping-strategies, among other factors, have a negative influence on the course of depression. In stroke patients, depression is associated with unfavorable outcomes, including death. Treatment and management strategies such as the administration of antidepressants and good coping skills have beneficial effects on stroke-associated depression.

increases the risk of institutionalization, and family and caregiver depression[22]. Depression in stroke survivors at 3 months after stroke does not predict cognitive impairment within 5 years after stroke, but is associated with an increased risk of anxiety[22].

Pathophysiology and biomarkers

Two magnetic resonance spectroscopy studies showed that patients with stroke-associated depressive disorder had increased glutamate levels in the frontal lobe[46,47]. Moreover, in stroke survivors with small vessel disease, white matter damage (measured by fractional anisotropy) in the anterior limb of the internal capsule has been shown to increase the risk of depression, possibly because it impairs the frontal–subcortical circuits[48]. This biological vulnerability, together with environmental stressors, could precipitate stroke-associated depressive disorder[35].

In one functional MRI (fMRI) study, disrupted default mode network connectivity in the middle temporal cortex and precuneus correlated with the severity of depressive symptoms[49]. In another study, poststroke depression was associated with dysfunction of the links between the different areas of the affective network (prefrontal cortex, amygdala, insula, ventral striatum, hippocampus and anterior cingulate gyrus), with a correlation between the intensity of depressive symptoms and altered functional connectivity of the left orbital frontal gyrus[50].

In addition to the alteration of imaging markers after stroke, blood-based biomarker levels can be modified in patients with poststroke depression. Patients with stroke-induced depression show high homocysteine[51] and bilirubin levels[52], proteomic evidence of perturbed lipid metabolism and altered immunoregulation[53], and increased levels of serum leptin[54] and plasma glutamate[55]. Some of these factors — in particular, bilirubin — are potential markers of depression; however, these results need replication, and the causal relationship between these potential markers and depression remains to be established.

In a meta-analysis of association studies of serotonin transporter gene (*SLC6A4*) polymorphisms, stroke patients who carried two 'short' variations of the 5-HTTLPR polymorphic region had a twofold increase in the risk of stroke-induced depressive disorder[56]. The expression of *SLC6A4* is influenced by DNA methylation: increased methylation in the *SLC6A4* promoter region can suppress *SLC6A4* expression, and has been linked to poststroke depression[57]. Brain-derived neurotrophic factor (*BDNF*) gene polymorphisms and the methylation status of *BDNF* also affect the susceptibility to depressive disorder after stroke[57]. *SLC6A4* and *BDNF* polymorphisms are potential genetic markers of depressive disorders associated with stroke.

Management and treatment

In general, management of depression includes psychotherapy, antidepressants and neurostimulation[58,59] (FIG. 1). In patients with stroke, the use of neurostimulation is strictly limited because these individuals are at increased risk of stimulation-triggered seizures. Psychotherapy has a small preventive effect on stroke-associated depressive disorder[60], but there is no robust evidence to support the use of psychotherapy to treat stroke-induced depressive disorder[61]. Sending a monthly postcard to patients — a practice that has been shown to reduce suicidal behaviour in psychiatric inpatients and self-poisoning patients — was not effective in patients with stroke[62].

According to the European Stroke Organization, pharmacotherapy is recommended for depressive disorder attributed to stroke[63], because antidepressants have been shown to reduce the number and severity of depressive symptoms and episodes, despite treatment-associated adverse events[61]. A Cochrane Review including 56 randomized controlled trials (RCTs) and 4,059 patients provided strong support for the use of selective serotonin reuptake inhibitors (SSRIs) in patients with stroke, most notably those with depression. SSRIs reduced dependence, disability, neurological impairment, anxiety and depression, but had no effect on mortality, cognitive function or motor deficits[64]. No increase in severe adverse effects (seizures or gastrointestinal bleeding) was reported. Time elapsed since stroke or stroke severity did not influence the beneficial effect of SSRIs. As no SSRI has consistently demonstrated superiority over the others[64], selection of the most appropriate antidepressant for the individual patient must take into account not only efficacy, but also the comorbidities and adverse effects[65,66] (TABLE 2).

Folic acid and vitamin B_1, B_6 and B_{12} supplements have some beneficial effects on depression associated with stroke[67]. The efficacy of alternative therapies in stroke-associated depressive disorder has also been assessed[68]. In Asia, the use of acupuncture[69], electroacupuncture[70] and music therapy[71] had encouraging beneficial effects, but these results need confirmation.

Despite the high prevalence of stroke-associated depressive disorder and the availability of affordable and efficacious treatments, depression remains underdiagnosed and undertreated in patients with stroke[24,72], and two-thirds of stroke survivors with depression do not

Table 2 | **Selection of an antidepressant for the individual patient with depression after stroke**

Class	Adverse effects	Drug	Co-morbidities leading to preferential use
Selective serotonin reuptake inhibitor (SSRI)	Nausea, vomiting, gastric pain, anxiety, tremor, decreased threshold for seizures, and withdrawal syndrome	Escitalopram	Anxiety
		Paroxetine	Anxiety, weight loss
		Fluoxetine	Hypersexuality, weight gain
		Sertraline	Weight gain
TeCA, TriCA	Dry mouth, blurred vision, increased ocular tension, drowsiness, increased heart rate, cardiac arrhythmias, constipation, urine retention, postural hypotension, tremor and decreased threshold for seizures	Mirtazapine (TeCA)	Sleep disturbances, weight loss
		Amitriptyline (TriCA)	Sleep disturbances, weight loss, pain
Serotonin–noradrenaline reuptake inhibitor (SNRI)	Nausea, headache, somnolence, ejaculation disorder, yawning, decreased threshold for seizures	Duloxetine	Pain
		Venlafaxine	Pain, weight gain
Serotonin antagonist and reuptake inhibitor (SARI)	Dry mouth, constipation, blurred vision, drowsiness	Trazodone	Sleep disturbances
Dopaminergic	Dry mouth, headache, nausea, weight loss, insomnia, agitation	Bupropion	Apathy, weight gain

TeCA, tetracyclic antidepressant; TriCA, tricyclic antidepressant.

receive antidepressants. Such figures could be improved by eradicating the misconception that low mood is a transient normal reaction to stroke, and that the associated deficits are not relevant to health outcomes. Implementation of routine screening for depression in stroke and rehabilitation units could also be beneficial.

Suicidality after stroke

As stated above, recurrent thoughts of death — that is, suicidal ideation — or suicide plans or attempts are among the diagnostic symptoms of a major depressive episode[4]. However, although the suicide rate is higher in patients with stroke than in the general population[73,74], suicide is still uncommon after stroke[75]. Suicidal thoughts, which can develop shortly after stroke but are more often observed after a delay[76], are particularly common in patients with low education, previous mood disorder, and/or stroke-associated depressive disorder[75]. Suicidality after stroke is also associated with younger age, functional limitations[73], insomnia, pain, apathy and lobar cerebral microbleeds[77–80].

In patients with acute depression after stroke, completed suicide has sometimes been linked with argyrophilic grain disease or early progressive supranuclear palsy, suggesting that an underlying tauopathy can aggravate poststroke depression, potentially leading to suicide. Such an effect could, plausibly, occur through frontal disinhibition[81].

Bipolar and related disorders

Manic episodes and bipolar disorder are rare psychiatric complications of stroke (reported in 1–2% of stroke survivors)[18,19]. Attribution of these disorders to stroke should only be made when the onset of mania coincides with or follows stroke: mania can occur concomitantly with stroke or follow it by days, months or years. The most common clinical manifestations of poststroke mania are elevated mood, hyperactivity, increased rate or amount of speech, and insomnia or decreased need for sleep[19] (TABLE 1). Other symptoms include irritability, flights of ideas, grandiosity, lack of insight, and social disinhibition. Mania is more common after infarcts of the right hemisphere than of the left hemisphere[19]. Patients with stroke-associated mania can experience recurrent episodes of mania or, as described in a few reports, alternate manic and depressive bouts (bipolar disorder)[19].

Evidence to support management strategies for manic episodes and bipolar disorder after stroke is limited to case reports and small case series[19]. Current treatment guidelines for bipolar disorder recommend mood stabilizers such as lithium, valproate or lamotrigine, neuroleptics during severe maniac episodes, and antidepressants in depressive periods[82].

Anxiety disorders

Clinical and diagnostic features

Anxiety disorders are common after stroke, but they are less well studied than depressive symptoms. Panic attacks and phobias attributed to stroke have been described in isolated reports, but the most common stroke-associated anxiety disorder is generalized anxiety disorder[83]. Generalized anxiety disorder is defined as almost permanent anxiety or worry about a variety of topics that is difficult to control, to the extent of having a negative impact on well-being and everyday functioning[4]. In addition to permanent anxiety, the DSM-5 criteria require that the patient presents with three or more other symptoms (restlessness, decreased energy, poor concentration, irritation, nervous tension and/or insomnia)[4]. The Hospital Anxiety and Depression Scale (HADS) is commonly used to screen and rate the intensity of the symptoms in patients with anxiety after stroke[15].

Prevalence

In a systematic review and meta-analysis of 42 observational studies comprising 5,760 patients with stroke, the prevalence of anxiety was 18% when assessed by clinical interview and 25% when assessed by a rating scale[84]. The prevalence of anxiety is stable over time: 20% of patients experience anxiety within the first month after stroke, compared with 23% 1–5 months and 24% >6 months after stroke[84]. Two community-based studies published after the meta-analysis confirmed most of these findings[27,85].

Predictors

Previous depression, previous anxiety and alcohol abuse are the most consistent psychiatric predictors of stroke-induced anxiety. Demographic predictors of anxiety include young age and female sex. Aphasia, history of insomnia and cognitive impairment also predict anxiety associated with stroke. Functional and social predictors of anxiety after stroke include impairment in activities of daily living, impairment in social functioning, inability to work, being single, and living alone or having no social contacts outside the family[85,86].

Clinical course and outcome

25–50% of patients with acute anxiety after stroke develop permanent chronic anxiety. The co-occurrence of depression with poststroke anxiety increases the likelihood that the anxiety will be permanent or long-standing[86]. Anxiety without depression does not influence functional recovery from stroke but is associated with worse social functioning and quality of life[85,87].

Advances in pathophysiology

Stroke-triggered anxiety could be especially common after strokes affecting the anterior circulation: one study suggested an association between anxiety and right frontal infarcts[88]. A small-sample genetic association study performed in China suggested that polymorphisms in the tryptophan hydroxylase 2 (*TPH2*) gene are involved in the development of stroke-associated anxiety[89].

Management and treatment

Management of generalized anxiety disorder includes patient education and lifestyle modifications, psychotherapy, and pharmacotherapy with antidepressants (SSRIs or serotonin–noradrenaline reuptake inhibitors), benzodiazepines, buspirone or pregabalin[90]. Pharmacological treatments are also efficacious in the treatment of anxiety attributed to stroke. In a systematic review that included two trials involving a total of 175 stroke patients with anxiety and comorbid depression, paroxetine and buspirone were found to substantially reduce anxiety scores[91]. A systematic review of SSRIs for stroke recovery assessed eight trials with a total of 413 participants, and reported that SSRIs decrease anxiety scores[64]. A few small pilot trials of relaxation therapies to reduce stroke-associated anxiety have produced encouraging results[92,93]. The use of benzodiazepines or pregabalin in patients with poststroke anxiety has not yet been evaluated by RCT.

Post-traumatic stress disorder

Clinical and diagnostic features

Stroke and TIA are unexpected events that have the potential to be life-threatening and cause serious disability; moreover, they can be re-experienced in an unpleasant and uncontrollable way after the actual event[94]. Stroke-associated post-traumatic stress disorder (PTSD) is characterized by intrusive symptoms (memories, dreams, and flashbacks of the stroke or TIA), persistent avoidance of stimuli associated with the stroke, negative alterations in cognition and mood, marked alterations in arousal, and increased reactivity (irritability, angry outbursts, exaggerated startle response)[4].

The PTSD Impact of Events Scale — Revised and Interview[95] can be used to screen patients for PTSD. PTSD can be diagnosed with questionnaires, scales or formal psychiatric interview, with varying results: when assessed with a scale, PTSD was diagnosed in 25% of patients with stroke, whereas only 10% of patients were diagnosed with PTSD when assessed with a formal psychiatric interview[96].

Prevalence

In stroke survivors, the estimated prevalence of PTSD ranges from 10% to 31%[94,96,97]. These percentages are probably overestimates because, in most studies, PTSD was diagnosed with questionnaires and scales[96,98], rather than with formal psychiatric interviews.

Predictors

PTSD after stroke is more common in women, younger patients, and patients with low educational level, recurrent strokes, more-severe disability, comorbidities (including depression and anxiety), prestroke neuroticism, or prior psychiatric morbidity. Moreover, PTSD is more common in patients with a subjectively rated high stroke risk or a negative appraisal of the stroke or TIA experience (peritraumatic distress)[94,96,97]. Peritraumatic distress predicts acute PTSD symptoms after a first stroke[99] and correlates with the intensity of PTSD symptoms, although this correlation tends to decline over time after the stroke[99].

Course and outcome

PTSD has a negative effect on mental health and quality of life. It is also associated with an increased risk of nonadherence to medication[100].

Management and treatments

The use of behavioural therapeutic strategies, such as exposure therapy, has been shown to reduce PTSD in combat veterans[101] and could be tested in patients with stroke. Approaches in which patients are taught more-effective coping skills and are cautiously briefed about the realistic risk of stroke recurrence should be tested for effectiveness in PTSD after stroke.

Personality changes

Personality has a complex two-way relationship with stroke. Some personality traits[4,102], including anger, type A behaviour and pessimism, increase stroke risk[103], and affect stroke outcome[104] and response to

therapeutic interventions. In a pooled analysis of three cohort studies, high extraversion was linked to an increased risk of stroke; high neuroticism was associated to increased stroke-related mortality, whereas high consciousness was associated with decreased mortality[105]. Neuroticism was also found to predispose to poststroke depression and poor quality of life[105]. Negative affectivity hampers improvement in response to speech therapy[106].

Conversely, stroke can affect personality; such personality changes are more marked and intense than those reported in association with other chronic diseases. In a pooled analysis of four cohort studies including 17,493 patients with chronic diseases, stroke induced a long-term change in personality traits, even after adjustment for age. Stroke was associated with a decrease in the 'positive pole' of personality traits domains (FIG. 2), including extraversion, emotional stability, consciousness and openness to experience. Furthermore, a trend towards a 'dose–response' relationship between the severity and chronicity of stroke and the intensity of personality trait changes was observed[107].

Clinical and diagnostic features

Personality disorders are grouped in three main clusters, A, B and C, according to the DSM-5 classification, and are defined as a repeated deviation of behaviour from what can be expected from the individual's culture[4]. Personality changes are classified into five types (labile, disinhibited, aggressive, apathetic, and paranoid)[4], and represent a change from the individual's previous personality pattern. Diagnosis of personality disorders and changes requires multiple examinations by a medical expert, usually a psychiatrist. Personality scales can help establish the correct diagnosis[104,108], and simple instruments, such as the Neuropsychiatric Inventory[109], are often used for screening purposes. In the sections that follow, we will focus on the apathetic and aggressive types of personality change, as the information on other personality changes after stroke is limited.

Apathetic personality change. Apathy is a disorder of motivation characterized by decreased spontaneous mental and physical activity and emotional indifference[110,111].

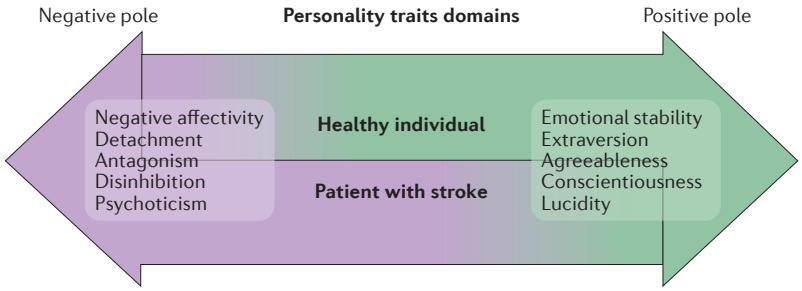

Figure 2 | **Shift towards the negative pole of personality trait domains after stroke.** Personality changes attributed to stroke can be conceptualized as changes towards the 'negative pole' of personality traits. Examples include detachment observed in apathetic personality, negative affectivity seen in labile personality, disinhibition in disinhibited personality, psychoticism in paranoid personality and negative affectivity, detachment, antagonism, disinhibition and/or psychoticism in aggressive personality.

Apathetic patients have markedly decreased motor, verbal and behavioural initiative: they do not start a new activity by themselves, but they can adequately perform the same activity following the commands or actions of others. Characteristic symptoms in apathetic patients are lack of interest in their previous activities and hobbies, and preference for passive activities. As apathetic patients are emotionally indifferent, even to their symptoms, they can seem depressed, but if questioned whether they are sad, they deny low mood, in contrast with depressed patients who express sadness and are affected by not being able to start and maintain actions and to experience pleasure in activities.

Some patients with apathy after stroke are also depressed[112–115], and depression is particularly common and severe in apathetic patients[114,116]. However, the co-occurrence of apathy and depression could be lower than reported, because apathy can be erroneously labelled as anhedonia or inhibition, thereby leading to an incorrect diagnosis of depression[110]. Indeed, apathy and depression are typically dissociated: apathy without depression was reported in 21% and depression without apathy in 12% of stroke survivors[113]. These disorders also have different evolutions during follow-up and different responses to treatment[112,117–120].

Apathetic personality change should be diagnosed by a skilled physician, using accepted diagnostic criteria[4]. Validated scales, such as the Apathy Scale, which was adapted from the original Apathy Evaluation Scale[121], can be used for screening and to grade the severity of apathy symptoms, but cannot replace the expert diagnosis of apathetic personality change.

Aggressive personality change. In patients with stroke, the three components of anger (emotional, cognitive and behavioural[122,123]), the subjective experience of anger, and anger-associated behaviour can be dissociated[124,125]. Patients with stroke and aggressive personality change can behave aggressively without feeling angry or, conversely, experience only hostility without showing aggressive behaviour.

In stroke survivors, anger or aggressive behaviour can be symptomatic of several neuropsychiatric disorders, including delirium, mania, psychosis, vascular cognitive impairment and catastrophic reaction[126]. A tendency to react and behave aggressively can also be the prominent feature of another type of long-standing personality change after stroke. Patients with dorsolateral prefrontal or basofrontal infarcts (for example, in the context of anterior communicating artery aneurysmal rupture) can display such personality change as part of a dysexecutive syndrome that impairs inhibition of aggressive responses and decreases mental flexibility. Similarly, patients with severe Wernicke aphasia are almost deprived of language comprehension and can develop intense suspicion, anger and aggressive behaviour[126].

Prevalence

Stroke-related personality disorders of the three clusters (A, B and C) are rare, and are estimated to occur in less than 1% of stroke survivors[127]. However, stroke-associated

personality changes seem to be quite common, although their frequency is not well defined, except in the case of apathy, as detailed below. Reasons for these heterogeneous results include different definitions of personality changes, and the multiplicity of instruments that have been used to detect and grade the severity of such changes of personality. The reported frequency of personality changes after subarachnoid haemorrhage is 59%[128]. Depending on the study, 8–32% of stroke survivors experience a labile personality change and 6–76% of patients with stroke show disinhibited personality change[3]. Similarly, a 2015 systematic review reported a high prevalence of anger, with high variability between studies (15–57%)[129].

Although stroke-associated apathy has received less attention than depression, potentially owing to the fact that apathy can be misdiagnosed as depression, their prevalence is similar. In a systematic review of 19 studies, we found a prevalence of stroke-associated apathy of 36.3%[116]. The prevalence was similar in acute (up to 15 days after stroke onset) and post-acute phases. Two studies, published in 2013 and 2015, confirmed the high prevalence of stroke-related apathy[117,130].

Predictors

In our systematic review, apathy was more common in older patients, and in patients with recurrent stroke, cognitive impairment or depression[116]. The prevalence of apathy was similar in both sexes, after ischaemic and haemorrhagic strokes, and after right and left hemispheric strokes[112–116].

Case reports and small case series have described apathy to be a prominent clinical feature in patients with strokes in locations that are essential for motivation, such as the anterior cingulate–pallidum–thalamic circuit. For example, apathetic personality changes were induced by unilateral or bilateral anterior cerebral artery infarcts[131], anterior and paramedian ischaemic thalamic strokes[132], striatocapsular strokes[118], and anterior communicating artery aneurysmal rupture with basofrontal or mesial infarcts[128,133]. However, in most systematically evaluated series of patients with apathy after stroke, the anatomical location of the stroke was not significantly associated with apathy, with the exception of one patient series[131], in which apathy was more common after bilateral lesions (67%), followed by left-hemisphere and right-hemisphere strokes (51% and 25%, respectively). In this study, apathy was more common when the stroke damaged the frontal pole, gyrus rectus, corpus callosum, cingulate gyrus or superior frontal lobe. In another study, pontine infarcts were linked to increased risk of apathy after stroke[134].

In patients with stroke, the association of anger with demographic, clinical, neuroradiological, psychological and social variables is not consistent between studies[129]. Some studies reported anger to be more frequent in patients with haemorrhagic strokes, with lesions close to the frontal pole, and in strokes involving the frontal, lenticulocapsular and basal pontine areas, whereas other studies found no association with a specific stroke type or localization[129].

Course and outcome

The course of apathy after stroke has been evaluated in only a few longitudinal studies[112,115,130,135]. In general, apathetic patients with stroke show little improvement of apathy over time. Apathy in the acute phase of stroke predicts longer-term poststroke apathy[112]. Persistent apathy after stroke is associated with cognitive impairment, more-severe functional deficits, less functional improvement, depression, recurrent strokes, and suicide[80]. Apathy interferes with rehabilitation, and impairs health-related quality of life[114,116,119,120,130,131,135,136]. Nevertheless, no difference in functional outcomes has been observed between patients with and without apathy[114].

Advances in pathophysiology

A few small functional neuroimaging studies have provided important hints concerning the cerebral network dysfunction that underlies apathy. Matsuoka *et al.* found delayed atrophy in the posterior cingulum in patients with poststroke apathy[137]. The fMRI study of a patient with poststroke apathy demonstrated aberrant functional connectivity in the default mode network and in the cingulo-opercular network, and identified these two networks as an apathy-related functional network[138]. A voxel-based analysis of fractional anisotropy in 54 patients with stroke demonstrated that apathy is related to damage of the genu and splenium of the corpus callosum, left anterior corona radiata and white matter of the right inferior frontal lobe[139]. Poor reward sensitivity, which is linked to damage to the ventral putamen and pallidum, dorsal thalamus, left insula and prefrontal cortex, was also associated with apathy in an fMRI study of 55 patients with stroke and 15 controls[140]. Another fMRI study showed that the pathways associated with affective (serotonergic) and apathetic (dopaminergic) depression after stroke were different[141].

In patients with acute stroke, failure of inhibitory control of behaviour is probably the primary cause of aggressive behaviour[126]. The hospital environment can be perceived as hostile or humiliating, thereby contributing to the development of angry behaviour. Premorbid anger can also increase the intensity of the manifestations of anger after stroke. fMRI studies in healthy individuals have implicated the ventromedial, prefrontal and orbitofrontal cortices in anger[142]. Stroke rarely involves these frontal areas, with the notable exception of subarachnoid haemorrhage caused by rupture of an aneurism in the anterior communicating artery. This type and location of stroke often results in aggressive behaviour[143]. Aggressiveness attributed to stroke can also be secondary to the loss of empathy. Recent MRI studies in patients with right hemispheric stroke point towards a crucial role for the right uncinate fasciculus in emotional empathy[144], and a function of the temporal pole and anterior insula in affective empathy[145].

Management and treatment

No large high-quality RCTs have yet been conducted to guide the treatment of apathetic personality change attributed to stroke. Evidence regarding potential treatments for apathy is limited to case reports and small

case series. Therefore, the treatment of apathy after stroke currently follows indirect low-level evidence collected in the context of apathy treatment in other neurological conditions.

Behavioural interventions for apathy prevention have been assessed in two small RCTs. Coping-strategy training[146] and problem-solving therapy[147] both show promise for the prevention of apathy.

Given the role of dopamine in motivation, dopaminergic agents could represent a first-line pharmacological treatment to ameliorate apathy[66,148]. If the patient is also depressed, antidepressants with dopaminergic activity (for example, buproprion) or noradrenergic activity (for example, reboxetine) could be used. A small randomized trial showed improvement of poststroke apathy with the nootropic nefiracetam, which enhances GABAergic, cholinergic and monoaminergic signalling[149]. Other cholinergic agents, such as donepezil[150], and stimulants, such as modafinil[151] or methylphenidrate[152], have also been reported to alleviate apathy, although their cardiovascular adverse effects limit their use in elderly patients with stroke and comorbid hypertension or cardiac diseases. Surprisingly, a case report claimed that the sedative zolpidem was effective in the treatment of poststroke apathy[153].

No studies have specifically evaluated interventions to manage severe aggressive personality change in patients with stroke. Recommendations have been made for dealing with aggressive behaviour after other neurological conditions, such as traumatic brain injury[154], but post-traumatic and poststroke aggressiveness might have different pathophysiologies. We advocate psychological counselling to establish realistic goals for recovery, coping strategies to deal with the stroke-associated deficits, and explaining to the caregiver how to deal with the aggressive patients. Anger after stroke can be treated with SSRIs such as fluoxetine[155]. In patients with severe aggressive behaviour, neuroleptics (either haloperidol or atypical neuroleptics) could be used to prevent harm to the patient and to others. The starting dose should be low and titrated according to the control of aggression gained with treatment and to the intensity of the adverse effects (sedation, confusion or cognitive impairment, rigidity, walking difficulty and falls). Cardiovascular adverse effects and lowering of the seizure threshold, especially if the drugs are prescribed concomitantly with SSRIs, should also be monitored. If aggressive behaviour is under control or decreases to acceptable levels, the dose should be reduced, and the drug should eventually be discontinued. In patients who do not respond to SSRIs and neuroleptics, antiepileptic drugs or beta blockers can be used[154].

Conclusions and future directions

Over the past decade, researchers have successfully described the high prevalence of the neuropsychiatric sequelae of stroke and their main clinical and psychosocial correlates. One-third to one-half of stroke survivors are affected by a neuropsychiatric disorder despite evidence that pharmacological treatment of neuropsychiatric disorders — in particular, depression — is efficacious in patients recovering from stroke. Moreover, the neuropsychiatric disturbances that occur after stroke are currently underdetected[25,72]. This underestimation is observed even in developed countries where access to health care is easy. Antidepressants can have the additional benefit of improving physical and cognitive recovery after stroke. These results could justify antidepressant prescription to almost all stroke survivors, but larger trials are needed before such a treatment policy is implemented[64,156].

Most of the studies published on the psychiatric complications of stroke have several recurrent methodological limitations. Almost all studies analysed patients from hospitals, clinics or rehabilitation centres, and very few were population-based. Patients with aphasia and cognitive deficits were often excluded. Stroke type and location were not always specified. The coexistence of imaging markers of cerebral small vessel disease or Alzheimer disease, which are confounding factors, was only rarely assessed. In general, the diagnosis of the psychiatric condition was made after a single examination, and by following cut-off scores on a scale. The diagnosis of a psychiatric condition requires the expertise of an experienced psychiatrist, using validated diagnostic criteria and multiple observations of the patient. Moreover, different studies used different scales, making interstudy comparisons and systematic reviews challenging. The use of scales also leads to the inclusion of mild cases and minor disturbances in the same group as psychiatric disorders, which can obscure or dilute the results of studies that investigate risk factors and prognostic variables. Another limitation of the studies on the neuropsychiatric sequelae of stroke is that psychiatric models, such as personality models, are only rarely integrated when testing hypotheses on the development of neuropsychiatric disorders after stroke.

The majority of the studies on the neuropsychiatric consequences of stroke failed to confirm consistent associations between psychiatric disturbances and anatomical locations of stroke lesions. Some studies indicate that lesions in particular locations trigger certain psychiatric conditions; however, such claims can only be validated by comparing patients with psychiatric disorders presumably caused by stroke lesions with a control group of patients with stroke-associated lesions in other locations. In addition, most fMRI studies that evaluated the influence of lesion location on psychiatric symptoms — for example, the study on right hemispheric stroke and apathy[144] — selected patients with a specific stroke location, and did not include a control group. The results of fMRI and network analysis studies are often difficult to interpret, owing to the multiple roles of functional nodes that are deemed important for a specific disturbance.

There is still a paucity of studies that analysed serum or cerebrospinal fluid biomarkers or examined genetic polymorphisms that could predispose individuals to psychiatric disturbances after stroke. Many of the available studies tested hypotheses that were too general, such as the catecholamine hypothesis, which premise is that depression is associated with a decrease in central catecholamine levels, or asked questions that were too broad (for example, "is inflammation involved in stroke-associated depressive disorder?"), and the results are yet to be replicated.

Improved study designs and expansion of the research on the biological determinants and pathophysiology of stroke-associated psychiatric disorders are clearly needed. Management of poststroke psychiatric symptoms also needs further investigation, which should include pilot studies of innovative behavioural interventions and large-scale RCTs of drugs that are safe to use in patients with stroke.

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Competing interests statement
The authors declare no competing interests.

Review criteria
In this narrative review, we did not follow the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). We retrieved background information from publications and books and performed a MEDLINE/PubMed search of relevant publications from 2010 to 2015 using the following keywords: "depression", "poststroke depression", "suicide", "bipolar", "mania", "psychosis", "anxiety", "post-traumatic stress disorder", "stress disorder", "personality", "personality disorders", "lability", "emotional control", "disinhibition", "aggressiveness", "aggression", "hostility", "irritability", "anger", "poststroke apathy" and "apathy AND stroke". We also searched the Cochrane Central Register of Controlled Trials, the Internet Stroke Centre and ClinicalTrials.gov. References were selected on hierarchy of evidence, study quality, clinical relevance and innovation.