Neuropsychiatric Symptoms of Neurological Disease

José M. Ferro *Editor*

Neuropsychiatric Symptoms of Cerebrovascular Diseases

Springer

Neuropsychiatric Symptoms of Neurological Disease

José M. Ferro
Editor

José M. Ferro
Series Editor

Neuropsychiatric Symptoms of Cerebrovascular Diseases

Springer

Editor
José M. Ferro
Faculty of Medicine
Institute of Molecular Medicine
University of Lisbon
Lisbon, Portugal

Department of Neurosciences
Neurology Service
Hospital de Santa Maria
Lisbon, Portugal

Series Editor
José M. Ferro
Faculty of Medicine
Institute of Molecular Medicine
University of Lisbon
Lisbon, Portugal

Department of Neurosciences
Neurology Service
Hospital de Santa Maria
Lisbon, Portugal

ISBN 978-1-4471-2427-6 ISBN 978-1-4471-2428-3 (eBook)
DOI 10.1007/978-1-4471-2428-3
Springer London Heidelberg New York Dordrecht

Library of Congress Control Number: 2013943264

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Foreword

Neuropsychiatric Symptoms of Cerebrovascular Diseases is the first book of a series of volumes on the psychiatric aspects of common neurological diseases, to be published by Springer-Verlag.

The first volume is dedicated to acute stroke and other cerebro-vascular diseases.

Stroke and chronic cerebro-vascular disease, namely vascular cognitive impairment and dementia, are among the commonest causes of longstanding disability due to diseases of the central nervous system. Neuropsychiatric complications are quite frequent both in the acute phase of stroke (e.g. delirium, denial) and in stroke survivors or in patients with vascular cognitive impairment (e.g. depression, apathy). In the acute phase of stroke, delirium and other neuropsychiatric complications become a focus of interest, because they disturb the process of care and are indicators of worse outcome.

In the long range, psychiatric disturbances strongly contribute to a lower Quality of Life among stroke survivors. The role of psychiatric disturbances in producing significant caregiver burden has also been recently recognised. Meanwhile several new drugs (new anti-psychotics, mood stabilizers, antidepressants, cholinergic agents) become available, that may be useful in the management of these patients.

Health care professionals are starting to realize the weight of neuropsychiatric complications in long-term disability. Unfortunately, few professional received formal training on the detection and management of emotional and behavioural disturbances. We hope that this book can contribute to fill such educational gap.

This book has several features to attract the interest of the reader. The 14 chapters cover not only the psychiatry of stroke and vascular cognitive impairment, but also the role of psychiatric disturbance and psychological events as triggers and risk factors for stroke and the contribution of cerebrovascular disease to primary psychiatric conditions. Chapters are up to date comprehensive reviews of different topics within the neuropsychiatry of stroke, by active authorities in the field, with emphasis on the diagnostic and management issues. There is a focus on the pharmacological aspects of management, to provide robust information on drug dosages, side

effects and interactions, in order to enable the reader to a safer management of these patients. Several chapters include one or two illustrative cases, which will make the reading more pleasurable and more close to mainstream practice.

Each chapter includes a critical appraisal of the methodological aspects and limitations of the current research on the neuropsychiatry of stroke and on unanswered questions. This feature makes this book of great interest for students and researchers in the area.

We hope this book will become a standard reference for clinicians of several specialities.

Lisbon, Portugal José M. Ferro

Acknowledgements

To all the authors for their generous and enthusiastic participation in this project.

To my mentors in Neuropsychology and Psychiatry: António Damásio, Andrew Kertesz, Simões da Fonseca and Silveira Nunes.

To the University of Lisbon research group on Psychiatry of Stroke: Luisa Figueira, Lara Caeiro, Ana C. Santos and Rudolfo Albuquerque.

To Isabel Santos and Luisa Pires for their help with the references and secretarial work.

Contents

Contributors

J. Bogousslavsky Center for Brain and Nervous System Disorders, Genolier Swiss Medical Network Neurocenter and Department of Neurology and Neurorehabilitation, Clinique Valmont, Glion, Switzerland

Simone Brockman School of Psychiatry and Clinical Neurosciences, University of Western Australia, Crawley, WA, Australia

Joanne A. Byars Department of Neurology, University of Florida College of Medicine, Gainesville, FL, USA

Lara Caeiro Faculty of Medicine, Institute of Molecular Medicine, University of Lisbon, Lisbon, Portugal

Department of Neurosciences, Neurology Service, Hospital de Santa Maria, Lisbon, Portugal

P. Calabrese Division of Molecular and Cognitive Neuroscience, Basel University, Basel, Switzerland

A. Carota Center for Brain and Nervous System Disorders, Genolier Swiss Medical Network Neurocenter and Department of Neurology, Clinique Genolier, Genolier, Switzerland

Hugues Chabriat Department of Neurology, Hopital Lariboisière, APHP, Université Paris VII, Denis Diderot, Paris, France

CERVCO, Université Paris VII, Denis Diderot, Paris, France

INSERM UMR740, Université Paris VII, Denis Diderot, Paris, France

Smi Choi-Kwon College of Nursing, Research Institute of Nursing Science, Seoul National University, Seoul, Korea

José M. Ferro Faculty of Medicine, Institute of Molecular Medicine, University of Lisbon, Lisbon, Portugal

Department of Neurosciences, Neurology Service, Hospital de Santa Maria, Lisbon, Portugal

Jess G. Fiedorowicz Department of Psychiatry, Roy J. and Lucille A. Carver College of Medicine, University of Iowa Hospitals and Clinics, Iowa City, IA, USA

Department of Internal Medicine, Roy J. and Lucille A. Carver College of Medicine, University of Iowa Hospitals and Clinics, Iowa City, IA, USA

Department of Epidemiology, College of Public Health, The University of Iowa, Iowa City, IA, USA

Vincent Guiraud Université Paris Descartes, Sorbonne Paris Cité, INSERM UMR S894, Service de Neurologie et Unité Neurovasculaire, Pôle Raymond Garcin, Hôpital Sainte-Anne, Paris, France

Brad Hayhow School of Psychiatry and Clinical Neurosciences, University of Western Australia, Crawley, WA, Australia

Hilde Henon E.A. 1046 Department of Neurology, Stroke Unit, University Hospital of Lille, Lille, France

Markku Kaste Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland

Jong S. Kim Department of Neurology, University of Ulsan College of Medicine, Asan Medical Center, Song-Pa, Seoul, South Korea

Emre Kumral Neurology Department, Stroke Unit, Ege University School of Medicine, İzmir, Turkey

Didier Leys E.A. 1046 Department of Neurology, Stroke Unit, University Hospital of Lille, Lille, France

Leonardo Pantoni NEUROFARBA Department, Neuroscience Section, University of Florence, Florence, Italy

Anna Poggesi NEUROFARBA Department, Neuroscience Section, University of Florence, Florence, Italy

Sonia Reyes Department of Neurology, Hopital Lariboisière, APHP, Université Paris VII, Denis Diderot, Paris, France

CERVCO, Université Paris VII, Denis Diderot, Paris, France

Arnaud Saj Department of Neurosciences, University of Geneva, Geneva, Switzerland

Department of Neurology, University Hospital of Geneva, Geneva, Switzerland

Catarina O. Santos Faculty of Medicine, Institute of Molecular Medicine, University of Lisbon, Lisbon, Portugal

Department of Neurosciences, Serviço de Neurologia (piso 6), Hospital de Santa Maria CEEM, Lisbon, Portugal

Sergio E. Starkstein School of Psychiatry and Clinical Neurosciences, University of Western Australia, Crawley, WA, Australia

Fremantle Hospital, T-7, Fremantle, WA, Australia

Alan J. Thomas Institute for Ageing and Health, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, UK

Emmanuel Touzé Université Paris Descartes, Sorbonne Paris Cité, INSERM UMR S894, Service de Neurologie et Unité Neurovasculaire, Pôle Raymond Garcin, Hôpital Sainte-Anne, Paris, France

Risto Vataja Department of the Neuropsychiatry and Geriatric Psychiatry, Kellokoski Hospital, Kellokoski, Finland

Roland Vocat Valais Hospital, Sion, Switzerland

University Hospital of Geneva, Geneva, Switzerland

Patrik Vuilleumier Department of Neurology, University Hospital of Geneva, Geneva, Switzerland

Department of Neurosciences, Medical Center, University of Geneva, Geneva, Switzerland

Département de Neurosciences Fondamentales, Centre Médical Universitaire, Geneva, Switzerland

Part I
Psychiatry of Stroke

Chapter 1
Delirium in Stroke Patients

Hilde Henon and Didier Leys

Abstract Delirium is an acute, transient, and fluctuating disorder of consciousness, attention, and cognition. It is frequent at the acute phase of stroke, occurring in approximately one-quarter of stroke patients. Despite this high frequency, the physiopathology of delirium in stroke patients remains largely unknown. Delirium may be the consequence of stroke itself but is, in a large number of cases, the consequence of a preexisting cognitive decline and of coexistent intercurrent disorders such as a metabolic disturbances or infections. This suggests that when delirium occurs in a stroke patient, a comprehensive search for precipitating factors must be performed. Delirium is a predictor of worse outcome after stroke: it is associated with a longer duration of hospital stay, a higher mortality, a worse functional outcome, and a higher risk of poststroke cognitive decline. No large randomized trial has been conducted in delirious patients, in particular after stroke. Treatment recommendations are therefore based on expert's opinions: supportive and environmental measures, treatment programs, and trained nurses may be useful; drug treatment must be restricted to selected patients, after a careful evaluation of the benefice/risk balance. Orally low dose of haloperidol or atypical antipsychotic drugs remains to date the first-choice treatment.

Keywords Stroke • Delirium • Confusional state • Cognition • Prognosis

Delirium is a neuropsychiatric disorder characterized by an altered level of consciousness associated to disturbances in orientation, memory, thought, and behavior, with an acute onset and a fluctuating course. It is frequent in stroke patients, although stroke is a rare cause of delirium. Many predisposing factors have been

H. Henon (✉) • D. Leys
E.A. 1046 Department of Neurology, Stroke Unit,
University Hospital of Lille, Lille 59037, France
e-mail: hilde.henon@chru-lille.fr

J.M. Ferro (ed.), *Neuropsychiatric Symptoms of Cerebrovascular Diseases*,
Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-1-4471-2428-3_1, © Springer-Verlag London 2013

identified. Stroke per se may however induce delirium. The occurrence of this disorder adversely influences outcome in stroke patients. The physiopathology remains however largely unknown, and no specific treatment has proven its efficacy in this condition.

Diagnosis of Delirium

Main Clinical Characteristics

Delirium is an acute, transient disorder of consciousness, attention, and cognition which develops over a short period of time and fluctuates during the course of the day [1] which is common in elderly hospitalized patients, occurring in 20–30 % of patients [2]. The clinical picture of delirium in stroke patients is identical to delirium occurring in other conditions and is characterized by an acute onset (hours to days) of consciousness disturbances usually presenting as a reduced awareness of the environment, with difficulties in focusing and sustaining attention on one stimulus and difficulties in shifting attention to new external stimuli. Attention disturbances are associated to other cognitive disturbances including disorders of memory, orientation, language (aphasia, incoherent speech, anomia), visuospatial dysfunction, and abnormalities of thinking and perception (illusions, hallucinations, or delusions). Sleep-wake abnormalities are often observed with reduced and fragmented sleep during the night with nocturnal agitation, shouting, and aggressiveness contrasting with daytime sleepiness. A wide range of emotional disturbances may occur, including fear, anxiety, euphoria, apathy, and depression, with sometimes rapidly changing emotions. The symptoms of delirium are wide ranging and nonspecific, but their abrupt or rapid onset and their fluctuating nature are highly characteristic and are a valuable diagnostic tool. The diagnostic criteria for delirium from the American Psychiatric Association [1] and from the ICD-10 [3] are given in Table 1.1.

Many individuals are restless and hyperactive, while others are lethargic. Based on psychomotor activity, three subtypes of delirium have been described: hyperactive, hypoactive, and mixed [4–6]. In the hyperactive type, patients are agitated, disoriented, and delusional, with motor hyperactivity, increased reactivity, logorrhea, stereotyped activities, and aggressive behavior. Patients with the hypoactive type are subdued and apathetic with facial inexpressiveness, motor and speech retardation, decreased reactivity, perplexity, and mental slowness [7]. Some authors restrict the term delirium to hyperactive type, suggesting that the different types of delirium might have different pathogenic mechanism and involve different part of the brain [8]. However, quick shifting from hyperactivity to reduced activity is frequently observed, and many patients will present both hyperactive and hypoactive subtypes of delirium [7].

The main differential diagnosis of delirium is dementia. However, it may also be difficult to differentiate delirium from psychotic disorders such as schizophrenia or psychiatric disorders such as depression or mania. Moreover, in stroke patients, the

Table 1.1 Diagnostic criteria for delirium

DSM-IV	A. Disturbance of consciousness (i.e., reduced clarity of awareness about the environment) with reduced ability to focus, sustain, or shift attention
	B. Change in cognition (e.g., memory deficit, disorientation, language disturbance) or development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia
	C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day
	D. Evidence from the history, physical examination, or laboratory findings indicates that the disturbance is caused by direct consequences of a general medical condition
ICD-10	For a definite diagnosis, symptoms, mild or severe, should be present in each of the following areas:
	Impairment of consciousness and attention (from clouding to coma and reduced ability to direct, focus, sustain, and shift attention)
	Global disturbance of cognition (perceptual distortions, illusions, and hallucinations, most often visual; impairment of abstract thinking and comprehension, with or without transient delusions but typically with some degree of incoherence; impairment of immediate recall and recent memory, with relatively intact remote memory; disorientation for time as well as in more severe cases for place and person)
	Psychomotor disturbances (hypoactivity or hyperactivity and unpredictable shifts from one to the other, increased reaction time, increased or decreased flow of speech, enhanced startle reaction)
	Disturbance of the sleep/wake cycle (insomnia or, in more severe cases, total sleep loss or reversal of the sleep/wake cycle; daytime drowsiness; nocturnal worsening of symptoms; disturbing dreams or nightmares, which may continue as hallucinations after awakening)
	Emotional disturbance (depression, anxiety or fear, irritability, euphoria, apathy or wandering, perplexity)

diagnosis of delirium may be even more difficult as loss of consciousness and neurological dysfunctions may be symptoms of stroke itself. The acute onset and the fluctuating nature of confusional state are however key features for the differential diagnosis.

Methods of Assessment

In clinical practice, delirium is frequently misdiagnosed and usually underdiagnosed with reported nondetection rates of 33–66 % [9]. Screening tools may therefore be useful to improve detection of delirium. Many assessments scales for delirium are available, some of them being dedicated to improve diagnosis of delirium, while others are more dedicated to the evaluation of the severity of delirium [6, 10]. Most of the delirium-evaluating instruments have been developed on the basis of the DSM criteria. Rating scales designed to be used by experts usually contain few items, while scales designed to be used by non-trained people are usually more detailed with many items.

The most widely used screening tool is the Confusion Assessment Method (CAM), based on DSM-III-R criteria. This scale is based on the presence of four criteria: acute onset and fluctuating course, inattention, disorganized thinking, or altered level of consciousness (Table 1.2) [11]. It has been developed for use by any health professional and is reliable, easy to administer, and applicable to a large variety of settings, with a high sensitivity and specificity [12]. Other diagnostic instruments are however available. The Organic Brain Syndrome Scale [13] was developed to determine elderly patients' disturbances of awareness and orientation to time, place, and own identity and assessment of various emotional and behavioral symptoms appearing in delirium, dementia, and other organic mental diseases: it has 39 items dedicated to confusion, has been developed for use by research assistant, and was reported taking up to 1 h to complete [14]. The Delirium Symptom Interview (DSI) [15] is a structured interview for diagnosing the presence of symptoms of delirium that can be administered by lay interviewers: normative data and validity are excellent, but it is long (consisting of 62 items) and somewhat difficult to administer even after rater's training [16].

Beside these diagnostic instruments determining the presence or absence of symptoms, other scales have been elaborated to quantify delirium severity, whose scores can sometimes be used for likelihood of diagnosis [16]. The Delirium Rating Scale (DRS) (Table 1.2) [17] is widely used for the evaluation of delirium severity. It comprises ten items exploring temporal onset of symptoms, perceptual disturbances, hallucinations, delusions, psychomotor and behavioral disturbances, cognitive status deficits, sleep-wake cycle disturbances, lability of mood, and variability of symptoms, with a maximum score of 32. It is also useful for the positive diagnosis with a cutoff score of ten indicating the presence of delirium [18] and for the differential diagnosis with dementia or depression [17, 19]. Delirium should however be rated over a 24-h period to detect fluctuations and sleep-wake cycle abnormalities. Other instruments have been developed specifically for measuring the severity of the delirium syndrome. The Memorial Delirium Assessment Scale (MDAS) [20] is a ten-item, four-point, observer-rated scale designed for use by experienced psychiatrists, which contains both objective cognitive testing and evaluation of behavioral symptoms: it explores level of consciousness, orientation, short-term memory, digit span, attention, thinking, perceptual disturbance, delusions, psychomotor activity, and sleep-wake cycle. Easy to administer, it has been designed to be repeatable at short intervals, allowing to evaluate time course and treatments effects. The Delirium Assessment Scale (DAS) [21], based on DSM-III-R criteria, is designed for use by physicians. It contains 11 items: the items measuring orientation, memory, and attention include subitems from MMSE and digit span; the other items evaluating perceptual disturbances, psychomotor activity/alertness, coherence, global accessibility, psychomotor activity, fluctuation of symptoms, and sleep-wake cycle are based on behavior observed during the interview and behavior reported by the patient and the staff. The Confusional State Evaluation (CSE) [22] was elaborated to assess delirium in elderly patients and, as the DAS, to measure changes of symptoms over time to evaluate effects of intervention. This scale designed to be used by trained nurses, doctors, and psychologists contains 22 items: 12 measure

Table 1.2 Assessment of delirium

CAM	(1) *Acute onset and fluctuating course*	
	(2) *Inattention* (difficulty focusing attention, being easily distractible, difficulty keeping track of what was being said)	
	(3) *Disorganized thinking* (with rambling or irrelevant conversation, unclear or illogical flow of ideas, unpredictable switching from subject to subject)	
	(4) Altered level of consciousness	
	The diagnosis of delirium requires the presence of both (1) and (2) and of either (3) or (4). When the diagnosis is established, the assessment of other delirium symptoms is possible including:	
	Disorientation	
	Memory impairment	
	Perceptual disturbances	
	Psychomotor agitation	
	Psychomotor retardation	
	Altered sleep-awake cycle	
CAM-ICU	Step 1: determination of the RASS score	
	RASS score > −4: go to step 2	
	RASS score ≤ −4: the patient must be reevaluated later	
	Step2: CAM-ICU	
	(1) *Acute onset and fluctuating course*	
	Modification of the basal mental status (may require to interview patient's relatives) or modification of the RASS score within the last 24 h. If absent: no delirium	
	(2) *Inattention*	
	The patient must read ten letters and stretch the hand when a designated letter occurs. If the number of errors <3: no delirium	
	(3) *Disorganized thinking*	
	5 logical questions (with simple responses) are asked to the patient. If the number of errors <2: no delirium	
	(4) *Altered level of consciousness*	
	If the RASS score = 0: no delirium	
	The diagnosis of delirium requires the presence of both (1) and (2) and of either (3) or (4)	
DRS	1. Temporal onset of symptoms	Quoted 0, 1, or 2
	2. Perceptual disturbances	Quoted 0, 1, or 2
	3. Hallucination type	Quoted 0, 1, or 2
	4. Delusions	Quoted 0, 1, or 2
	5. Psychomotor behavior	Quoted 0, 1, or 2
	6. Cognitive status during formal testing	Quoted 0, 1, 2, 3, or 4
	7. Physical disorder	Quoted 0, 1, or 2
	8. Sleep-awake cycle disturbances	Quoted 0, 1, 2, 3, or 4
	9. Lability of mood	Quoted 0, 1, or 2
	10. Variability of symptoms	Quoted 0, 1, 2, 3, or 4

CAM Confusion Assessment Method, *CAM-ICU* Confusion Assessment Method-Intensive Care Unit, *DRS* Delirium Rating Scale

key symptoms of delirium leading to a confusion score, 7 deal with symptoms frequently observed in delirious patients, and 3 relate to the duration and intensity of the episode of delirium. The Delirium Index [23] is also used to assess

the severity of delirium: it is reliable and valid in patients with delirium, with or without dementia. It is however time-consuming.

The choice of an evaluation instrument will depend on the purpose (screening, diagnosis, rating, follow-up), on time constraints, and on the examiner, some scales requiring trained and experimented psychiatrists. The CAM scale, despite its simplicity, has a high sensitivity and specificity. The DRS is perhaps the most widespread scale and is in use in many countries [5, 10]. It is however important to notice that none of these scales have been specifically established for stroke patients and that none, with the exception of the CAM-ICU [24], has been validated in populations of stroke patients, which may be difficult to assess because stroke patients can present with non-fluctuating disturbances of memory, perception, or attention resulting from brain lesions, prestroke dementia, or depression and because communication deficits are frequent. The CAM-ICU [25, 26] (Table 1.2), an adapted version of the CAM, is currently the most widely used method for assessing delirium in critically ill patients. It is based on DSM-III-R criteria and incorporates the four key features (acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness) that constitute the definition of delirium, as taken from the original CAM algorithm [12]. It consists of a brief interview with the patient and includes nonverbal tasks designed to be completed by nonverbal, mechanically ventilated, or restrained patients in ICU settings. In a study conducted in a stroke population [24], the CAM-ICU demonstrated a high sensitivity (76 %) and a very high specificity (98 %) with a high inter-rater reliability, compared to the DSM-IV criteria applied by experimented raters. Serial evaluations are however necessary because of the fluctuating nature of delirium [24].

Incidence of Delirium in Stroke Patients

After having been reported as single case reports or in retrospective studies, systematic investigations of delirium have been prospectively performed in stroke patients [27–38]: delirium was found to occur in 10–48 % of stroke patients. The main characteristics of the study populations reported in the literature are detailed in Table 1.3. A recent review on poststroke delirium reported an incidence rate of delirium in acute stroke and SAH of 26 % with a 95 % CI of 19–33 % [39].

Time Course of Delirium

The natural history of poststroke delirium remains largely unknown. Available data suggest that delirium usually occurs in the first days after stroke [33, 37], occurring within the first 24 h after stroke onset in about two-thirds of patients [24]. In the

Table 1.3 Incidence of delirium in stroke patient cohorts

Authors	Population	Age	Number of patients	Type of stroke (number of patients)	Delirium assessment	Time of assessment	Incidence (%)	Incidence according to stroke type
Gustafson et al. [27]	Consecutive patients admitted in a stroke unit	73[a]	145	Ischemic stroke (113) TIA (21) ICH (8)	DSM-III	≤7 days of admission	48.3	Ischemic stroke: 50 % TIA: 29 % ICH: 88 %
Henon et al. [28]	Consecutive patients admitted in a stroke unit whose	75[b]	202	Ischemic stroke (177) ICH (25)	DSM-IV DRS	During hospital stay	24.3	Ischemic stroke: 24.3 % ICH: 24 %
Caeiro et al. [29]	Consecutive patients admitted in a stroke unit	57.3	218	Ischemic stroke (142) ICH (48) SAH (28)	DSM-IV DRS≥10	≤4 days of admission	13	Ischemic stroke: 9 % ICH: 27 % SAH: 11 %
Caeiro et al. [30]	Consecutive patients admitted for a SAH	55.5	68	NA	DSM-IV DRS≥10	≤4 days of admission	16	NAp
Sheng et al. [31]	Elderly stroke patients (≥65 years) admitted in a stroke unit	79.2	156	Ischemic stroke (123) ICH (23)	DSM-IV	≤3 days of admission	25	Ischemic stroke: 10 % ICH: 48 %
Dostovic et al. [32]	Consecutive patients admitted for a first-ever stroke	70	233	Ischemic stroke (NAv) ICH (NAv) SAH (NAv)	DSM-IV DRS-R-98>16	≤4 days of admission	25.3	NAv
McManus et al. [33, 34]	Consecutive patients admitted in a stroke	66.4	82	Ischemic stroke (NAv) ICH (NAv)	CAM	≤4 days of admission then	28	NAv
Dahl et al. [35]	Consecutive patients admitted in a stroke	73	178	Ischemic stroke (NAv) ICH (NAv)	CAM twice daily DSM-IV	≤7 days of admission	10	NAv

(continued)

Table 1.3 (continued)

Authors	Population	Age	Number of patients	Type of stroke (number of patients)	Delirium assessment	Time of assessment	Incidence (%)	Incidence according to stroke type
Melkas et al. [36]	Stroke patients from the Helsinki Stroke Aging Memory Cohort (55–85 years)	70.8[a]	263	Ischemic stroke (surviving at month 3)	DSM-IV (retrospective assessment)	≤7 days of admission	19	NAp
Oldenbeuving et al. [37]	Consecutive patients admitted in a stroke unit	72[a]	527	Ischemic stroke (470)	CAM±DRS	At day 2–4 and 5–7 from admission	11.8	Ischemic stroke: 11.5 %
				ICH (57)				ICH: 12.9 %
Kostalova et al. [38]	Consecutive patients admitted in a stroke	73.5[a]	100	Ischemic stroke (80)	DSM-IV	≤24 h of admission then daily for 7 days	43	Ischemic stroke: 37.5 %
		77[b]		ICH (20)	CAM-ICU			ICH: 65 %

NAv not available, *NAp* not applicable

[a]Mean

[b]Median

study of Mitasova et al. [24], delirium developed within 5 days of stroke onset in all delirium-positive patients.

Data concerning delirium duration in stroke patients are more controversial. One study, however, performed in a small number of patients [33], found that near half of patients had symptoms lasting more than 4 weeks. This finding was consistent with other studies conducted in medical inpatients that have shown that delirium is slow to resolve, with delirium still present in 32 % of medical inpatients on discharge [40]. However, in other studies, duration of delirium after stroke was shorter. Dostovic et al. [32] reported an average duration of delirium of 4 days in patients with ischemic stroke and 3 days in patients with cerebral hemorrhage [32]: in the whole population, the average duration of delirium in the acute stage of stroke was 4 days (range 1–18), with a longer duration in women, in patients older than 65 years, and in patients with right hemispheric lesions. In a study evaluating the efficacy of rivastigmine in the treatment of delirium after stroke [41], the mean duration of delirium was 6.7 days (range 2–17). In another study published by Oldenbeuving [37], among 62 patients out of 527 who developed delirium, 52 were diagnosed between day 2 and 4 and 10 between day 5 and 7: about two-thirds of patients with delirium at the first screening moment did not have delirium during the second screening. The mean duration of delirium was 4.8 days (range 1–15 days). Last, in the study by Sheng et al. [31], of the 39 patients who had delirium, 18 patients had delirium lasting 24 h or less, and 21 had delirium lasting longer than 24 h (7 for 24–48 h, 14 for more than 48 h). The duration of delirium may however be important as it has been suggested that transient delirium of 24 h or less was associated with better long-term functional outcome than delirium lasting longer than 24 h: patients with delirium lasting longer than 24 h had a worse outcome than those with transient delirium for 6-month mortality and 1- and 12-month FIM scores [31].

Risk Factors

Many predictors of delirium in hospitalized patients have been identified irrespective of the cause of admission: age, male gender, drugs (in particular drugs with anticholinergic effect), somatic or metabolic disorders, dementia, vision and hearing impairment, and focal brain lesions of any origin, especially stroke [42–46]. Stroke remains a rare cause of delirium in patients without focal neurological signs [47], at least when stroke diagnosis is based on CT scan. Whether it remains true when MRI is used remains unsettled. Indeed, delirium is more common in acute stroke than in acute coronary patients, suggesting a causal relationship between brain damage and the occurrence of delirium after stroke [29]. In fact both stroke characteristics and patient's characteristics may predispose to delirium. The main risk factors identified in cohorts of stroke patients are detailed in Tables 1.4 and 1.5.

Table 1.4 Demographic data, vascular risk factors, and clinical data associated with delirium in stroke patients

	Age	Sex	High Blood Pressure	Diabetes	Alcohol	AF	Sensorial deficit	Previous stroke	Prestroke dementia/ cognitive decline	Previous delirium	Drugs
Gustafson et al. [27]	+	–	–	–				–		+	+ Drugs with anticholinergic effect
Henon et al. [28]	+ (only in univariate analysis)	–	+ in patients without prestroke cognitive decline	–	+ in patients without prestroke cognitive decline	–		–	+ IQCODE score		– Drugs known to induce ACS
Caeiro et al. [29]	+	–		–	–			–	+		
Sheng et al. [31]	+	–	–	–	–	–		–	+		– Anticholinergic medication preadmission
McManus et al. [33]	+						+ Poor vision		IQCODE score >3		
Dahl et al. [35]	+	–		–				–	+ Prestroke dementia		–
Melkas et al. [36]	–	–	–	–		–			+ Prestroke cognitive decline (no standardized assessment)		
Oldenbeuving et al. [37]	– (after adjustment on brain atrophy)	–							+ IQCODE>50		– Anticholinergic medication preadmission
Kostalova et al. [38]	+	–	–	–	–	–	–		Suspected dementia (BDS≥3)		+ Number of drugs at delirium onset

Table 1.5 Stroke characteristics associated with delirium in stroke patients

	Stroke type	Stroke location	Stroke severity	Stroke etiology	Medical complications	Neglect
Gustafson et al. [27]	+ ICH	+ Left-sided lesions	+ Severity of motor deficit			
Henon et al. [28]	–	No clear influence of stroke location. Delirium more frequent in hemispheric vs. posterior fossa lesion	Orgogozo's score (only in univariate analysis)	– (TOAST)	Metabolic and infectious disorders	
Caeiro et al. [29]	+ ICH	No clear influence of stroke location. Delirium more frequent in hemispheric vs. posterior fossa lesion	GCS ≤ 9		+ Medical complications and metabolic disorders	+
Sheng et al. [31]	+ ICH		Admission Glasgow coma scale <15 Ability to lift both arms on admission	+ Cardioembolic stroke	+ Metabolic disorders Urinary tract infection (only in univariate analysis)	+ (only in univariate analysis)
McManus et al. [33]		Delirium more frequent in TACI	Barthel at admission <10	– TOAST	CRP > 5 mg/dl	
Dahl et al. [35]			–	– TOAST	Infection Cardiac events	
Melkas et al. [36]		Delirium more frequent in TACI	+ mRS 3–5			
Oldenbeuving et al. [37]	–	Right-sided lesion	NIHSS		No influence of metabolic disorders Influence of infection	
Kostalova et al. [38]	+ ICH	No clear influence of stroke location. Delirium more frequent in TACI	NIHSS > 10	– TOAST	+ Medical complications defined according to the sequential organ failure assessment (SOFA) score	–

Influence of Stroke Characteristics

Stroke Type

Delirium seems to be more frequent in patients with cerebral hemorrhage (Table 1.5) [27, 29, 31, 38] compared to patients with ischemic stroke. The small number of patients included in published studies however precludes definite conclusion.

Delirium can also occur after subarachnoid hemorrhage [30, 48, 49]. The only prospective study conducted in patients with subarachnoid hemorrhage found delirium in 16 % of patients, with a higher incidence in cases of intraventricular bleeding, hydrocephalus, and basofrontal hemorrhage [30]. Basofrontal lesions may involve the cingulum, frontal projections from the thalamus, the septal area, and the Meynert nucleus, leading to disruption of the cholinergic projections to the cerebral cortex and the hippocampus. Moreover, structures close to the lateral and the third ventricles (anterior and medial thalamic nuclei, fornix, mammillary bodies, caudate, and hippocampus) are important in attention, memory, and executive functions [30].

Stroke Location

No clear influence of stroke location has been demonstrated in prospective studies conducted in stroke cohorts (Table 1.5). Delirium has however been reported in patients with strategic lesions involving structures subserving attention, memory, and emotional behavior.

Thalamic Strokes

Thalamic vascular lesions may induce acute cognitive disturbances, which usually do not fulfill criteria of delirium. Cases of delirium have however been reported after medial thalamic lesion [50] or stroke involving anterior and dorsomedial thalamic locations [51]. The thalamus acting as a filter allowing only relevant information to travel to the cortex, stroke could compromise this gating function, leading to sensory overload and hyperarousal [52].

Uni- and Bilateral Posterior Cerebral Artery Territory Infarcts

Delirium may occur after uni- or, more frequently, bilateral lesions involving medial temporo-occipital lobes [53–56], in particular in bilateral lesions involving occipital and temporal lobe cortex below the calcarine sulcus, including the lingual and fusiform gyri [55]. In this case, delirium is considered as a consequence of dysfunction of the fusiform-parahippocampal and hippocampal regions, with impairment of focal attention, loss of memory, and disruption of temporal sequencing resulting

from destruction of neocortical association area or its disconnection from limbic structures. Delirium may also occur after unilateral posterior cerebral artery territory infarct, in particular in case of lesion of the left hemisphere [53, 56] which leads to focal attention impairment, loss of linguistically organized memory, and disruption of temporal sequencing [53]. However, the influence of the left hemisphere was not consistently found [54].

Anterior Cerebral Artery Territory Infarcts

Delirium may be the consequence of lesion of the medial frontal lobe [57], in particular in case of bilateral or right unilateral lesions, involving the prefrontal cortex and anterior cingulate gyrus.

Stroke Lesions in the Head of the Caudate Nucleus

Delirium has been reported in lesions involving the caudate nucleus [58, 59], in right as in left lesion, probably more frequently in bilateral lesion and in lesions involving the head of the caudate nucleus [59]. The caudate nucleus connects associative cortex with deeper anatomic structures by cortico-pallido-nigra-thalamocortical loops, and delirium could be the consequence of the interruption of striato-pallido-thalamo-frontal circuit [60].

Stroke Lesions in the Inferior Part of the Genu of the Internal Capsule

Lesions of the inferior part of the genu of the internal capsule may lead to delirium with fluctuating alertness, inattention, memory loss, apathy, abulia, and psychomotor retardation [61], resulting from a functional deactivation of the ipsilateral frontal cortex secondary to an interruption of the inferior and anterior thalamic peduncles by the capsular genu infarct.

Right Middle Cerebral Artery Territory Infarcts

Right middle cerebral artery territory infarction is probably the most common stroke leading to delirium [62, 63], which was reported to occur in up to 61 % of patients with acute middle cerebral artery territory infarct [63], sometimes leading to chronic confusional state [64]. The role of fronto-striatal lesions [62, 63] and damage to the right temporal lobe [63], in particular in middle temporal gyrus, may have been suggested.

However, in the majority of the descriptions of the focal form of delirium, patients do not strictly meet DSM-IV criteria of delirium. In case reports with first generations of CT scans, another vascular lesion of the brain cannot be excluded

and may interfere with the clinical presentation [65]. Finally, in elderly patients, the contribution of an underlying dementia is possible.

Stroke Severity

All available data suggest a higher incidence of delirium in severe stroke [27–29, 31, 33, 36–38] (Table 1.5).

Stroke Etiology

No association has usually been found between stroke etiologies defined according to TOAST criteria [66] with the exception of one study, which found delirium to be more frequent in cardioembolic stroke [31]. Delirium has also more frequently been reported in patients with TACI, defined according Bamford's [67] classification [33, 36, 38]. It is however probable that this association reflects more the influence of the severity of stroke than the influence of its etiology.

Consequences of Stroke

Left hemineglect has in some studies been considered as a risk factor for delirium [29, 31]. Neglect usually occurs after right hemisphere lesions, the right hemisphere being dominant for attention [68]: this may play a role in delirium, which is characterized by an inability to focus, sustain, and shift attention.

As in other inpatient populations [42, 69, 70], medical complications occurring after stroke (infections, metabolic disorders, cardiac complications) were usually found to be associated with a higher incidence of delirium in stroke patients [27–29, 31, 33, 35, 37, 38, 71], suggesting that when delirium occurs in a stroke patient, a comprehensive search for precipitating factors must be performed [5].

Influence of Patients Characteristics

Demographic Data

Older age is usually considered as a risk factor for delirium [27–29, 31, 33, 35, 38], while there is no influence of sex (Table 1.4). In one study [37], the influence of age disappeared after adjustment on brain atrophy, suggesting that the association of age and delirium could be mediated by confounding factors such as cerebral atrophy, which had been reported to be associated with a higher incidence of delirium after stroke in an older paper [28]. Another confounding factor could be the increasing presence and severity of leukoaraiosis in older patients, as leukoaraiosis has also been found to be a risk factor for delirium in stroke patients [28].

Vascular Risk Factors

No influence of traditional risk factor on the risk of delirium after stroke has been demonstrated (Table 1.4).

Prestroke Cognitive Status

Dementia is an important factor of delirium in elderly hospitalized patients [72, 73]. In stroke patients, preexisting cognitive disturbances and dementia [28, 29, 31, 33, 35–38] have constantly been reported as a risk factor for delirium. A history of delirium also appears as a risk factor for poststroke delirium [27].

Previous or Current Use of Drugs with Anticholinergic Effect

An association between delirium and anticholinergic drugs has been inconsistently observed [27, 28, 31, 37, 38]. Measurement of serum anticholinergic activity could be more reliable to identify cholinergic deficiency due to medication or loss of cholinergic reserves [74]. Polypharmacy might however be of importance [37].

Physiopathology

The physiopathology of delirium remains largely unknown [5, 42, 75].

Central cholinergic deficiency is to date the leading hypothesized mechanism for delirium [76, 77], the decrease synthesis of acetylcholine and epinephrine resulting from a reduced oxidative metabolism. It has been shown that anticholinergic medications could precipitate delirium in stroke patients [45] as in medical patients [78]. Anticholinergic medications were also found to increase the severity of delirium in patients with diagnosed delirium [44]. Delirious patients have increased plasmatic levels of acetylcholinesterase [74]. Cholinergic drugs can improve delirium induced by lithium and anticholinergic drugs [79, 80]. Neuroimaging data have suggested that delirious patients had brain abnormalities coinciding with areas involved in cholinergic pathways [81, 82]. The age-related loss of cholinergic reserves might explain why delirium is more common in older patients and in patients with dementia [83, 84]. The increased production of endogenous anticholinergic substances during acute illness might explain why delirium is more common after stroke [85]. Other neuromediators, such as dopamine, might play a role, delirium being a common side effect of dopamine and of drugs decreasing glutamate release [86]. Delirious symptom could result from an imbalance in the cholinergic and dopaminergic neurotransmitter systems [77, 86].

Another hypothesis is that delirium is a manifestation of acute stress mediated by abnormally increased levels of cortisol. Corticosteroids may have deleterious effects on mood and memory in case of prolonged excessive secretion [87]. Stroke, pain,

and infections are stressful conditions, leading to an increase of the glucocorticoid formation, which could in some cases not be adequately suppressed and lead to delirium. Higher post-dexamethasone cortisol levels [71] and increased levels of ACTH in the first hours after onset [88] have indeed been observed in delirious stroke patients.

The role of other neuromediators has been suggested. Stroke or poststroke complications may induce upregulation of cytokines such as interleukin-1, interleukin-2, interleukin-6, tumor necrosis factor, and interferon. Cytokines may contribute to delirium by increasing the permeability of the blood–brain barrier and altering neurotransmission [6]. Alterations in the metabolism of melatonin may also play a role in the development of delirium [89], where sleep disorders are frequent [90]: disturbed circadian pattern of melatonin secretion has been observed in delirious postoperative patients [91], and differences in urinary melatonin metabolite concentrations were found during delirium and after recovery from delirium in medical patients [92]. Moreover, two randomized clinical trials have shown that prophylactic treatment with melatonin could reduce the occurrence of delirium in medical and elective surgical patients [93, 94].

Beside the influence of neurotransmitters, it has also been suggested that delirium could involve particular neural pathways and that lateralization to the right may be relevant. Two main neuronal networks underlie attention, the first being diffuse, involving thalamic and bihemispheric pathways, and the second being focal, involving frontal and parietal cortex in the right hemisphere [95]. Delirium is characterized by a widespread disruption of higher cortical function, with evidence of dysfunction in several brain areas including subcortical structures, brainstem and thalamus, nondominant parietal lobe, fusiform, and prefrontal cortices, as well as the primary motor cortices [95]. These brain areas may be the "final common pathway" for delirium from a variety of etiologies, which could be responsible for certain "core symptoms" (disorientation, cognitive deficits, sleep-wake cycle disturbance, disorganized thinking, and language abnormalities), while other symptoms (delusions, hallucinations, illusions, and affective lability) may occur depending on the etiology causing delirium [86].

Influence of Delirium on Stroke Outcome

Published data concerning the influence of delirium on outcome in stroke patients suggest a worse vital, functional, and cognitive outcome in patients with delirium, with a longer duration of hospital stay, a higher risk of death and of dependency, and a higher risk of cognitive deterioration. The results of the main studies that have evaluated the influence of delirium on stroke outcome are detailed in Table 1.6. A meta-analysis published in 2012 [97] revealed that stroke patients with delirium had higher inpatient mortality (OR, 4.71; 95 % CI, 1.85–11.96) and mortality at 12 months (OR, 4.91; 95 % CI, 3.18–7.6) compared to non-delirious patients. Patients with delirium also tended to stay longer in hospital compared to those who did not

Table 1.6 Influence of delirium on outcome in stroke patients

Authors	Length of stay	Inhospital mortality	Mortality after discharge	Functional outcome	Institutionalization	Poststroke dementia and cognitive decline
Gustafson et al. [27, 71]	+ 19 vs. 13 days	+ 16 % vs. 3 %			+ Less likely to be discharged at home (48 % vs. 85 %)	
Henon et al. [28]	+ 13 vs. 12 days	– 14 % vs. 13 %	– At M6: no significant difference 35 vs. 28 %	+ Less likely to be discharged at home (29 vs. 50 %) Median mRS 3 vs. 2 at discharge Median mRS 2 vs. 1 at M6 More severe loss of IADL at M6	+ Less likely to live at home at M6 (59 vs. 86 %)	+ Median MMS 23 vs. 27 at M6
Caeiro et al. [29]				+ 24 % of confused patients and 67 % of nonconfused patients had a Rankin 0–2 at discharge		
Sheng et al. [31]	+ 33 vs. 25 days	+ 8 vs. 4 %	At M1: no significant difference 10 vs. 4 % Mortality significantly increased at M6 (30 % vs. 13 %) and Y1 (41 vs. 17 %)	+ Less likely to be discharged to usual accommodation (51 vs. 81 %) Lower FIM scores at M1, M6, and Y1	+ Less likely to live at home at 1 year (38 vs. 78 %)	+ Mean MMS score 18 vs. 25 at Y1

(continued)

Table 1.6 (continued)

Authors	Length of stay	Inhospital mortality	Mortality after discharge	Functional outcome	Institutionalization	Poststroke dementia and cognitive decline
Dostovic et al. [32]		+ 18.6 % vs. 1.7 %				
McManus et al. [33]	+ 62 vs. 29 days	+ 30.4 % vs. 1.7 %			+ More likely to be institutionalized at discharge 43.7 % vs. 5.2 %	
Dahl et al. [35]	+ 12 vs. 8 days					
McManus et al. [34]			No significant influence on mortality post-discharge up to 1-year poststroke (25 vs. 7.4 %) and mortality from 1 to 2 years post-discharge (8.3 vs. 10.2 %).			
Melkas et al. [36]			Shorter median survival (6 years vs. 9 years) in patients with poststroke delirium[c]			+ Dementia 3 months after stroke more frequent 50 % vs. 17 %

Oldenbeuving et al. [37]	+	+	Barthel Index at M1 worse in patients with delirium Unfavorable outcome (death or BI < 12) at M1 more frequent in patients (67 % vs. 21 %)		
	24 vs. 14 days	19.4 % vs. 6.5%[b]			
Van Rijsbergen et al. [96][a]				+	Delirium was an independent predictor of dementia (CDR and R-CAMCOG) 2 years after stroke

M1 month 1, *M6* month 6, *Y1* year 1, *Y2* year 2

[a]This study was conducted in the population included in the study of Oldenbeuving et al. [37]

[b]The effect disappeared after adjustment for age, IQCODE, and NIHSS scores

[c]This effect disappeared after adjustment on age and severity of stroke

have delirium (mean difference, 9.39 days; 95 % CI, 6.67–12.11) and were more likely to be discharged to nursing homes or other institutions (OR, 3.39; 95 % CI, 2.21–5.21).

Management of Delirium

No large randomized trial concerning delirium in acute stroke patients has been performed. Recommendations about prevention and treatment of delirium in stroke patients are to date similar to management of delirium occurring in other diseases. Data on the management of delirium, whatever the underlying condition, remain however scarce and are mainly issued from studies which included postsurgery patients [98].

Prevention

According to literature data, 30–40 % of delirium could be preventable [2]. A broad spectrum of systematic interventions appeared to be effective in preventing delirium in surgical patients more than in elderly medical patients, systematic detection and treatment programs, and special nursing adding benefits to traditional medical care [99, 100]. Providing support and orientation and providing an unambiguous environment appear useful. The application of practical interventions targeted towards six risk factors (cognitive impairment, immobility, sleep deprivation, vision impairment, hearing impairment, and dehydration) leads to an effective prevention of delirium [101].

Recent studies have examined the role of pharmacological strategies in delirium prophylaxis in selected populations. Haloperidol has been shown to reduce the incidence of delirium in elderly patients after noncardiac surgery [102]. This reduction in incidence was however not constantly found [103]. The few randomized, controlled clinical trials of cholinesterase inhibitors that have been performed to date have shown no benefit for these drugs in the prevention of postoperative delirium, but these studies were small and underpowered [104, 105]. The efficacy of neither haloperidol nor cholinesterase inhibitors in preventing delirium in stroke patients has been evaluated.

Treatment

The treatment of delirium requires identification and treatment of precipitants, when existing. When delirium occurs in a stroke patient, a comprehensive search for precipitating factors must be performed [5] including search for metabolic disorders,

Table 1.7 Treatments usually recommended in delirium

Drug	Posology	Comment	Adverse effects
Conventional antipsychotics			
Haloperidol	0.5–1 mg orally twice daily	Agent of choice Avoid intravenous use due to short duration of action; avoid in patients with withdrawal syndrome, hepatic insufficiency, or neuroleptic malignant syndrome	Extrapyramidal signs Prolonged corrected QT interval
Atypical antipsychotics			
Risperidone	0.5 mg twice daily	Few available data	Extrapyramidal signs
Olanzapine	2.5–5 mg daily		Prolonged corrected QT interval
Quetiapine	25 mg twice daily		
Benzodiazepines			
Lorazepam	Initial 0.5- to 1 mg dose orally; repeat every 4 h, as needed	Not recommended in the absence of alcohol or benzodiazepine withdrawal, Parkinson disease, or neuroleptic malignant syndrome	Paradoxical excitation, respiratory depression, and oversedation
Cholinesterase inhibitors			
Rivastigmine	1.5–6 mg twice daily	Few available data Has been suggested to increase mortality in delirious patients	Vomiting Cardiac conduction disturbances

infections, fever, cardiopulmonary disorders, epilepsy, ethanol, sedatives or drug intoxication at stroke onset or withdrawal during the next days, iatrogenic complication, pain (headache, abdominal pain from fecal impaction or erocolia, vesical distension, bed sores), and subdural hematoma (especially in case of fall secondary to stroke onset), and adequate measures must be undertaken. Supportive care (including management of hypoxia, hydration and nutrition, minimizing the time spent lying in bed, and mobilization) is required [106]. Nonpharmacological interventions are usually recommended, but randomized controlled trials have shown that input from a specialist, protocol-based multidisciplinary team was no better than usual ward care [107]. Physical restraints should be avoided because they tend to increase agitation and injury.

Benefit/risk balance of drug treatment in delirious patients must be carefully considered: sedative drugs may improve behavioral disturbances but worsen cognitive impairment [108]. Drug treatment should then be reserved for patients who might be dangerous for themselves or others. Treatments usually recommended in delirium are detailed in Table 1.7. Neuroleptics, effective on a wide range of symptoms of delirium, with a rapid onset of action, seem more effective than benzodiazepines to treat delirium in the absence of alcohol or benzodiazepine withdrawal [109, 110]. The use of low-dose oral haloperidol (1–10 mg/day) is usually recommended [109, 110]. It has also been suggested that atypical antipsychotics (olanzapine, risperidone, quetiapine) could be useful in delirious patients

[111–113]. No consistent differences in efficacy and tolerability between first- and second-generation antipsychotics have however been reported [114, 115]. Benzodiazepines, and in particular lorazepam, which is sedative and has a rapid onset and a short duration of action, can sometimes be useful, in particular in patients with contraindication to or who do not tolerate antipsychotic drugs. However, to date, no adequately controlled trials were found to support the use of benzodiazepines in the treatment of nonalcohol withdrawal-related delirium among hospitalized patients [116]. Based on the cholinergic deficiency hypothesis underlying delirium and on case reports reporting a successful treatment of severe delirium by cholinesterase inhibitors [79, 117, 118], it has been postulated that cholinesterase inhibitors could be useful. In stroke patients, two small open studies have suggested that the use of low-dose rivastigmine was safe and could be effective to reduce duration of poststroke delirium [41, 119]. However, a recent randomized study conducted in critically ill patients and whose aim was to evaluate the effect of rivastigmine on the duration of delirium when used as an adjunct to usual care based on haloperidol was prematurely stopped because of a higher mortality in the rivastigmine group, without clear benefit on the duration of delirium [120]. Concerning melatonin, its interest to treat or prevent delirium in stroke patients remains to be evaluated.

References

1. American Psychiatric Association. Delirium, dementia and amnestic and other cognitive disorders. In: Diagnostic and statistical manual of mental disorders: DSM-IV. 4th ed. Washington, D.C.: American Psychiatric Association; 2000. p. 135–80.
2. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients. Age Ageing. 2006;35:350–64.
3. WHO. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. Geneva: World Health Organization; 1992.
4. Lipowski ZJ. Delirium: acute confusional state. Oxford: Oxford University Press; 1990.
5. Ferro JM, Caeiro L, Verdelho A. Delirium in acute stroke. Curr Opin Neurol. 2002;15:51–5.
6. Oldenbeuving AW, de Kort PL, Jansen BP, Roks G, Kappelle LJ. Delirium in acute stroke: a review. Int J Stroke. 2007;2(4):270–5.
7. Camus V, Gonthier R, Dubos G, et al. Etiologic and outcome profiles in hypoactive and hyperactive subtypes of delirium. J Geriatr Psychiatry. 2000;13:38–42.
8. Adams RD, Viktor M, Ropper AH. Principles of neurology. 6th ed. New York: McGraw-Hill; 1997. p. 405–16.
9. Inouye SK. The dilemma of delirium: clinical and research controversies regarding diagnosis and evaluation of delirium in hospitalized elderly medical patients. Am J Med. 1994;97:278–88.
10. Robertsson B. Assessment scales in delirium. Dement Geriatr Cogn Disord. 1999;10:368–79.
11. Monette J, Galbaud du Fort G, Fung SH, Massoud F, Moride Y, Arsenault L, Afilalo M. Evaluation of the Confusion Assessment Method (CAM) as a screening tool for delirium in the emergency room. Gen Hosp Psychiatry. 2001;23:2025.
12. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113:941–8.

13. Björkelund KB, Larsson S, Gustafson L, Andersson E. The Organic Brain Syndrome (OBS) scale: a systematic review. Int J Geriatr Psychiatry. 2006;21(3):210–22.
14. Sandberg O, Gustafson Y, Brännström B, Bucht G. Clinical profile of delirium in older patients. J Am Geriatr Soc. 1999;47(11):1300–6.
15. Albert MS, Levkoff SE, Reilly C, Liptzin B, Pilgrim D, Cleary PD, Evans D, Rowe JW. The delirium symptom interview: an interview for the detection of delirium symptoms in hospitalized patients. J Geriatr Psychiatry Neurol. 1992;5:14–21.
16. Smith MJ, Breitbart WS, Platt MM. A critique of instruments and methods to detect, diagnose, and rate delirium. J Pain Symptom Manage. 1995;10(1):35–77.
17. Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. Psychiatry Res. 1988;23:89–97.
18. McManus J, Pathansali R, Stewart R, Macdonald A, Jackson S. Delirium post-stroke. Age Ageing. 2007;36(6):613–8.
19. Trzepacz PT, Mittal D, Torres R, Kanary K, Norton J, Jimerson N. Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. J Neuropsychiatry Clin Neurosci. 2001;13:229–42.
20. Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S. The memorial delirium assessment scale. J Pain Symptom Manage. 1997;13:128–37.
21. O'Keeffe ST. Rating the severity of delirium: The delirium Assessment Scale. Int J Geriatr Psychiatry. 1994;9:551–6.
22. Robertsson B, Karlsson I, Styrud E, Gottfries CG. Confusional State Evaluation (CSE): an instrument for measuring severity of delirium in the elderly. Br J Psychiatry. 1997;170: 565–70.
23. McCusker J, Cole M, Bellavance F, Primeau F. Reliability and validity of a new measure of severity of delirium. Int Psychogeriatr. 1998;10:421–33.
24. Mitasova A, Kostalova M, Bednarik J, Michalcakova R, Kasparek T, Balabanova P, Dusek L, Vohanka S, Ely EW. Poststroke delirium incidence and outcomes: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med. 2012;40:484–90.
25. Ely EW, Inouye S, Bernard GL, et al. Delirium in mechanically ventilated patients: validity and reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). JAMA. 2001;286:2703–10.
26. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAMICU). Crit Care Med. 2001;29:1370–9.
27. Gustafson Y, Olsson T, Eriksson S, Asplund K, Bucht G. Acute confusional states (delirium) in stroke patients. Cerebrovasc Dis. 1991;1:257–64.
28. Henon H, Lebert F, Durieu I, Godefroy O, Lucas C, Pasquier F, Leys D. Confusional state in stroke: relation to preexisting dementia, patient characteristics, and outcome. Stroke. 1999;30:773–9.
29. Caeiro L, Ferro JM, Albuquerque R, Figueira ML. Delirium in the first days of acute stroke. J Neurol. 2004;251:171–8.
30. Caeiro L, Menger C, Ferro JM, Albuquerque R, Figueira ML. Delirium in acute subarachnoid haemorrhage. Cerebrovasc Dis. 2005;19:31–8.
31. Sheng AZ, Shen Q, Cordato D, Zhang YY, Yin Chan DK. Delirium within three days of stroke in a cohort of elderly patients. J Am Geriatr Soc. 2006;54:1192–8.
32. Dostović Z, Smajlović D, Sinanović O, Vidović M. Duration of delirium in the acute stage of stroke. Acta Clin Croat. 2008;48:13–7.
33. McManus J, Pathansali R, Hassan H, Ouldred E, Cooper D, Stewart R, Macdonald A, Jackson S. The course of delirium in acute stroke. Age Ageing. 2009;38:385–9.
34. McManus J, Pathansali R, Oulred E, Stewart R, Jackson S. Association of delirium post-stroke with early and late mortality. Age Ageing. 2011;40:271–86.
35. Dahl MH, Rønning OM, Thommessen B. Delirium in acute stroke–prevalence and risk factors. Acta Neurol Scand Suppl. 2010;190:39–43.

36. Melkas S, Laurila JV, Vataja R, Oksala N, Jokinen H, Pohjasvaara T, Leppävuori A, Kaste M, Karhunen PJ, Erkinjuntti T. Post-stroke delirium in relation to dementia and long-term mortality. Int J Geriatr Psychiatry. 2012;27(4):401–8.
37. Oldenbeuving AW, de Kort PL, Jansen BP, Algra A, Kappelle LJ, Roks G. Delirium in the acute phase after stroke: incidence, risk factors, and outcome. Neurology. 2011;76(11):993–9.
38. Kostalova M, Bednarik J, Mitasova A, Dusek L, Michalcakova R, Kerkovsky M, Kasparek T, Jezkova M, Balabanova P, Vohanka S. Towards a predictive model for post-stroke delirium. Brain Inj. 2012;26(7–8):962–71.
39. Carin-Levy G, Mead GE, Nicol K, Rush R, van Wijck F. Delirium in acute stroke: screening tools, incidence rates and predictors: a systematic review. J Neurol. 2012;259(8):1590–9.
40. McCusker J, Cole M, Dendukuri N, Belzile E, Primeau F. Delirium in older medical inpatients and subsequent cognitive and functional status: a prospective study. CMAJ. 2001;165:575–83.
41. Oldenbeuving AW, de Kort PL, Jansen BP, Kappelle LJ, Roks G. A pilot study of rivastigmine in the treatment of delirium after stroke: a safe alternative. BMC Neurol. 2008;8:34.
42. Lipowski ZJ. Delirium in the elderly patient. N Engl J Med. 1989;320:578–82.
43. Rahkonen T, Luukkainen-Markkula R, Paanila S, Sivenius J, Sulkava R. Delirium episode as a sign of undetected dementia among community dwelling elderly subjects: a 2 year follow up study. J Neurol Neurosurg Psychiatry. 2000;69:519–21.
44. Han L, McCusker J, Cole M, Abrahamowicz M, Primeau F, Elie M. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. Arch Intern Med. 2001;161:1099–105.
45. Caeiro L, Ferro JM, Claro MI, Coelho J, Albuquerque R, Figueira ML. Delirium in acute stroke: a preliminary study of the role of anticholinergic medications. Eur J Neurol. 2004;11:699–704.
46. Edlund A, Lundström M, Karlsson S, Brännström B, Bucht G, Gustafson Y. Delirium in older patients admitted to general internal medicine. J Geriatr Psychiatry Neurol. 2006;19:83–90.
47. Naughton BJ, Moran M, Ghaly Y, Michalakes C. Computed tomography scanning and delirium in elder patients. Acad Emerg Med. 1997;4:1107–10.
48. Mobbs RJ, Chandran KN, Newcombe RL. Psychiatric presentation of aneurysmal subarachnoid haemorrhage. ANZ J Surg. 2001;71:69–70.
49. Reijneveld JC, Wermer M, Boonman Z, van Gijn J, Rinkel GJ. Acute confusional state as presenting feature in aneurysmal subarachnoid hemorrhage: frequency and characteristics. J Neurol. 2000;247:112–6.
50. Castaigne P, Lhermitte F, Buge A, Escourolle R, Hauw JJ, Lyon-Caen O. Paramedian thalamic and midbrain infarct: clinical and neuropathological study. Ann Neurol. 1981;10:127–48.
51. Graff-Radford NR, Eslinger PJ, Damasio AR, Yamada T. Nonhemorrhagic infarction of the thalamus: behavioural, anatomic, and physiologic correlates. Neurology. 1984;34:14–23.
52. Gaudreau JD, Gagnon P. Psychotogenic drugs and delirium pathogenesis: the central role of the thalamus. Med Hypotheses. 2005;64:471–5.
53. Devinsky O, Bear D, Volpe BT. Confusional states following posterior cerebral artery infarction. Arch Neurol. 1988;45:160–3.
54. Milandre L, Brosset C, Botti G, Khalil R. A study of 82 cerebral infarctions in the area of posterior cerebral arteries. Rev Neurol (Paris). 1994;150:133–41.
55. Caplan LR. Posterior circulation disease: clinical findings. Diagnosis and management. Boston: Butterworth-Heinemann; 1996.
56. Shih HT, Huang WS, Liu CH, Tsai TC, Lu CT, Lu MK, Chen PK, Tseng CH, Jou SB, Tsai CH, Lee CC. Confusion or delirium in patients with posterior cerebral arterial infarction. Acta Neurol Taiwan. 2007;16:136–42.
57. Kumral E, Bayulkem G, Evyapan D, Yunten N. Spectrum of anterior cerebral artery territory infarction: clinical and MRI findings. Eur J Neurol. 2002;9:615–24.
58. Caplan LR, Schmahmann JD, Kase CS, Feldmann E, Baquis G, Greenberg JP, Gorelick PB, Helgason C, Hier DB. Caudate infarcts. Arch Neurol. 1990;47:133–43.

59. Kumral E, Evyapan D, Balkir K. Acute caudate vascular lesions. Stroke. 1999;30:100–8.
60. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci. 1986;9:357–81.
61. Tatemichi TK, Desmond DW, Prohovnik I, Cross DT, Gropen TI, Mohr JP, Stern Y. Confusion and memory loss from capsular genu infarction: a thalamocortical disconnection syndrome? Neurology. 1992;42:1966–79.
62. Mesulam MM, Waxman SG, Geschwind N, Sabin TD. Acute confusional states with right middle cerebral artery infarctions. J Neurol Neurosurg Psychiatry. 1976;39:84–9.
63. Mori E, Yamadori A. Acute confusional state and acute agitated delirium. Occurrence after infarction in the right middle cerebral artery territory. Arch Neurol. 1987;44:1139–43.
64. Mullaly W, Ronthal M, Huff K, Geschwind N. Chronic confusional state. N J Med. 1989;86:541–4.
65. Godefroy O, Rousseaux M, Pruvo JP, Cabaret M, Leys D. Neuropsychological changes related to unilateral laterostriatal infarcts. J Neurol Neurosurg Psychiatry. 1994;57:480–5.
66. Adams Jr HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, 3d Marsh EE. Classification of subtypes of acute ischemic stroke. Definitions for use in a multicenter clinical trial. Stroke. 1993;24:35–41.
67. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet. 1991;337(8756):1521–6.
68. Pardo JV, Fox PT, Raichle ME. Localization of a human system for sustained attention by positron emission tomography. Nature. 1991;349:61–4.
69. Koponen HJ, Stenbäck U, Mattila E, Soininen H, Reinikainen K, Riekkinen PJ. Delirium among elderly persons admitted to a psychiatric hospital: clinical course during the acute stage and one-year follow-up. Acta Psychiatr Scand. 1989;79:579–85.
70. Koponen HJ, Riekkinen PJ. A prospective study of delirium in elderly patients admitted to a psychiatric hospital. Psychol Med. 1993;23:103–9.
71. Gustafson Y, Olsson T, Asplund K, Hägg E. Acute confusional state (delirium) soon after stroke is associated with hypercortisolism. Cerebrovasc Dis. 1993;3:33–8.
72. Pompei P, Foreman M, Rudberg MA, Inouye SK, Braund V, Cassel CK. Delirium in hospitalized older persons: outcomes and predictors. J Am Geriatr Soc. 1994;42:809–15.
73. Erkinjuntti T, Wikstrom J, Palo J, Autio L. Dementia among medical inpatients: evaluation of 2000 consecutive admissions. Arch Intern Med. 1986;146:1923–6.
74. Mussi C, Ferrari R, Ascari S, Salvioli G. Importance of serum anticholinergic activity in the assessment of elderly patients with delirium. J Geriatr Psychiatry Neurol. 1999;12:82–6.
75. Maclullich AM, Ferguson KJ, Miller T, de Rooij SE, Cunningham C. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. J Psychosom Res. 2008;65:229–38.
76. Inouye SK. Delirium in older persons. N Engl J Med. 2006;16:1157–65.
77. Hshieh TT, Fong TG, Marcantonio ER, Inouye SK. Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence. J Gerontol A Biol Sci Med Sci. 2008;63:764–72.
78. Karlsson I. Drugs that induce delirium. Dement Geriatr Cogn Disord. 1999;10:412–5.
79. Wengel SP, Roccaforte WH, Burke WJ. Donezepil improves symptoms of delirium in dementia: implications for future research. J Geriatr Psychiatry Neurol. 1998;11:159–61.
80. Fisher P. Successful treatment of nonanticholinergic delirium with a cholinesterase inhibitor. J Clin Pharmacol. 2001;21:118.
81. Alsop DC, Fearing MA, Johnson K, Sperling R, Fong TG, Inouye SK. The role of neuroimaging in elucidating delirium pathophysiology. J Gerontol A Biol Sci Med Sci. 2006;61:1287–93.
82. Fong TG, Bogardus Jr ST, Daftary A, Auerbach E, Blumenfeld H, Modur S, Leo-Summers L, Seibyl J, Inouye SK. Cerebral perfusion changes in older delirious patients using 99mTc HMPAO SPECT. J Gerontol A Biol Sci Med Sci. 2006;61:1294–9.
83. Macdonald AJ, Treloar A. Delirium and dementia: are they distinct? J Am Geriatr Soc. 1996;44:1001–2.
84. Reyes-Ortiz CA. Delirium, dementia and brain reserve. J Am Geriatr Soc. 1997;45:778–9.

85. Flacker JM, Wei JY. Endogenous anticholinergic substances may exist during acute illness in elderly medical patients. J Gerontol A Biol Sci Med Sci. 2001;56:M353–5.
86. Trzepacz PT. Update on the neuropathogenesis of delirium. Dement Geriatr Cogn Disord. 1999;10:330–4.
87. Olsson T. Activity in the hypothalamic-pituitary-adrenal axis and delirium. Dement Geriatr Cogn Disord. 1999;10:345–9.
88. Fassbender K, Schmidt R, Mossner R, Daffertshofer M, Hennerici M. Pattern of activation of the hypothalamic-pituitary-adrenal axis in acute stroke. Relation to acute confusional state, extent of brain damage, and clinical outcome. Stroke. 1994;25:1105–8.
89. Lewis MC, Barnett SR. Postoperative delirium: the tryptophan dysregulation model. Med Hypotheses. 2004;63:402–6. doi:10.1016/j.mehy.2004.01.033.
90. Gupta N, de JJ, Schieveld J, Leonard M, Meagher D. Delirium phenomenology: what can we learn from the symptoms of delirium? J Psychosom Res. 2008;65:215–22. doi:10.1016/j.jpsychores.2008.05.020.
91. Shigeta H, Yasui A, Nimura Y, Machida N, Kageyama M, Miura M, Menjo M, Ikeda K. Postoperative delirium and melatonin levels in elderly patients. Am J Surg. 2001;182:449–54. doi:10.1016/S0002-9610(01)00761-9.
92. Balan S, Leibovitz A, Zila SO, Ruth M, Chana W, Yassica B, Rahel B, Richard G, Neumann E, Blagman B, Habot B. The relation between the clinical subtypes of delirium and the urinary level of 6-SMT. J Neuropsychiatry Clin Neurosci. 2003;15:363–6. doi:10.1176/appi.neuropsych.15.3.363.
93. Al-Aama T, Brymer C, Gutmanis I, Woolmore-Goodwin SM, Esbaugh J, Dasgupta M. Melatonin decreases delirium in elderly patients: a randomized, placebo-controlled trial. Int J Geriatr Psychiatry. 2010;26(7):687–94.
94. Sultan SS. Assessment of role of perioperative melatonin in prevention and treatment of postoperative delirium after hip arthroplasty under spinal anesthesia in the elderly. Saudi J Anaesth. 2010;4:169–73. doi:10.4103/1658-354X.71132.
95. Filley CM. The neuroanatomy of attention. Semin Speech Lang. 2002;23:89–98.
96. van Rijsbergen MW, Oldenbeuving AW, Nieuwenhuis-Mark RE, Nys GM, Las SG, Roks G, de Kort PL. Delirium in acute stroke: a predictor of subsequent cognitive impairment? A two-year follow-up study. J Neurol Sci. 2011;306((1–2)):138–42.
97. Shi Q, Presutti R, Selchen D, Saposnik G. Delirium in acute stroke: a systematic review and meta-analysis. Stroke. 2012;43(3):645–9.
98. Bourne RS, Tahir TA, Borthwick M, Sampson EL. Drug treatment of delirium: past, present and future. J Psychosom Res. 2008;65:273–82.
99. Cole MG. Delirium: effectiveness of systematic interventions. Dement Geriatr Cogn Disord. 1999;10:406–11.
100. Tabet N, Howard R. Non-pharmacological interventions in the prevention of delirium. Age Ageing. 2009;38(4):374–9.
101. Inouye SK, Bogardus Jr ST, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, Cooney Jr LM. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med. 1999;340:669–76.
102. Wang W, Li HL, Wang DX, Zhu X, Li SL, Yao GQ, Chen KS, Gu XE, Zhu SN. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial. Crit Care Med. 2012;40(3):731–9.
103. Kalisvaart KJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc. 2005;53:1658–66.
104. Liptzin B, Laki A, Garb JL, Fingeroth R, Krushell R. Donepezil in the prevention and treatment of post-surgical delirium. Am J Geriatr Psychiatry. 2005;13:1100–6.
105. Sampson EL, et al. A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. Int J Geriatr Psychiatry. 2007;22:343–9.
106. Young J, Inouye SK. Delirium in older people. BMJ. 2007;334(7598):842–6.

107. Holroyd-Leduc JM, Khandwala F, Sink KM. How can delirium best be prevented and managed in older patients in hospital? CMAJ. 2010;182(5):465–70.
108. Meagher DJ. Delirium: optimising management. BMJ. 2001;322:144–9.
109. American Psychiatric Association. Practice guidelines for the treatment of delirium. Am J Psychiatry. 1999;156:1–20.
110. Breitbart W, Marotta R, Platt MM, Weisman H, Derevenco M, Grau C, Corbera K, Raymond S, Lund S, Jacobson P. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry. 1996;153:231–7.
111. Sipahimalani A, Masand PS. Use of risperidone in delirium: case reports. Ann Clin Psychiatry. 1997;9:105–7.
112. Beuzen JN, Taylor N, Wesnes K, Wood A. A comparison of the effects of olanzapine, haloperidol and placebo on cognitive and psychomotor functions in healthy elderly volunteers. J Psychopharmacol. 1999;13:152–8.
113. Devlin JW, Roberts RJ, Fong JJ, Skrobik Y, Riker RR, Hill NS, Robbins T, Garpestad E. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. Crit Care Med. 2010;38(2):419–27.
114. Campbell N, Boustani MA, Ayub A, Fox GC, Munger SL, Ott C, Guzman O, Farber M, Ademuyiwa A, Singh R. Pharmacological management of delirium in hospitalized adults–a systematic evidence review. J Gen Intern Med. 2009;24:848–53.
115. Lonergan E, Britton AM, Luxenberg J, Wyller T. Antipsychotics for delirium. Cochrane Database Syst Rev. 2007;(2):CD005594.
116. Lonergan E, Luxenberg J, Areosa Sastre A. Benzodiazepines for delirium. Cochrane Database Syst Rev. 2009;(4):CD006379.
117. Burke WJ, Roccaforte WH, Wengel SP. Treating visual hallucinations with donepezil. Am J Psychiatry. 1999;156:1117–8.
118. Kobayashi K, Higashima M, Mutou K, Kidani T, Tachibana O, Yamashita J, Koshino Y. Severe delirium due to basal forebrain vascular lesion and efficacy of donepezil. Prog Neuropsychopharmacol Biol Psychiatry. 2004;28:1189–94.
119. Litvineneko IV, Odinak MM, Khlystov IV, Perstnev SV, Fedorov BB. Efficacy and safety of rivastigmine (exelon) in the confusion syndrome in the acute phase of ischemic stroke. Zh Nevrol Psikhiatr Im S S Korsakova. 2010;110(11 Pt 2):36–41.
120. van Eijk MM, Roes KC, Honing ML, Kuiper MA, Karakus A, van der Jagt M, Spronk PE, van Gool WA, van der Mast RC, Kesecioglu J, Slooter AJ. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. Lancet. 2010;376:1829–37.

Chapter 2
Poststroke Illusions and Hallucinations

Emre Kumral

Abstract Illusions are misperceptions or perceptual distortions of an existing external stimulus, and hallucination is a perception in the absence of a stimulus. Both phenomena can occur in the course of a large number of cerebrovascular pathological processes, and they may develop in either isolated or combined modalities. Isolated auditory, olfactory, and tactile hallucinations are a rare event and have been associated with a number of stroke subtypes. Charles-Bonnet syndrome is characterized by the occurrence of visual hallucinations that are formed, complex, persistent or repetitive, and stereotyped; fully or partially retained insight; and absent delusions. Peduncular hallucinosis may develop following rostral brainstem lesion and characterized by seeing animals of bizarre appearance, transformation of the animals into human figures, mobile and multiple-colored images, and visuotactile associations. Isolated or combination of visual and auditory hallucinations following multi-infarct dementia with lesions involving occipitotemporal regions may occasionally occur. In most of the patients, auditory hallucinations were observed mostly after ischemic and hemorrhagic stroke involving posterior parts of the cerebral hemisphere and more frequently in the right than in the left. Patients with syncope and transient cerebral hypoxia may experience visual and auditory hallucinations such as gray haze, colored patches, or bright lights consisting of rushing or roaring noises, screaming, or voices.

Keywords Visual hallucinations • Charles-Bonnet syndrome • Peduncular hallucinosis • Auditory • Olfactory • Tactile hallucinations • Ischemic stroke • Hemorrhagic stroke

E. Kumral, MD
Neurology Department, Stroke Unit,
Ege University School of Medicine, İzmir, Turkey
e-mail: emre.kumral@ege.edu.tr

J.M. Ferro (ed.), *Neuropsychiatric Symptoms of Cerebrovascular Diseases*,
Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-1-4471-2428-3_2, © Springer-Verlag London 2013

Illusions are misperceptions or perceptual distortions of an existing external stimulus. They differ from hallucinations in that the perceptual activity has its original stimulus in the external environment. Illusional perceptions of single features of object such as size, shape, and color are named as metamorphopsia. According to classification of Hécaen and Albert, illusions may be manifested as visual, auditory, and somatognostic [1]. Elementary illusions may be presented as misperceptions of simple features, while complex illusions are manifested as misperception of objects and scenes. Elementary illusions may have several forms, including distortion of shape, size, and color. Misperception of object size, so-called metamorphopsia, causes real objects and entire scenes to look either smaller (micropsia) or bigger (macropsia) than their actual size. Metamorphopsia of color is a modification of object color, including achromatopsia, which is the disappearance of color, and erythropsia which is a perception of a uniform tint of a particular color. Complex illusions may be presented as telescopy which is a perception of smaller object moving farther away and pelopsia which is a perception of larger object approaching the subject, and a loss of stereoscopic vision is characterized by the perception of three-dimensional objects in two-dimensional space. In polypsia, the number of objects may multiply or infinitely extend the number of objects as perceived in either sagittal or frontal planes. Alloesthesia is manifested by the doubling of any sensory modalities and feeling or seeing any sensorial input in the symmetrical position of the body or visual field.

Illusions and hallucinations can be differentiated clinically; the distinctions have little etiology significance, since both phenomena may be found in the same disorders. Illusions may oftenly occur in epilepsy, migraine, narcolepsy, and infectious disorders and with hallucinogens.

Esquirol described a hallucination as a perception in the absence of a stimulus [2]. In a stricter sense, hallucinations are defined as perceptions in a conscious and awake state in the absence of external stimuli which have qualities of real perception in that they are vivid, substantial, and located in external objective space. A patient may see a hallucinatory object in a real visual scene or may hear hallucinatory voices while engaging in conversation with a real individual. Hallucinations may be appreciated objectively as false events not corresponding to external reality and may not be able to voluntarily suppress them (sometimes called pseudohallucinations), or they may be thought to represent actual external events. The latter are hallucinations with delusional endorsement and comprise part of a psychotic experience. Hallucinations occur in the course of a large number of pathological processes and may occasionally occur in normal individuals in the absence of a disease. They may occur in any sensory modality visual, auditory, somatic (tactile), olfactory, or gustatory. Elementary hallucinations involve primary sensations, such as light flashes and noises, and complex hallucinations include animals, humans, or sometimes complex vivid scenes. Hallucinations similar to dreams may develop in the course of falling asleep (hypnagogic hallucinations) or while waking up (hypnopompic hallucinations). Synesthesias are cross-modal experiences reported by patients who have one sensory-modal experience (e.g., color) when another is stimulated (e.g., sound).

In a stroke unit during a period of 10 years, there were five patients who developed different modalities of hallucinations following a stroke [3]. All five patients had suffered from a right-hemisphere lesion with cortical lesions in four, with extensions into the two or three adjacent lobes. One patient had subcortical lesions involving the head of the caudate, the putamen, and the internal capsule. Different modalities of illusions and hallucinations following stroke with various clinical symptoms and pathophysiology could be present. Herein different modalities of poststroke illusions and hallucinations will be presented below.

Visual Illusions and Hallucinations

The most common modality includes the phenomena of seeing things which are not present or visual perception which does not reconcile with the consensus reality in which the patient claims to see something or behaves as though having seen something that the observer cannot see. Visual hallucinations occur in a wide variety of ophthalmologic, neurological, psychiatric, toxic-metabolic, and idiopathic disorders.

Visual hallucinations may occur following acute vascular pathology, particularly in the acute period of vascular lesion, such as involving brainstem or occipital-parietal cortices. Retinal ischemia in the course of amaurosis fugax associated with carotid artery disease may be manifested as blindness (typically a "descending curtain") or as visual hallucinations [4]. The hallucinations are typically unformed and appear as scintillations, colored streaks, blobs, or flashing lights. These visual changes closely resemble those of migraine and may lead to misdiagnosis. Optic nerve disease, particularly optic neuritis, is also associated with brief unformed visual hallucinations [5]. The phosphenes occur with movement of the eyes or may be induced by sounds. Focal lesions in a number of locations in the brain are associated with visual hallucinations.

Charles-Bonnet Syndrome

Charles-Bonnet syndrome (CBS) is a disorder that causes mentally healthy patients with visual loss to have complex visual vivid and complex recurrent visual hallucinations (fictive visual percepts), first described by Charles-Bonnet in 1760 and first introduced into English-speaking psychiatry in 1982 [6]. This syndrome is characterized by the occurrence of visual hallucinations that are formed, complex, persistent or repetitive, and stereotyped; fully or partially retained insight; absent delusions; and no hallucinations in other modalities. Both ocular and brain disorders, especially ischemic or hemorrhagic stroke involving occipital region, can produce this syndrome (Fig. 2.1). Charles-Bonnet syndrome may occur in the absence of cognitive changes or emotional disturbances. Following impairment or loss of

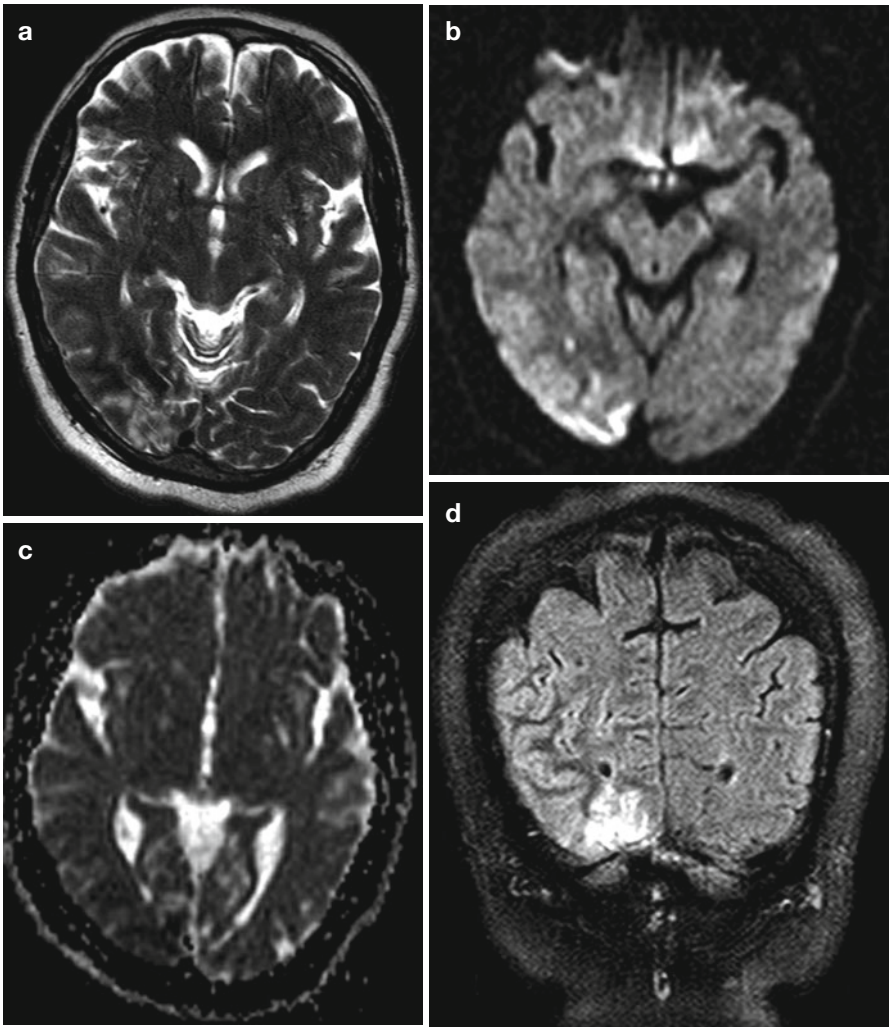


Fig. 2.1 (**a**) T_2-weighted MRI demonstrated the right medial occipital lobe infarction in a patient with Charles-Bonnet syndrome. (**b**) Diffusion MRI showed acute right occipital pole ischemic lesion involving gyrus descendens, inferior part of middle occipital gyrus. (**c**) ADC mapping demonstrates decreased signal intensity in the right occipital lobe. (**d**) Coronal MRI showed involvement of the medial occipital lobe

vision, hallucinations usually develop after a latency period and disappear within several weeks or months. While the pathophysiology of CBS is generally interpreted either a release phenomenon (deafferentation) [7, 8], it may be caused by sensory deprivation and "phantom vision" [9, 10] or by an abnormal focus activating neuronal network [11]. Its preponderance in patients with structural damage such as infarction or vascular malformation [4, 11, 12] has suggested that isolated lesions to the occipital lobe can lead to complex visual and somatosensory hallucinations.

Patients suffering from eye disease showed asymmetric hyperperfusions in the lateral temporal cortex, striatum, and thalamus, with visual hallucinations precipitated by excessive cortical compensation [13]. It is important to determine if the visual hallucinations are caused by persisting occipital lobe seizures or by newly developed ischemic lesion causing deafferentation of the occipital association areas. Occipital lobe epilepsy can be differentiated through a detailed medical history of the nature of the visual hallucinations and through video-EEG monitoring.

Peduncular Hallucinosis

Lesions in the midbrain region produce the syndrome of peduncular hallucinosis. Peduncular hallucinosis was originally described by Lhermitte in association with rostral brainstem lesion in a patient seeing animals of bizarre appearance and when trying to touch them, they disappeared through the floor [14]. The patient perceived these images as unreal illusions. She also reported the transformation of the animals into human figures, such as children playing the dolls. The patient also suffered from afternoon somnolence and insomnia at night. L'Hermitte pointed the similarity of the visual hallucinations to dreaming, according to their incoherent nature, the prevalence of mobile and multiple-colored images, and visuotactile associations. This type of hallucination was called hypnagogic because of the predilection for appearance during the late evening, but later, Van Bogaert suggested the term "peduncular hallucinosis" after a pathological verification of a patient with mesencephalic infarction [15]. De Morsier reported three patients with posterior thalamic infarct [16], and Feinberg and Rapscak observed peduncular hallucinosis in a patient with paramedian thalamic infarct [17]. Hallucinations may mostly start a few days after infarction and subside a few weeks later, but they may persist for years. The hallucinations usually last minutes to several hours, but sometimes they may persist throughout waking. There are complex visual hallucinations that typically occur in the evenings and are associated with disturbances of the sleep-wake cycle and are usually viewed as benign, entertaining phenomena. They are occasionally accompanied by tactile and auditory hallucinations. Auditory-visual synesthesia has also occasionally been described by patients with lesions involving the upper brainstem. There is often an associated disturbance of consciousness and somnolence, and they have difficulty distinguishing dreams from reality (oneroid states). When the temporal or occipital lobes are infarcted, an agitated delirium may occur. Patients have insight into hallucinations, and once they understand the phenomenon, they cope with it well, without features of paranoia or psychiatric disturbance. In this condition peduncular hallucinosis has been associated with bilateral lesions of the substantia nigra (pars reticulata), infarction of the right paramedian (nucleus reticularis thalami) or posterior thalamus, and focal insults of the right midbrain tegmentum and cerebral peduncle. A pathologic study revealed lesions restricted to the medial substantia nigra pars reticulata and concluded that destruction of the pars reticulata may be the essential feature to the development of peduncular hallucinosis [18].

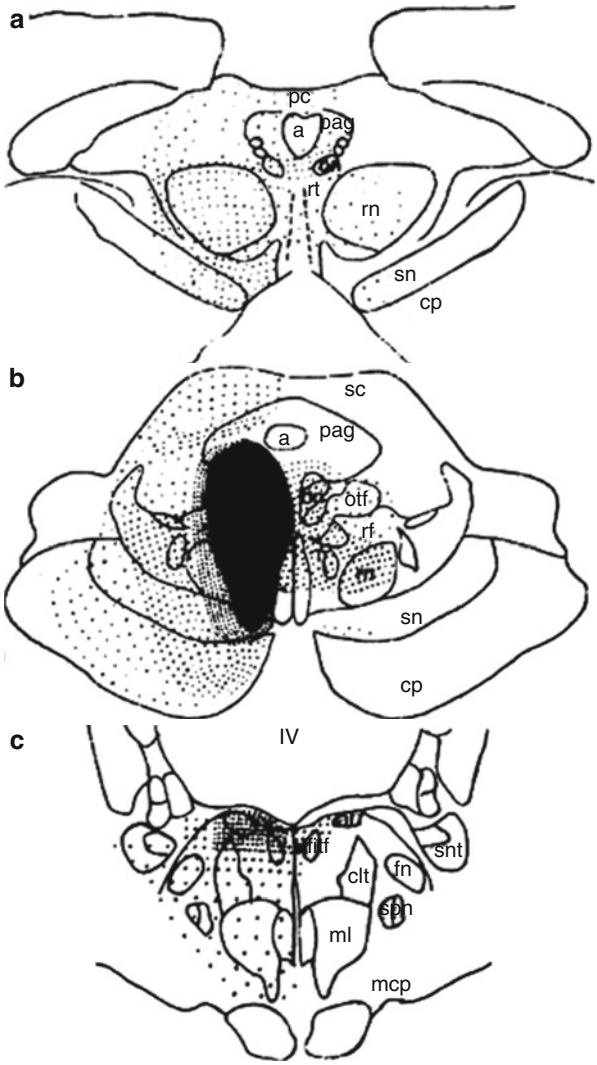


Fig. 2.2 Representative horizontal sections showing lesion localization through brainstem in patients with peduncular hallucinosis. (**a**) The level of the posterior commissure, (**b**) the oculomotor nucleus, (**c**) the abducens nucleus. *a* aqueduct, *an* abducens nucleus, *cp* cerebral peduncle, *ctt* central tegmental tract, *fn* facial nucleus, *IV* fourth ventricle, *ml* medial lemniscus, *mlf* medial longitudinal fasciculus, *mcp* middle cerebral peduncle, *on* oculomotor nucleus, *pag* periaqueductal gray matter (includes raphe nuclei), *pc* posterior commissure, *rf* reticular formation, *rn* red nucleus, *sc* superior colliculus, *son* superior olivary nucleus, *sn* substantia nigra, *snt* spinal nucleus and tract of the trigeminal nerve. Lesions appear to be concentrated in the paramedian reticular formation from pontine to midbrain levels, with the maximum density of lesions in the midbrain, close to the level of the oculomotor and raphe nuclei (With permission of Manford and Andermann [19])

The nigra pars reticulata receives inputs from both serotonergic raphe neurons and cholinergic cells of the pedunculopontine tegmental nucleus and sends reciprocal efferents to the pedunculopontine tegmental nucleus and reticular formation as well as to the parafascicular nucleus of the thalamus (Fig. 2.2) [19]. The nigra pars reticulata is thus closely connected to nuclei more commonly implicated in peduncular hallucinosis. The upper region of the brainstem is perfused by the basilar artery, and occlusion of the upper basilar produces the "top of the basilar syndrome [20]." This specific syndrome includes abnormalities of ocular movement, eyelid retraction, and skew deviation. Thalamic disorders have occasionally been associated with visual hallucinations (Fig. 2.3). Noda et al. reported two patients with an infarct

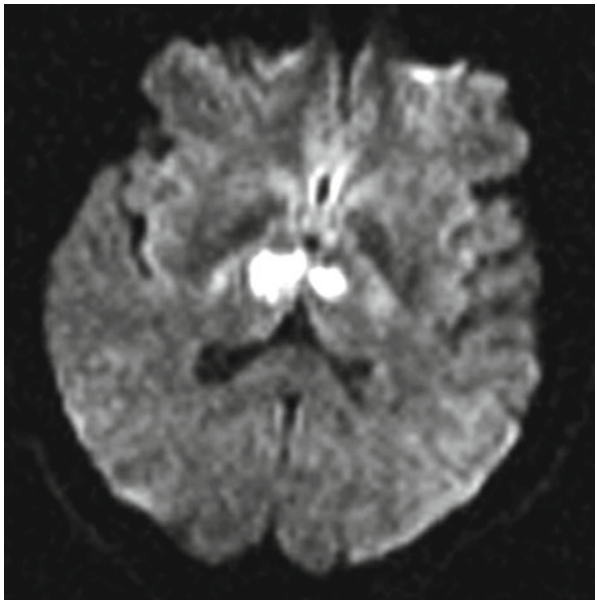


Fig. 2.3 A patient having bilateral thalamic infarction on diffusion MRI presented vivid visual hallucination as walking animals on the wall and touching to his body. Hallucinations continued along 1 month and the patient had prominent anxiety

limited to the thalamus developed auditory and visual experiential hallucinations [21]. Neuropathological study in one patient showed a small cavity in the right intralaminar nuclei surrounded by focal spongiform change, partly involving the right dorsomedial nucleus. Neuroradiological data in another patient indicated that the same nuclei in the left thalamus were also affected. It was concluded that a unilateral thalamic lesion could cause experiential hallucinations, and the intralaminar and dorsomedial nuclei might be important structures to explain the phenomenon [22]. Fisher (1959) reported data on five patients with unilateral thalamic hemorrhage who developed visual hallucinations [23].

Focal hemispheric lesions can produce visual hallucinations in two clinical circumstances: as part of focal seizure activity or as release (deafferentation) phenomena associated with visual field defects. Release hallucinations are generally formed images, lasting from minutes to weeks. They are variable in content, may be modified by altering the visual input as opening or closing the eyes, and tend to occur within the field defect. The underlying pathological lesion is usually an infarction, but any focal lesion within the visual pathways in the temporal, parietal, or occipital lobes may produce release hallucinations [24]. Following onset of hemianopia due to posterior cerebral artery (PCA) infarction, there are hallucinations of colors, objects, and figures. These illusions are often at the edge of the hemianopic field; they can appear later in the clinical course as the visual field defect is improving. In a case report [25], an 80-year-old right-handed woman, previously in good health, developed flashing lights of different colors in her right visual field while watching television. These continued for about half an hour. She then saw “a red curtain” descend over her right field, followed at once by a right field hallucination of “four or five men,” variably dressed (two or three in business suits, one in a cowboy suit

and hat, one in a plaid shirt), moving about, not speaking, and not relating to one another. She could not make out their faces: "It was as if they were in shadows." The figures were not frightening and did not remind her of any past experience. They persisted in her right visual field as long as she watched the television screen, disappearing when she looked away and returning abruptly when she looked back. For the next 2 weeks, they occurred nightly while she watched television, lasting as long as she viewed the screen, on one occasion for 4 h. One evening they appeared while she was reading a book, disappearing when she stopped, and another time they occurred throughout a church service, whether or not she was reading the hymnal.

Another type of illusion is visual perseverations described by the patient in relation to their hemianopia. When they look to the hemianopic field, they may see an object formerly in front of them now projected into their blind field. Trains of multiple objects may seem to be duplicated in the near edge of the blind field [26, 27].

Palinopsia (Greek: *palin* for "again" and *opsia* for "seeing") is a visual misperception that causes images to persist to some extent even after their corresponding stimulus has left. These images are known as after images and occur in persons with normal vision. However, a person with palinopsia experiences them to a significantly greater degree, to the point where they become difficult or impossible to ignore. Palinopsia sometimes appears on its own but is more often accompanied by other visual disturbances such as visual snow and can be attributed to a number of conditions affecting the brain including occipital lobe or visual pathway ischemic lesions, subcortical hemorrhage, and dural arteriovenous malformations [28, 29]. The phenomenon usually begins abruptly with a cerebral infarction and persists only a few days, but in some cases it has endured for years. Palinopsia can occur with lesions of either hemisphere but is most common with acute damage to the posterior aspect of the right hemisphere. Meadows and Munro described a patient who experienced a severe headache lasting only a few hours and then suffered palinopic images and congruous left upper quadrantanopia beginning the next day and recurring for the remaining 7 days of her life [30]. The autopsy showed a predominantly subcortical infarct undermining the right lingual and fusiform gyri. Michel and Troost studied three patients whose palinopic images also occurred in the affected visual field after presumed unilateral large occipital infarction affecting the right side in two and the left in one [31]. Hayashi et al. wrote of a patient who exhibited transient palinopsia and visual hallucinations [32]. Disturbances initially included an auditory component and increasingly were localized to the left visual field. These events occurred during recovery from a right subcortical hematoma with left homonymous hemianopia. Single-photon emission computed tomography (SPECT) demonstrated extensive perilesional hyperperfusion involving parts of the right parietal, temporal, and occipital cortex. Perilesional hyperperfusion disappeared as the visual abnormalities diminished. It has been accepted that excitatory neuronal activation in perilesional cortex during recovery contributed importantly to the transient abnormal perceptions. In addition to subcortical hemorrhage and posterior pathway lesions being possible underlying conditions for this visual phenomenon, palinopsia also seems to occur in those with dural arterial defects which affect blood flow to the occipital regions of the brain. Kupersmith et al. described

seven patients with visual disturbances, including palinopsia, which all have dural arteriovenous malformations (DAVMs) [29]. They describe that such malformations, if caught early, should be amenable to treatment before irreversible damage or visual field loss should occur through surgical intervention. In such patients, neurological and visual illusions can be correlated to venous hypertension, from incorrect occipital venous emptying.

Metamorphopsias of different types have also been noted in patients with PCA infarction, especially when the lesion is bilateral or occipitotemporal. In a limited portion of the visual field, they report enlargement (macropsia) or diminution (micropsia) of objects. Objects can be distorted or angulated. In a report, the patient described objects as tiny or minute, "like dollhouse furniture," in her left visual field and unusually large and "misshapen" in parts of the right visual field. Faces were grotesque because of the strange contrast between the two sides [28]. Yamada et al. reported a 63-year-old man whose micropsia occurred suddenly and was associated with an acute amnestic state and a right upper quadrantanopia due to large left PCA territory infarction [33]. Another patient reported having a migraine history and postmortem right inferolateral occipital cerebral infarction. The syndrome started as left homonymous hemianopia with prominent prosopagnosia. As these complaints faded over a week's time, the patient experienced that objects seemed somewhat shrunk and compressed in his left visual field, making the plotting of visual fields difficult and producing an awareness that pictures seemed asymmetric. He drew the left-hand side of a pattern larger than the right so it would look symmetrical to him [34].

Misperception of colors has been observed when infarction is localized to the lower bank of calcarine cortex, especially when the infarct is bilateral [35–38]. Unilateral large lesions undercutting the lingual gyrus can cause an abnormality of color perception in the contralateral half field [39]. Infarction of the lateral geniculate body may also affect color perception [40]. In some cases color perception is disturbed and seems dim, washed out, or pale, or the environment is said to have switched from "technicolor to black and white." In some instances, color perception is normal but colors are misnamed. The patient can match colors or say what color an object usually is, select and appropriately color objects from a set of crayons, yet give the wrong color name [40, 41].

Hallucinations may occur in the course of acute confusional states following acute stroke. They have been noted in 40–75 % of delirious patients [42]. In delirium, the hallucinations are relatively brief, are often nocturnal, and may be regarded as real. Hallucinations in delirium are usually clear, brightly colored visions that are experienced as three-dimensional images in nearby space. The patients are often fearful and respond to the hallucinations with self-protective measures. The visions are typically formed, moving, silent images but in some cases may be accompanied by auditory or tactile hallucinations. This is particularly common in patients with associated vascular or Alzheimer's dementia syndrome [43]. Autoscopy (beutoscopy) is another striking hallucinatory experience in which one sees one's own image. Such hallucinations may occur in subarachnoid hemorrhage, epilepsy, brain tumors, cerebral trauma, cerebral syphilis, migraine, postencephalitic parkinsonism, typhus

and other infectious diseases, drug intoxications, schizophrenia, and depression. If the patient endorses the vision as a true double or believes that a double exists, even though invisible, the syndrome merges into the delusion of the double, or the doppelgänger [44, 45].

Hallucinations following multi-infarct dementia may occasionally develop. Cummings et al. described visual hallucinations in 4 of 15 patients with multi-infarct dementia in the earlier stages of the disease [46]. Three patients experienced visual hallucinations including one patient with a combination of visual and auditory hallucinations. Visual hallucinations were observed in the homonymous field defect in two of the three patients, and a patient had marked visual acuity decrease. Hallucinations were explained by peripheral sensory loss or hemianopia. Another report noticed that a 79-year-old woman with vascular dementia seeing several males sitting around the table and discussing something on the deck of her house. CT scan revealed large occipital lobe and subcortical white matter infarction [47].

There are no etiologically specific or pathognomonic types of hallucinations, but features of visual hallucinations may facilitate identification of the clinical disorders from which they originate [48, 49]. For instance, posterior occipital lesions produce unformed, simple flashes; the patterns become more complex if the lesion located in visual association cortex; and more anteriorly placed lesions in the medial temporal lobe produce complex, formed images and visual memories. Foerster described a variety of visual hallucinations induced by electrical stimulation of different areas of the occipital cortex [50]. Stimulation of occipital pole or posterior area striae (area 17) led to hallucinations of "a stationary light or stars" immediately in front of the subject. Stimulating area 17 more anteriorly produced light "seen in the peripheral parts of the visual field and moving toward the center of the field." Stimulation of area 18 caused similar sensations. But stimulating the occipital cortex on the convex surface (area 19) produced more formed hallucinations: figures, people, or animals. Penfield and Jasper reported similar findings but believed stimulation had to be anterior to area 19, in the temporal or parietal cortex, to evoke formed or "psychical" hallucinations [51]. The remarkable similarity of many aspects of visual hallucinations suggests that a few basic CNS mechanisms are responsible for generation of most of the images. The most common situation in which hallucinations merge involves the reduction of visual input. This occurs in sensory isolation, enucleation, cataract formation, retinal disorder, choroidal change, macular disease, and optic nerve and tract disease and with hemispheric lesions involving the geniculocalcarine pathways. The blindness may be partial or total monocular or hemianopic and in all cases may be associated with hallucinations of similar character. West proposed for explanation of these hallucinations a "perceptual release theory," which suggests that decreased sensory input results in release of spontaneous activity of CNS structures normally mediating perceptual experience [52].

Cholinergic mechanisms may also have important role in mechanisms associated with hallucinosis. Anticholinergic toxicity is accompanied by prominent hallucinations, and treatment with cholinergic agents may reduce visual hallucinations. Visual hallucinations respond poorly to treatment except in specific circumstances. Visual hallucinations in patients with vascular dementia associated with degenerative

disorders, such as Alzheimer's disease and Parkinson's disease with dementia, may improve with therapy with cholinesterase inhibitors. Antipsychotic agents reduce both hallucinations and delusions in patients with delirium. Dopaminergic and serotonergic mechanisms have been implicated [19, 24].

Auditory Hallucination

Auditory hallucinations (also known as paracusia) are the perception of sound without outside stimulus. Auditory hallucinations can be divided into two categories: elementary and complex. Elementary hallucinations are the perception of sounds such as hissing, whistling, an extended tone, and more. In many cases, tinnitus is an elementary auditory hallucination. However, some people who experience certain types of tinnitus, especially pulsatile tinnitus, are actually hearing the blood rushing through vessels near the ear. Because the auditory stimulus is present in this situation, it does not count as a hallucination. Complex hallucinations are those of voices, music, or other sounds which may or may not be clear; may be familiar or completely unfamiliar; and may be friendly or aggressive, among other possibilities [43, 47].

Auditory hallucinations, unlike visual hallucinations, are more characteristic of idiopathic psychiatric disorders. Auditory hallucinations are caused uncommonly by acute stroke, mostly described after lesions of the brainstem and very rarely reported after cortical strokes. Lampl et al. observed poststroke auditory hallucinations in 4 of 641 patients, and all of them occurred after an ischemic lesion of the right temporal lobe [53]. After no more than 4 months, all patients were symptom-free and without therapy. The phenomenon may be completely reversible after a couple of months. Auditory hallucination is uncommon at onset of stroke; in such a case report, a 48-year-old right-handed woman had complaints of hearing abnormal sounds, including clicks, grunts, and other nonword vocalizations. These auditory hallucinations occurred intermittently for 10–15 min, during which time she was unable to speak but had retained comprehension. She had a very mild language disturbance, with occasional semantic and phonemic paraphasic errors and impaired naming. The initial formulation was that the etiology of her symptoms was most likely migraine. CT angiogram showed a filling defect in the distal M2 segment of the left MCA, and the perfusion study was consistent with acute ischemia [54].

Levine and Finkelstein presented eight patients of the development of hallucinations, delusions, and agitated aggressive behavior following a posterior right-hemisphere stroke in seven cases and a head injury with a right temporoparietal in one case [55]. The stroke lesions included a right occipitoparietal hemorrhage in two patients, a right temporoparietal hemorrhage in two patients, a right temporoparietal infarction in one case, and a right temporoparietal-occipital infarction in one patient. Time interval between stroke and hallucinations was 1–8 months in six patients and 11 years in one patient. The types of hallucinations were as follows: in patient 1 there was hallucinatory experience, and there were persecutory

delusions; in patient 2, a soft cloak was thought to be placed over the patient's left arm and both shoulders, and at night a broadcaster's voice was heard repeating the same things, classical music interrupted by "Happy Birthday" was heard, loud and insulting voices were perceived, and God was seen as a glorious light that followed her, but she was lucid in the daytime; in patient three, there were visual hallucinations and illusions in human forms, delusions of being spied upon, and delusions that listening devices have been placed in her house; in patients two, seven, and eight, there were pure hallucinations; and in other patients persecutory ideation, agitation, aggressive behavior, fluctuating disorientation, and incoherent thoughts were noted. Another report described a patient 63-year-old right-handed man with a right homonymous hemianopia due to right putaminal hemorrhage experienced metamorphopsia and visual hallucinations as "the right half of the curtain in front of him suddenly transforms into an animal's face [56]. It rotates there for a while and finally flows to the right, and then disappears." On the fourth day of stroke, he complained that the doctor's left cheek seemed to have been scraped, that the doctor's left hand seemed tortuous, and that some of the fingers of the hand seemed to be missing.

Peroutka, Sohmer, Kumar, Folstein, and Robinson reported the development of auditory and visual hallucinations in the course of a stroke in a 72-year-old woman [57]. The patient reported seeing and hearing various people sitting at her kitchen table, were discussing about her among themselves, and were making derogatory and vulgar remarks about her. Elementary auditory hallucinations included a loud buzzing noise, which the patient perceived as coming from a large bee. She occasionally experienced tactile hallucinations of having her hair pulled out by her visitors. CT scan demonstrated a small region of hypodensity with rim enhancement at the junction of the temporal, parietal, and occipital regions. Patient experienced an episode of uncontrolled movements, which began in the left shoulder and subsequently spread to the entire left upper extremity, lasting for approximately 1 min.

Musical hallucinations are a unique type of auditory hallucination that often surprise the individual who begins to experience them for the first time; the patient may try to find the radio or television that think is the origin of the sound [58, 59]. Musical hallucinations are also relatively common in terms of complex auditory hallucinations and may be the result of a wide range of causes ranging from hearing loss (such as in musical ear syndrome, the auditory version of CBS), arteriovenous malformation, acute ischemic lesions, lateral temporal lobe epilepsy, abscess, or tumor. For instance, a 50-year-old man presented to the emergency department with a generalized tonic-clonic seizure. Before the onset of his seizure, he experienced a vivid auditory hallucination of his favorite song by the band Pink Floyd, "A Brick in the Wall." He had been diagnosed with epilepsy 25 years previously. On presentation, his neurological examination was normal, but a computed tomography scan of the brain revealed a large arteriovenous malformation (AVM) occupying the left temporal lobe [60].

Musical hallucination may also develop in patients with brainstem stroke. Lanska, Lanska, and Mendez reported a 55-year-old patient, after suffering left-sided pontine hemorrhage involving the caudal part of the pontine tegmentum and

the dorsal and medial acoustic striate, complained of hearing low-pitched, slow musical sounds in both ears [61]. Several days later, the auditory hallucinations became "like people talking" and "like continuous rain falling on a roof." Cascino and Adams presented three patients with hearing loss and brainstem auditory hallucinations [62]. Two patients had suffered from a vascular lesion of the rostral pontine tegmentum; the third patient had a lower midbrain tumor. Later, in another case report, a patient with hearing loss developed auditory musical hallucinations lateralized to the right ear following a stroke with a hemorrhage at the right pontine tegmentum. Two years prior to the stroke, the patient had a lacunar stroke involving the right internal capsule [58].

In most of the patients, auditory hallucinations were observed mostly after ischemic and hemorrhagic stroke involving posterior parts of the cerebral hemisphere and more frequently in the right than in the left. Imaging studies have also compared brain activity during hallucination versus non-hallucination periods, identifying widespread brain activation related to auditory verbal hallucinations. These activations frequently include the inferior frontal gyri (IFG), the anterior cingulate cortex, the parahippocampal gyrus, and the superior and middle temporal gyri [63, 64].

Syncope may be associated with hallucinations. Thirty-six percent of individuals who experienced transient cerebral hypoxia had auditory hallucinations, and 60 % had visual changes such as gray haze, colored patches, or bright lights consisting of rushing or roaring noises, screaming, or voices [65]. Poststroke auditory hallucinations must be differentiated from primary auditory manifestation of schizophrenia, psychoses, hysterical conversion reactions, multiple personality disorders, and posttraumatic stress disorder. Auditory hallucinations may also develop in patients with palinacousis, in which there is a persistence or late recurrence of existing auditory stimuli [66]. Palinacousis has been associated with a variety of cerebral lesions (particularly infarctions and neoplasms), and the lesions usually involve the temporal lobe.

Wearing headphones has decreased auditory hallucinations in some patients, and others report temporary amelioration of the hallucinations with humming or mouth opening (maneuvers that disrupt subvocalization) [67]. Antipsychotic agents may relieve auditory hallucinations in some patients with vascular auditory hallucinations, but there is no large case series to prove the efficacy of these drugs.

Tactile Illusions and Hallucinations

Little study has been conducted on the topic of poststroke tactile hallucinations or delusions, as compared to the much larger body of research dedicated to visual hallucinations. Reported cases of tactile hallucinations vary from more basic tactile sensations, such as imaginary itches, formication (i.e., the abnormal sensation as of insects crawling in or upon the skin), pinching, rubbing, and having the skin covered in fur, to far more complex perceptual experiences, such as being kissed, having someone lying by one's side, and more or less bizarre sexual experiences

[68]. In a number of different cases, tactile hallucinations have been associated with ischemic stroke. For instance, Halligan et al. reported a patient with tactile (as well as visual) hallucinatory sensations following right-hemisphere stroke affecting the right temporal pole, caudate nucleus, lower basal ganglia, insular cortex, putamen, and posterior frontal cortex [69]. The patient exhibited a number of hallucinations (compatible with a diagnosis of CBS) with a moderate left-sided neglect and left visual field deficits. On different occasions, the patient experienced tactile sensations related to the object of her hallucinations. For example, she not only experienced the presence of a dog (actually one of her dogs that had died many years earlier) but also reported the sensation that the dog's fur was wet to touch, the same as when he had come back to her following a walk in the rain. She also reported the tactile feeling associated with poking her husband's arm in order to wake him up. Neuroimaging studies have shown that both the posteroventral insula and perirhinal cortex are involved in the storage of tactile information regarding haptically explored stimuli [70]. It can be speculated that tactile (as well as visual) hallucinations might be caused by the faulty activation of those brain areas responsible for tactile memories. Eventually, a misfiring of the circuit that sustains tactile memories (and that includes the somatosensory cortex as well as areas responsible for the active exploration of the stimuli) could, at least in part, explain the hallucinatory tactile phenomena [71].

Delusional parasitosis is a syndrome characterized by the conviction (accompanied by reports of tactile and sometimes visual sensations) that small creatures are infesting one's skin. Previous studies concluded that delusions of parasitosis commonly occur after damage to subcortical or cortical brain regions, often in the temporoparietal region of the right hemisphere [72–74]. Huber et al. found that in patients with delusions of parasitosis, there were structural lesions in the striatum, predominantly the putamen which might account for this syndrome [75]. The itching and tactile hallucinations, as well as somatic delusions seen in patients, are mediated through a striato-thalamo-parietal network.

Supernumerary of limbs is a tactile misperception as artificial hand, arm, or leg that appeared to be connected to the participants' own body to give the impression that they had a supernumerary third arm or leg (in a central location between the real hands or legs). Halligan et al. reported a patient affected by the delusional perception of a supernumerary phantom limb after damage to the right basal ganglia [76]. A following case report described a patient who experienced the presence of a third hand, and less frequently leg, after lesion to the right frontal lobe and corpus callosum [77]. Invisible doppelgänger (double of a living person) and left arm amputation impression in the right frontal opercular stroke was described in a patient. These body scheme disorders have both been described after (right) parietal lesions. Diffusion tensor imaging showed that the stroke involved the ventral bundle of the superior longitudinal fasciculus that connects the parietal to the frontal lobe. The unusual clinical presentation of this frontal lesion may have been due to a "diaschisis"-like phenomenon via the superior longitudinal fasciculus [78]. The results of the studies on tactile illusions, together with those on supernumerary limbs, suggest possibility that the awareness of tactile stimulation can somehow be

"rebuilt" or "rewired" in patients who have suffered from deafferentation by directly acting upon somatosensory cortex.

Illusory sensations of movement can be elicited in patients with right brain damage. An anomalous sensation of the right hand induced a very clear sensation of movement of the left, contralesional hand in two patients affected by body image disorders. Remarkably, this occurred mainly while subjects were looking in the mirror, that is, when conflicts between visual, somatic, and motor information were maximal. Illusory movements of the left plegic hand contingent upon sensorimotor conflicts can be evoked in brain-damaged patients with body image disorders [79]. Illusion of longitudinal body axis (LBA) rotated in the frontal plane can be developed in stroke patients. In a recent study, in eight patients with stroke (six right stroke, two left stroke), the perceived LBA was rotated from true body orientation in the direction opposite to the lesioned side (range 3–9.5°, mean 5.2°) [80]. The rotation of perceived LBA was more pronounced for right-hemisphere strokes.

Olfactory and Gustatory Illusions and Hallucinations

Olfactory and gustatory (taste) hallucinations are the least common hallucinations recorded in stroke investigations. Isolated olfactory hallucinations are a rare event and have been associated with a number of etiologies including medial temporal lobe lesion, complex partial seizures (uncinate seizures), migraines, psychiatric illnesses, multi-infarct dementia, and Alzheimer's disease. A recent report described a 58-year-old woman self-presented to the emergency department with an increasing frequency of experiencing abnormal olfactory sensations due to hemorrhagic lesion in the left uncinate lobe [81]. She complained of episodically smelling a very unpleasant odor that was like "burning paint mixed with rotting flesh." The odor would increase in intensity before subsiding, and the duration of each episode was 2–3 min. The only symptoms reported between episodes were of food tasting different, as if it had lost some taste.

The initial connection of the olfactory tract is to the primary olfactory cortex and the amygdala. The primary olfactory cortex, called the piriform cortex, is located in the uncus and anterior parahippocampal gyrus and is thought to be associated with the perception of smell. Olfactory hallucinations have most often been associated with lesions of the mesial temporal lobe; however, they have also been reported in association with lesions of the orbitofrontal region. In a report, the patient felt a sweet pleasant smell coming from behind her right side every time before the attack. Cranial magnetic resonance imaging and CT angiography revealed a large aneurysm at the bifurcation of the right middle cerebral artery and compression of the right orbitofrontal cortex. Small spikes were recorded from the right orbitofrontal and superior temporal gyri and from the uncus by the cortical electrodes during clipping of the aneurysm [82].

Gustatory illusions are commonly reported as the perception of a bad taste. Symptoms reported included dysgeusia which is a qualitative gustatory disturbance

relating to a distorted taste perception or to a persistent taste sensation in the absence of stimulation. Frequently, gustatory stimuli are reported to be different from what they used to be; they are perceived as bitter, sour, or metallic. Taste phantoms (phantogeusia) have been reported in patients with epilepsy and schizophrenia [83]. Gustatory misperceptions have been infrequently reported in patients following stroke [84, 85]. Patients with taste misperception may have either ischemic or hemorrhagic lesion in the anterior circulation or posterior circulation. These patients presented inability to detect real tastes and experienced different bad tastes. Patients reported heavily salting or sweetening their food to mask the distorted and unpleasant taste perception. More recent investigations in patients who have had strokes indicated that dysgeusia was present contralaterally to a thalamic or corona radiata infarction, thus supporting the idea that gustatory fibers ascend contralaterally in the cerebral hemisphere and that the pathway ascends from the thalamus to the insular cortex, frontal operculum, opercular part of the superior temporal gyrus, and inferior part of the precentral and postcentral gyri, via the posterior part of the corona radiata [86].

References

1. Hécaen H, Albert M. Human neuropsychology. New York: Wiley; 1978.
2. Esquirol JED. Les maladies mentales. Paris: Ballieres: 1814. Mental malady. New York: Hafner Press; 1965.
3. Starkstein SE, Robinson RG, Berthier ML. Post-stroke hallucinatory delusional syndromes. Neuropsychiatry Neuropsychol Behav Neurol. 1992;5:114–8.
4. Teunisse RJ, Cruysberg JR, Verbeek AL, Zitman FG. The Charles Bonnet syndrome: a large prospective study in the Netherlands: a study of the prevalence of the Charles Bonnet syndrome and associated factors in 500 patients attending the University Department of Ophthalmology at Nijmegen. Br J Psychiatry. 1995;166:254–7.
5. Sonnenblick M, Nesher R, Rozenman Y, Nesher G. Charles Bonnet syndrome in temporal arteritis. J Rheumatol. 1995;22:1596–7.
6. de Morsier G. Le syndrome de Charles Bonnet: hallucinations visuelles des vieillards sans deficience mentale (in French). Ann Med Psychol. 1967;125:677–701.
7. Kolmel HW. Complex visual hallucinations in the hemianopic field. J Neurol Neurosurg Psychiatry. 1985;48:29–38.
8. Siatkowski RM, Zimmer B, Rosenberg PR. The Charles Bonnet syndrome: visual perceptive dysfunction in sensory deprivation. J Clin Neuroophthalmol. 1990;10:215–8.
9. Schultz G, Melzack R. The Charles Bonnet syndrome: phantom visual images. Perception. 1991;20:809–25.
10. Mewasingh LD, Kornreich C, Christiaens F, Christophe C, Dan B. Pediatric phantom vision (Charles Bonnet) syndrome. Pediatr Neurol. 2002;26:143–5.
11. Beniczky S, Keri S, Voros E, et al. Complex hallucinations following occipital lobe damage. Eur J Neurol. 2002;9:175–6.
12. Kurata A, Miyasaka Y, Yoshida T, Kunii M, Yada K, Kan S. Venous ischemia caused by dural arteriovenous malformation: case report. J Neurosurg. 1994;80:552–5.
13. Adachi N, Watanabe T, Matsuda H, Onuma T. Hyperperfusion in the lateral temporal cortex, the striatum and the thalamus during complex visual hallucinations: single photon emission computed tomography findings in patients with Charles Bonnet syndrome. Psychiatry Clin Neurosci. 2000;54:157–62.

14. L'Hermitte J. Syndrome de la calotte du pédoncle cérébral. Les troubles psycho-sensorieles dans les lésions du mesencéphale. Rev Neurol. 1922;38:1359–65.
15. Van Bogaert L. Syndrome inférieur du noyau rouge, troubles psycho-sensoriels d'origine mésocéphalique. Rev Neurol. 1924;40:417–23.
16. De Morsier G. Les hallucinations visuelles dans les lésions du diencéphale (section 2). Revue Neuro-Oto Ophtalmologie. 1938;16:244–352.
17. Feinberg WM, Rapcsak SZ. Peduncular hallucinosis after paramedian thalamic infarction. Neurology. 1989;39:1535–6.
18. McKee AC, Levine DN, Kowall NW, Richardson EP. Peduncular hallucinosis associated with isolated infarction of the substantia pars reticulata. Ann Neurol. 1990;27:500–4.
19. Manford M, Andermann F. Complex visual hallucinations. Clinical and neurobiological insights. Brain. 1998;121:1819–40.
20. Caplan LR. Top of the basilar syndrome. Neurology. 1980;30:72.
21. Noda S, Mizoguchi M, Yamamoto A. Thalamic experiential hallucinosis. J Neurol Neurosurg Psychiatry. 1993;56:1224–6.
22. Catafau JS, Rubio F, Seera JP. Peduncular hallucinosis associated with posterior thalamic infarction. J Neurol. 1992;239:89–90.
23. Fisher CM. The pathologic and clinical aspects of thalamic hemorrhage. Trans Am Neurol Assoc. 1959;84:56–9.
24. Santhouse AM, Howard RJ, ffyttche DH. Visual hallucinatory syndromes and the anatomy of the visual brain. Brain. 2000;123:2055–64.
25. Brust JCM, Behrens MM. Release hallucinations as the major symptom of posterior cerebral artery occlusion: a report of 2 cases. Ann Neurol. 1977;2:432–6.
26. Critchley M. The parietal lobes. London: Edward Arnold; 1953.
27. Kinsbourne M, Warrington EK. A study of visual perseveration. J Neurol Neurosurg Psychiatry. 1963;26:468–75.
28. Caplan LR. Posterior cerebral artery syndromes. In: Toole JF, editor. Handbook of clinical neurology. Vascular diseases. Part I, vol. 9(53). Netherlands: Elsevier Science BV; 1988.
29. Kupersmith MJ, Berenstein A, Nelson PK, Simon HT, Setton A. Visual symptoms with dural arteriovenous malformations draining into occipital veins. Neurology. 1999;52:156–62.
30. Meadows JC, Munro SS. Palinopsia. J Neurol Neurosurg Psychiatry. 1977;40:5–8.
31. Michel EM, Troost BT. Palinopsia. Cerebral localization with computed tomography. Neurology. 1980;30:887–9.
32. Hayashi R, Shimizu S, Watanabe R, Katsumata Y, Mimura M. Palinopsia and perilesional hyperperfusion following subcortical hemorrhage. Acta Neurol Scand. 2002;105:228–31.
33. Yamada A, Miki H, Nishioka M. A case of posterior cerebral artery territory infarction with micropsia as the chief complaint. Rinsho Shinkeigaku. 1990;30:894–7.
34. Cohen L, Gray F, Meyrignac C. Selective deficit of visual size perception: Two cases of hemimicropsia. J Neurol Neurosurg Psychiatry. 1994;57:73–8.
35. Critchley MK. Acquired anomalies of color perception of central origin. Brain. 1965;88:711–24.
36. Pearlman AL, Birch J, Meadows JC. Cerebral color blindness: an acquired defect in hue discrimination. Ann Neurol. 1978;5:253–61.
37. Damasio A, Yamada Y, Damasio H, Corbett J, MacKee J. Central achromatopsia: behavioral, anatomic, and physiological aspects. Neurology. 1980;30:1064–71.
38. Meadows JC. Disturbed perception of colours associated with localized cerebral lesions. Brain. 1974;97:615–32.
39. Polyak SL. The vertebrate visual system. Chicago: University of Chicago Press; 1957.
40. Mohr JP, Leicester J, Stoddard LT, Sidman M. Right hemianopia with memory and color deficits in circumscribed left posterior cerebral artery territory infarction. Neurology. 1971;21:1104–11.
41. Geschwind N, Fusillo M. Color-naming defects in association with alexia. Arch Neurol. 1965;15:137–46.
42. Lipowski ZJ. Delirium: acute confusional states. New York: Oxford University Press; 1990.

43. Cummings JL, Mega MS. Neuropsychiatry and behavioral neuroscience. Oxford: Oxford University Press; 2003. p. 187–99.
44. Dening RE, Brrios GE. Autoscopic phenomena. Br J Psychiatry. 1994;165:808–17.
45. Lhermitte J. Visual hallucinations of the self. BMJ. 1951;1:431–4.
46. Cummings J, Miller B, Hill MA, Neshkes R. Neuropsychiatric aspects of multi-infarct dementia and dementia of the Alzheimer type. Arch Neurol. 1987;44:389–93.
47. Tonkonogy JM, Puente AE. Localization of clinical syndromes in neuropsychology and neuroscience. New York: Springer; 2009. p. 187–220.
48. Lance JW. Simple formed hallucinations confined to the area of a specific visual field defect. Brain. 1976;99:719–34.
49. La Mancusa JC, Cole AR. Visual manifestations of occipital lobe infarction in three patients on a geriatric psychiatry unit. J Geriatr Psychiatry Neurol. 1988;1:231–4.
50. Foerster O. The cerebral cortex in man. Lancet. 1931;2:309–31.
51. Penfield W, Jasper H. Epilepsy and functional anatomy of the human brain. Boston: Little, Brown; 1954.
52. West LJ. Hallucinations. New York: Grune and Stratton; 1962.
53. Lampl Y, Lorberboym M, Gilad R, Boaz M, Sadeh M. Auditory hallucinations in acute stroke. Behav Neurol. 2005;16:211–6.
54. Boyd JG, Jin AY. "Alien voice" auditory hallucinations as the presenting symptom of acute left middle cerebral artery (MCA) infarction. Stroke. 2010;41:e473–510.
55. Levine DN, Finkelstein S. Delayed psychosis after right temporoparietal stroke and trauma: relation to epilepsy. Neurology. 1982;32:267–73.
56. Shiga K, Makino M, Ueda Y, Nakajima K. Metamorphopsia and visual hallucinations restricted to the right visual hemifield after a left putaminal haemorrhage. J Neurol Neurosurg Psychiatry. 1996;61:420–1.
57. Peroutka SJ, Sohmer B, Kumar AJ, Folstein M, Robinson RG. Hallucinations and delusions following a right temporooccipital infarction. Johns Hopkins Med J. 1982;151:181–5.
58. Murata S, Naritomi H, Sawada T. Musical auditory hallucinations by a brainstem lesion. Neurology. 1994;44:154–8.
59. Evers S, Ellger T. The clinical spectrum of musical hallucinations. J Neurol Sci. 2004;227:55–65.
60. Ozsarac M, Aksay E, Kiyan S, Unek O, Gulec FF. De novo cerebral arteriovenous malformation: Pink Floyd's song 'Brick in the Wall' as a warning sign. J Emerg Med. 2012;43(1):e17–20. doi:10.1016/j.jemermed.2009.05.035. ISSN 0736–4679.
61. Lanska DJ, Lanska MJ, Mendez M. Brainstem auditory hallucinosis. Neurology. 1987;37:1685.
62. Cascino GD, Adams RD. Brainstem auditory hallucinosis. Neurology. 1986;36:1042–7.
63. Hoffman RE, Hampson M, Wu K, Anderson AW, Gore JC, Buchanan RJ, et al. Probing the pathophysiology of auditory/verbal hallucinations by combining functional magnetic resonance imaging and transcranial magnetic stimulation. Cereb Cortex. 2007;17:2733–43.
64. Sommer IE, Diederen KM, Blom JD, Willems A, Kushan L, Slotema K, et al. Auditory verbal hallucinations predominantly activate the right inferior frontal area. Brain. 2008;131:3169–77.
65. Lempert T, Bauer M, Schmidt D. Syncope: a videometric analysis of 56 episodes of transient cerebral hypoxia. Ann Neurol. 1994;36:233–7.
66. Malone GL, Leiman HI. Differential diagnosis of palinacousis in a psychiatric patient. Am J Psychiatry. 1983;140:1067–8.
67. Feder R. Auditory hallucinations treated by radio headphones. Am J Psychiatry. 1982;139:1188–90.
68. Berrios GE. Tactile hallucinations: conceptual and historical aspects. J Neurol Neurosurg Psychiatry. 1982;45:285–93.
69. Halligan PW, Marshall JC, Ramachandran VS. Ghosts in the machine: a case description of visual and haptic hallucinations after right hemisphere stroke. Cogn Neuropsychol. 1994;11:459–77.
70. Bonda E, Petrides M, Evans A. Neural systems for tactual memories. J Neurophysiol. 1996;75:1730–7.

71. Gallace A, Spence C. The cognitive and neural correlates of tactile memory. Psychol Bull. 2009;135:380–406.
72. Nagaratnam N, O'Neile L. Delusional parasitosis following occipito-temporal cerebral infarction [letter]. Gen Hosp Psychiatry. 2000;22:129–32.
73. Adunsky A. Early post-stroke parasitic delusions. Age Ageing. 1997;26:238–9.
74. Blasco-Fontecilla H, Bragado Jimenez MD, Garcia Santos LM, Barjau Romero JM. Delusional disorder with delusions of parasitosis and jealousy after stroke: treatment with quetiapine and sertraline. J Clin Psychopharmacol. 2005;25:615–7.
75. Huber M, Karner M, Kirchler E, Lepping P, Freudenmann RW. Striatal lesions in delusional parasitosis revealed by magnetic resonance imaging. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:1967–71.
76. Halligan PW, Marshall JC, Wade DT. Three arms: a case study of supernumerary phantom limb after right hemisphere stroke. J Neurol Neurosurg Psychiatry. 1993;56:159–66.
77. Hari R, Karhu J, Hamalainen M, Knuutila J, Salonen O, Sams M, Vilkman V. Functional organization of the human first and second somatosensory cortices: a neuromagnetic study. Eur J Neurosci. 1993;5:724–34.
78. Perren F, Chabwine JN, Vargas MI, Aboulaffia T, Caratsch L, Schnider A, Landis T. Simultaneous Doppelgänger and limb amputation impression in right frontal opercular stroke. J Neurol Neurosurg Psychiatry. 2011;82:1209–11.
79. Zampini M, Moro V, Aglioti SM. Illusory movements of the contralesional hand in patients with body image disorders. J Neurol Neurosurg Psychiatry. 2004;75:1626–8.
80. Barra J, Chauvineau V, Ohlmann T, Gresty M, Pérennou D. Perception of longitudinal body axis in patients with stroke: a pilot study. J Neurol Neurosurg Psychiatry. 2007;78:43–8.
81. Nye E, Arendts G. Intracerebral haemorrhage presenting as olfactory hallucinations. Emerg Med (Fremantle). 2002;14:447–9.
82. Mizobuchi M, Ito N, Tanaka C, Sako K, Sumi Y, Sasaki T. Unidirectional olfactory hallucination associated with ipsilateral unruptured intracranial aneurysm. Epilepsia. 1999;40:516–9.
83. Hausser-Hauw C, Bancaud J. Gustatory hallucinations in epileptic seizures: electrophysiological, clinical and anatomical correlates. Brain. 1987;110:339–59.
84. Landis BN, Leuchter I, San Millán Ruíz D, Landis T. Transient hemiageusia in cerebrovascular lateral pontine lesions. J Neurol Neurosurg Psychiatry. 2006;77:680–3.
85. Heckmann JG, Stössel C, Lang CJ, Bernhard G, Neundörfer B, Tomandl B, Hummel T. Taste disorders in acute stroke. A prospective observational study on taste disorders in 102 stroke patients. Stroke. 2005;36:1690–4.
86. Sanchez-Juan P, Combarros O. Gustatory nervous pathway syndromes. Neurologia. 2001;16:262–71.

Chapter 3
Depression After Stroke

Sergio E. Starkstein, Simone Brockman, and Brad Hayhow

Abstract Poststroke depression (PSD) is among the most common neuropsychiatric sequelae of stroke. Cross-sectional studies have demonstrated that about one-third of patients develop depression during the acute stage after stroke and more than 50 % suffer depression at some later point. PSD is strongly associated with negative outcomes, such as increased length of hospital stay, increased severity of neurological and functional deficits, more severe cognitive deficits, worse quality of life, and increased mortality. Randomized controlled trials have demonstrated the efficacy of nortriptyline, citalopram, and reboxetine to treat PSD. Recent studies also suggest that prophylactic treatment with antidepressants may significantly decrease the incidence of PSD, although more research in this area is needed.

Keywords Poststroke depression • Cognition • Mortality • Prevention • Treatment • Physical impairment

Introduction

Depression is one of the most frequent psychiatric complications after stroke. Cross-sectional studies have reported that about 20 % of patients suffer from major depression after an acute stroke and an additional 20 % develop minor

S.E. Starkstein (✉)
School of Psychiatry and Clinical Neurosciences,
University of Western Australia, Crawley, WA 6009, Australia

Fremantle Hospital, T-7, Fremantle, WA 6959, Australia
e-mail: sergio.starkstein@uwa.edu.au

S. Brockman • B. Hayhow
School of Psychiatry and Clinical Neurosciences,
University of Western Australia, Crawley, WA 6009, Australia

J.M. Ferro (ed.), *Neuropsychiatric Symptoms of Cerebrovascular Diseases*,
Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-1-4471-2428-3_3, © Springer-Verlag London 2013

depression [1]. Poststroke depression (PSD) has a negative impact on functional recovery and is associated with more severe cognitive deficits, poor quality of life, and higher mortality [1]. This chapter will first discuss current conceptual limitations in the diagnosis of depression after stroke. It will then address the prevalence, natural course, clinical correlates, and treatment and prevention of PSD.

Diagnosis of PSD

One of the most challenging problems in neuropsychiatry is how to diagnose depression when the symptoms of the neurological illness overlap with those of the affective disorder. Stroke patients frequently complain of insomnia, loss of appetite, poor concentration, loss of libido, and poor energy, which are all commonly identified through assessment with generic depression scales.

Four strategies have been proposed to minimize the overlap dilemma. In the "inclusive approach," symptoms of depression are counted as present regardless of whether they may be related to physical illness [2]. In the "exclusive approach," symptoms are removed from the diagnostic criteria whenever there is a potential overlap between depression and the neurological condition [3]. In the "substitutive approach," somatic symptoms of depression are replaced with psychological symptoms [4]. Finally, in the "etiological approach," symptoms of depression are included only when the examiner considers the symptoms not to be related to the neurological disorder [5].

In recent years several studies have been conducted to determine the specificity of depressive symptoms in stroke. Paradiso and coworkers [6] followed a group of acute stroke patients for 2 years and found that suicide ideation, ideas of reference, and pathological guilt were the only depressive symptoms not to be significantly more frequent in patients with DSM-IV major depression vs. those with no depression at 3 months poststroke. They also found 100 % sensitivity of standard DSM-IV criteria for major depression during the acute stroke period and 96 % sensitivity at the 2-year follow-up. Cumming and coworkers [7] carried out a factor analysis of 10 depressive symptoms in depressed and nondepressed stroke patients and found no significant differences between PSD and primary major depression for either psychological or somatic symptoms of depression. Based on these and previous findings, Robinson and Spalletta [8] suggested that no modification of the DSM-IV criteria for major depression is needed for the diagnosis of PSD. Nevertheless, future studies should further examine the validity of these criteria, specifically on stroke patients that are difficult to assess with current techniques (e.g., patients with aphasia or dementia).

Prevalence of PSD

Most studies assessing patients in acute settings reported a frequency of major depression of about 20 %, while another 20 % had minor depression [1]. For patients living in the community, the frequency of major depression was reported to be of

about 14 %, with 9 % for minor depression [1]. Robinson [1] suggested that this difference may be explained by more severe strokes among patients cared for in hospital settings as compared to patients living in the community.

Natural Course of PSD

There are few prospective studies of patients with untreated PSD with a relatively long follow-up. Robinson's studies found that about 50 % of patients with acute major depression remained depressed 6 months later, with the frequency dropping to 11 % 12 months poststroke, and none at the 24-month follow-up [9]. On the other hand, patients with minor depression seem to have a more chronic course, with about 50 % showing major or minor depression throughout the 2-year follow-up period [9]. Astrom and coworkers [10] reported a frequency of major depression of 30 % at 3 months poststroke. One year later, 60 % of them were nondepressed, while the remaining 40 % continued to be depressed.

The mechanism underlying the variability in the duration of depression remains poorly understood. In a small study that compared six depressed patients who spontaneously recovered from depression 6 months poststroke and ten depressed patients who did not recover, the main finding was that the non-recovered group had a higher frequency of cortical lesions and more severe in-hospital impairment in activities of daily living than the recovered group [11].

In conclusion, if left untreated, PSD is a long-lasting mood disorder, and duration may be influenced by lesion location and severity of acute impairments.

Clinical Correlates of PSD

Relationship to Lesion Variables

Pioneering studies by Robinson's group [1] showed a significant association between the frequencies of PSD and left frontal lesions. Starkstein and coworkers [12] later found this association to be true for both cortical and subcortical strokes in anterior regions of the left hemisphere. Another important finding from Robinson's studies [1] was a significant correlation between the distance of the lesion from the frontal pole and depression scores (i.e., the closer the lesion to the frontal pole, the higher the depression score). Later studies by other investigators produced heterogeneous results, ranging from replication of Robinson's findings [10, 13, 14] to no association between PSD and lesion variables [15]. Potential reasons for these discrepancies have been extensively discussed [1] and include differences in the time since stroke, demographic factors, recruitment bias, and source of patients (e.g., acute stroke units, rehabilitation services, patients living in the community). Time since stroke was identified as the main confounder by Shimoda and Robinson [16]. They reported that

the frequency of depression 2 weeks after stroke was significantly higher for patients with left vs. right hemisphere strokes, but there were no significant between-group differences in the frequency of depression at 3–6 months and 1–2 years after stroke. A meta-analysis that only included patients assessed up to 2 months after stroke found a significant association between left anterior lesions and depression (OR = 2.29, 95 % CI = 1.6–3.4, $p < 0.001$) [17]. Bhogal and coworkers [13] reported that the association between PSD and lesion location is influenced by source of patients (inpatients vs. individuals living in the community) and by time since stroke.

Relationship to Physical Impairment

A significant association between PSD and both physical and functional deficits has been consistently demonstrated, but this association is a complex one. Several studies showed that while PSD is a significant predictor of poorer recovery, more severe functional and physical impairments in the acute stage are strong predictors of depression [1].

Parikh and coworkers [18] and Pohjasvaara and coworkers [19] reported that depression at baseline predicts poor long-term functional and physical outcome. Donnellan and coworkers [20] recently examined the impact of depression on stroke outcomes. After controlling for relevant confounders, they found acute PSD was significantly associated with increased functional disability and poorer quality of life at 1 month poststroke. A review by Hackett and Anderson [21] found that 9 of 11 studies assessing physical and functional impairments in PSD demonstrated that greater functional and physical disability was associated with a greater frequency of depression.

Narushima and Robinson [22] reported that 34 patients (with or without depression) who received a 12-week treatment within the first 30 days after stroke with either fluoxetine (up to 40 mg/day) or nortriptyline (up to 100 mg/day) showed a greater recovery on activities of daily living than 28 patients receiving the same medications but who started treatment at 140 days poststroke. This finding suggests that early treatment with antidepressant drugs, even in the absence of depression, may have a positive impact upon functional recovery. These preliminary findings should be confirmed in large-scale randomized controlled trials (RCTs).

Relationship with Cognitive Impairment

A significant association between PSD and more severe cognitive impairment has been consistently demonstrated in both hospital and community settings. Robinson and coworkers [23] were the first to demonstrate significantly lower scores on the Mini Mental State Examination (MMSE) for patients with major depression as compared to nondepressed patients. These findings were later replicated by Spalletta and coworkers [24], Downhill and Robinson [25], and Morris and coworkers [26]. To

control for lesion variables, Starkstein and coworkers [27] matched 11 patients with PSD with 11 nondepressed stroke patients for lesion location and volume. They replicated the finding of significantly lower MMSE scores for patients with major depression as compared to lesion-matched nondepressed individuals. Bolla-Wilson and coworkers [28] assessed a series of patients with an acute stroke using a comprehensive neuropsychological battery. They found that patients with PSD and left hemisphere lesions had significantly more severe deficits on temporal orientation, language, and executive functions than nondepressed patients with left hemisphere strokes. On the other hand, there were no significant differences on any cognitive domain between patients with right hemisphere strokes with or without depression.

The question now arises as to whether antidepressant treatment may have a beneficial effect upon cognition in PSD. Kimura and coworkers [29] reported that 24 patients with PSD who responded to treatment with nortriptyline had a greater improvement on MMSE scores than nonresponders ($N=23$). This improvement in cognition was reported to last for 2 years or more, even after the antidepressant was ceased [30] suggesting that antidepressant medication may improve cognitive deficits among patients with PSD.

Relationship to Mortality

Several studies have demonstrated an increase in both short-term (1–2 years poststroke) and long-term (5–10 years) mortality in patients with PSD. Morris and coworkers [31] reported that patients with PSD were 3.4 times more likely to have died during 10 years of follow-up than nondepressed patients. House and coworkers [32] reported that patients scoring 1 or more points on the depression subscale of the General Health Questionnaire had a mortality rate 2.4 times greater than patients who scored zero. In a retrospective study, Williams and coworkers [33] replicated the finding of greater mortality 6 years poststroke for patients with depression as compared to nondepressed patients. Jorge and coworkers examined mortality data 9 years after 104 acute stroke patients were randomly assigned to receive treatment with nortriptyline, fluoxetine, or placebo. The main finding was that 67 % of patients who were given full-dose antidepressants were alive at follow-up, as compared to only 35 % of placebo-treated patients. This suggests that treatment with antidepressants within the first 6 months after stroke is associated with increased survival of stroke victims with or without depression.

Treatment of Poststroke Depression

Given the poor prognosis of patients with PSD, it is not surprising that several RCTs have been conducted to investigate both the treatment and prevention of PSD. We will now discuss the most relevant RCTs and meta-analyses, including both pharmacological and psychosocial interventions.

Pharmacological Treatments

Antidepressants

The first randomized controlled trial (RCT) of antidepressants in PSD was carried out by Lipsey and coworkers [34] who used nortriptyline for 6 weeks with doses increasing from 25 to 100 mg/day. The main finding was greater efficacy of the nortriptyline over placebo. Side effects from the nortriptyline group were delirium, drowsiness, confusion, and agitation in three patients which were severe enough to require discontinuation. Since this seminal study, a number of RCTs have been reported, most of them using selective serotonin reuptake inhibitors (SSRIs). Andersen and coworkers [35] examined the efficacy of citalopram (10–20 mg/day) in a 6-week RCT that included 59 completers. The main finding was a significant reduction on the HAM-D in the citalopram group as compared to the placebo group, with only minor side effects in the active treatment group.

Robinson and coworkers [36] carried out the only RCT to compare the efficacy of a tricyclic drug (nortriptyline) against an SSRI (fluoxetine) and placebo. This was a 12-week study, and patients with contraindications to the use of fluoxetine (intracerebral hemorrhage) or nortriptyline (cardiac conduction abnormalities, cardiac arrhythmia, narrow-angle glaucoma, sedation, or orthostatic hypotension) were excluded. Patients in the fluoxetine group were started on 10 mg/day for the first 3 weeks, and the dose was increased up to 40 mg/day. Patients on nortriptyline were started on 25 mg/day for the first week, and the dose was increased up to 100 mg/day. The main finding was that patients on nortriptyline showed a significantly greater decrease on HAM-D scores as compared to patients on fluoxetine or placebo (Fig. 3.1). On the other hand, there were no significant differences between the fluoxetine and the placebo groups. Based on these findings, Robinson and coworkers recommended a slow increase of nortriptyline, with a goal of achieving a serum concentration between 50 and 150 ng/mL.

The only RCT to use a norepinephrine reuptake inhibitor was conducted by Rampello and coworkers [37] who assessed the efficacy of reboxetine among patients with PSD and psychomotor retardation. Patients on reboxetine (4 mg/day) showed a significant decline on depression scores as compared to patients on placebo over the 16-week trial.

The efficacy of antidepressants was examined in two meta-analyses. Chen and coworkers [38] identified 16 relevant RCTs: 12 assessed SSRIs, 2 assessed tricyclics, and the remaining trials assessed other compounds. There was a significantly greater improvement in depression with active treatment as compared to placebo (pooled response rates of 65 and 44 %, respectively). Positive effects were observed after 3–4 weeks of treatment, and longer duration of treatment was associated with a greater response. Based on this important finding, the time-dependent effect of antidepressants in PSD should be further studied, and maintenance treatment should be perhaps recommended. Hackett and coworkers [39] conducted a meta-analysis that included seven RCTs of antidepressants: 4 RCTs used SSRIs (fluoxetine,

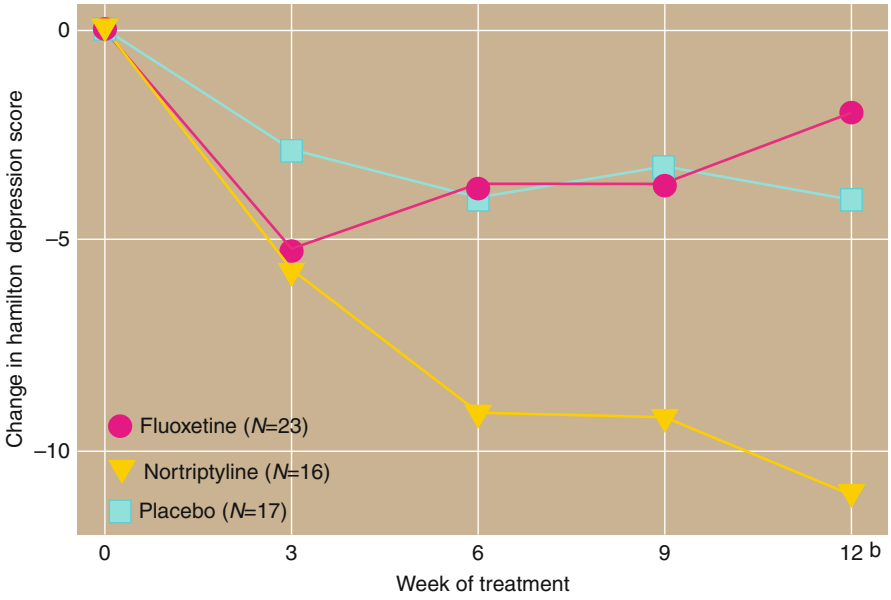


Fig. 3.1 Change in depression scores for depressed poststroke patients entered in a study comparing fluoxetine, nortriptyline, and placebo. Significant time-by-treatment interaction ($F = 3.45$, df = 8, 212, $p = 0.004$). Significantly greater change in patients treated with nortriptyline than in those taking fluoxetine or placebo (post hoc tests with Duncan's statistic, $p < 0.05$) [36] (Reprinted with permission)

sertraline, and citalopram), one RCT used a tricyclic compound (nortriptyline), and 2 RCTs assessed other antidepressants (aniracetam and trazodone). The main finding was that antidepressants were not associated with overall benefit as compared to placebo, but there was a significant effect in favor of active treatment on response rates and reduction in depression scores. Nevertheless, outcomes were quite heterogeneous, and active treatment was associated with increased frequency of adverse events.

Psychostimulants

Psychostimulants were mostly assessed in open-label studies using dextroamphetamine and methylphenidate and generally reported good efficacy of these compounds in treating PSD [40, 41]. However, the only RCT carried out to date failed to demonstrate significant treatment efficacy [42].

Several important limitations of RCTs for PSD should be noted. First, the recruitment periods of different studies ranged from that the acute stroke period to months or years after the stroke. Patients have also been recruited from different sources, such as acute stroke units, rehabilitation settings, or from the community. Second, some studies have excluded patients with a pre-stroke history of depression, while

other studies have included patients regardless of a previous positive psychiatric history. Third, the diagnosis of depression has been heterogeneous, ranging from scoring above a specific cutoff point on a depression scale to using more appropriate standardized diagnostic criteria for major depression. Finally, duration of treatment has ranged from 4 to 8 weeks, and primary outcome measures have varied from full remission (i.e., no longer meeting the criteria for depression), response (a reduction of 50 % or more on the baseline depression score), or a significant reduction in depression scores.

Non-pharmacological Treatments

Psychosocial Interventions

Few studies have examined the efficacy of psychosocial interventions as a treatment for PSD. Lincoln and coworkers [43] showed cognitive-behavioral treatment to be no more effective than a placebo treatment. One meta-analysis examined the efficacy of psychotherapy for PSD and showed no significant effects for active treatment [39]. Nevertheless, a recent RCT of a care management intervention (Activate-Initiate-Monitor intervention) showed that care management of PSD resulted in greater remission of depression and reduction of depressive symptoms than usual care alone [44]. Positive results were also found with the use of an integrated case model of depression treatment and a physical exercise program [45]. Treatment took place in the home three times a week for a total of 36 sessions and was supervised by a physical or occupational therapist. One limitation of this study is that there was no formal psychiatric interview to ascertain a diagnosis of PSD. Nevertheless, these findings suggest that adding patient activation and telephone-based treatment monitoring may enhance the efficacy of antidepressants to treat PSD.

Repetitive Transcranial Magnetic Stimulation (rTMS)

Two RCTs examined the efficacy of rTMS in PSD. The first study included 20 patients who received 10 sessions of rTMS or sham stimulation on the left dorsolateral prefrontal cortex [46]. Patients receiving active treatment showed a significant reduction of depressive symptoms as compared to sham treatment. The treatment was well tolerated, with only mild side effects in both groups. The second study [47] included 18 patients who were randomly assigned to low-frequency (1 Hz), high-frequency (10 Hz), or sham stimulation. The main finding was that high-frequency rTMS resulted in a significant decrease in depression scores as compared to sham treatment. Future studies are needed to further examine the efficacy and safety of rTMS for PSD.

Electroconvulsive Therapy (ECT)

There are no RCTs of ECT in PSD, but retrospective studies suggest that elderly individuals with stroke and depression may show moderate or marked improvement after ECT without further neurological complications except for prolonged postictal confusion and amnesia [48]. ECT could become a useful alternative for patients refractory to antidepressants or psychotherapy, but the efficacy and safety of ECT should be examined in appropriate RCTs.

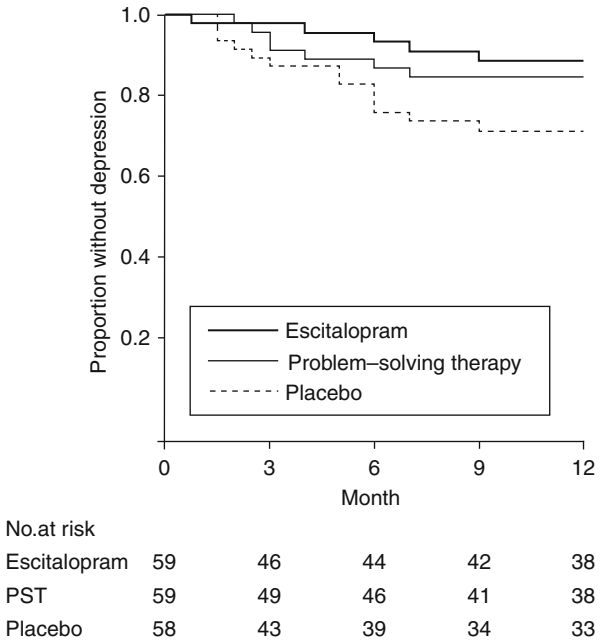
Prevention of Poststroke Depression

Given that PSD is associated with greater functional impairment, more severe cognitive deficits, and higher mortality, prevention is of great relevance. Both pharmacological and psychotherapeutic interventions have been explored in preventing PSD, with variable success.

Pharmacological Interventions

The first prevention study was carried out by Palomaki and coworkers [49], who compared the efficacy of mianserin (60 mg/day) against placebo during a 12-month period in a sample of 100 acute stroke patients. The authors found no significant differences between active treatment and placebo in preventing PSD. Rasmussen and coworkers [50] have examined the efficacy of sertraline (mean dose 63 mg/day) to prevent PSD in a series of 137 acute stroke patients who received acute treatment or placebo during 12 months. About 8 % of patients on sertraline developed depression as compared to 22 % of patients on placebo. Treatment with sertraline was well tolerated, and side effects were minor. On the other hand, using sertraline 50 mg/day, Almeida and coworkers [51] were unable to find significant efficacy for the active treatment. However, the study was methodologically limited given the short follow-up period (3 months only), and the study may have lacked power to detect significant differences between sertraline and placebo.

More recently, Robinson and coworkers [52] conducted a multicenter RCT that included 176 nondepressed patients within 3 months after stroke who were followed for 12 months. Patients were randomized to escitalopram, a non-blinded problem-solving therapy, or placebo. The main finding was that both active treatments were superior to placebo in preventing PSD. In another study, Robinson's group reported that nortriptyline treatment increased the vulnerability to depression after its discontinuation, suggesting that patients may develop tolerance to this antidepressant [53]. Finally, Jorge and coworkers [54] reported that a 12-week trial with nortriptyline (25–100 mg/day) or fluoxetine (10–40 mg/day) may significantly decrease the



No.at risk					
Escitalopram	59	46	44	42	38
PST	59	49	46	41	38
Placebo	58	43	39	34	33

Fig. 3.2 Risk comparison of depression onset for patients receiving escitalopram, problem-solving therapy (PST), or placebo over 1 year [52] (Reprinted with permission)

9-year mortality as compared to depressed or nondepressed stroke patients treated with placebo (Fig. 3.2).

Yi and coworkers [55] carried out a meta-analysis on the efficacy of fluoxetine for the prophylaxis of PSD. The analysis included six studies and the main finding was a significant reduction of PSD, increased recovery on neurological function, and improved independence on activities of daily living. On the other hand, there were no significant differences between the fluoxetine and placebo groups on depression scores at the end of the studies. There were no differences on side effects between patients on fluoxetine or placebo, although nausea, insomnia, and seizures were more frequent in the fluoxetine group. Of note, reductions in the incidence of PSD were related to onset of fluoxetine administration, with patients receiving fluoxetine 1 week after the stroke showing the best results. Side effects in the different trials were minimal, and the analysis of adverse events suggests a high risk-benefit ratio in favor of antidepressants.

Anderson and coworkers conducted a Cochrane review to examine whether pharmacological interventions can prevent PSD [56]. They included data from 10 RCTs, and main outcome measures of which were the presence of major depression or dysthymia or scoring above specific cutoff points for depressive disorder on specific depression rating scales. They reported no consistent evidence that antidepressant treatment prevents PSD, although the overall rate of depression was lower among patients treated with antidepressants. The negative finding may be explained by major differences between studies, such as time from stroke to onset of antidepressant intake, and the use of different drugs (fluoxetine, sertraline,

trazodone, piracetam, maprotiline, mianserin, nortriptyline, indeloxazine, and methylphenidate). Furthermore, treatment duration varied from 2 weeks to 12 months, and outcome measures differed between studies.

In conclusion, it is still unclear whether all stroke patients should receive prophylactic treatment with antidepressants. Ramasubbu [57] discussed several limitations to implement generic treatment, consequent to the fact that 50 % of stroke patients may never develop depression. For instance, patients and their families may not accept antidepressant treatment in the absence of depression, and clinicians may be reluctant to prescribe these medications due to concerns about side effects and potential drug interactions.

Psychosocial Interventions

Anderson's and coworkers Cochrane review [56] also assessed the efficacy of psychotherapy to prevent PSD. They included four RCTs and quasi-RCTs comparing different types of psychotherapy against standard care. Psychotherapeutic interventions consisted of problem-solving therapy, motivational interviewing, and multidisciplinary home-based therapy targeting psychosocial stressors. The main finding was a significant improvement on psychological distress after psychotherapy, but there were no significant differences on depression outcome. More evidence is required before a definite recommendation about using psychotherapy to prevent PSD is made.

Conclusion

PSD is a frequent finding after stroke and is significantly associated with negative physical, functional, and cognitive outcomes. RCTs have demonstrated the efficacy of nortriptyline and citalopram to treat PSD, but patients should be adequately selected to avoid severe side effects. Psychosocial interventions may also have efficacy for PSD and could enhance the effect of antidepressants. Prevention of PSD with antidepressants is still a debated issue, and future studies should identify the population of stroke patients that may significantly benefit from this intervention.

References

1. Robinson RG. The clinical neuropsychiatry of stroke. 2nd ed. Cambridge: Cambridge University Press; 2006.
2. Rifkin A, Reardon G, Siris S, Karagji B, Kim YS, Hackstaff L, et al. Trimipramine in physical illness with depression. J Clin Psychiatry. 1985;46(2 Pt 2):4–8.

3. Bukberg J, Penman D, Holland JC. Depression in hospitalized cancer patients. Psychosom Med. 1984;46(3):199–212.
4. Endicott J. Measurement of depression in patients with cancer. Cancer. 1984;53(10 Suppl):2243–9.
5. Rapp SR, Vrana S. Substituting nonsomatic for somatic symptoms in the diagnosis of depression in elderly male medical patients. Am J Psychiatry. 1989;146(9):1197–200.
6. 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(2):137–57.
7. Cumming TB, Churilov L, Skoog I, Blomstrand C, Linden T. Little evidence for different phenomenology in poststroke depression. Acta Psychiatr Scand. 2010;121(6):424–30.
8. Spalletta G, Robinson RG. How should depression be diagnosed in patients with stroke? Acta Psychiatr Scand. 2010;121(6):401–3.
9. Robinson RG, Spalletta G. Poststroke depression: a review. Can J Psychiatry. 2010;55(6):341–9.
10. Astrom M, Adolfsson R, Asplund K. Major depression in stroke patients. A 3-year longitudinal study. Stroke. 1993;24(7):976–82.
11. Starkstein SE, Robinson RG, Price TR. Comparison of spontaneously recovered versus nonrecovered patients with poststroke depression. Stroke. 1988;19(12):1491–6.
12. Starkstein SE, Robinson RG, Price TR. Comparison of cortical and subcortical lesions in the production of poststroke mood disorders. Brain. 1987;110(Pt 4):1045–59.
13. 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(3):794–802.
14. Morris PL, Robinson RG, Raphael B, Hopwood MJ. Lesion location and poststroke depression. J Neuropsychiatry Clin Neurosci. 1996;8(4):399–403.
15. 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(9224):122–6.
16. Shimoda K, Robinson RG. The relationship between poststroke depression and lesion location in long-term follow-up. Biol Psychiatry. 1999;45(2):187–92.
17. Narushima K, Kosier JT, Robinson RG. A reappraisal of poststroke depression, intra- and inter-hemispheric lesion location using meta-analysis. J Neuropsychiatry Clin Neurosci. 2003;15(4):422–30.
18. 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(7):785–9.
19. Pohjasvaara T, Vataja R, Leppavuori A, Kaste M, Erkinjuntti T. Depression is an independent predictor of poor long-term functional outcome post-stroke. Eur J Neurol. 2001;8(4):315–9.
20. Donnellan C, Hickey A, Hevey D, O'Neill D. Effect of mood symptoms on recovery one year after stroke. Int J Geriatr Psychiatry. 2010;25(12):1288–95.
21. Hackett ML, Anderson CS. Predictors of depression after stroke: a systematic review of observational studies. Stroke. 2005;36(10):2296–301.
22. 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(10):645–52.
23. Robinson RG, Bolla-Wilson K, Kaplan E, Lipsey JR, Price TR. Depression influences intellectual impairment in stroke patients. Br J Psychiatry. 1986;148:541–7.
24. Spalletta G, Guida G, De Angelis 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):1541–51.
25. Downhill Jr JE, Robinson RG. Longitudinal assessment of depression and cognitive impairment following stroke. J Nerv Ment Dis. 1994;182(8):425–31.
26. Morris PL, Robinson RG, Raphael B. Prevalence and course of depressive disorders in hospitalized stroke patients. Int J Psychiatry Med. 1990;20(4):349–64.

27. Starkstein SE, Robinson RG, Price TR. Comparison of patients with and without poststroke major depression matched for size and location of lesion. Arch Gen Psychiatry. 1988;45(3):247–52.
28. Bolla-Wilson K, Robinson RG, Starkstein SE, Boston J, Price TR. Lateralization of dementia of depression in stroke patients. Am J Psychiatry. 1989;146(5):627–34.
29. Kimura M, Robinson RG, Kosier JT. Treatment of cognitive impairment after poststroke depression : a double-blind treatment trial. Stroke. 2000;31:1482–6.
30. Narushima K, Chan KL, Kosier JT, Robinson RG. Does cognitive recovery after treatment of poststroke depression last? A 2-year follow-up of cognitive function associated with post-stroke depression. Am J Psychiatry. 2003;160(6):1157–62.
31. Morris PL, Robinson RG, Samuels J. Depression, introversion and mortality following stroke. Aust N Z J Psychiatry. 1993;27(3):443–9.
32. House A, Knapp P, Bamford J, Vail A. Mortality at 12 and 24 months after stroke may be associated with depressive symptoms at 1 month. Stroke. 2001;32(3):696–701.
33. Williams LS, Ghose SS, Swindle RW. Depression and other mental health diagnoses increase mortality risk after ischemic stroke. Am J Psychiatry. 2004;161(6):1090–5.
34. Lipsey JR, Robinson RG, Pearlson GD, Rao K, Price TR. Nortriptyline treatment of post-stroke depression: a double-blind study. Lancet. 1984;1(8372):297–300.
35. Andersen G, Vestergaard K, Lauritzen L. Effective treatment of poststroke depression with the selective serotonin reuptake inhibitor citalopram. Stroke. 1994;25(6):1099–104.
36. Robinson RG, Schultz SK, Castillo C, Kopel T, Kosier JT, Newman RM, 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(3):351–9.
37. Rampello L, Alvano A, Chiechio S, Raffaele R, Vecchio I, Malaguarnera M. An evaluation of efficacy and safety of reboxetine in elderly patients affected by “retarded” post-stroke depression. A random, placebo-controlled study. Arch Gerontol Geriatr. 2005;40(3):275–85.
38. Chen Y, Guo JJ, Zhan S, Patel NC. Treatment effects of antidepressants in patients with post-stroke depression: a meta-analysis. Ann Pharmacother. 2006;40(12):2115–22.
39. Hackett ML, Anderson CS, House AO. Interventions for treating depression after stroke. Cochrane Database Syst Rev. 2004;3:1–48.
40. Masand P, Murray GB, Pickett P. Psychostimulants in post-stroke depression. J Neuropsychiatry Clin Neurosci. 1991;3(1):23–7.
41. Lazarus LW, Moberg PJ, Langsley PR, Lingam VR. Methylphenidate and nortriptyline in the treatment of poststroke depression: a retrospective comparison. Arch Phys Med Rehabil. 1994;75(4):403–6.
42. Grade C, Redford B, Chrostowski J, Toussaint L, Blackwell B. Methylphenidate in early post-stroke recovery: a double-blind, placebo-controlled study. Arch Phys Med Rehabil. 1998; 79(9):1047–50.
43. Lincoln NB, Flannaghan T. Cognitive behavioral psychotherapy for depression following stroke: a randomized controlled trial. Stroke. 2003;34(1):111–5.
44. Williams LS, Kroenke K, Bakas T, Plue LD, Brizendine E, Tu W, et al. Care management of poststroke depression: a randomized, controlled trial. Stroke. 2007;38(3):998–1003.
45. Joubert J, Joubert L, Reid C, Barton D, Cumming T, Mitchell P, et al. The positive effect of integrated care on depressive symptoms in stroke survivors. Cerebrovas Dis. 199;26(2).
46. Jorge RE, Robinson RG, Tateno A, Narushima K, Acion L, Moser D, et al. Repetitive transcranial magnetic stimulation as treatment of poststroke depression: a preliminary study. Biol Psychiatry. 2004;55(4):398–405.
47. Kim D-Y, Lim J-Y, Kang EK, You DS, Oh M-K, Oh B-M, et al. Effect of transcranial direct current stimulation on motor recovery in patients with subacute stroke. Am J Phys Med Rehabil. 2010;89(11):879–86.
48. Murray GB, Shea V, Conn DK. Electroconvulsive therapy for poststroke depression. J Clin Psychiatry. 1986;47(5):258–60.
49. Palomaki H, Kaste M, Berg A, Lonnqvist R, Lonnqvist J, Lehtihalmes M, et al. Prevention of poststroke depression: 1 year randomised placebo controlled double blind trial of mianserin with 6 month follow up after therapy. J Neurol Neurosurg Psychiatry. 1999;66(4):490–4.

50. 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(3):216–21.
51. Almeida OP, Waterreus A, Hankey GJ. Preventing depression after stroke: results from a randomized placebo-controlled trial. J Clin Psychiatry. 2006;67(7):1104–9.
52. Robinson RG, Jorge R, Moser D, Acion L, Solodkin A, Small SL, et al. Escitalopram and problem-solving therapy for prevention of poststroke depression: a randomized controlled trial. JAMA. 2008;28:2391–400.
53. Narushima K, Kosier JT, Robinson RG. Preventing poststroke depression: a 12-week double-blind randomized treatment trial and 21-month follow-up. J Nerv Ment Dis. 2002; 190(5):296–303.
54. Jorge RE, Robinson RG, Arndt S, Starkstein S. Mortality and poststroke depression: a placebo-controlled trial of antidepressants. Am J Psychiatry. 2003;160(10):1823–9.
55. Yi ZM, Liu F, Zhai SD. Fluoxetine for the prophylaxis of poststroke depression in patients with stroke: a meta-analysis. Int J Clin Pract. 2010;64(9):1310–7.
56. Anderson CS, Hackett ML, House A. Interventions for preventing depression after stroke. Cochrane Database Syst Rev. 2004;2:1–55.
57. Ramasubbu R. Therapy for prevention of post-stroke depression. Expert Opin Pharmacother. 2011;12(14):2177–87.

Chapter 4
Mania

Catarina O. Santos, Lara Caeiro, and José M. Ferro

Abstract Mania is a rare consequence of stroke, and according to the sparse published information, it is difficult to describe its demographic, clinical, and prognostic characteristics. We defined poststroke mania as a mood disorder characterized by an elevated, expansive, or irritable mood, pressured speech, distractibility, grandiosity, hyperactivity, and disinhibition. The diagnosis is based on DSM-IV-TR and Krauthammer and Klerman criteria. A recent systematic review of all cases of poststroke mania allows the collection of 49 studies describing 74 cases. Although there are some cases of mania after left-sided strokes, the majority of cases referred to right-sided lesions. These lesions were more frequently located in the area of orbitofrontal circuit that includes the orbitofrontal cortex, the basotemporal region, the thalamus, and the caudate nucleus. This circuit is crucial for mood regulation and social behavior. The typical patient with mania associated to stroke was a male, without personal/family history of psychiatric disorder, with at least one vascular risk factor, without subcortical atrophy, and with a right cerebral infarct. Similar to primary mania, treatment consists of mood stabilizers and typical or atypical antipsychotics. Mania has high potential disruptive impact after stroke, during the acute care and in the post-acute and rehabilitation phase.

C.O. Santos, PsyD (✉)
Faculty of Medicine, Institute of Molecular Medicine,
University of Lisbon, Lisbon, Portugal

Department of Neurosciences, Serviço de Neurologia (piso 6),
Hospital de Santa Maria CEEM,
Av. Professor Egas Moniz, 1649-035 Lisbon, Portugal
e-mail: acosta@fm.ul.pt

L. Caeiro, PsyD • J.M. Ferro, MD, PhD
Faculty of Medicine, Institute of Molecular Medicine,
University of Lisbon, Lisbon, Portugal

Department of Neurosciences, Neurology Service,
Hospital de Santa Maria, Lisbon, Portugal

J.M. Ferro (ed.), *Neuropsychiatric Symptoms of Cerebrovascular Diseases*,
Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-1-4471-2428-3_4, © Springer-Verlag London 2013

Keywords Poststroke mania • Mood disorder, DSM-IV-TR • Elevated, expansive, or irritable mood • Increased rate or amount of speech • Overactivity • Flight of ideas • Grandiose ideation • Orbitofrontal circuit • Mood stabilizers • Antipsychotics

Definition

Mania is the main symptom for the diagnosis of bipolar disorder, a mood disorder with a prevalence in community studies between 0.4 and 1.6 % and which causes a significant personal and social impairment [1]. Mania is characterized by affective disturbances, such as an elevated, expansive, or irritable mood; changes in speech, with an increased rate or amount; disturbances in language thought and content, with flight of ideas, grandiose ideation, and lack of insight; and behavioral disturbances characterized by overactivity and social disinhibition [1–4]. Primary mania refers to the psychiatric condition itself without a documented brain lesion, and secondary mania describes the manic symptoms caused by neurological, metabolic, or toxic disorders [5]. The term secondary mania was introduced by Krauthammer and Klerman in 1978. Starkstein et al. did not find significant differences between primary and secondary mania clinical profiles [6].

DSM-IV-TR presents the criteria for mood disorder due to a general condition. These criteria should be used for the diagnosis of depression and/or mania after stroke. In Table 4.1, we present the DSM-IV-TR criteria and also the Krauthammer and Klerman criteria for secondary mania.

The literature of mania after stroke is composed predominantly by case reports, small case series, and a few systematic studies. Although mania can be very disrupting during stroke hospitalization and recovery, its low prevalence limits the description of its clinical, demographic, and prognostic features and the identification of

Table 4.1 Diagnostic criteria for poststroke mania

1. DSM-IV-TR diagnostic criteria for 293.83 mood disorder due to stroke with manic features
A. A prominent and persistent disturbance in mood predominates in the clinical picture and is characterized by elevated, expansive, or irritable mood
B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a stroke
C. The disturbance is not accounted for by another mental disorder
D. The disturbance does not occur exclusively during the course of a delirium
E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
2. Krauthammer and Klerman [5] criteria for secondary mania
A. Symptoms duration of at least 1 week
B. Presence of elevated or irritable mood
C. Presence of at least two of the following symptoms: hyperactivity, pressured speech, flight of ideas, grandiosity, decreased sleep, distractibility, and lack of judgment
D. There was no previous history of manic depressive or other affective illness and symptoms of a confusional state (such as delirium) co-occurring with the mania

evidence-based strategies for dealing with it. Recently, we performed a systematic review of all cases of mania associated with stroke, published until December 2010, aiming to answer to those questions, in order to increase the robustness of the evidence of this neuropsychiatric complication of stroke [7].

We included studies that were required to fulfill the following inclusion criteria: (1) all cases of mania associated with stroke; (2) patients with diagnosis of cerebral infarct (INF), intracerebral hemorrhage (ICH), or subarachnoid hemorrhage (SAH); and (3) adult patients (≥18 years old). From 265 abstracts identified by electronic search, reference lists of the studies collected, and handbooks of neuropsychiatry of stroke, 139 were potentially relevant, of which 49 studies (35 %) met the inclusion criteria. These 49 studies describing 74 cases of poststroke mania were included in the first analysis to determine the most important characteristics of those cases. In a second analysis, from those 49 studies, we selected 32 studies (49 cases), corresponding to cases in whom an explicit temporal and causal relationship between manic symptoms and stroke was documented. The results and conclusions of the systematic review will be discussed throughout this chapter along with data from previous studies and case reports.

Epidemiology

Mania is a rare consequence after stroke and its prevalence seems to be around 1 % [8]. In large community-based studies, such as the Oxfordshire Community Stroke Project and the Perth Community Stroke Study, no cases of poststroke mania were found [9, 10].

In 1922, Babinski first associated a right hemispherical lesion with euphoria, indifference, and anosognosia [11]. Since then, nearly a hundred cases have been described. In our systematic review, we had confirmed the rarity of poststroke mania, identifying only 74 cases of adult stroke patients with mania symptoms published since the 1970s (Table 4.2).

Cohen and Niska described a case of a 59-year-old man, who 2 years after a right temporal hematoma presented manic symptoms, compatible with secondary mania criteria [58]. Jampala and Abrams reported the cases of a 52-year-old man and a 40-year-old man admitted with mania after a left and right hemispherical stroke lesion, respectively [57]. After a review of the cases with mania and the type and location of intracerebral lesions, the authors questioned the association between mania and right lesions. One year later, Cummings and Mendez strengthened the relationship between right hemispheric strokes and mania, while presenting two patients with lesions in the right thalamus, followed by mania [56].

In successive studies, Starkstein et al. collected the highest number of poststroke mania patients. Until 1987, the authors found only three patients with mania among 700 stroke patients [8]. In 1987, they included 11 consecutive patients in a group of secondary mania, four of whom had stroke [6]. The same authors performed a series of studies about mania and depression and collected 17 patients with mania, of whom 9 with a stroke [61].

Table 4.2 Studies ($n=49$) and cases ($n=74$) included in systematic review

	Date	Type of study	Diagnostic criteria	Assessment	Cases	HPPD	HFPD	Laterality
Semiz et al. [12]	2010	Case study	Krauthammer and Klerman	Clinical + scale	1			R
Duggal and Singh [13]	2009	Case study	DSM	Clinical	1	1		L
López et al. [14]	2009	Case study	unknown	Clinical	1			R
Havle et al. [15]	2009	Case study	DSM	Clinical	1			unknown
Rocha et al. [16]	2008	Case study	DSM	Clinical + scale	1		unknown	R
Dervaux and Levasseur [17]	2008	Case study	DSM	Clinical	1			R
Rocha et al. [18]	2008	Case study	DSM	Clinical + scale	1			R
Nagaratnam et al. [19]	2006	Case series	DSM	Clinical	2		unknown	L; R
Goyal et al. [20]	2006	Case study	ICD	Clinical + scale	1		1	R
Mimura et al. [21]	2005	Case study	unknown	Clinical + scale	1	1		R
Celik et al. [22]	2004	Case study	unknown	Clinical + scale	1			R
Huffman and Stern [23]	2003	Case study	unknown	Clinical	1	1	1	R
Gafoor and O'Keane [24]	2003	Case series	unknown	Clinical	1		unknown	R
Colenda [25]	2002	Case study	unknown	Clinical	1		unknown	R
Benke et al. [26]	2002	Case study	unknown	Clinical + scale	1			B
Caeiro et al. [27]	2002	Cohort	DSM	Clinical + scale	1			B
Inzelberg et al. [28]	2001	Case study	DSM	Clinical	1			R
Franco and Chughtai [29]	2000	Case study	unknown	Clinical	1			R
Leibson [30]	2000	Case study	unknown	Clinical + scale	1			R
Fenn and George [31]	1999	Case study	unknown	Clinical	1			L
De León et al. [32]	1999	Case study	unknown	Clinical	1		unknown	R
Börnke et al. [33]	1998	Case study	DSM	Clinical	1			R
Kumar et al. [34]	1997	Case study	ICD	Clinical	1			B
Kulisevsky and Berthier [35]	1997	Case study	DSM	Clinical + scale	1			R
Liu et al. [36]	1996	Case study	DSM	clinical	1			L
Trillet et al. [37]	1995	Case study	unknown	Clinical	1			L

Kulisevsky et al. [38]	1995	Case study	unknown	Clinical + scale	1			R
Tohen et al. [39]	1994	Cohort	unknown	Clinical	7	unknown	unknown	1L; 6?
Kumar and Kuruvilla [40]	1994	Case study	DSM	Clinical	1			R
Berthier and Kulisevsky [41]	1993	Case study	DSM	Clinical + scale	1			R
Turecki et al. [42]	1993	Case study	unknown	Clinical	1			L
Kulisevsky et al. [43]	1993	Case study	DSM	Clinical + scale	1			R
Berthier [44]	1992	Case study	unknown	Clinical + scale	1			R
Starkstein et al. [45]	1991	Cohort	DSM	Clinical + scale	10		unknown	10R
Blackwell [46]	1991	Case study	unknown	Clinical	1	unknown	unknown	R
Fawcett [47]	1991	Case study	unknown	unknown	1	unknown	unknown	R
Snowdon [48]	1991	Retrospective	ICD	unknown	1	unknown		unknown
Drake et al. [49]	1990	Case series	unknown	unknown	2			L; R
Starkstein et al. [50]	1990	Cohort	DSM	Clinical + scale	5			5R
Danel et al. [51]	1989	Case series	unknown	Clinical	1		unknown	R
Mendez [52]	1989	Case series	unknown	Clinical	2	unknown	unknown	L; R
Stone [53]	1989	Retrospective	unknown	unknown	2	unknown	unknown	L; R
Goldschmidt et al. [54]	1988	Case study	unknown	Clinical + scale	1		unknown	B
Bogousslavsky et al. [55]	1988	Case study	unknown	Clinical	1		unknown	R
Cummings and Mendez [56]	1984	Case series	DSM	Clinical	2	1		2R
Jampala and Abrams [57]	1983	Case series	Krauthammer and Klerman	Clinical	2		1	L; R
Cohen and Niska [58]	1980	Case study	Krauthammer and Klerman	Clinical	1			R
Shulman and Post [59]	1980	Retrospective	unknown	unknown	1	unknown	unknown	unknown
Rosenbaum and Barry [60]	1975	Case study	unknown	Clinical	1		unknown	R
					74	4	3	50R, 11L, 4B

Caeiro et al., in a study of neuropsychiatric disturbances in consecutive acute stroke patients, investigated the presence of mania, using the Mania Rating Scale (MRS) [27]. MRS is a widely used mania scale with 11 items, in which mania is operationally defined if patients score at least 12 points [62]. Of the 188 patients, with a mean age of 56.9 and a mean of 6.6 years of education, only one (0.5 %) fulfilled the criteria for mania. This patient presented emotional and behavioral changes characteristic of a manic episode, such as an elevated mood, talkativeness, overactivity, and denial (Case 1).

Celik et al. described a case of a 69-year-old woman with vascular risk factors that after a right temporoparietal stroke had an acute change in her behavior with manic symptoms [22]. Nagaratnam et al. studied two patients with secondary mania following left- and right-sided infarctions [19]. Rocha et al. followed a 47-year-old woman without personal or familiar history of psychiatric disorder and with a right medial frontal lobe, which seems to cause elated mood, irritability, agitation, pressured speech, grandiosity, insomnia, and denial [18].

Mania can manifest in the acute phase but there are reported cases of mania until 2 years after stroke [8]. In fact, the majority of mania cases appeared in the first days after stroke, with 53 % immediately after stroke, 23 % during the first month after stroke, and 23 % after this first month. This delayed presentation may cause difficulties in the identification of manic symptoms.

As stated earlier, the clinical profile of poststroke mania is very similar to the symptom profile of primary mania. We found that the first symptom of mania associated with stroke is the presence of elevated mood, which in some cases alternates with an irritable mood. Other frequent symptoms are an increased rate or amount of speech, insomnia, and agitation. We also counted the number of core symptoms of mania and found that the majority of the patients presented five or more symptoms of mania. The difference between primary and secondary mania seems to be the symptom duration, which is longer in secondary mania probably due to the presence of other comorbidities and the usage of lower doses of antimanic agents.

Risk Factors

Since the first reported cases, the association between poststroke mania and right-sided lesions has been the most quoted risk factor for poststroke mania. Indeed, the majority of patients described in case studies and small case series had right-sided lesions. However, this association has been challenged by the description of cases of mania following left hemispheric lesions [31, 36, 42, 57]. Of the 74 cases of mania and stroke, 50 (68 %) had right-sided lesions, while only 11 (15 %) presented left-sided lesions, a difference which reaches statistical significance (Table 4.3).

With respect to stroke location, almost all cases refer to lesions in the right corticolimbic pathways, an integrated system that includes the limbic system and the

Table 4.3 Description of the 74 cases of stroke and mania

Variables		*N*=74	*p*
Age	<65	35	0.19*
	≥65	22	
	Range (years)	27–91	
	No information	17	
Gender	Female	17	0.00*
	Male	44	
	No information	13	
History of personal psychiatric disorder	Yes	4	0.00*
	No	55	
	No information	15	
Family history of psychiatric disorder	Yes	3	0.00*
	No	38	
	No information	33	
Vascular risk factors	Yes	26	0.00*
	No	7	
	No information	41	
Stroke type	Cerebral Infarct	56	0.00**
	Intracerebral hemorrhage	7	
	Subarachnoid hemorrhage	9	
	No information	2	
Stroke laterality	Right	50	0.00**
	Left	11	
	Bilateral	4	
	No information	9	
Subcortical atrophy	Yes	2	0.00*
	No	36	
	No information	36	
Relation with stroke	Causal and temporal relationship	49	0.00**
	Secondary to treatment	4	
	Previous affective disorder[a]	4	
	Unknown	17	

*Binomial test for proportions; **chi-square test for proportions

[a]Three cases of depression and one case of cyclothymia

basal ganglia. The orbitofrontal circuit is a complex functional network that includes the orbitofrontal cortex, the basotemporal region, the thalamus, and the caudate nucleus. This circuit is crucial for mood regulation and social behavior [6, 19, 26]. Basotemporal and orbitofrontal lesions are frequently associated with mood and behavior changes such as disinhibition, lack of spontaneity and affective control, irritability and aggression, decreased social sensitivity, and confabulation. Secondary mania caused by degenerative, infectious, and traumatic disorders was also frequently related with lesions in basal ganglia [6].

Dysregulation at this level results in decreased prefrontal modulation and mood changes expressed as manic symptoms.

Imaging studies and the systematic review of all the cases evidenced that the majority of patients had large middle cerebral artery infarctions, with lesions in the basal ganglia and frontal and temporal lobes [7]. Blumberg et al. found a decreased activation on the right rostral and orbital prefrontal cortex in patients with mania [63].

Cases of mania with left-sided stroke could be explained by a disconnection between left medial and anterior thalamus with the frontal lobe, which could cause a frontal dysfunction. In this situation the frontal lobes induce an inhibitory effect on the limbic system, which ceases to have its modulating role [24].

Mania could also be related with a biochemical dysfunction caused by right hemisphere stroke, which increases the level of brain serotonin. This mechanism seems to occur in mania caused by antidepressant therapy [13, 45]. Mood-stabilizing drugs seem to be effective in the treatment of manic symptoms due to their effect on serotonin system [18].

Establishing the causal relationship between stroke and mania has also been based on other factors than right-sided lesions, namely, a predisposing genetic factor and/or the presence of subcortical brain atrophy. Starkstein et al. found that stroke patients with mania had more subcortical atrophy than the remaining stroke patients matched by lesion size and location [6]. Krauthammer and Klerman excluded patients with previous affective disorder in the diagnosis of secondary mania [5]. In an epidemiological study about geriatric mania, the authors found that the majority of patients did not have personal or family history of affective disorder [64]. However, in our systematic review, we did not find evidence in favor of these two factors. The majority of poststroke mania cases did not have history of family or personal psychiatric disorder or subcortical atrophy (Table 4.3).

The presence of vascular risk factors, such as hypertension and diabetes, is another factor that characterizes late-onset mania [22, 65]. Fujikawa found a significant association between silent cerebral infarcts and mood disorders in elderly [66]. The desirable control of vascular risk factors has impact not only on the prevalence of stroke and other cardiovascular diseases but also on the prevalence of poststroke consequences, such as mania.

Looking at the range and average age of the poststroke mania cases reported in the literature, we observe that the onset of mania occurs much later in life than that what is characteristic of primary mania. The more recent published exception is a case of mania in a 27-year-old female with a right cerebral infarct and heart surgery 1 year and 6 months before, respectively, and without family or personal history of affective disorder [12]. Cassidy and Carroll suggested a cutoff of 47 years old to distinguish between early-onset and late-onset mania [65].

In the systematic review of poststroke mania, we found that the typical patient with mania associated to stroke was a male, without personal/family history of psychiatric disorder, with at least one vascular risk factor, without subcortical atrophy, and with a right cerebral infarct.

Outcome

The follow-up of these patients was described in a minority of cases. Some patients had recurrent episodes of mania or presented hypomania. We could not confirm that about 30 % of patients may develop a bipolar disorder [61].

Management

The mood, cognitive, and behavioral changes that characterize mania can have a strong impact in stroke management and rehabilitation. In this context, the treatment of manic symptoms should be similar to that which is recommended for primary mania. Treatment consists of mood stabilizers and typical or atypical antipsychotics [13, 18, 67, 68]. These drugs should be prescribed to poststroke mania patients with precautions for three main reasons: older patients have a highly sensitivity to psychotropic drugs, the presence of stroke itself could change their efficacy, and stroke patients had frequently other medical comorbidities [68]. Dosages should be lower and increased slower than in primary mania.

Lithium was frequently used with favorable results, but its use is controversial in cases with cerebral lesions because the stroke itself may alter the sensitivity to lithium neurotoxicity [6, 42, 69]. Anticonvulsant mood stabilizers, such as carbamazepine and valproic acid, were effective in other patients, with the advantage of also preventing poststroke seizures [18]. Antipsychotics were used in cases of severe mania with psychotic symptoms, and in recent years atypical antipsychotics have been preferred because they had comparatively less side effects. Antipsychotics are associated with the emergence of extrapyramidal symptoms and parkinsonian syndromes [25]. Other relevant side effects of neuroleptics include drowsiness, increased risk of falls, prolonged QT interval, cardiac arrhythmias including sudden death, increased risk of cardiovascular events including stroke, decreased threshold for seizures, and weight gain. Benzodiazepines were also used as adjunctive treatment for hyperactivity and insomnia [17].

Different neurotransmitters are involved in the orbitofrontal circuit and their excess seems to mediate the relation between and affective disorder. In addition to serotonin, other neurotransmitters could be involved in poststroke mania, what could explain the diversity of therapeutic response to different substances [19].

In systematic review, we have data on the treatment for only 47 (64 %) of the 74 cases included. Mood stabilizers (lithium, carbamazepine, and valproic acid) were used in 62 %, typical antipsychotics (haloperidol) in 32 %, atypical antipsychotics (olanzapine, risperidone) in 19 %, and benzodiazepines (diazepam, lorazepam) in 13 %. We found three cases of stroke patients with depression that developed mania after antidepressant treatment [33, 36, 42]. Data on dosages, duration of

the treatment, and efficacy were so scarce that it was impossible to provide any meaningful results.

The lack of placebo-controlled and double-blind trials and the marked differences in efficacy between the same or similar drugs in different cases reinforce doubts about the role of pharmacological treatment in the resolution of symptoms and impede the definition of targeted and evidence-based treatment guidelines [6, 17, 68].

Conclusion

Although rare, mania has high potential disruptive impact after stroke, during the acute care and later, in the post-acute and rehabilitation phase. A manic patient has difficulty in understanding why he is in hospital. He resists treatment and rehabilitation strategies, denying and depreciating the disease symptoms. Manic symptoms could be a part of a clinical profile characterized by other neuropsychiatric changes, such as delirium, denial, post-traumatic stress disorder, psychotic disorders, and personality changes due to stroke. We have carefully examined the patient in order to establish the differential diagnosis with these other conditions, because all of them have common symptoms which may mislead the diagnosis. Only a detailed psychiatric/psychological assessment can detect not only the more frequent neuropsychiatric poststroke changes but other rare consequences, such as mania.

Poststroke mania should also be considered in any manic patient who presents concomitant neurological focal deficits and is older than expected for the onset of primary mania. As stressed above, typically these patients are male, without psychiatric antecedents or subcortical atrophy, with vascular risk factors and right infarct.

Case 1: Mania in the Acute Phase of Subarachnoid Hemorrhage

A 65-year-old female, without vascular risk factors and no personal or family history of mood disorders, was admitted because of acute onset of severe headache, vomiting, and brief loss of consciousness. She was alert but somnolent, oriented, and collaborative, with neck stiffness and left hemiparesis (Hunt and Hess' grade 2). CT scan revealed subarachnoid hemorrhage with hematic densities in the basal cisterns, posterior fossa, third and fourth ventricles, and left lateral ventricle, with moderate hydrocephalus (Fig. 4.1). Angiography revealed an intracranial left vertebral artery dissection.

Psychiatric/psychological assessment was performed on the third day of hospitalization. The patient was oriented, but she presented attention and short-term memory mild defects. In the Mania Rating Scale, she presented an elevated mood, with euphoria, elation, and ecstasy (item 1). This period of intense self-satisfaction and optimism alternates with anger (item 9). She

presented a mild overactivity (item 2), a severe increased rate or amount of speech (item 6), and hyper-religiosity (item 8). The patient reported also a decreased need for sleep (item 4) and eating. She admitted a change in his behavior but denied his neurological disease and psychiatric disturbances (item 11), alluding that there was nothing really wrong with her and presenting a carefree, cheerful, and jovial approach to life, with coolness behavior. She scored 12 on Mania Rating Scale. Her behavioral changes were treated with diazepam (5–20 mg). Thirteen days after the first psychiatric assessment, the manic symptoms had regressed, remained only a hyper-religiosity and a decreased need for sleep. The patient was discharge on the 21st day with a modified Rankin Scale score of 1.

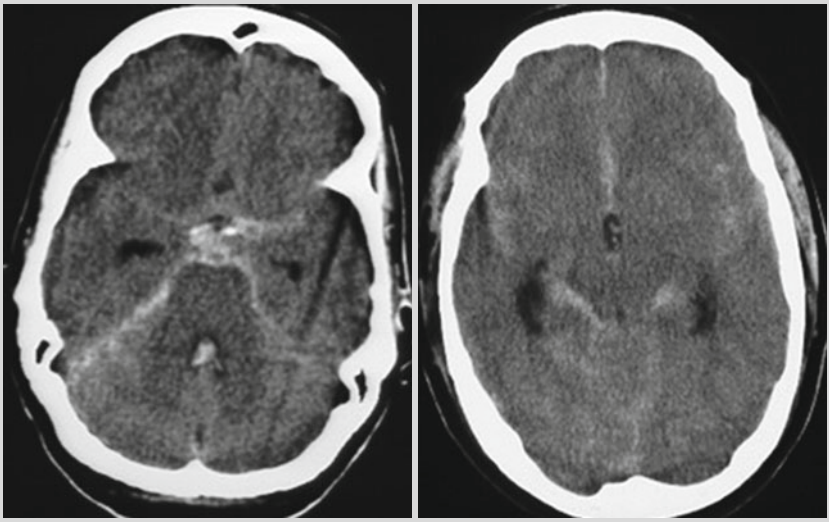


Fig. 4.1 Acute brain CT showing typical features of generalized acute subarachnoid hemorrhage

Case 2: Bipolar Disorder After Stroke

A 68-year-old male, active University Professor, with diabetes, hypertension, and coronary heart disease suffered a minor left hemispheric deep parietal ischemic stroke (Fig. 4.2). He had anomic aphasia, alexia with agraphia, and a slight distal upper limb paresis. No cardiac cause of embolism was detected, and apart from <50 % ipsilateral carotid stenosis, no other abnormal results were found in a comprehensive workup in search of the cause of his stroke. He recovered completely and returned to his previous academic and social

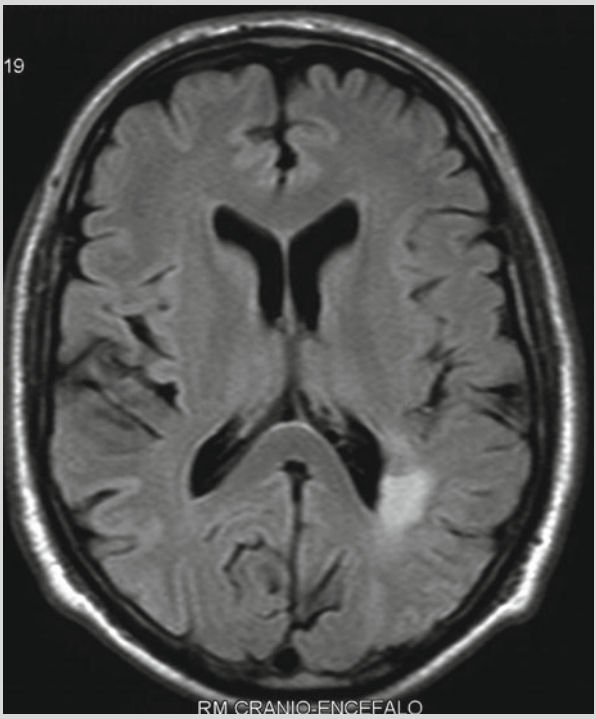


Fig. 4.2 DWI MR showing subcortical left parietal infarct

activities. Two months later he had a fist hypomanic episode characterized by multiple and grandiose plans, optimism, and decreased sleep, which was shortly followed by a prolonged major depressive episode, during which the patient had very depressed mood, pessimism, and decreased energy, avoiding social contacts and staying in bed for prolonged periods. Except for what could be judged retrospectively as a hyperthymic temperament, he had no previous psychiatric history. During the next 2 years, he alternated depressive and manic episodes. Although the patient complained mainly of his depressive symptoms, manic episodes were particularly disturbing because of overactivity, engagement in multiple commitments, decreased sleep, and excessive spending including traveling to foreign countries. Depressive episodes were treated with venlafaxine and manic episodes controlled with haloperidol, although the patient frequently missed medical appointments during these periods. The clinical condition was finally stabilized with lithium and lamotrigine.

References

1. American Psychiatric Association. Mood disorders. In: Diagnostic and statistical manual of mental disorders. 4th ed, text revision. Washington, D.C.: American Psychiatric Association; 2002. p. 345–428.
2. Ferro JM, Caeiro L, Santos C. Poststroke emotional and behavior impairment: a narrative review. Cerebrovasc Dis. 2009;27 Suppl 1:197–203.
3. Sadock BJ, Sadock VA. Mood disorders. In: Sadock BJ, Sadock VA, editors. Kaplan and Sadock's synopsis of psychiatry. Behavioural sciences/clinical psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2003. p. 534–72.
4. Vuilleumier P, Ghika-Schmid F, Bogousslavsky J, Assal G, Regli F. Persistent recurrence of hypomania and prosoaffective agnosia in a patient with right thalamic infarct. Neuropsychiatry Neuropsychol Behav Neurol. 1998;11:40–4.
5. Krauthammer C, Klerman G. Secondary mania. Manic syndromes associated with antecedent physical illness or drugs. Arch Gen Psychiatry. 1978;35:1333–9.
6. Starkstein SE, Pearlson GD, Boston JD, Robinson RG. Mania after brain injury. A controlled study of causative factors. Arch Neurol. 1987;44:1069–73.
7. Santos CO, Caeiro L, Ferro JM, Figueira ML. Mania and stroke: a systematic review. Cerebrovasc Dis. 2011;32:11–21.
8. Starkstein SE, Boston JD, Robinson RG. Mechanisms of mania after brain injury. 12 case reports and review of the literature. J Nerv Ment Dis. 1988;176:87–100.
9. House A, Dennis M, Mogridge L, Warlow C, Hawton K, Jones L. Mood disorders in the year after first stroke. Br J Psychiatry. 1991;158:83–92.
10. 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.
11. Babinski J. Réflexes de défense. Brain. 1922;45:149–84.
12. Semiz M, Kavakçı O, Yontar G, Yıldırım O. Case of organic mania associated with stroke and open heart surgery. Psychiatry Clin Neurosci. 2010;64:587.
13. Duggal HS, Singh I. New-onset vascular mania in a patient with chronic depression. J Neuropsychiatry Clin Neurosci. 2009;21:480–2.
14. López JD, Araúxo A, Páramo M. Late-onset bipolar disorder following right thalamic injury. Actas Esp Psiquiatr. 2009;37:233–5.
15. Havle N, Ilnem MC, Yener F, Dayan C. Secondary mania after brain stem infarct. Anadolu Psikiyatri Dergisi. 2009;10:163–4.
16. Rocha FF, Carneiro JG, Pereira Pde A, Correa H, Teixeira AL. Poststroke manic symptoms: an unusual neuropsychiatric condition. Rev Bras Psiquiatr. 2008;30:173–4.
17. Dervaux A, Levasseur M. Risperidone and valproate for mania following stroke. J Neuropsychiatry Clin Neurosci. 2008;20:247.
18. Rocha FF, Correa H, Teixeira AL. A successful outcome with valproic acid in a case of mania secondary to stroke of the right frontal lobe. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:587–8.
19. Nagaratnam N, Wong KK, Patel I. Secondary mania of vascular origin in elderly patients: a report of two clinical cases. Arch Gerontol Geriatr. 2006;43:223–32.
20. Goyal R, Sameer M, Chandrasekaran R. Mania secondary to right-sided stroke-responsive to olanzapine. Gen Hosp Psychiatry. 2006;28:262–3.
21. Mimura M, Nakagome K, Hirashima N, et al. Left frontotemporal hyperperfusion in a patient with post-stroke mania. Psychiatry Res. 2005;139:263–7.
22. Celik Y, Erdogan E, Tuglu C, Utku U. Poststroke mania in late life due to right temporoparietal infarction. Psychiatry Clin Neurosci. 2004;58:446–7.

23. Huffman J, Stern TA. Acute psychiatric manifestations of stroke: a clinical case conference. Psychosomatics. 2003;44:65–75.
24. Gafoor R, O'Keane V. Three case reports of secondary mania: evidence supporting a right frontotemporal locus. Eur Psychiatry. 2003;18:32–3.
25. Colenda CC. Mania in late life. The challenges of treating older adults. Geriatrics. 2002;57(50):53–4.
26. Benke T, Kurzthaler I, Schmidauer C, Moncayo R, Donnemiller E. Mania caused by a diencephalic lesion. Neuropsychologia. 2002;40:245–52.
27. Caeiro L, Ferro JM, Albuquerque R, Figueira ML. Mania no AVC agudo. Sinapse. 2002;2:90.
28. Inzelberg R, Nisipeanu P, Joel D, Sarkantyus M, Carasso RL. Acute mania and hemichorea. Clin Neuropharmacol. 2001;24:300–3.
29. Franco K, Chughtai H. Steroid-induced mania in poststroke patient involving the right basal ganglion and right frontal region. Psychosomatics. 2000;41:446–7.
30. Leibson E. Anosognosia and mania associated with right thalamic haemorrhage. J Neurol Neurosurg Psychiatry. 2000;68:107–8.
31. Fenn D, George K. Post-stroke mania late in life involving the left hemisphere. Aust N Z J Psychiatry. 1999;33:598–600.
32. De León OA, Furmaga KM, Kaltsounis J. Mirtazapine-induced mania in a case of post-stroke depression. J Neuropsychiatry Clin Neurosci. 1999;11:115–6.
33. Börnke C, Postert T, Przuntek H, Büttner T. Acute mania due to a right hemisphere infarction. Eur J Neurol. 1998;5:407–9.
34. Kumar S, Jacobson RR, Sathananthan K. Seasonal cyclothymia to seasonal bipolar affective disorder: a double switch after stroke. J Neurol Neurosurg Psychiatry. 1997;63:796–7.
35. Kulisevsky J, Berthier ML. A new case of fluoxetine-induced mania in post-stroke depression. Clin Neuropharmacol. 1997;20:180–1.
36. Liu CY, Wang SJ, Fuh JL, Yang YY, Liu HC. Bipolar disorder following a stroke involving the left hemisphere. Aust N Z J Psychiatry. 1996;30:688–91.
37. Trillet M, Vighetto A, Croisile B, Charles N, Aimard G. Hemiballismus with logorrhea and thymo-affective disinhibition caused by hematoma of the left subthalamic nucleus. Rev Neurol (Paris). 1995;151:416–9.
38. Kulisevsky J, Avila A, Berthier ML. Bipolar affective disorder and unilateral parkinsonism after a brainstem infarction. Mov Disord. 1995;10:799–802.
39. Tohen M, Shulman KI, Satlin A. First-episode mania in late life. Am J Psychiatry. 1994;151:130–2.
40. Kumar KR, Kuruvilla K. Secondary mania following stroke. Indian J Psychiatry. 1994;36:33.
41. Berthier ML, Kulisevsky J. Fluoxetine-induced mania in a patient with post-stroke depression. Br J Psychiatry. 1993;163:698–9.
42. Turecki G, Mari Jde J, Del Porto JÁ. Bipolar disorder following a left basal-ganglia stroke. Br J Psychiatry. 1993;163:690.
43. Kulisevsky J, Berthier ML, Pujol J. Hemiballismus and secondary mania following a right thalamic infarction. Neurology. 1993;43:1422–4.
44. Berthier ML. Post-stroke rapid cycling bipolar affective disorder. Br J Psychiatry. 1992;160:283.
45. Starkstein SE, Fedoroff P, Berthier ML, Robinson RG. Manic-depressive and pure manic states after brain lesions. Biol Psychiatry. 1991;29:149–58.
46. Blackwell MJ. Rapid-cycling manic-depressive illness following subarachnoid haemorrhage. Br J Psychiatry. 1991;159:279–80.
47. Fawcett RG. Cerebral infarct presenting as mania. J Clin Psychiatry. 1991;52:352–3.
48. Snowdon J. A retrospective case-note study of bipolar disorder in old age. Br J Psychiatry. 1991;158:485–90.
49. Drake ME, Pakalnis A, Phillips B. Secondary mania after ventral pontine infarction. J Neuropsychiatry Clin Neurosci. 1990;2:322–5.
50. Starkstein SE, Mayberg HS, Berthier ML, Fedoroff P, Price TR, Dannals RF, et al. Mania after brain injury: neuroradiological and metabolic findings. Ann Neurol. 1990;27:652–9.

51. Danel T, Comayras S, Goudemand M, et al. Troubles de l' humeur et infarcts de l'hémisphère droit. Encéphale. 1989;15:549–53.
52. Mendez MF, Adams NL, Lewandowski KS. Neurobehavioral changes associated with caudate lesions. Neurology. 1989;39:349–54.
53. Stone K. Mania in the elderly. Br J Psychiatry. 1989;155:220–4.
54. Goldschmidt TJ, Burch EA, Gutnisky G. Secondary mania from cerebral embolization with nonfocal neurologic findings. South Med J. 1988;81:1309–11.
55. Bogousslavsky J, Ferrazzini M, Regli F, Assal G, Tanabe H, Delaloye-Bischof A. Manic delirium and frontal-like syndrome with paramedian infarction of the right thalamus. J Neurol Neurosurg Psychiatry. 1988;51:116–9.
56. Cummings JL, Mendez MF. Secondary mania with focal cerebrovascular lesions. Am J Psychiatry. 1984;141:1084–7.
57. Jampala VC, Abrams R. Mania secondary to left and right hemisphere damage. Am J Psychiatry. 1983;140:1197–9.
58. Cohen MR, Niska RW. Localized right cerebral hemisphere dysfunction and recurrent mania. Am J Psychiatry. 1980;137:847–8.
59. Shulman K, Post F. Bipolar affective disorder in old age. Br J Psychiatry. 1980;136:26–32.
60. Rosenbaum AH, Barry Jr MJ. Positive therapeutic response to lithium in hypomania secondary to organic brain syndrome. Am J Psychiatry. 1975;132:1072–3.
61. Robinson RG, Boston JD, Starkstein SE, Price TR. Comparison of mania and depression after brain injury: causal factors. Am J Psychiatry. 1988;145:172–8.
62. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978;133:429–35.
63. Blumberg HP, Stern E, Ricketts S, Martinez D, de Asis J, White T, et al. Rostral and orbital prefrontal cortex dysfunction in the manic state of bipolar disorder. Am J Psychiatry. 1999;156:1986–8.
64. McDonald WM. Epidemiology, etiology, and treatment of geriatric mania. J Clin Psychiatry. 2000;61 Suppl 13:3–11.
65. Cassidy F, Carroll BJ. Vascular risk factors in late onset mania. Psychol Med. 2002;32:359–62.
66. Fujikawa T, Yamawaki S, Touhouda Y. Silent cerebral infarctions in patients with late-onset mania. Stroke. 1995;26:946–9.
67. Robinson RG. Neuropsychiatric consequences of stroke. Annu Rev Med. 1997;48:217–29.
68. Wijeratne C, Malhi GS. Vascular mania: an old concept in danger of sclerosing? A clinical overview. Acta Psychiatr Scand Suppl. 2007;116 Suppl 434:35–40.
69. Evans DL, Byerly MJ, Greer RA. Secondary mania: diagnosis and treatment. J Clin Psychiatry. 1995;56 Suppl 3:31–7.

Chapter 5
Anxiety Disturbances in Stroke Patients

Risto Vataja and Markku Kaste

Abstract Anxiety is present in at least 20 % of stroke patients already in the acute phase and once present tends to run a chronic course. Of the different anxiety disorders, generalized anxiety disorder is the most common. The concept of "post-stroke anxiety," as a direct consequence of biological mechanisms associated to stroke is controversial. More likely, the etiology of anxiety after stroke is probably multifactorial, associated with, e.g., personality traits, psychosocial stressors, and yet unknown biological mechanisms. The role of the stroke lesion location is unknown, although posterior right hemisphere location has been suggested in generalized anxiety, right temporal location in panic disorder, and lesions affecting the frontal-subcortical circuitry in the obsessive-compulsive disorder (OCD). Compared to post-stroke depression, anxiety has been far less studied. Yet it has a strong negative impact on the quality of life of the stroke victims and their caregivers, and it is associated with impaired activities of daily living and probably also premature institutionalization. Although the validity of structured methods and rating scales is probably suboptimal, their routine use is recommended to improve detection of this often neglected disorder. There are no randomized controlled high-quality studies of the management or pharmaceutical treatment. In clinical practice most of the patients seem to benefit from the serotonin-selective reuptake inhibitors and other antianxiety drugs that are widely used in general psychiatry. However, neuroleptics, benzodiazepines, and tricyclic antidepressants should be used with caution in this fragile patient population.

R. Vataja, MD, PhD (✉)
Department of the Neuropsychiatry and Geriatric Psychiatry,
Kellokoski Hospital, Kellokoski 04500, Finland
e-mail: risto.vataja@hus.fi

M. Kaste, MD, PhD, FAHA, FANA, FESO
Department of Neurology, Helsinki University Central Hospital,
00290 Helsinki, Finland
e-mail: markku.kaste@hus.fi

J.M. Ferro (ed.), *Neuropsychiatric Symptoms of Cerebrovascular Diseases*,
Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-1-4471-2428-3_5, © Springer-Verlag London 2013

Keywords Anxiety • Post-stroke • Generalized anxiety • GAD • OCD • PTSD • Neuropsychiatric • Behavioral • Quality of life • Lesion location

Introduction

Anxiety as a post-stroke symptom or syndrome has received only relatively little attention in clinical work or research, and its impact, clinical correlations, and management are far less understood than those of post-stroke depression. Yet vascular diseases and risk factors are associated with anxiety or excessive worrying, as has been shown in adult cohort studies like the one carried out by Fiedorowicz et al. [1]. They found in a representative cohort of 5,692 individuals, that vascular disease and risk factors (diabetes, high BP, and obesity) were associated with anxiety (diagnosis of generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD), especially in men (OR = 1.62, CI 1.19.2.21). Furthermore, in a meta-analysis of data from five large cohorts of community-dwelling older people, history of TIA or stroke was associated with anxiety (the Hospital Anxiety and Depression Scale score 8 or higher; OR 1.55; CI 1.23–1.97) [2]. Such cohort studies demonstrate that anxiety is a significant neuropsychiatric problem in patients with cerebrovascular disorders (CVD) and their risk factors, but they leave the questions of causality and mechanisms unanswered.

Fearful emotions and worry are normal emotions in patients with acute stroke, but they often continue despite physical recovery and sometimes develop into anxiety syndromes that seriously interfere with the patients' emotional and cognitive functioning and adaptation to the illness [3]. Ruminating worries may focus on wide range of concerns, like having a new stroke or other new debilitating illness, not coping with activities of daily living, or getting abandoned by near ones. Sudden panic-like outbursts of anxiety may be triggered by fear of falling. Agitated anxiety may occur in sudden complex situations that a patient with cognitive difficulties finds overwhelming, typically in situations where the disabled individual is assisted in daily life. Numerous physiological arousal symptoms associated with anxiety like heart pounding, shortness of breath and choking sensations, numbness and tingling, nausea, and increased muscle tone may lead to repeated unnecessary emergency room visits. "Fear of fear" experienced by many patients, and the rapid calming effect that benzodiazepines and alcohol have on it may predispose vulnerable patients to excessive use of these agents and to all the motor, cognitive, and psychiatric side effects that they bring on. Depersonalization and feelings of unreality associated with anxiety may bring about fear of going insane in a patient or misinterpretation of the symptoms as a psychotic disorder by a clinician. Irritated, tense and apprehensive emotional state of mind, insomnia, fear of being left alone, tendency for social isolation, and continuous anxious apprehension of things to come may seriously affect the quality of living of the patients and their caregivers alike.

Table 5.1 Anxiety disorders in the DSM-IV [4]

Generalized anxiety disorder (GAD)
Post-traumatic stress disorder (PTSD)
Panic disorder
Agoraphobia (with or without panic disorder)
Specific phobias
Obsessive-compulsive disorder (OCD)
Anxiety disorder due to a general medical condition
Substance-induced anxiety disorder

Table 5.2 Diagnostic criteria for generalized anxiety disorder according to the DSM-IV [4]

A. Excessive anxiety and worry, occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance)
B. The person finds it difficult to control the worry
C. The anxiety and worry are associated with three or more of the following six symptoms
   1. Restlessness or feeling keyed up or on edge
   2. Being easily fatigued
   3. Difficulty concentrating or mind going blank
   4. Irritability
   5. Muscle tension
   6. Sleep disturbance (difficulty falling or staying asleep or restless unsatisfying sleep)
D. The focus of the anxiety and worry is not confined to features of another Axis I disorder, e.g., panic disorder, anorexia nervosa, and somatization disorder
E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
F. The disturbance is not due to the direct physiological effects of a substance or a general medical condition and does not occur exclusively during a mood disorder or a psychotic disorder

Too often anxiety is interpreted as a normal consequence of serious illness by the patients and their near ones, not to be reported to health-care professionals, who also too often fail to recognize anxiety disorders or have nihilistic attitudes towards their management. In this chapter we want to emphasize the high prevalence and significance of anxiety in stroke patients and present the treatment options available for them.

Anxiety in General Psychiatry

The anxiety syndromes are classified according to the circumstances (triggering internal or external factors) and temporal associations (continuous vs. paroxysmal) in which the pathological anxious affect arises. The classification of anxiety disorders in the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) is presented in Table 5.1.

GAD (Table 5.2) is the most prevalent anxiety disorder in general practice [5]. It is characterized by excessive anxiety and worry, which the patients find hard to control. Most of the patients report onset of symptoms in childhood, adolescence,

or early adulthood, and the course is usually chronic or fluctuating, with symptom exacerbation during times of stress. Of the individuals with generalized anxiety, 20–45 % have comorbid depression [6].

In elderly population, the prevalence of any anxiety symptoms ranges from 15 to 52 % in community samples and 15 to 56 % in clinical samples. The high variance of the reported prevalences is attributable to the conceptual and methodological inconsistencies that characterize the literature. In those studies that have used the criteria most often used in stroke literature (e.g., DSM-IIR or DSM-IV criteria or a rating scale cut point), the reported prevalence of anxiety in elderly community-dwelling people varies between 10 and 14 % [7]. Of the more specific anxiety syndromes in the older population (55–85 years), Beekman et al. [5] reported GAD as the most prevalent disorder (7.3 %), followed by phobic disorder (3.0 %), panic disorder (1.0 %), and OCD (0.6 %).

Diagnostic Issues in Patients with Post-stroke Anxiety

Applying the diagnostic criteria for anxiety disorders in patients with post-stroke anxiety is often difficult. In patients with new onset anxiety after stroke, the disorder is often less clear and only partly fulfils the criteria required by the DSM. Furthermore, many patients that are not anxious may fulfil some of the somatic and cognitive criteria of the GAD (being easily fatigued, having difficulties in concentration, or having sleep difficulties), because they are often part of the neurological stroke syndrome.

R.G. Robinson has studied the specificity of anxiety symptoms in a sample of 357 stroke patients by dividing the patients in those with excess anxiety or worry and those without [8]. The anxious patients had significantly higher frequency of all of the anxiety symptoms of DSM-IV GAD, suggesting that the generalized anxiety criteria may have face validity also in stroke patients.

Also, the requirement of symptom persistence of 6 months for the GAD cannot be fulfilled in studies addressing anxiety in acute and subacute stages of stroke. Therefore, many of the studies in this field have used modified diagnostic criteria, e.g., neglecting the time criteria [9, 10].

The DSM-IV classification also gives an opportunity to diagnose “true” post-stroke anxiety, i.e., anxiety that is a direct physiological consequence of stroke (Table 5.3). Prominent anxiety in any form is sufficient for inclusion in the A. criteria, so that the symptom criteria are much more permissive than, for example, in the GAD syndrome. Using this diagnosis, however, is challenging, as is the case in any other post-stroke neuropsychiatric syndromes. The criterion C of the diagnostic criteria for anxiety disorder due to general medical condition (e.g., stroke) requires that anxiety is judged to be a direct *physiological* consequence of a specific medical condition and that it is not better accounted for by any other mental disorder (e.g., adjustment disorder in which anxiety emerges as *psychological consequence* caused by stressor, for example, developing stroke).

Table 5.3 The DSM-IV criteria for anxiety disorder due to stroke [4]

A. Prominent anxiety, panic attacks, or obsessions or compulsions predominate in the clinical picture
B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition
C. The disturbance is not better accounted for by another mental disorder (e.g., adjustment disorder in which the stressor is stroke)
D. The disturbance does not occur exclusively during the course of a delirium
E. The disturbance causes clinically significant distress of impairment in social, occupational, or other important areas of functioning

However, there is no way to make a reliable distinction between psychological and physiological etiologies in stroke patients, and such dichotomy is artificial at best. The "direct physiological consequence," e.g., a stroke affecting neurocircuitry or neurochemistry associated with fear regulation is probably only one factor among others that results in anxiety disorder. Previous personality traits, above all neuroticism, an enduring personality tendency to experience anxiety and guilt, may increase risk for anxiety also in post-stroke patients. Genetic factors, somatic complaints and medications, previous psychiatric disorders, current interpersonal relations, psychosocial stressors, and also protective factors yet to be identified most likely play an important part in the pathogenesis of post-stroke anxiety. Such a multifactorial approach is analogous to what has been suggested for the etiology and risk factors of post-stroke depression [11]. Furthermore, in stroke patients, the knowledge of the pathophysiological mechanisms between the brain infarct process and subsequent anxiety symptoms is limited at present, e.g., association between the lesion characteristics like location and anxiety is yet unclear. The use of the "anxiety disorder associated with a medical condition" or "post-stroke anxiety" diagnosis is probably best justified in patients with no history of pathological anxiety, and a clear temporal association between the stroke and the onset of anxiety disorder. The criteria of "anxiety disorder associated with another medical condition" in the upcoming DSM-V [12] will probably remain essentially similar with the "anxiety disorder due to stroke" of the DSM-IV.

In the clinical studies, most investigators have worked around the diagnostic criteria problem by using rating scales described below.

Assessment of Post-stroke Anxiety

The use of structured in-depth diagnostic tools as a part of psychiatric practice has been shown to improve the quality of patient management. Such systematic interview procedures increase the relevancy of diagnostic process in a clinical field, where exact biological measurements like neuroimaging or laboratory tests have often only an exclusive role, whereas inclusive diagnostics often depend on more vague observations of the patients' behavior and self-report. Thus, the DSM-IV-based

Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID) is the golden standard for diagnosing anxiety syndromes after stroke [13].

In neurological clinical practice, the use of less exhaustive, easy-to-give formal screening instruments (see below) and rating scales are valuable in detecting neuropsychiatric symptoms that might otherwise be missed [14]. However, the use of these screening instruments as a sole method in diagnosing post-stroke anxiety in clinical research has been questioned, as it has been shown that, e.g., associations between stroke lesion location and post-stroke anxiety vary within same patient groups when different rating scales and cut points are used [15]. The most widely used rating scales are probably sensitive but lack specificity in post-stroke patients and may in fact measure "general distress" more than specific anxiety syndrome [16]. Thus, they should probably be used as robust screening instruments at best or as a measurement of the changes in the severity of the anxiety symptoms both in research and in clinical work. Clinical psychiatric evaluation is needed to confirm the diagnosis of the anxiety syndromes.

Having said that, a formal screening at certain time points after stroke would probably increase the detection of treatable anxiety symptoms and disorders. Anxiety is often overlooked by the patients and their caregivers as a "natural consequence" after a frightening or devastating acute illness and underdiagnosed in clinical practice. Presence of anxiety symptoms within 2 weeks after stroke is strongly associated with persisting anxiety symptoms and disorders at 4-month follow-up, and the individuals at risk for such emotional complications can be identified by appropriate questionnaires [17]. Thus, screening for anxiety—along with depression—is recommended already at the acute-subacute phase, as well as at 3–4 months after stroke as a part of routine follow-up procedures in stroke patients.

The Hospital Anxiety and Depression Scale (HADS) is the most commonly used screening instrument for anxiety symptoms in post-stroke patients [18]. It is a self-rating scale for detecting and grading states of depression (HADS-D) and anxiety (HADS-A) in general hospitals with seven items assessing depressive, and seven items assessing anxiety symptoms. Its internal construct, e.g., ability to differentiate anxiety and depression is good in general psychiatry [19]. It is an instrument with good psychometric properties in terms of factor structure, subscale intercorrelation, homogeneity, and internal consistency. Screening cut point for anxiety is usually 8 points or higher, although recent studies comparing HADS with DSM-IV criteria for anxiety disorders after stroke have recommended much lower cutoff at 4 points or higher [20].

The second most widely used screening instrument is the Beck Anxiety Inventory (BAI), also a self-inventory instrument that screens not only the presence of, but also the severity of (graded from 0 to 3) 21 symptoms of anxiety [21]. The total score ranges from 0 to 63, with scores 8–5 indicating mild, 20–28 moderate, and 29–63 severe anxiety. The somatic symptoms are heavily weighted.

The Hamilton Anxiety Rating Scale (HAM-A) has been widely used in clinical and research settings for more than 50 years [22]. It consists of 14 items defined by a series of psychic and somatic anxiety symptoms. However, its usability in stroke

patients is limited because of many somatic items that are often present also in non-anxious patients after stroke.

The presence and severity of anxiety symptoms in post-stroke patients as a part of neuropsychiatric symptom spectrum or the presence of comorbid psychiatric symptoms in stroke patients presenting with anxiety symptoms can be assessed with the Neuropsychiatric Inventory (NPI) [23]. It is a caregiver-rated scale composed of 12 subscales that measure different behavioral symptoms: delusions, hallucination, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, nighttime behavioral disturbances, and eating abnormalities. The NPI was originally designed to assess the variety of neuropsychiatric symptoms of dementia patients, but it performs well also in patients with moderate or severe stroke [24, 25].

Although the diagnostic criteria like the DSM-IV as well as structured scales for identifying and rating the severity of anxiety are essential in clinical neuropsychiatry, their extensive use in everyday neurological practice may be too time-consuming and require some psychiatric expertise. In real-life clinical situations, the key screening questions for GAD, the most important form of anxiety syndromes, are:

- During the past month, have you been feeling worried, anxious, or tense most of the time?
- Are you frequently fearful, irritable, or having trouble sleeping?

If the answer is "yes" for either or both of these questions, more in-depth assessment of the anxiety symptoms or referral to consulting psychiatrist is probably warranted for.

GAD and Anxious Symptoms in Stroke Patients

Most of the studies addressing anxiety in stroke patients focus on the GAD. However, the total number of these studies is small, and the methodological inconsistencies and shortcomings of them probably explain the discrepancies reported. Thus, different patient populations (community based vs. stroke unit patients), variation in the diagnostic criteria used (DSM criteria vs. rating scales), different approaches to comorbid depression (analysis of "pure anxiety" or any anxiety, i.e., also with comorbid depression), and overlapping of the published patient populations in some studies (previous study populations included in a later study) shadow the overall picture of this field. The pivotal studies of the prevalence and clinical correlates of GAD and anxiety symptoms after stroke are presented in Table 5.4. Here it can be seen, that in spite of the heterogeneous data, the prevalence of anxiety syndromes is probably higher in post-stroke patients than in the general elderly population.

The breakthrough study of post-stroke anxiety was carried out in 1972 by Gainotti [35]. He described catastrophic reactions (anxiety, tears, or aggression in cognitively challenged patients provoked by a request to perform a task beyond their capacity) in altogether 160 left and right hemisphere infarcts. He found out

Table 5.4 Prevalence and clinical correlates of post-stroke anxiety

Study	Number of patients	Patient population	Time after stroke	Definition of anxiety	Prevalence of any anxiety (w. and without comorbid depression)	Prevalence of "pure" GAD (no comorbid depression)	Lesion location	Clinical correlates of post-stroke anxiety	Comment
House et al., 1991 [26]	128	Community-based cohort	1 month after stroke, 1-year follow-up	DSM-III and ICD 9 clinical diagnosis	NR	DSM-III: 1 %, ICD-9: 3 % "anxiety neurosis"	NR	NR	
Castillo et al., 1993 [27]	309	NR	NR	DSM-III R clinical assessment	GAD 26.9 %	11.1 %	GAD alone associated with posterior right hemisphere lesion, anxiety with depression left cortical lesion on CT	NR	
Burvill et al., 1994 [28]	294	All residents of the Perth metropolitan who had a stroke 1989–1990	Acute phase and after 4 months follow-up	DSM-III clinical assessment	Agoraphobia 9 %. GAD 2 % in acute phase, any anxiety disorder 21 % at 4 months after stroke	2 %	NR	Any anxiety: 12 % of men and 28 % of women	
Åström et al., 1996 [10]	80	All patients admitted to a stroke unit in 1 year	At discharge, and after 3, 12, 24, and 36 months follow-up	DSM-III R clinical assessment	GAD 28 % in acute phase, 31 % at 3 months, 24 % after 1 year, 19 % after 3 years	13 %	GAD alone associated with right hemisphere lesion on CT and depression with GAD with left hemisphere lesion	Few social contacts, dependence in ADL, cortical and subcortical atrophy on CT at 3 years	62 % of the surviving patients, who had GAD at acute phase still had it at 3 years follow-up

Schultz et al., 1997 [29]	142	Acute stroke patients	Acute phase, 3,6,12, and 24 months after stroke	DSM-IV clinical assessment	GAD 19 % in acute phase, 22 % at 3 months, 25 % at 6 months, 11 % at 12 months, 18 % at 24 months	NR	NR	Depression severity associated with presence of GAD, female sex, younger age	
Leppavuori et al., 2003 [9]	277	Consecutive stroke patients admitted to general hospital	3 months	DSM-IV, structured clinical assessment	GAD 20.6 %	4 %	Anterior circulation stroke. No correlation between anxiety and hemispheric lesion location on MRI (personal communication)	History of epilepsy or migraine, heavy use of alcohol, presence and severity of depression, female sex, worse psychosocial functioning, more severe brain infarct, more impaired into the ADLs	Comorbidity anxiety + depression 80.7 %

(continued)

Table 5.4 (continued)

Study	Number of patients	Patient population	Time after stroke	Definition of anxiety	Prevalence of any anxiety (w. and without comorbid depression)	Prevalence of "pure" GAD (no comorbid depression)	Lesion location	Clinical correlates of post-stroke anxiety	Comment
Fure et al., 2006 [30]	178	Consecutive stroke unit patients	3–7 days	HADS-A≥8	26.4 %	NR	No difference between left/right hemisphere or cerebellum/ brainstem on CT	Living alone, MMSE<26	
Barker-Collo, 2007 [31]	73	Consecutive rehabilitation unit patients	3 months	BAI	Moderate to severe anxiety 21.1 %	NR	Left hemisphere	NR	Comorbidity with depression 12.3 %
De wit et al., 2008 [32]	532	Consecutive rehabilitation unit patients, 4 European countries	2,4,6, months after stroke	HADS-A≥8	22–25 %	NR	NR	NR	
Sagen et al., 2009 [20]	104	Consecutive stroke unit patients	4 months	SCID (DSM-IV)	GAD 6 %, PTSD 3 %, phobias 9 %, social phobia 3 %, OCD 2 %, panic disorder 10.6 %, any anxiety disorder 23 %	NR	NR	Disability	Comorbity of depression with any anxiety 59 %

Bergersen et al., 2010 [33]	162	Stroke patients discharged from rehabilitation hospital	2–5 years after discharge	HADS-A > 7, postal survey	36.4 %	NR	NR	NR	32 % of the patients reported of anxiety or anxiety-depression episodes during 2–5 years period
Castellanos-Pinedo, 2011 [34]	89	Acute hospital admission	Admission, 4, 12, 26 weeks	HAM-A; NPI	Admission: 15.7 %, week 4: 29.2 %, week 12: 25.0 %, week 26: 20.0 %	NR	NR	NR	

ADL activities of daily living, *BAI* Beck Anxiety Inventory, *GAD* generalized anxiety disorder, *MMSE* the Mini-Mental State Examination, *OCD* obsessive-compulsive disorder, *PTSD* post-traumatic stress disorder, *HADS-A* the Hospital Anxiety and Depression Scale, anxiety subscale, *HAM-A* the Hamilton Anxiety Rating Scale, *NR* not reported

that anxious-depressive catastrophic reactions were associated with left hemisphere lesion location. Many of the early papers addressing frequency, phenomenology, and clinical correlates of post-stroke anxiety were published by a study group of Robinson [29, 36–38]. The pooled data from these studies including 357 acute stroke patients was partially reanalyzed and published by Robinson in a monograph [8]. The overall prevalence of GAD in the stroke cohort was 22 %. However, 86 % of those patients had comorbid minor or major depression. Ten percent of the 357 patients had "pure" GAD, without any depression.

House and colleagues reported a significantly lower prevalence of GAD between 1 % (DSM-III) and 3 % (ICD-9) in 128 patients within a yearlong follow-up. The frequency of anxiety syndromes was similar to that of an age-sex-matched control group of 111 individuals [26].

Burvill et al. reported a high prevalence of 24 % (12 % of the men and 28 % of the women) of any anxiety (mostly agoraphobia) from a community-based acute stroke cohort from Australia [39]. Two thirds of the patients were symptom free at 1 year without any specific treatments. The authors suggested that anxiety symptoms disappear with time, as the patients adapt to the illness, and that the etiology of anxiety would thus be more "psychological" than "biological."

Conflicting results were published in Sweden in a population-based cohort of 80 consecutive stroke patients by Monica Åström, who found a high prevalence of GAD (in 28 % of patients) at the acute stage [10]. Similar results were reported by Leppävuori et al., who studied 277 consecutive acute stroke patients at 3 months after stroke [9]. They found that altogether 20.6 % of the patients had GAD, and 9.4 % of the patients had GAD due to stroke (i.e., GAD judged to be a direct physiological consequence of stroke, according to the DSM-IV). History of pre-stroke anxiety disorder was present in 32 % of the patients, a strikingly higher prevalence than that of GAD in Finnish general population (1.5 %).

Numerous studies have used self-report questionnaires (as opposed to structured psychiatric assessment) to detect anxiety symptoms after stroke. As discussed above, such methods are unspecific and may measure, e.g., general distress rather than anxiety. From the clinical point of view, such studies may be valuable, as clinicians treating post-stroke patients often face unspecific or atypical clusters of anxiety symptoms rather than the precise syndromes described in the diagnostic manuals and textbooks. Fure et al. reported that 26 % of their 178 patients suffered from anxiety symptoms (HADS-A > 7) already at 3–7 days after admittance to the stroke unit [30], and after 3-month follow-up, Barker-Collo et al. found that 21 % of their 73 stroke patients suffered from moderate to severe anxiety symptoms (BAI > 15) [31].

Using the NPI, Angelelli and coworkers reported that prevalence of anxiety symptoms was present in 23 % of 124 patients within one year after stroke, compared to 3 % of 61 healthy control patients [25]. The anxiety was associated primarily with programmed events (71 %), subjective tension and inability to relax (58 %), and fear of being separated from caregivers or near ones (33 %).

In 532 consecutive stroke patients from rehabilitation centers of four European countries, de Wit et al. found that prevalence of anxiety (HADS-A score 8 or higher) at 2, 4, and 6 months after stroke was almost constant (between 22 and 25 %),

whereas the severity of anxiety symptoms tended to wane. Almost half of the patients with anxiety symptoms at 2 months were anxiety-free at 6 months. The prevalence and severity of anxiety symptoms were similar in four countries (Belgium, Germany, Switzerland, and UK) participating in this study [32].

Anxiety is common also in patients with vascular cognitive impairment. Ballard and colleagues compared the neuropsychiatric profiles between 92 patients with Alzheimer's disease and 92 patients with vascular dementia (VaD) [40]. Anxiety was assessed using the DSM-IV symptom checklist. If two or more of the symptoms on the list (anxiety, worry, restlessness, fatigue, irritability, poor concentration, muscular tension, panic attacks, social phobia, or agoraphobia) were present, anxiety was diagnosed. Patients with vascular dementia showed twice as much anxiety symptoms as patients with Alzheimer disease (72 % vs. 38 %), most commonly of the GAD type. The prevalence of anxiety increased in the more cognitively impaired VaD patients, so that in patients with MMSE < 20 anxiety was present in 68 % of the patients, whereas in patients with MMSE < 10 anxiety was present in almost everyone (94 %).

The Clinical and Neuroradiological Correlates of GAD and Anxiety Symptoms

Analogously to the studies in post-stroke depression, some investigators have tried to identify significant lesion locations associating with post-stroke anxiety (Table 5.4). Tang et al. [41] studied a large cohort of 693 patients, and diagnosed anxiety using a cut point of 8 points or more on HADS-A ($n = 42$). The number of acute right frontal infarcts was four times higher in patients with higher anxiety scores, and in a multivariate regression model (including age, sex, geriatric depression scale score, presence of acute infarcts), the presence of right frontal infarct was independently associated with anxiety (OR = 3.87, CI 1.5–9.6, $p = 0.004$). However, the probable high comorbidity of depression was unaccounted for, and thus the impact of depression to the results remains unclear.

Robinson's group has reported that in patients with right hemisphere infarcts, patients with GAD had more posterior lesions than those without anxiety or depression. In patients with left hemisphere lesions, those who had anxiety and comorbid depression had significantly more cortical lesions than those patients with depression and without anxiety [8, 42].

Analogously, Monica Åström found that GAD with depression was associated with left hemisphere lesion, whereas GAD alone was more common in patients with right hemisphere infarcts [10].

In the Helsinki Aging Stroke study, MRI (1T) was used to identify neuroanatomical correlates of post-stroke anxiety using a sophisticated protocol for lesion location (hemispheres, brain lobes, cerebellum, pons, detailed white and grey matter subcortical structures, and circulation territories), infarct volume, brain atrophy, and white matter changes associating with DSM-IV-defined anxiety syndromes in 277 patients [9]. However, 80 % of the patients with anxiety were also depressed,

which made it impossible to identify independent anatomical explanatory variables for anxiety [9].

Of the clinical correlates of post-stroke anxiety (Table 5.4), female sex, impairment and disability, few social contacts or living alone, and severity of depression are reported to be associated with anxiety in more than one of the studies. Migraine and epilepsy or central and cortical cerebral atrophy may also contribute to anxiety. Robinson has reported that post-stroke anxiety is associated with younger age and history of alcohol abuse [8]. Patients with anxiety were more impaired in their activities of daily living (as measured by the Johns Hopkins Functioning Inventory) and social functioning (as measured by the social ties checklist). There were no differences in stroke symptoms or aphasia in patients with and without anxiety, or cognitive function as measured by the Mini-Mental Score Examination (MMSE). Not surprisingly, the use of anxiolytic drugs or history of anxiety disorders or other psychiatric disorders is also associated with anxiety in stroke patients [9]. Severity of stroke as measured with stroke scales, other somatic illnesses, aphasia, or length of formal education, on the other hand, have not been associated with post-stroke anxiety.

Most of the studies report a high comorbidity of anxiety disorders and depression in stroke patients, varying between 25 and 80 %. The possible causative association between these two disturbances is unknown, but strong evidence from general psychiatry suggests that anxiety disorders may be primary to depression [43]. Also, in around 30 % of post-stroke patients who have depression, comorbid anxiety disorder significantly interacts with depression and has a negative impact on the severity and course of depression as well as on the activities of daily living and social functioning [38].

Once present, anxiety symptoms tend to persist. Thus, Åström reported that after a 1-year follow-up, only 23 % of the patients diagnosed with GAD at acute phase had recovered, and almost all of those who had not recovered run a chronic course and had not recovered at 3 years after stroke [10]. In a cross-sectional study using HADS-A cut point >7 points, Bergersen et al. found that anxiety symptoms are surprisingly prevalent at 2–5 years after stroke, with 36 % reporting anxiety symptoms in the HADS-A [33]. About half of the patients reported "having been through episodes of anxiety" at some point during the long follow-up.

Other Anxiety Syndromes After Stroke

Post-traumatic stress disorder (PTSD) may follow exposure to an extremely traumatic experience that induces fear of death, severe injury, or threat to physical integrity of self and others. Acute severe illness or being diagnosed with a life-threatening, fearful condition like stroke may be sufficient as triggering experiences. PTSD is in many ways associated with memory. It includes intrusion of recurrent, intrusive memories of the traumatic event, recurrent distressing dreams with the content or affect of the event, intense anxiety with physiological reactions when exposed to cues of the stressor, and sudden spontaneous "flashbacks," reliving the incident and

associated emotions unexpectedly. Patients with PTSD tend to avoid circumstances like places and activities that could serve as a cue to the traumatic event. Their memories of the incident are usually patchy at best. Anxiety, hypervigilance, self-destructive or aggressive behavior, sleep disturbances, concentration difficulties, negative cognitions about one's self or others, and pervasive negative emotional state are common psychological symptoms in the PTSD.

Sembi and coworkers were the first to study the prevalence of PTSD in their cohort of 61 patients who had experienced a first-ever stroke or transient ischemic attack [44]. Using structured diagnostic interview and self-reported measures they found that 10 % of the patients had PTSD, compared to the reported prevalence of PTSD of less than 2 % in general population. The features and symptom spectrum of post-stroke PTSD did not differ from that of patients with PTSD after an assault, combat, or traffic accident. In later studies, the prevalence of PTSD in stroke patients has varied between 6 and 31 % [45]. Long-term prognosis of PTSD after stroke is unknown, but at 3 months follow-up the symptom spectrum and severity remains unchanged and may be chronic in course, as has been suggested in studies of other critical illnesses [46]. Even non-severe stroke may induce long-lasting PTSD syndrome, especially in patients with more negative cognitive appraisals of the acute stroke experience [47]. Little is known of proper treatment of post-stroke PTSD, but emphasis should probably be placed on prevention by reducing the initial fear and confusion by an encouraging attitude combined with adequate information when treating patients with acute stroke. In later phases, antidepressive medication with serotonin-selective reuptake inhibitors, psychosocial support, and in some cases trauma-related cognitive-behavioral therapy can be recommended [48].

Obsessive-compulsive disorder (OCD) is characterized by unwanted, recurrent intrusive thoughts or obsessions (e.g., of violent or sexual content or doubts of forgetting important things like locking doors) that typically increase anxiety, and repetitive, not appropriate behavior patterns or compulsions (e.g., washing hands, checking). Obsessions are often described as anxiety-producing and compulsions as anxiety-releasing symptoms [49].

There are some case reports of OCD following stroke and other local brain injuries [50]. Basal ganglia infarcts [51] or frontal lesions [52], mostly right-sided are the most typical lesion locations in these cases. The current neuroanatomical model of OCD is dysfunction of frontal-subcortical circuitry, which regulates anxiety-generating memories and associated obsessions, repetitive behavior, and executive functions [53]. The structures involved are orbitofrontal cortex and anterior cingulate cortex, caudate nucleus, substantia nigra, globus pallidus and thalamus, and the white matter connections, e.g., internal capsule that connects these structures completing the frontal-subcortical-frontal loops [54]. Lesions affecting the inhibitory elements within these loops, e.g., by brain infarcts may cause overactivation of the direct pathway and lead to symptoms of OCD [49].

Panic disorder is a syndrome with sudden, unexpected panic attacks of severe anxiety and several physical symptoms like tachycardia, hyperventilation, and gastrointestinal symptoms [55]. The key cognition of the patients is a feeling of a total loss of control, which can be experienced, for example, as a fear of losing

consciousness or fear of sudden death. In addition to these attacks, the syndrome includes worry about the possibility of future attacks, phobic avoidance of situations and places which might elicit panic attacks (agoraphobia), and in stroke patients quite often fear of a new incipient stroke and "unnecessary" visit to emergency room. Reports of post-stroke panic disorders are anecdotal case reports [56]. Those studies and case reports of patients with other focal brain damage (i.e., brain tumor, AV malformations) suggest that lesions affecting anterior cingulate cortex and temporal lobe structures, especially on the right side are associated with panic disorder [57, 58].

Social anxiety disorder (social phobia) is another common anxiety disorder, characterized by a fear of social situations. The patients avoid the scrutiny of others and are afraid of embarrassment or humiliation caused by doing or saying something "funny" or looking somehow striking to others. Patients suffering from social phobia may shun most interpersonal encounters. Apart from single case reports [59], the studies of social phobia after stroke are practically nonexistent. However, clinicians treating stroke victims in the rehabilitation phase and after often find this disorder in their patients. The role changes of the patient (e.g., from a highly functional family breadwinner to an ailing stroke patient needing assistance in activities of daily living), the psychological stigma associated with stroke and subsequent withdrawal from social contacts is a fairly common complaint of post-stroke patients. Some of these behavioral changes are associated with anxious ideation that fulfil the criteria for social phobia but remain undiagnosed and untreated.

Although some case reports of phobias after specific brain lesion locations (thalamus and frontal-subcortical connections) exist [60], specific phobias (i.e., phobic fear of spiders, thunderstorms, or high places) after stroke are probably rare and are not specific to pathophysiology of stroke per se. Rather, the unfamiliar circumstances that the patient with acute stroke faces may trigger fear reactions that then may be learned, for example, a phobia of needles after painful blood taps in the hospital.

The prevalence of the above-mentioned anxiety disorders in stroke patients in general is relatively unknown. In an early study, Burvill et al. reported high prevalence of agoraphobia (often associated with panic disorder) at 9 % [39]. Sagen et al. [17] reported in their 104 consecutive stroke unit patients 4 months after stroke a prevalence of panic disorder (prevalence in elderly population in parenthesis) 10.6 % (1.0 %), specific phobias 8.7 % (3.0 %), and OCD 1.9 % (0.6 %). These studies suggest that the whole anxiety disorder spectrum not just the GAD or unspecific anxiety symptoms may be overrepresented in post-stroke patients. However, we found in the Helsinki Stroke Aging study of 486 consecutive stroke patients [9], that when using the DSM-IV criteria and a structured clinical psychiatric assessment, the prevalence of panic disorder, specific phobias, and OCD were all under 2 % and did not exceed the prevalence of these syndromes in the Finnish general population (unpublished data).

Like the association between CVD and depression, the association between anxiety and CVD may be bidirectional: anxiety is overrepresented in patients with stroke, and on the other hand, anxiety seems to be a risk factor for cerebrovascular symptoms and stroke [61]. This pre-stroke anxiety or anxiety disorders as a risk factor for

subsequent stroke has been studied in different patient groups. For example, in a large telephone health survey of 770 patients with ischemic heart disease or congestive heart failure discharged from a cardiology department, Kornerup et al. reported that a high HADS-A score (11–21 vs. 0–10) at 1 year after discharge predicted consequent stroke during a 5-year follow-up (HR 2.25, 95 % CI 1.05–4.82) [62].

Likewise, preliminary studies in PTSD [63] and panic disorder [64] suggest increased risk for subsequent stroke in individuals who are diagnosed with these disorders.

Several possible intermediary mechanisms for these associations have been suggested, but they are probably multifactorial. Thus, effect of anxiety on blood pressure, heart rate and vagal control, unhealthy lifestyle, increased activity of the catecholamines and stress hormones, and increased inflammatory mediators and oxidative stress may all contribute to the adverse outcome. Phobic and acute anxiety may also activate coagulation and fibrinolysis in the direction of a hypercoagulable state [65].

Significance of Post-stroke Anxiety

Many studies have shown that in different neurological disorders depression is the most important psychiatric disorder to have a negative impact on the quality of life (QoL), and this is the case also in stroke patients. However, anxiety is also an independent inverse correlate of QoL in stroke patients [66, 67]. Especially, important aspects of quality of life like social functioning, role limitations, mental health, and vitality measured by the health-related quality of life scale (HRQOL) are significantly impaired in patients with post-stroke anxiety, compared with non-anxious stroke patients [68]. Furthermore, social functioning and inability in activities of daily living (ADL) are more affected in patients with anxiety than in those without [38]. The patients with comorbid depression and anxiety fare even worse than patients with depression alone in these domains that are known to associate with worse QoL [38]. Almost half of the patients with acute stroke suffer from exaggerated fear of falling, which is often accompanied by anxiety and depression [69]. Fear of falling affects negatively the outcome of stroke patients, decreasing independence, physical and social activities, and QoL [70].

Anxiety has also a deleterious impact on the families and caregivers of the patients. Psychiatric symptoms, especially anxiety and depression in patients have repeatedly been shown to be independent predictors of caregiver burden and worse caregiver QoL [71]. Furthermore, anxiety is common not only in patients but also in their informal caregivers. Half of the caregivers score 8 points or higher on the HADS-A at 1–3 months post-stroke [72], which may indicate the “contagious” nature of this symptom between chronically ill individuals and their near ones.

Fear of psychiatric stigma or unawareness of treatment possibilities may be reasons for the patients’ reluctance to seek help for their anxiety and other emotional problems after stroke. Thus, Bergersen et al. reported that only half of the stroke

patients discharged from a rehabilitation hospital and experiencing anxious or anxious-depressive episodes 2–5 years after discharge had consulted health-care professionals about their emotional problems [33].

Although relatively little is known about the nature or correlates of cognitive deficits associated with anxiety and anxiety disorders in general, GAD probably affects working memory, visual memory, semantic memory, and verbal memory [73]. Disorders of attention are common, especially hyperattention and hypervigilance for possibly threatening external or internal (somatic) cues disturb concentration. In addition, PTSD and OCD are also associated with problems in executive functions [74]. Patients with post-stroke anxiety were at increased risk of general cognitive decline during a 6-month follow-up in a study by Rasquin et al. [75], but otherwise the significance of post-stroke anxiety to cognitive outcome is unknown.

Although the economical burden associated with anxiety after stroke is unknown, it is probably significant. Anxious individuals after stroke are heavy users of health-care services. Increased dependency in daily living, sometimes leading to premature institutionalization, increases the costs associated with stroke in patients with anxiety. The expenses associated with stroke and anxiety could be extrapolated from what is known of costs of anxiety in general. In Europe, the total direct and indirect costs of all anxiety disorders in 2010 has been estimated as having been 74.4 billion €, higher than, e.g., stroke (64.1 billion €) or traumatic brain injury (33.3 billion €), but less than dementia (105.2 billion €) or mood disorders (113.4 billion €) [76].

Pathophysiology of Anxiety

Research on the neuroanatomy of anxiety disorders has rapidly increased during the last 15 years, following the evolution of sophisticated neuroimaging techniques (PET, MRS, fMRI, and DTI). Dysregulation of the neurocircuitry that controls the primary emotion (fear), thus leading to a more pervasive state (anxiety), may be the common pathophysiological mechanism behind different anxiety syndromes [77]. The classical limbic structures regions associated with anxiety disorders are the amygdala, the hippocampus, and the insula. Hyperreactivity to fearful cues or resting overactivity of amygdala is the most consistent finding in functional neuroimaging studies of different anxiety disorders [78]. The amygdala integrates information from sensory modalities, prior learning (memory), and threat response and together with hippocampus gives an emotional valence to conscious and subconscious memories. Activation of the amygdala in reaction to fearful cues is associated with autonomic fear response and arousal [79]. The insula has been suggested to be the key region in integrating the internal bodily information (interoception) with the emotional information from the amygdala and cognitive executive control information from the prefrontal cortex. Anxious affect with maladaptive behavioral and cognitive response, e.g., avoidance behavior is reflected by the abnormal fMRI findings in insula in patients with anxiety disorders [80]. Finally, the medial prefrontal cortex

(medial orbitofrontal cortex and anterior cingulate cortex) provides the conscious and subconscious control of fearful and threatening emotions and behavior [81].

It is intriguing to speculate that post-stroke anxiety could at least in part be explained by disrupted neurocircuitry, analogously to what has been suggested of the pathophysiology of post-stroke depression. In post-stroke depression, lesions affecting frontal-subcortical or limbic circuitry, e.g., a critical infarct affecting the anterior cingulate circuits, have been proposed to mediate the effect of stroke to depressed affect [82]. However, the studies addressing the association between stroke lesion location and post-stroke anxiety are contradictory and suffer from methodological problems. The very high prevalence of comorbid depression with post-stroke anxiety makes the task of identifying critical lesion locations and disrupted circuits associated purely with post-stroke anxiety challenging, and the association between lesion location and subsequent anxiety remains controversial [9].

Neurochemistry of anxiety disorders is a complex and rapidly evolving field. Corticotrophins, hypothalamus-hypophyse-adrenal cortex axis, monoamines regulating mood and emotions (noradrenaline, serotonin, and dopamine), GABA system, neuropeptides (substance P, neuropeptide Y, oxytocin, vasopressin, orexine, and galanine), glutamate system, and endogenous opiates all probably have a role in regulating fear and anxious affect [77, 83]. However, at present there are no studies or influential theories of the possible specific neurochemical mechanisms of post-stroke anxiety.

Pre-stroke personality traits probably associate with presence and severity of anxiety symptoms after stroke, as has been shown in post-stroke depression [84]. However, the only study in which pre-stroke personality and subsequent anxiety has been studied found only weak correlation between neuroticism and anxiety in stroke patients [24].

Treatment of Post-stroke Anxiety

As there are no randomized, controlled studies of the treatment of anxiety disorders in patients with the GAD after stroke, the clinical recommendations have to be extrapolated from what is known of the management of anxiety syndromes in general. Guidelines for intrinsic anxiety syndromes apply, as long as the susceptibility of stroke patients to side effects and to drug-drug interactions is accounted for. Table 5.5 is a synthesis from current studies and guidelines of the pharmacological treatments of anxiety in non-stroke populations (e.g., by Davidson et al. [85] and by Baldwin et al. [86]), modified for stroke patients.

Serotonin-selective reuptake inhibitors (SSRI's) are the first-line choice for post-stroke anxiety, based on their good performance in other related patient groups, i.e., patients with post-stroke depression, Parkinson's disease, or elderly depressive patients in general. Within the SSRIs, sertraline, citalopram, and escitalopram are recommended because of their favorable interaction profile and rapid elimination half-time, which is an advantage if side effects occur or if preparation change is

Table 5.5 Pharmacological treatment of anxiety in stroke patients

	Dosing (mg)	Comments
Serotonin-selective reuptake inhibitors		First-line choice. Beware of hyponatremia and GI bleeding, headache, sexual dysfunction
Sertraline	50–150	
Escitalopram	5–20	
Citalopram	10–40	
Fluoxetine	10–40	Extended half-life
Paroxetine	10–40	
Other antidepressants		Second-line choice
Duloxetine	30–60	
Venlafaxine	37.5–150	Dose-related risk of elevated blood pressure
Bupropion	100–150	Increases risk for convulsions in susceptible individuals
Mirtazapine	15–30	Favorable profile for patients with insomnia, beware of akathisia, sedation, weight gain
Buspirone	10–60	
Trazodone	50–300	Favorable profile for patients with insomnia
Nortriptyline	50–100	
Anticonvulsants		Third-line choice
Pregabalin	150–300	Beware of sedation, falls
Antipsychotics		Third-line choice
Quetiapine	25–200	Beware of sedation, falls, hypotension
Benzodiazepines		Short-period use. Beware of sedation, falls, cognitive disturbances, dependency
Lorazepam	0.5–2	
Clonazepam	0.5–1.5	

considered. Anxiety and agitation may transitionally increase during the first days after the initiation of these drugs, of which the patients and their caregivers should be informed. Positive response should be expected within 2–6 weeks, and the dose should be increased after 2–6 weeks if no improvement has occurred. The SSRIs are moderately effective in GAD, and they are usually well tolerated. However, some caveats should be remembered when using these drugs in stroke patients. Hyponatremia, falls, and bone fractures have recently been associated with chronic use of the SSRIs [87], as well as gastrointestinal bleedings especially when other drugs affecting platelet function and coagulation (e.g., anti-inflammatory agents or warfarin) are prescribed [88].

Other new-generation and tetracyclic antidepressants are recommended if the SSRIs fail or are not tolerated. Drugs affecting both serotonergic and noradrenergic systems (e.g., duloxetine, venlafaxine, and mirtazapine) and dopamine and noradrenergic systems (e.g., bupropion) can be considered on post-stroke GAD, based on what is known of their profile in GAD in general. Some case reports have associated the use of mirtazapine with akathisia, which can both mimic and increase anxiety. Venlafaxine and duloxetine have been reported to increase blood pressure in some patients, and bupropion has been associated with epileptiform EEG changes and

dose-dependent risk of seizures [89]. Trazodone is a tetracyclic antidepressant with sedative properties, which can be utilized in patients whose primary complaint among the anxiety symptoms is insomnia.

Of the atypical antipsychotics, quetiapine has been shown to be effective in GAD, and risperidone is probably effective in OCD in nonelderly adults. However, in elderly patients with dementia, they are associated with an increased mortality (OR 1.5), risk of cardiovascular (OR 1.1–2.3) and cerebrovascular accident (0.7–3.2). The safety profile for these serious outcomes seems to be the worst for risperidone and olanzapine, and more favorable for quetiapine. Although there are no high-quality trials of neuroleptics for neuropsychiatric symptoms in stroke patients, these drugs should be used with caution in this frail patient population [90].

Tricyclic antidepressant nortriptyline for post-stroke GAD was studied by the Robert G. Robinson's study group of the Iowa University. They pooled secondary data from their three nortriptyline studies in post-stroke depression to study the efficacy of that drug in post-stroke GAD [91]. These three studies were carried out in different times, but in all the studies the same semistructured interview (Present State Examination, PSE) was used in altogether 27 patients, of whom 13 were randomly assigned to nortriptyline and 14 to placebo. All patients had also comorbid minor or major depression. Nortriptyline was increased stepwise to 100 mg/day within 3–4 weeks. They found out that the reduction of the Hamilton Rating Scale for Anxiety (HAM-A) score was more than 50 % in 9 of the 13 patients in the nortriptyline group and in 3 of the 14 patients in the placebo group (Fisher's exact test: $p = 0.02$). The rate of the improvement of anxiety symptoms was significantly faster than the improvement of neurological deficits caused by stroke. This study with its many potential severe flaws is the only one that even tries to approach the pharmacological treatment of post-stroke anxiety in a randomized, controlled trial. Nortriptyline and other tricyclic antidepressants are, however, associated with anticholinergic side effects, decreased cardiac conduction, orthostatic hypotension, and a narrow therapeutic dose window. They should be used in stroke patients only when the safer options like the SSRIs and pregabalin have failed in the treatment of severe post-stroke anxiety.

Both paroxetine (an SSRI) at 20 mg/day alone or together with psychiatrist administered supportive psychotherapy and buspirone at 40–60 mg/day have been reported to diminish anxiety symptoms in patients with comorbid anxiety and depression significantly as measured by the HAM-A compared with "standard care." These two separate Chinese studies with altogether 175 patients were reviewed by Cambell Burton et al. [92]. They concluded that evidence from these studies was insufficient because of methodological issues (e.g., no placebo-control groups were used).

Numerous anticonvulsants (e.g., phenytoin, gabapentin, levetiracetam, carbamazepine, oxcarbazepine, tiagabine, and valproate) have emerged as possible treatment options for anxiety disorders in general psychiatry [93]. Of these pregabalin, a novel gamma-aminobutyric acid (GABA) analog that is approved for the treatment of neuropathic pain and partial-onset seizures, has emerged as the most promising. It has been approved for the treatment of GAD in the European Union. Pregabalin has been shown to be both safe and effective in eight controlled trials, and its use has rapidly increased in patients who are either treatment resistant or

intolerant to other antianxiety drugs [94]. The response is usually rapid, with alleviation of anxiety symptoms within first week of the treatment. No trials of pregabalin for patients with post-stroke anxiety exists, but in one 13-week randomized, controlled, double-blind multicenter study of 219 patients, it was found to be both effective and safe in central post-stroke pain at doses of 150–600 mg/day [95]. However, common side effects of dizziness and somnolence may limit its use in post-stroke patients. Also, emerging reports of potential abuse of this drug must be borne in mind in susceptible patients [96].

Transcranial magnetic brain stimulation is a promising, novel method for a wide range of psychiatric disorders, including OCD and post-traumatic stress disorder [97]. It is probably effective and safe for depression in elderly patients with established CVD (patients with "vascular depression") [98] and may be helpful also in patients with anxiety, given the high comorbidity of anxiety and depression in post-stroke patients.

Various forms of psychological therapies are available for treating anxiety, but there are no clinical studies of their use in post-stroke anxiety. However, in other neuropsychiatric syndromes, modified cognitive-behavioral techniques (CBT) are the most studied and recommended forms of psychotherapy. In elderly somatic ill patient such therapies may concentrate on stress management, relaxation, sleep hygiene, learning to cope with negative cognitions, problem solving, establishing meaningful activities, and encouraging positive cognitions, e.g., meaningfulness and positive expectations [99]. Thus, in patients with depression in Parkinson's disease, 10 weekly individual 60–75 min sessions of manualized CBT combined with four separate individual caregiver educational sessions reduced significantly both depression and anxiety symptoms, and the effect in those patients was at least as good as that reported from antidepressive trials of the same disorder [100]. The use of CBT has been encouraged in post-stroke depression, although the empirical evidence of its efficacy is still controversial [101].

The psychological well-being and neuropsychiatric symptoms like anxiety can also be improved in stroke patients by focusing interventions on the carers, as was shown by Lalit Kalra et al. in their single-blind randomized controlled trial of 300 patients and their caregivers and a control group. The active intervention group of caregivers was trained in basic nursing and personal care techniques (lifting, handling techniques, assistance in personal activities of daily living, common stroke-related nursing problems like prevention of pressure sores, nutrition, continence, etc.), whereas the control group received treatment and support as usual. It was found that anxiety significantly reduced in the trained group of the caregivers, as well as in the patients that they took care of (as measured by the HADS-A scores: 3 vs. 4.5, $p<0.0001$) [102].

Conclusions

Post-stroke depression is underdiagnosed and undertreated both among stroke patients and their caregivers, and the same is true in post-stroke anxiety. There are safe and effective treatments for post-stroke anxiety which, however, have not been

evaluated in clinical randomized trials. Post-stroke anxiety impairs the quality of life of patients and their caregivers and increases the health-care costs of stroke patients, which already are high and due to the age structure of populations will increase in the coming years. Therefore, the physicians treating stroke patients should have a high suspicion index for post-stroke anxiety, and they should ask two simple questions, which could reveal the presence of post-stroke anxiety and lead to its treatment after a more in-death assessment. Serotonin-selective reuptake inhibitors are the first choice, but also other antidepressants and even anticonvulsants can be effective. Proper diagnosis and treatment of post-stroke anxiety will reduce both human suffering and economic burden of post-stroke anxiety.

References

1. Fiedorowicz JG, He J, Merikangas KR. The association between mood and anxiety disorders with vascular diseases and risk factors in a nationally representative sample. J Psychosom Res. 2011;70(2):145–54.
2. Gale CR, Sayer AA, Cooper C, Dennison EM, Starr JM, Whalley LJ, et al. Factors associated with symptoms of anxiety and depression in five cohorts of community-based older people: the HALCyon (Healthy Ageing across the Life Course) Programme. Psychol Med. 2011; 41(10):2057–73.
3. Mukherjee D, Levin RL, Heller W. The cognitive, emotional, and social sequelae of stroke: psychological and ethical concerns in post-stroke adaptation. Top Stroke Rehabil. 2006;13(4): 26–35.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed revised. Text revision. Washington, D.C.: Psychiatric Press, Inc.; 2000.
5. Beekman AT, Bremmer MA, Deeg DJ, van Balkom AJ, Smit JH, de Beurs E, et al. Anxiety disorders in later life: a report from the Longitudinal Aging Study Amsterdam. Int J Geriatr Psychiatry. 1998;13(10):717–26.
6. Mittal D, Fortney JC, Pyne JM, Wetherell JL. Predictors of persistence of comorbid generalized anxiety disorder among veterans with major depressive disorder. J Clin Psychiatry. 2011;72(11):1445–51.
7. Bryant C, Jackson H, Ames D. The prevalence of anxiety in older adults: methodological issues and a review of the literature. J Affect Disord. 2008;109(3):233–50.
8. Robinson RG. Poststroke anxiety disorders. In: Robinson RG, editor. The clinical neuropsychiatry of stroke. 2nd ed. Cambridge: Cambridge University Press; 2006. p. 317–47.
9. Leppavuori A, Pohjasvaara T, Vataja R, Kaste M, Erkinjuntti T. Generalized anxiety disorders three to four months after ischemic stroke. Cerebrovasc Dis. 2003;16(3):257–64.
10. Åström M. Generalized anxiety disorder in stroke patients. A 3-year longitudinal study. Stroke. 1996;27(2):270–5.
11. Whyte EM, Mulsant BH. Post stroke depression: epidemiology, pathophysiology, and biological treatment. Biol Psychiatry. 2002;52(3):253–64.
12. DSM V. Proposed draft diagnostic criteria. 2011. Available at: http://www.dsm5.org/Pages/Default.aspx
13. Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I: history, rationale, and description. Arch Gen Psychiatry. 1992;49(8):624–9.
14. Edwards DF, Hahn MG, Baum CM, Perlmutter MS, Sheedy C, Dromerick AW. Screening patients with stroke for rehabilitation needs: validation of the post-stroke rehabilitation guidelines. Neurorehabil Neural Repair. 2006;20(1):42–8.
15. Schramke CJ, Stowe RM, Ratcliff G, Goldstein G, Condray R. Poststroke depression and anxiety: different assessment methods result in variations in incidence and severity estimates. J Clin Exp Neuropsychol. 1998;20(5):723–37.

16. Johnson G, Burvill PW, Anderson CS, Jamrozik K, Stewart-Wynne EG, Chakera TM. Screening instruments for depression and anxiety following stroke: experience in the Perth community stroke study. Acta Psychiatr Scand. 1995;91(4):252–7.
17. Sagen U, Finset A, Moum T, Morland T, Vik TG, Nagy T, et al. Early detection of patients at risk for anxiety, depression and apathy after stroke. Gen Hosp Psychiatry. 2010;32(1):80–5.
18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361–70.
19. Johnston M, Pollard B, Hennessey P. Construct validation of the hospital anxiety and depression scale with clinical populations. J Psychosom Res. 2000;48(6):579–84.
20. Sagen U, Vik TG, Moum T, Mørland T, Finset A, Dammen T. Screening for anxiety and depression after stroke: comparison of the hospital anxiety and depression scale and the Montgomery and Åsberg depression rating scale. J Psychosom Res. 2009;67(4):325–32.
21. Beck TA, Steer RA. Beck anxiety inventory manual. San Antonio: Harcourt Brace and Company; 1993.
22. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32(1): 50–5.
23. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44(12):2308–14.
24. Greenop KR, Almeida OP, Hankey GJ, van Bockxmeer F, Lautenschlager NT. Premorbid personality traits are associated with post-stroke behavioral and psychological symptoms: a three-month follow-up study in Perth, Western Australia. Int Psychogeriatr. 2009;21(6): 1063–71.
25. Angelelli P, Paolucci S, Bivona U, Piccardi L, Ciurli P, Cantagallo A, et al. Development of neuropsychiatric symptoms in poststroke patients: a cross-sectional study. Acta Psychiatr Scand. 2004;110(1):55–63.
26. House A, Dennis M, Mogridge L, Warlow C, Hawton K, Jones L. Mood disorders in the year after first stroke. Br J Psychiatry. 1991;158:83–92.
27. Castillo CS, Schultz SK, Robinson RG. Clinical correlates of early-onset and late-onset poststroke generalized anxiety. Am J Psychiatry. 1995;152(8):1174–79.
28. Burvill PW, Johnson GA, Jamrozik KD, Anderson CS, Stewart-Wynne EG, Chakera TM. Anxiety disorders after stroke: results from the Perth Community Stroke Study. Br J Psychiatry. 1995;166(3):328–32.
29. Schultz SK, Castillo CS, Kosier JT, Robinson RG. Generalized anxiety and depression. Assessment over 2 years after stroke. Am J Geriatr Psychiatry. 1997;5(3):229–37.
30. Fure B, Wyller TB, Engedal K, Thommessen B. Emotional symptoms in acute ischemic stroke. Int J Geriatr Psychiatry. 2006;21(4):382–7.
31. Barker-Collo SL. Depression and anxiety 3 months post stroke: prevalence and correlates. Arch Clin Neuropsychol. 2007;22(4):519–31.
32. De Wit L, Putman K, Baert I, Lincoln NB, Angst F, Beyens H, et al. Anxiety and depression in the first six months after stroke. A longitudinal multicentre study. Disabil Rehabil. 2008;30(24):1858–66.
33. Bergersen H, Froslie KF, Stibrant Sunnerhagen K, Schanke AK. Anxiety, depression, and psychological well-being 2 to 5 years poststroke. J Stroke Cerebrovasc Dis. 2010;19(5):364–9.
34. Castellanos-Pinedo F, Hernandez-Perez JM, Zurdo M, Rodriguez-Funez B, Hernandez-Bayo JM, Garcia-Fernandez C, et al. Influence of premorbid psychopathology and lesion location on affective and behavioral disorders after ischemic stroke. J Neuropsychiatry Clin Neurosci. 2011;23(3):340–7.
35. Gainotti G. Emotional behavior and hemispheric side of the lesion. Cortex. 1972;8(1): 41–55.
36. Morris PL, Robinson RG, Raphael B. Prevalence and course of depressive disorders in hospitalized stroke patients. Int J Psychiatry Med. 1990;20(4):349–64.
37. Castillo CS, Schultz SK, Robinson RG. Clinical correlates of early-onset and late-onset poststroke generalized anxiety. Am J Psychiatry. 1995;152(8):1174–9.

38. Shimoda K, Robinson RG. Effects of anxiety disorder on impairment and recovery from stroke. J Neuropsychiatry Clin Neurosci. 1998;10(1):34–40.
39. Burvill PW, Johnson GA, Jamrozik KD, Anderson CS, Stewart-Wynne EG, Chakera TM. Anxiety disorders after stroke: results from the Perth Community Stroke Study. Br J Psychiatry. 1995;166(3):328–32.
40. Ballard C, Neill D, O'Brien J, McKeith IG, Ince P, Perry R. Anxiety, depression and psychosis in vascular dementia: prevalence and associations. J Affect Disord. 2000;59(2):97–106.
41. Tang WK, Chen Y, Lu J, Liang H, Chu WC, Mok VC, et al. Frontal infarcts and anxiety in stroke. Stroke. 2012;43(5):1426–8.
42. Starkstein SE, Cohen BS, Fedoroff P, Parikh RM, Price TR, Robinson RG. Relationship between anxiety disorders and depressive disorders in patients with cerebrovascular injury. Arch Gen Psychiatry. 1990;47(3):246–51.
43. Wittchen H, Beesdo K, Bittner A, Goodwin RD. Depressive episodes—evidence for a causal role of primary anxiety disorders? Eur Psychiatry. 2003;18(8):384–93.
44. Sembi S, Tarrier N, O'Neill P, Burns A, Faragher B. Does post-traumatic stress disorder occur after stroke: a preliminary study. Int J Geriatr Psychiatry. 1998;13(5):315–22.
45. Wang X, Chung MC, Hyland ME, Bahkeit M. Posttraumatic stress disorder and psychiatric co-morbidity following stroke: the role of alexithymia. Psychiatry Res. 2011;188(1):51–7.
46. Sukantarat K, Greer S, Brett S, Williamson R. Physical and psychological sequelae of critical illness. Br J Health Psychol. 2007;12(Pt 1):65–74.
47. Bruggimann L, Annoni JM, Staub F, von Steinbuchel N, Van der Linden M, Bogousslavsky J. Chronic posttraumatic stress symptoms after nonsevere stroke. Neurology. 2006;66(4):513–6.
48. National Institute for Clinical Excellence (NICE). Post-traumatic stress disorder (PTSD): the management of PTSD in adults and children in primary and secondary care. London: National institute for Clinical excellence; 2005.
49. Abramowitz JS, Taylor S, McKay D. Obsessive-compulsive disorder. Lancet. 2009;374(9688):491–9.
50. Coetzer BR. Obsessive-compulsive disorder following brain injury: a review. Int J Psychiatry Med. 2004;34(4):363–77.
51. Carmin CN, Wiegartz PS, Yunus U, Gillock KL. Treatment of late-onset OCD following basal ganglia infarct. Depress Anxiety. 2002;15(2):87–90.
52. Swoboda KJ, Jenike MA. Frontal abnormalities in a patient with obsessive-compulsive disorder: the role of structural lesions in obsessive-compulsive behavior. Neurology. 1995;45(12):2130–4.
53. Huey ED, Zahn R, Krueger F, Moll J, Kapogiannis D, Wassermann EM, et al. A psychological and neuroanatomical model of obsessive-compulsive disorder. J Neuropsychiatry Clin Neurosci. 2008;20(4):390–408.
54. Chow TW, Cummings JL. Frontal-subcortical circuits. In: Miller BL, Cummings JL, editors. The human frontal lobes. 2nd ed. New York: The Guilford Press; 2007. p. 25–44.
55. Roy-Byrne PP, Craske MG, Stein MB. Panic disorder. Lancet. 2006;368(9540):1023–32.
56. Maricle RA, Sennhauser S, Burry M. Panic disorder associated with right parahippocampal infarction. J Nerv Ment Dis. 1991;179(6):374–5.
57. Kellner M, Hirschmann M, Wiedemann K. Panic attacks caused by temporal tumors: an exemplary new case and a review. Depress Anxiety. 1996–1997;4(5):243–5.
58. Shinoura N, Yamada R, Tabei Y, Otani R, Itoi C, Saito S, et al. Damage to the right dorsal anterior cingulate cortex induces panic disorder. J Affect Disord. 2011;133(3):569–72.
59. Nagaratnam N. The development of panic attacks and social phobia after stroke. J Stroke Cerebrovasc Dis. 2000;9(2):82–5.
60. Kazui H, Mori E, Hashimoto M, Hirono N. Phobia after bilateral thalamic hemorrhage. Cerebrovasc Dis. 2001;12(3):283–4.
61. Olafiranye O, Jean-Louis G, Zizi F, Nunes J, Vincent M. Anxiety and cardiovascular risk: Review of Epidemiological and Clinical Evidence. Mind Brain. 2011;2(1):32–7.
62. Kornerup H, Zwisler AD, Prescott E, DANREHAB Group C, Denmark. No association between anxiety and depression and adverse clinical outcome among patients with cardiovascular disease: findings from the DANREHAB trial. J Psychosom Res. 2011;71(4):207–14.

63. Coughlin SS. Post-traumatic stress disorder and cardiovascular disease. Open Cardiovasc Med J. 2011;5:164–70.
64. Smoller JW, Pollack MH, Wassertheil-Smoller S, Jackson RD, Oberman A, Wong ND, et al. Panic attacks and risk of incident cardiovascular events among postmenopausal women in the Women's Health Initiative Observational Study. Arch Gen Psychiatry. 2007;64(10):1153–60.
65. Geiser F, Conrad R, Imbierowicz K, Meier C, Liedtke R, Klingmuller D, et al. Coagulation activation and fibrinolysis impairment are reduced in patients with anxiety and depression when medicated with serotonergic antidepressants. Psychiatry Clin Neurosci. 2011;65(5): 518–25.
66. Sturm JW, Donnan GA, Dewey HM, Macdonell RA, Gilligan AK, Srikanth V, et al. Quality of life after stroke: the North East Melbourne Stroke Incidence Study (NEMESIS). Stroke. 2004;35(10):2340–5.
67. Fruhwald S, Loffler-Stastka H, Eher R, Saletu B, Baumhackl U. Relationship between symptoms of depression and anxiety and the quality of life in multiple sclerosis. Wien Klin Wochenschr. 2001;113(9):333–8.
68. de Weerd L, Rutgers WA, Groenier KH, van der Meer K. Perceived wellbeing of patients one year post stroke in general practice – recommendations for quality aftercare. BMC Neurol. 2011;11:42.
69. Schmid AA, Van Puymbroeck M, Knies K, Spangler-Morris C, Watts K, Damush T, et al. Fear of falling among people who have sustained a stroke: a 6-month longitudinal pilot study. Am J Occup Ther. 2011;65(2):125–32.
70. Murphy SL, Williams CS, Gill TM. Characteristics associated with fear of falling and activity restriction in community-living older persons. J Am Geriatr Soc. 2002;50(3):516–20.
71. McCullagh E, Brigstocke G, Donaldson N, Kalra L. Determinants of caregiving burden and quality of life in caregivers of stroke patients. Stroke. 2005;36(10):2181–6.
72. Greenwood N, Mackenzie A. An exploratory study of anxiety in carers of stroke survivors. J Clin Nurs. 2010;19(13–14):2032–8.
73. Castaneda AE, Tuulio-Henriksson A, Marttunen M, Suvisaari J, Lonnqvist J. A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. J Affect Disord. 2008;106(1–2):1–27.
74. Millan MJ, Agid Y, Brune M, Bullmore ET, Carter CS, Clayton NS, et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nat Rev Drug Discov. 2012;11(2):141–68.
75. Rasquin S, Lodder J, Verhey F. The association between psychiatric and cognitive symptoms after stroke: a prospective study. Cerebrovasc Dis. 2005;19(5):309–16.
76. Olesen J, Gustavsson A, Svensson M, Wittchen H-U, Jönsson B, CDBE2010 study group, et al. The economic cost of brain disorders in Europe. Eur J Neurol. 2012;19(1):155–62.
77. Mathew SJ, Price RB, Charney DS. Recent advances in the neurobiology of anxiety disorders: implications for novel therapeutics. Am J Med Genet C Semin Med Genet. 2008;148C(2): 89–98.
78. Shin LM, Liberzon I. The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology. 2010;35(1):169–91.
79. Phelps EA, LeDoux JE. Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron. 2005;48(2):175–87.
80. Paulus MP, Stein MB. An insular view of anxiety. Biol Psychiatry. 2006;60(4):383–7.
81. Ressler KJ, Mayberg HS. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. Nat Neurosci. 2007;10(9):1116–24.
82. Vataja R, Pohjasvaara T, Mantyla R, Ylikoski R, Leppavuori A, Leskela M, et al. MRI correlates of executive dysfunction in patients with ischaemic stroke. Eur J Neurol. 2003; 10(6):625–31.
83. Garakani A, Murrough JW, Charney DS, Bremner JD. The neurobiology of anxiety disorders. In: Charney DS, Nestler EJ, editors. Neurobiology of mental illness. 3rd ed. New York: Oxford University Press Inc.; 2009. p. 655–90.

84. Aben I, Denollet J, Lousberg R, Verhey F, Wojciechowski F, Honig A. Personality and vulnerability to depression in stroke patients: a 1-year prospective follow-up study. Stroke. 2002;33(10):2391–5.
85. Davidson J, Zhang W, Connor K, Ji J, Jobson K, Lecrubier Y, et al. Review: a psychopharmacological treatment algorithm for generalised anxiety disorder (GAD). J Psychopharmacol. 2010;24(1):3–26.
86. Baldwin D, Woods R, Lawson R, Taylor D. Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. BMJ. 2011;342:d1199.
87. Draper B, Berman K. Tolerability of selective serotonin reuptake inhibitors: issues relevant to the elderly. Drugs Aging. 2008;25(6):501–19.
88. de Abajo FJ. Effects of selective serotonin reuptake inhibitors on platelet function: mechanisms, clinical outcomes and implications for use in elderly patients. Drugs Aging. 2011;28(5):345–67.
89. Macaluso M, Zackula R, D'Empaire I, Baker B, Liow K, Preskorn SH. Twenty percent of a representative sample of patients taking bupropion have abnormal, asymptomatic electroencephalographic findings. J Clin Psychopharmacol. 2010;30(3):312–7.
90. Maher AR, Maglione M, Bagley S, Suttorp M, Hu JH, Ewing B, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. JAMA. 2011;306(12):1359–69.
91. Kimura M, Tateno A, Robinson RG. Treatment of poststroke generalized anxiety disorder comorbid with poststroke depression: merged analysis of nortriptyline trials. Am J Geriatr Psychiatry. 2003;11(3):320–7.
92. Campbell Burton CA, Holmes J, Murray J, Gillespie D, Lightbody CE, Watkins CL, et al. Interventions for treating anxiety after stroke. Cochrane Database Syst Rev. 2011;12, CD008860.
93. Mula M, Pini S, Cassano GB. The role of anticonvulsant drugs in anxiety disorders: a critical review of the evidence. J Clin Psychopharmacol. 2007;27(3):263–72.
94. Wensel TM, Powe KW, Cates ME. Pregabalin for the treatment of generalized anxiety disorder. Ann Pharmacother. 2012;46(3):424–9.
95. Kim JS, Bashford G, Murphy TK, Martin A, Dror V, Cheung R. Safety and efficacy of pregabalin in patients with central post-stroke pain. Pain. 2011;152(5):1018–23.
96. Schwan S, Sundstrom A, Stjernberg E, Hallberg E, Hallberg P. A signal for an abuse liability for pregabalin – results from the Swedish spontaneous adverse drug reaction reporting system. Eur J Clin Pharmacol. 2010;66(9):947–53.
97. Wassermann EM, Zimmermann T. Transcranial magnetic brain stimulation: therapeutic promises and scientific gaps. Pharmacol Ther. 2012;133(1):98–107.
98. Jorge RE, Moser DJ, Acion L, Robinson RG. Treatment of vascular depression using repetitive transcranial magnetic stimulation. Arch Gen Psychiatry. 2008;65(3):268–76.
99. Stanley MA, Wilson NL, Novy DM, Rhoades HM, Wagener PD, Greisinger AJ, et al. Cognitive behavior therapy for generalized anxiety disorder among older adults in primary care: a randomized clinical trial. JAMA. 2009;301(14):1460–7.
100. Dobkin RD, Menza M, Allen LA, Gara MA, Mark MH, Tiu J, et al. Cognitive-behavioral therapy for depression in Parkinson's disease: a randomized, controlled trial. Am J Psychiatry. 2011;168(10):1066–74.
101. Broomfield NM, Laidlaw K, Hickabottom E, Murray MF, Pendrey R, Whittick JE, et al. Post-stroke depression: the case for augmented, individually tailored cognitive behavioural therapy. Clin Psychol Psychother. 2011;18(3):202–17.
102. Kalra L, Evans A, Perez I, Melbourn A, Patel A, Knapp M, et al. Training carers of stroke patients: randomised controlled trial. BMJ. 2004;328(7448):1099.

Chapter 6
Apathy

Lara Caeiro and José M. Ferro

Abstract Apathy is a disorder of motivation. Apathetic patients have difficulties in starting, sustaining, or finishing any goal-directed activity. They lose self-activation or self-initiated behavior and may present emotional indifference. Apathy is mostly related to damage to subcortical brain structures linked to the anterior cingulate circuit, the so-called motivational circuit. Stroke lesions encompassing the frontal lobe, the cingulum, or subcortical structures such as the pallidus, internal capsule, caudate, putamen, and anterior or medial thalamic nuclei are associated with apathy. Validated scales are used to assess apathy in stroke patients.

Apathy is frequent in stroke patients affecting 1 in every 3 patients. Apathetic patients are older than non-apathetic patients. Cognitive impairment is three times more frequent in apathetic than in non-apathetic stroke patients. Although some studies claimed an association between apathy and right-sided stroke lesions, there is no consistent evidence to support this association. Apathy without depression is about two times more frequent than depression without apathy, reinforcing the view that although these two neuropsychiatric disturbances can be associated, one can occur separately from the other.

The management of apathy includes pharmacological and non-pharmacological interventions. Drugs with potential effect in improving apathy include dopaminergic agents, stimulants, antidepressants with dopaminergic or noradrenergic activity, and acetylcholinesterase inhibitors. However, there are no randomized controlled trials to prove the efficacy and safety of these interventions in apathetic stroke patients.

Keywords Apathy • Motivation • Abulia • Athymhormia • Emotional indifference • Goal-directed activity • Self-activation • Basal ganglia • Anterior cingulated circuit

L. Caeiro, PsyD (✉) • J.M. Ferro, MD, PhD
Faculty of Medicine, Institute of Molecular Medicine,
University of Lisbon, Lisbon, Portugal

Department of Neurosciences, Neurology Service,
Hospital de Santa Maria, Av. Professor Egas Moniz,
1649-035 Lisbon, Portugal
e-mail: laracaeiro@fm.ul.pt

J.M. Ferro (ed.), *Neuropsychiatric Symptoms of Cerebrovascular Diseases*,
Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-1-4471-2428-3_6, © Springer-Verlag London 2013

Definition of Apathy and Related Concepts

Etymologically, apathy is a word with a Latin and a Greek origin. From the Greek "apátheia" (απάθεια), it means absence of sensibility, indifference, impassibility, absence of pain. From the Latin "apathia," it corresponds to an absence of passion, calm, and insensibility of the soul [1]. Apathy is an insensibility to suffering, an absence of any kind of emotion, and a lack of interest in or concern for things that others find moving or exciting [1]. What characterizes an apathetic state is the inability of an organism to be motivated, to be aroused, or to be activated by any external or internal stimulus and consequently the inability to react emotionally or by motion [2, 3].

Motivation is "the process of starting, directing and maintaining physical and psychological activities" and "includes mechanisms involved in preferences for one activity over another and the vigour and persistence of responses" [4]. Motivation is distinct from emotion which is "a complex reaction pattern involving experiential, behavioural and physiological elements, by which the individual attempts to deal with a personality significant matter or event" [4]. Behavior corresponds to "actions by which an organism adjusts to its environment". Action, as part of behavior, is a "self-initiated sequence of movements, usually with respect to some goal" [4]. Lack of motivation often results in an absence of any goal-directed or any other type of physical activity [5]. Sometimes, actions or emotions cannot be triggered by the subject himself but are prompted by others, who represent a motivational external stimulus for action.

Motivation incorporates others concepts, such as impetus or drive, need, motive, will, and volition. Impetus or drive is a "generalized state of readiness precipitating an activity or course of action." It is "created by deprivation of a needed substance, of negative stimuli or of negative events" [4] either from outside or within the organism. Impetus or drive is a psychic and biological force, which will prompt the satisfaction of a primary need or of a learned need. Need is a "condition of tension in an organism resulting from deprivation of something required for survival, well-being or personal fulfilment" [4], which induces an action to satisfy the need. Motive is a specific physiological or psychological state of arousal that directs the energies of an organism towards a goal [4]. Will is the "capacity by which human beings are able to make choices and determine their own behavior in spite of the influences external to them" [4]; Will is fundamental for motivation and subsequent behavior. Volition is a cognitive process, a "faculty by which an individual decides upon and commits to a particular course of action, especially when this occurs without direct external influence… includes choice and decision, self-control, intentional action and an active rather than passive response to events" [4].

Clinical concepts related to apathy comprise abulia, athymhormia, anhedonia, and/or emotional indifference [2, 6]. Abulia is a severe form of apathy [3, 7–9]. Abulia is a lack of will, expressed by an absence or reduction of spontaneous acting and thinking. Athymhormia defines the loss of psychic, motor, or affective autoactivation. Individuals are able to be hetero-activated (activated by others), but not activated by their own will [3, 7–10]. Anhedonia describes the lack of pleasure or

interest in activities that the patient once enjoyed. It is the "inability to enjoy experiences or activities that would normally be pleasurable" [4]. Emotional indifference represents a lack of emotions that usually arouse an individual [3, 7–9, 11].

Personality is "the unique psychological quality of an individual that influence a variety of characteristic behavior patterns (both overt and covert) across different situations and over time." A personality change is a "chronic, inflexible, maladaptative pattern of perceiving, thinking and behaving" [4]. Personality change defines a pattern of inner experience and behavior that deviates from the expectations of the culture of an individual. It is stable over time and impairs the ability of the individual to function in social or other settings. The apathetic type of a personality change is characterized by severe apathy and indifference [11].

The Concept of Apathy in Clinical Practice

In clinical practice, apathy includes an absence of motivation and of feelings, emotions, and interests [3] and of the corresponding behavior. A subclassification of apathy was attempted by Marin [5] who described three apathy syndromes: (1) cognitive apathy, a motivational disturbance with impairment of executive functions and related to dysfunction of the fronto-dorso-lateral cortex; (2) motor apathy, a motivational disturbance with extrapyramidal motor dysfunction, due to an impairment of the motor-striate regions; (3) sensory apathy, a motivational disturbance, which is manifested also by anosognosia, due to a dysfunction of the right parietal or prefrontal cortex; (4) emotional apathy without any of previous associated disturbances, related to dysfunction of neuronal circuits involving the amygdala and the cingulum [5, 6, 12, 13].

Apathetic patients have difficulties in starting, sustaining, and finishing any goal-directed activity or voluntary movements. They lose self-activation or self-initiated behavior [3]. Patients often report "not having plans," "not caring about things," or having "low interest in doing things." In the emotional field, apathetic patients may present placidity and emotional indifference. Occasionally, apathetic patients may show impaired control of the expression of emotions and impulses such as aggressiveness [2, 5, 14–20].

Starkstein and Leentjens [7] proposed an international clinical criteria, for psychiatrists, neurologists, psychologists, or other clinical practitioners, which was adapted from Marin et al. [2, 3] criteria. The proposal of diagnostic criteria for apathy resumes to "(A) Lack of motivation relatively to the previous level of functioning of the patient or the standards of his or her age and culture, as indicated either by subjective account or observation by others, (B) Presence for at least 4 weeks during most of the day, of at least one symptom belonging to each of the following three domains: 1) diminished goal-directed behaviour, 2) diminished goal-directed cognition and 3) diminished concomitants of goal-directed behaviour, (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 diminished level of consciousness or the direct physiological effects of a substance."

Following the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [11], apathy associated with stroke is classified as a "Personality Change Due to a General Medical Condition" if the predominant feature of the personality change is marked apathy and indifference. The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) [21] describes apathy as a "Personality and Behavioural Disorders Due to Brain Disease, Damage and Dysfunction" in which are affected the (I) expression of emotions and needs, (II) cognitive functioning with disturbance on planning and anticipating personal and social consequences of behavior/absence of behavior, and (III) ability to sustain goal-directed activities and emotional behavior.

The DSM-IV-TR [11] criteria of "Personality Change Due to a General Medical Condition" apathetic type is the most suitable to diagnose apathy in the post-acute phase of stroke. However, this criterion is not completely suitable to diagnose apathy in acute phase of stroke. To diagnose a personality change, it is necessary a permanent change from a previous pattern of the behavior and cognition of the patient. Thus, it is not appropriate to diagnose a permanent change of personality in the acute phase of stroke.

How to Assess Apathy

Marin et al. [3] developed the 18-item Apathy Evaluation Scale (AES), which is the most used scale in the study of apathy in stroke patients (See [14, 22–24]). Originally, it aimed to characterize and quantify apathy in patients older than 55 years old, based on clinical, self-rated, or informant opinion. Factor analysis of AES [3] identified three main factors important in the assessment of apathy: cognitive (items 1, 3, 4, 5, 8, 11, 13, and 16), behavioral (items 2, 6, 9, 10, and 12), and emotional (items 7 and 14). Internal consistency is high for the clinical-rated (coefficient $\alpha = 0.90$), for the self-rated (coefficient $\alpha = 0.86$), and for informant-rated (coefficient $\alpha = 0.94$) versions (Table 6.1).

Leuken et al. [25] created a 10-item short version of the AES adapted for demented nursing home residents, easier and faster to accomplish and with more acceptance by professional caregivers. The Leuken et al. [25] short version of the AES has high internal consistency (short AES clinical version: Cronbach $\alpha = 0.95$; AES self-rated version: Cronbach $\alpha = 0.92$). Caeiro et al. [26] also developed a 10-item version of the AES, to assess apathy in acute stroke units' settings. This version also has good construct validity and internal consistency (10-item AES clinical version: Cronbach $\alpha = 0.70$; Split-half = 0.79; 10-item AES self-rated version: Cronbach $\alpha = 0.65$; Split-half = 0.57) (Table 6.1).

Starkstein et al. [27] developed the Apathy Scale (AS), which is an adapted version of the AES, validated in patients with Parkinson's disease but also used in stroke patients. This scale had high internal consistency (coefficient $\alpha = 0.76$) and good inter-rater reliability ($r = 0.81$, $p < 0.01$).

Table 6.1 Long and short version of the AES

Apathy evaluation scale
1. S/he is interested in things.[a]
2. S/he gets things done during the day.
3. Getting things started on his/her own is important to him/her.
4. S/he is interested in having new experiences.
5. S/he is interested in learning new things.
6. S/he puts little effort into anything.[a]
7. S/he approaches life with intensity.
8. Seeing a job through to the end is important to her/him
9. S/he spends time doing things that interest her/him.
10. Someone has to tell her/him what to do each day.[a]
11. S/he is less concerned about her/his problems than s/he should be.[a]
12. S/he has friends.[a]
13. Getting together with friends is important to her/him.[a]
14. When something good happens, s/he gets excited.[a]
15. S/he has an accurate understanding of her/his problems.[a]
16. Getting things done during the day is important to her/him.
17. S/he has initiative.[a]
18. S/he has motivation.[a]

[a]Items included in the 10-item Apathy Evaluation Scale [26]

The Neuropsychiatric Inventory (NPI) [28] assesses neurobehavioral and emotional disturbances secondary to a neurological, psychiatric, or other medical disease and includes the assessment of apathy. The NPI is useful if the rating of a caregiver is needed. Habib [29] also proposed a questionnaire to assess disorders of action and motivation in neurological practice. Recently, Sockeel et al. [30] and Dujardin et al. [31] developed the Lille Apathy Rating Scale, mostly used for patients with Parkinson's disease.

Pathophysiology of Apathy

Motivational disturbances such as apathy, lack of spontaneity, and indifference, with loss of motor and affective initiative, may occur after several types and locations of brain lesions (uni or bilateral). These lesions may involve the caudate, internal globus pallidus, putamen, or a part of a wide circuit (the motivational circuit) that includes the medial nucleus of the thalamus and certain frontal regions connected with the limbic system such as the anterior part of the cingulate gyrus [8, 10, 20, 29, 32–36]. Reports of patients with so-called frontal lobe syndrome with apathetic characteristics, secondary to bilateral lesion of both globus pallidus (motor/self-activation) and of both caudate nucleus (motivation/apathy), suggest that these two brain structures are part of a network, connected with the frontal cortex, essential for organization of motivational behavior [10, 34, 37].

Apathy due to damage of the projections from the globus pallidus to the nigrostriatum dopaminergic area or lesions of several mesencephalon nuclei disturbs locomotor goal-directed behavior [19, 38]. The caudate nucleus is important for spontaneous activity, as a prefrontal activity regulator [34]. Malfunctioning of thalamic projections disturbs the normal activity of the ipsilateral frontal cortex [18, 39]. Caudate nucleus and thalamus have limbic afferents from the amygdala and orbital gyrus (inferior or orbital surface of the frontal lobe) and thus have a role in coding the emotional meaning of the events. The influences of the limbic signals into the striate-thalamic-cortical circuits, and consequently in motor or cognitive inhibition, in depression or in apathy secondary to a medical condition are well known [35, 40, 41].

The frontal network comprises five circuits, three neurobehavioral (dorsolateral, orbitofrontal, and anterior cingulate), and two motor (oculomotor and motor) [42]. The anterior cingulate circuit is the most important cortico-subcortical circuit for motivation, whose damage is responsible for apathetic states following several neurological conditions including stroke.

The anterior cingulate circuit allows intentional selection of the exterior stimulus, which is sustained by internal needs and by a combination of emotional information with motivation. A lesion at any level of the anterior cingulate circuit (anterior cingulate gyrus, caudate, globus pallidus, thalamus, and interconnecting pathways) can be followed by apathy, abulia, loss of psychic self-activation or even akinetic mutism, and catatonia [43].

Limbic areas also have major importance for the processes of motivation. The information from the exterior reaches the limbic structures and the associated motivational circuit, through the posterior hemispheric systems, where it is translated, recognized, and included in preexisting supports [5]. The posterior systems provide a representation of the environment, which is incorporated in the anterior areas of the temporal lobe and in the insula.

Incidence of Apathy in Stroke Patients

In a recent meta-analysis [44], we searched for publications on apathy secondary to cerebral infarcts or intracerebral hemorrhages, in online databases. From the initial 1,399 publications, we included 19 studies (2,221 patients). Overall, in studies on apathy secondary to stroke, the incidence of apathy ranged between 15.2 and 71.1 % (Fig. 6.1). Pooled incidence of apathy in stroke was 36.3 % (95 % CI: 30.3–42.8 %), with some heterogeneity (I^2 = 46.8 %) among the studies (Fig. 6.1). Thus, apathy secondary to stroke is a frequent neuropsychiatric disturbance affecting 1 in every 3 stroke patients. The pooled estimate of incidence of "pure" apathy (apathy without concomitant depression) was 21.4 % (95 % CI: 15.6–28.7 %) (Fig. 6.2), twice more frequent than the pooled estimate incidence of "pure" depression (depression without concomitant apathy: 12.1 %, 95 % CI: 8.2–17.3 %).

In this meta-analysis [44], the incidence of apathy secondary to stroke was comparable after left- or right-sided hemispheric stroke lesions (Odds ratio [OR] = 1.14;

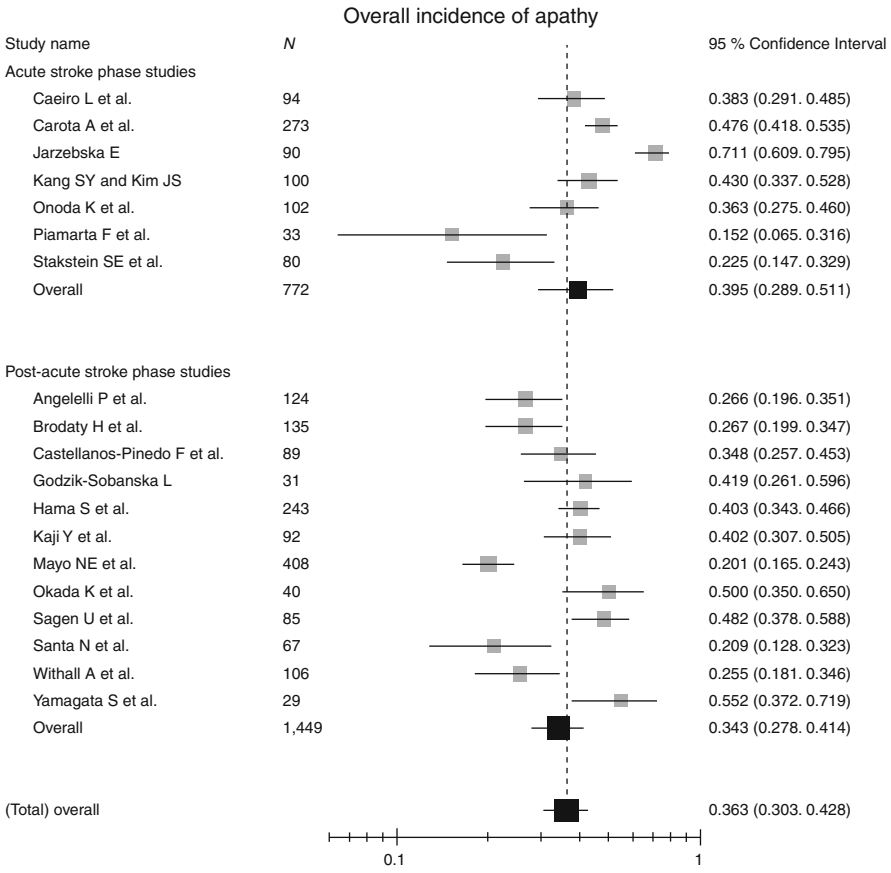


Fig. 6.1 Overall Incidence of apathy (Reproduced with permission from [44])

95 % CI: 0.60–2.15; $I^2 = 63$ %) (Fig. 6.3). The incidence of apathy was also similar after hemorrhagic or ischemic strokes (OR = 1.16; 95 % CI: 0.25–5.26; $I^2 = 79$ %) (Fig. 6.3).

Incidence of Apathy in the Acute Phase of Stroke (Apathy in Acute Stroke)

In most of the studies with acute stroke patients, the operational diagnosis of apathy includes abulia or avolition, athymhormia, and/or emotional indifference [2, 6]. There is no nosological definition for apathetic syndromes either in the DSM-IV-TR or in the ICD-10 which can be used in the acute phase of stroke [7, 11, 21]. In the systematic review [44], the meta-analysis identified an incidence of apathy in acute stroke of 39.5 % (95 % CI: 28.9–51.1 %; $I^2 = 47.0$ %) (Fig. 6.1).

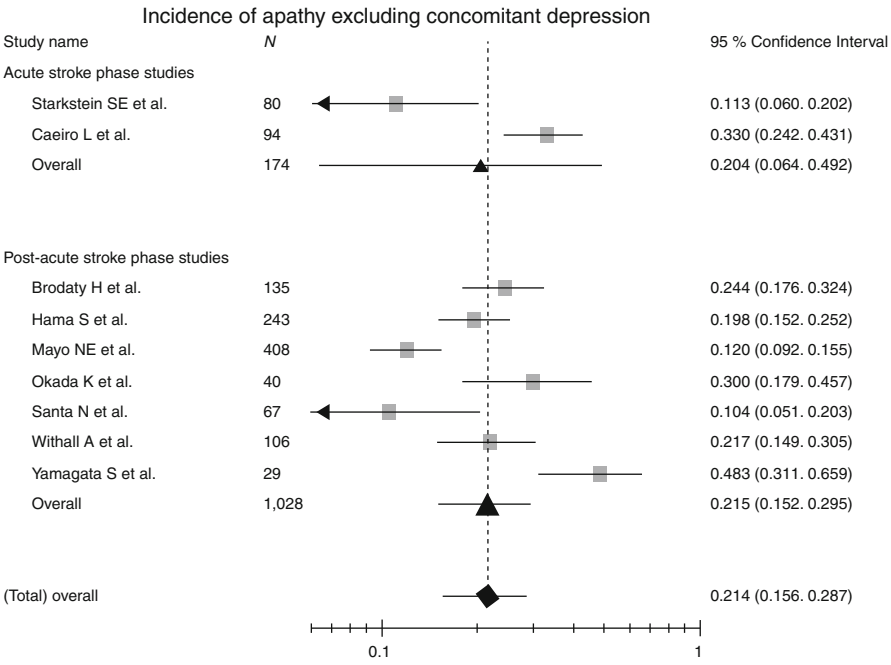


Fig. 6.2 Incidence of apathy (excluding concomitant depression) in stroke (Reproduced with permission from [44])

Incidence of Apathy in the Post-acute Phase of Stroke (Poststroke Apathy)

Studies on poststroke apathy may be supported by nosological criteria as defined in the DSM-IV-TR [11] or by ICD-10 [21]. However, most of the studies defined apathy based on the cutoff point of the scale used to assess apathy in that particular study. The frequency of apathetic patients in post-acute phase of stroke range is 20.1–91.7 % [45–54]. In the meta-analysis [44], we estimated a pooled incidence of post-stroke apathy of 34.3 % (95 % CI: 27.8–41.4 %; $I^2 = 45.7$ %) (Fig. 6.1).

Location of Lesions Causing Apathy in Stroke Patients

Apathy may be associated with infarcts at paramedian diencephalon-mesencephalon [33, 34, 55, 56]. The most commonly subcortical stroke lesions causing apathy are located in the cingulate gyrus [57], the anterior limb of the internal capsule [8], the lenticular nucleus or the globus pallidus, and in the anterior and medial thalamic nuclei [18, 39]. A review from Jorge and colleagues [32], based on the findings from

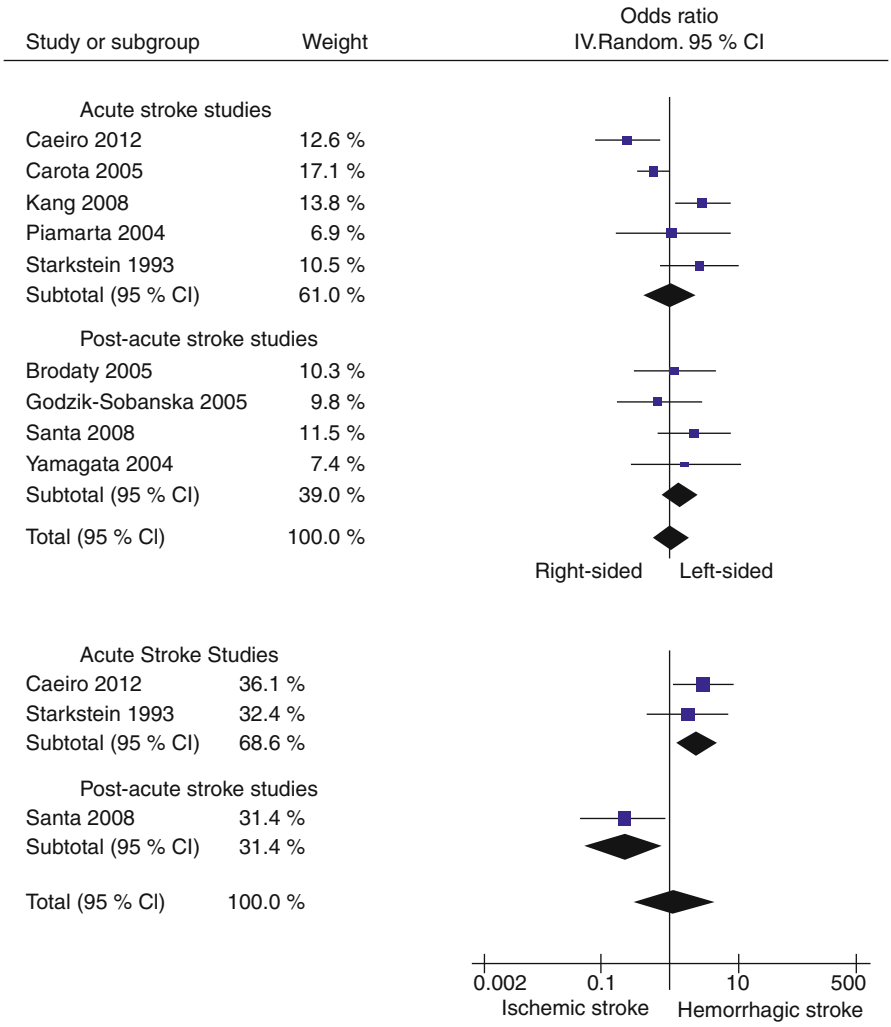


Fig. 6.3 Incidence of apathy in left versus right-sided stroke lesions and in hemorrhagic versus ischemic strokes (Reproduced with permission from [44])

five studies, suggested that stroke involving subcortical areas of the cortico-subcortical frontal circuits is associated with apathy.

Right-sided stroke lesions involving fronto-subcortical circuits or cortico-limbic-reticular subsystems, encompassing the frontal region, anterior cingulated gyrus, basal ganglia, anterior limb of the internal capsule, and thalamus cause apathy [12, 17, 18, 43, 46, 51–54, 57, 58] or indifference [59]. To explain the importance of the right-sided lateralization of brain lesion in patients with apathy, Davidson [60] suggested that the anterior regions of the left and right hemisphere are specialized in the process of approach and withdrawal, respectively.

Patients with bilateral lesions or with left-sided stroke lesions at the corpus callosum and cingulate gyrus or at the superior frontal lobe area and basal ganglia may present hypobulia or apathy or indifference [45, 48, 49, 57] or profound behavior changes such as athymhormia [61].

In CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), apathy is common affecting 37.8–41 % of the patients [62, 63]. The presence of white matter and lacunar lesions [63] and reduction of cortical surface or infarcts at the mediofrontal and orbitofrontal areas [62] are independently associated with apathy.

In the acute phase of subarachnoid hemorrhage (SAH), 42.4 % of the patients can be apathetic. Apathy is present in 22 % of the patients with perimesencephalic SAH and in 61.5 % of the patients with anterior communicating artery (ACoA) aneurysms [64]. Higher hematic densities in the left and in the right lateral ventricles are associated with apathy [64]. Apathy is one of the possible behavioral sequelae of ACoA rupture, although in some systematic studies no cases of apathy were found among SAH survivors [65].

Apathy has also been reported after cerebral venous sinus thrombosis, in cases with thrombosis of the deep venous system and thalamic infarcts or in patients with superior sagittal sinus thrombosis and cingulated infarcts [66–68].

Evidence from Lesion Studies in Cases with Apathy in Acute Stroke

Apathy in acute stroke is associated with stroke lesions involving the posterior limb of the internal capsule [38], caudate or putamen [5], but also with lesions in the territories supplied by the anterior cerebral artery [57] or the internal carotid artery [69]. Right hemispherical stroke lesions are commonly reported and increase the risk of apathy in acute stroke, mostly if the lesion is striatocapsular or thalamic [14, 51].

Only two studies on apathy in acute stroke provide information [14, 38] for the analysis between the incidence of apathy and stroke type. Patients with hemorrhagic stroke have a slight higher risk to present apathy in the acute phase (OR = 2.58; 95 % CI: 1.18–5.65; $I^2 = 0$ %) [44]. Incidence of apathy in acute stroke [14, 38, 57, 70, 71] is comparable in patients either with left- or right-sided hemispheric lesions (OR = 1.03; 95 % CI: 0.39–2.74; $I^2 = 78$ %) [44] (Fig. 6.3).

Evidence from Lesion Studies in Cases with Poststroke Apathy

Poststroke apathy associated with subcortical strokes is the most commonly reported, mostly if strokes involve the thalamus [52] or the striatum, globus pallidus, substantia nigra, and the subthalamic nucleus [45, 48, 49]. Single infarcts or hemorrhages in strategic subcortical locations interfere with specific circuits that

link the prefrontal cortex to basal nucleus or with nonspecific thalamic-cortical projections [72–75].

In the most recent meta-analysis [44], only one study on poststroke apathy [48] included data on ischemic and intracerebral hemorrhage. Ischemic patients presented a higher risk of poststroke apathy (OR = 4.35; 95 % CI: 1.11–16.7). Incidence of poststroke apathy [48, 51, 53, 58] was similar in patients with left- or right-sided hemispheric lesions (OR = 1.41; 95 % CI: 0.70–2.85; $I^2 = 0$ %) [44] (Fig. 6.3).

Evidence from Functional Studies: Poststroke Apathy

A case study using brain single-photon emission computed tomography (SPECT) [36] described a patient presenting psychosis and apathetic behavior after an acute bilateral thalamic infarct. SPECT showed bilateral hypoperfusion of the frontal lobes, which highlighted the role of thalamo-frontal circuits in the pathogenesis of apathy. Onoda et al. [45] using brain SPECT gave further evidence that hypoperfusion of the basal ganglia is associated to poststroke apathy. Habib [34] reported a patient with an infarct involving the head of the caudate nucleus. SPECT demonstrated an area of decreased perfusion in the right basal ganglia. Habib [34] concluded that the striate and the ventral globus pallidus are the brain areas where motivations are translated into behaviors and thus are an interface between motivation and action. Yamagata et al. [53] study provided further neurophysiological (event-related evoked potential) evidence of dysfunction of the frontal-subcortical system in apathetic patients with subcortical stroke. The apathetic group of stroke patients showed (1) prolonged latency of the novelty P3; (2) reduced novelty P3 amplitude over the frontal site, resulting in posterior shift of the scalp topography; and (3) correlations between the changes in novelty P3 measures and degree of apathy state.

Recently, Glodzik-Sobanska et al. [58] examined proton MRI spectroscopy findings in unaffected frontal lobes of stroke patients and demonstrated a correlation between apathy and reduction in the *N*-acetylaspartate/creatine ratio in the right frontal lobe.

Risk Factors and Associated Conditions for Apathy in Stroke Patients

Several publications suggest that aging increases the risk of poststroke apathy [47, 48, 51, 76, 77]. In our systematic review [44], among ten studies [14, 38, 45, 47, 48, 51, 53, 54, 58, 76] providing data for comparison of ages, apathetic patients were 3 years older than non-apathetic patients (mean difference [MD]: 2.74 years old [95 % CI: 1.25–4.23]; $I^2 = 0$ %), especially in the post-acute phase of stroke (MD = 2.99 [95 % CI: 1.36–4.61]; $I^2 = 0$ %). In the acute phase [14, 38, 45], apathetic patients were not older than non-apathetic patients (MD = 1.42 [95 % CI: −2.35–5.20]; $I^2 = 0$ %).

Other demographic factors such as male gender and low educational level or social condition were also pointed as risk factors for poststroke apathy, although of

less significance than age. In our meta-analysis (Fig. 6.4), the frequency of patients with apathy secondary to stroke was similar in males (OR = 0.88; 95 % CI: 0.66–1.17; $I^2 = 0$ %) and females (OR = 1.07; 95 % CI: 0.80–1.42; $I^2 = 0$ %), either in the acute phase or in post-acute phase of stroke [44].

The presence of cognitive impairment before stroke is a risk factor for post-stroke apathy [51, 53]. Poststroke cognitive impairment was also an important factor associated with poststroke apathy [45, 47, 48, 51, 76, 77]. Cognitive impairment is three times more frequent in apathetic than in non-apathetic patients (OR = 2.90;

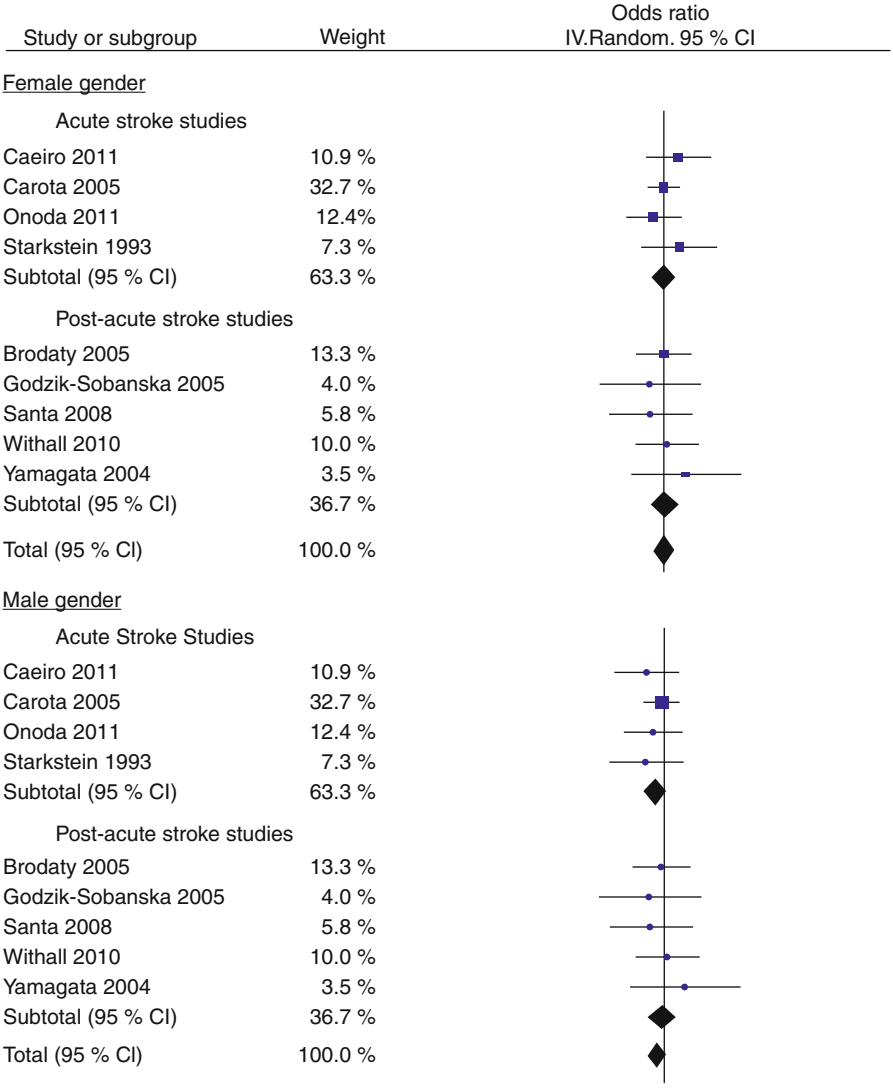


Fig. 6.4 Gender, depression, and cognitive Impairment in apathetic versus non-apathetic patients [44]

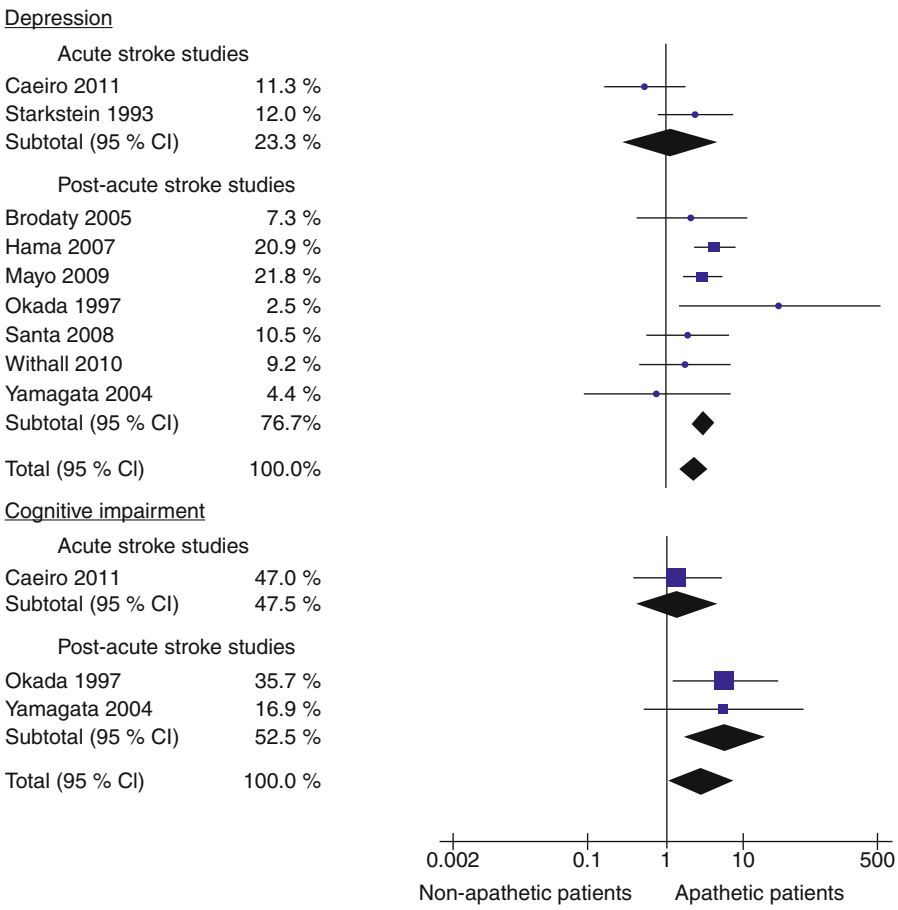


Fig. 6.4 (continued)

95 % CI: 1.09–7.72; $I^2 = 14$ %) [44] (Fig. 6.4), although this estimate is based on data from only three studies [14, 53, 54]. Severity of cognitive impairment, as assessed by the Mini-Mental State Examination [78] and the Hasegawa Dementia Rating Scale Revised, was higher in apathetic than in non-apathetic patients (standardized mean difference [SMD] = 0.68; 95 % CI: 0.50–0.85; $I^2 = 0$ %). However, severity of cognitive impairment was similar in the studies performed in acute (SMD = 0.66; 95 % CI: 0.40–0.92; $I^2 = 0$ %) and in post-acute (SMD = 0.69; 95 % CI: 0.46–0.92; $I^2 = 0$ %) stroke phases. In some studies, patients presenting post-stroke apathy showed impairments in verbal fluency tasks [53] but also other executive-type dysfunctions [18, 71, 76, 79, 80] including of attention and mental flexibility [37, 51, 61, 76, 81].

A review on apathy following stroke [32], both in acute and in post-acute phases of stroke, concluded that apathy is often associated with depression, but that one can occur separately from the other. In the acute phase of stroke, half of the patients with

apathy also present depression [38]. Our meta-analysis [44] identified nine studies [14, 42–49] providing information on depression (Fig. 6.4). Depression was more common in apathetic than in non-apathetic patients (OR = 2.29; 95 % CI: 1.41–3.72; I^2 = 44 %). The overall pooled incidence of apathy without depression was twice (21.4 %; 95 % CI: 15.6–28.7 %; I^2 = 45.6 %) (Fig. 6.2) that of depression without apathy (12.1 %; 95 % CI: 8.2–17.3 %; I^2 = 43.4 %), further reinforcing the notion that these are different clinical entities. In only half of the apathetic or of the depressive patients, an overlap between these two neuropsychiatric disturbances is seen. Depression severity, as assessed through validated scales (Montgomery and Asberg Depression Rating Scale [82], Hamilton Depression Rating Scale [83], Self-Rating Depression Scale [84]), was borderline higher in apathetic patients (SMD = 0.38; 95 % CI: −0.03–0.79; I^2 = 73 %, p = 0.003) [44]. This difference was significant only for the acute phase studies (SMD = 0.65; 95 % CI: 0.35–0.95; I^2 = 13 %) but not for the post-acute phase stroke studies (SMD 0.06; 95 % CI: −0.69–0.81; I^2 = 80 %) [44]. Apathy and depression are linked probably because they share symptoms such as diminishing interest in daily activities. Patients with both poststroke apathy and poststroke depression also share common neuropsychological features such as low MMSE scores [76] and working memory impairment [51]. Specific subcortical stroke locations can induce both poststroke apathy and poststroke depression [51, 76]. Poststroke apathy has been linked to right hemispheric subcortical lesions [49, 51, 85], while poststroke depression has been linked to left anterior lesions in one publication [49].

In acute stroke phase, apathy is present among patients with depression; however, non-depressive patients can also become apathetic [14, 15, 45, 69]. In the meta-analysis, we found that in the two publications [14, 38] reporting apathy and depression in acute phase of stroke, apathetic patients were not more frequently depressed compared with non-apathetic patients (OR = 1.18; 95 % CI: 0.28–5.02; I^2 = 71 %). Apathetic acute stroke patients often do not have the emotional experiences of loss [14] and do not feel sad but may show anhedonia [70], a symptom which may be confused with depressive mood. Apathetic patients often do not complain neither express their mood and emotional state [14], in contrast to the behavior usually displayed by depressed patients.

The association between poststroke apathy and poststroke depression is frequent; Fourteen percent to 51 % of the stroke patients present an overlap of poststroke apathy and poststroke depression [45, 51, 58, 76]. In post-acute phase of stroke, apathetic patients have 3 times more depression compared with non-apathetic patients (OR = 3.04 [95 % CI: 2.13–4.35], I^2 = 5 %) [47–49, 51, 53, 54, 76]. The pooled incidence of poststroke apathy without concomitant poststroke depression was 21.5 % (95 % CI: 15.2–29.5 %; I^2 = 45.4 %) [44] (Fig. 6.2).

Associated Neuropsychological Disturbances

Poststroke apathy is among the most troublesome stroke sequelae and may eclipse intellectual deficits [86]. In the elderly, the association between apathy and executive dysfunction increases [81].

Above all, apathetic patients present difficulties in executive tasks related to goal-directed abilities and spontaneous psychomotor initiative, motor slowness and diminished spontaneous movements, and increasing number of motor and verbal perseverations [18, 71, 87, 88].

In the acute phase of stroke, apathy is associated with global cognitive impairment (low MMSE scores) [14, 38, 45, 69]. The majority of the patients assessed in the acute phase of stroke have, at least, one cognitive domain disturbed such as memory and executive functions [77, 81, 89].

Patients with poststroke apathy have worse cognitive performances (low MMSE scores) than patients without apathy [48, 49, 51, 53, 54, 76, 90]. Apathy, as an inability of the organism to be motivated and to drive acts and relationships, is associated with executive impairments [48, 80]. The most frequent neuropsychological impairments are in the domains of attention and concentration, speed of information processing, working memory, and reasoning [51, 76, 90]. These neuropsychological impairments remain even after statistical correction for the presence of depression [51].

Outcome of Apathy in Stroke Patients

The timing of apathy assessment after stroke varied across studies from 1 day to 15 months from stroke onset. Three studies reported the evolution of apathy secondary to stroke over a year [16, 47, 90] and another over a 15-month period [76].

Caeiro et al. [90] evaluated 76 patients in the acute phase of stroke and at 1-year follow-up. In the acute phase of stroke, 17 patients were apathetic, and at 1-year follow-up, poststroke apathy was present in 18 patients. Apathy in acute stroke was an independent risk factor for poststroke apathy (OR = 3.1, 95 % CI = 0.8–12.8). Fourty-one percent of the acute apathetic patients remained apathetic at 1-year follow-up. Eleven new cases of poststroke apathy were identified at 1-year follow-up. Angelelli et al. [16] identified a three-time higher risk of development of poststroke apathy, at 6 months/1-year follow-up in patients presenting poststroke apathy at 2-month poststroke. Mayo et al. [47] studied a cohort of stroke survivors over a 1-year period and found that 50 % stroke patients were apathetic. The extent of apathetic behavior remained stable over the first year after stroke.

Withall et al. [76] followed a sample of stroke patients, 2–15 months after stroke. Two months after stroke, 21.7 % patients had poststroke apathy. Of these, at 15 months, 21.7 % remained apathetic, 30.4 % presented apathy and depression, and 43.4 % did not present any of these neuropsychiatric disturbances. Logistic regression analysis identified early cognitive impairment as a risk factor for poststroke apathy.

In conclusion, nearly half of the patients with apathy in the acute phase of stroke remain apathetic. Apathy in the acute phase of stroke is a predictor of long-term poststroke apathy.

Influence of Apathy in Stroke Outcome

Apathy is a risk factor for poor outcome or recovery after stroke [50, 51] because the patients are unable to return to their previous occupational and social activities [71, 79, 80]. The opposite is also true; the absence of apathy within the first year of poststroke is a predictor of a favorable outcome following stroke [91]. Apathy interferes with the ability of stroke patient to seek out rehabilitation services and to carry out rehabilitation exercises [48, 92, 93] or return to social relationships [48, 77].

Although a previous systematic review including five studies supported the association between apathy secondary to stroke and a lower functional status [32], our meta-analysis did not confirm those claims. The severity of the clinical global outcome, as assessed through validated scales (Modified Ranking Scale [14, 45], Johns Hopkins Functioning Inventory [38], Instrumental Activities of Daily Living [51, 76], Functional Independence Measurement [49], and Barthel Index [47, 48], was not significantly different between apathetic and non-apathetic patients (SMD = −0.01 [95 % CI: −0.39–0.36]; I^2 = 86 %)) [44]. Clinical outcome was not worse for apathetic patients either in acute (SMD = 0.27 [95%CI: −0.22–0.75]; I^2 = 71 %) and in post-acute stroke studies (SMD = −0.18 [95 % CI: −0.71–0.35]; I^2 = 91 %). Stroke is a component of physical health and also impairs psychological health, which has a negative influence in other domains of health [94]. One should note that apathetic patients may be less aware or report fewer complains about their functional loss.

Patients presenting apathy in acute stroke have a greater degree of cognitive, emotional, and physical disturbances [14, 38, 45, 48, 69, 85, 95]. Apathy is a main determinant of longer hospital stay following stroke and of nursing home and hospitalization in demented patients [96]. Apathy secondary to stroke increases the burden of caregivers, who may misattribute the pathological loss of drive to laziness or defiance [12, 97].

Management of Apathy

The management of apathy includes pharmacological and non-pharmacological interventions, namely, behavioral psychotherapy [98].

Drugs with potential effect in improving apathy include (1) dopaminergic agents [99] such as amantadine and dopaminergic agonists (e.g., bromocriptine [98] and ropinirole [100]); (2) stimulants, such as methylphenidate [101] and modafinil [102], because of its effect on stimulation of dopamine and norepinephrine release; (3) antidepressants with dopaminergic (e.g., bupropion) or noradrenergic (e.g., venlafaxine) activity; and (4) acetylcholinesterase inhibitors (e.g., donepezil [103]) and nootropics (e.g., nefiracetam [104]).

There are, however, no randomized controlled trials to prove the efficacy and safety of these medications in apathetic stroke patients.

Clinical Case

A 50-year-old male suffered a right-sided subcortical ischemic stroke. He had type II diabetes and hypercholesterolemia. He had no history of previous psychiatric or neurological disease. His wife described him as having an anxious and irritable temperament.

In the acute phase of stroke, he had left-sided brachial and facial paresis, apathy, drowsiness, and disorientation, with fluctuations during the day and all over the following week. CT scan showed a right-sided anterior thalamic infarct. Transcranial Doppler disclosed a mild left-sided middle cerebral artery stenosis. At discharge, he was considered recovered without any apparent neurologic deficits (modified Rankin scale score of 1).

He performed a neuropsychiatry evaluation 2 weeks after stroke onset. He had no language, memory, or executive impairments. He described himself as being unmotivated, with low energy and consequently having difficulties in starting, sustaining, and finishing any goal-directed activity. He also reported emotional indifference and of being less concerned about things. He characterized his state as apathetic (Apathy Scale = 13 points). At clinical observation, we confirmed all these apathetic characteristics but also athymhormia and low initiative (10-item Apathy Evaluation Scale = 17 points).

During the following year, his wife described him as a different person, not showing his usual irritable or anxious behavior. He remained without motivation, initiative, or self-activation and was emotionally indifferent. He would do things only if prompted by his wife. He had insight about his present condition, but he really did not care about his personality changes. His days were preferentially spent in front of a TV screen, changing channels.

At 8 months after stroke, he returned for a follow-up neuropsychological evaluation. He scored 29 on the MMSE. He showed impairments on sustained attention/speed, motor control, concentration, verbal fluency, abstract reasoning, and set shifting. He continued to describe himself as being apathetic (Apathy Scale = 28 points). His wife confirmed the same apathetic characteristics but in a severer degree than the patient (18-items Apathy Evaluation Scale score = 49 points). Clinical observation also confirmed apathy (18-item Apathy Evaluation Scale = 48 points).

Serotoninergic and noradrenergic antidepressants, bromocriptine, and modafinil were tried without effect.

References

1. Cresswell J. The Oxford dictionary of word origins. Oxford: Oxford University Press; 2009. Available from: http://www.oxfordreference.com/views/BOOK_SEARCH.html?book=t292
2. Marin RS. Apathy: a neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci. 1991;3: 243–54.

3. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res. 1991;38:143–62.
4. American Psychological Association. In: VandenBos GR, editor in Chief. APA dictionary of psychology. Washington, D.C.: American Psychological Association; 2007.
5. Marin RS. Apathy: concept, syndrome, neural mechanisms, and treatment. Semin Clin Neuropsychiatry. 1996;1:304–14.
6. Marin RS, Wilkosz PA. Disorders of diminished motivation. J Head Trauma Rehabil. 2005; 20:377–88.
7. Starkstein SE, Leentjens AF. The nosological position of apathy in clinical practice. J Neurol Neurosurg Psychiatry. 2008;79:1088–92.
8. Ghika-Schmid FS, Bogousslavsky J. Emotional behavior in acute brain lesions. In: Bogousslavsky J, Cummings JL, editors. Behavior and mood disorders in focal brain lesions. Cambridge: University Press; 2000. p. 65–94.
9. Sadock BJS, Sadock VAS. Synopsis of psychiatry. Behavioural sciences/clinical psychiatry. 9th ed. Philadelphia: Lippincott Williams and Wilkins; 2003.
10. Laplane D. Loss of psychic self-activation. Rev Neurol (Paris). 1990;146:397–404.
11. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Text revision ed. Washington, D.C.: American Psychiatric Press; 2002. p. 345–428.
12. Morris J. Effects of right hemisphere strokes on personality functioning. Top Stroke Rehabil. 2009;16:425–30.
13. Duffy J. Apathy in neurologic disorders. Curr Psychiatry Rep. 2000;2:434–9.
14. Caeiro L, Ferro JM, Figueira ML. Apathy in acute stroke patients. Eur J Neurol. 2012;19:291–7.
15. Aybek S, Carota A, Ghika-Schmid F, Berney A, Melle GV, Guex P, et al. Emotional behavior in acute stroke: the Lausanne emotion in stroke study. Cogn Behav Neurol. 2005;18: 37–44.
16. Angelelli P, Paolucci S, Bivona U, Piccardi L, Ciurli P, Cantagallo A, et al. Development of neuropsychiatric symptoms in poststroke patients: a cross-sectional study. Acta Psychiatr Scand. 2004;110:55–63.
17. Schmahmann JD. Vascular syndromes of the thalamus. Stroke. 2003;34:2264–78.
18. Ghika-Schmid F, Bogousslavsky J. The acute behavioral syndrome of anterior thalamic infarction: a prospective study of 12 cases. Ann Neurol. 2000;48:220–7.
19. Marin RS, Fogel BS, Hawkins J, Duffy J, Krupp B. Apathy: a treatable syndrome. J Neuropsychiatry Clin Neurosci. 1995;7:23–30.
20. Marin RS. Differential diagnosis and classification of apathy. Am J Psychiatry. 1990;147: 22–30.
21. World Health Organization. International classification of diseases and related health problems. 10th ed. Genève: World Health Organization; 1992.
22. Lee SH, Wen MC, Chao CC, Chen YJ, Yen CF. Apathy in late-life depression among Taiwanese patients. Int Psychogeriatr. 2008;20:328–37.
23. Clarke DE, Van Reekum R, Patel J, Simard M, Gomez E, Streiner DL. An appraisal of the psychometric properties of the Clinician version of the Apathy Evaluation Scale (AES-C). Int J Methods Psychiatr Res. 2007;16:97–110.
24. Lueken U, Seidl U, Schwarz M, Völker L, Naumann D, Mattes K, et al. Psychometric properties of a German version of the Apathy Evaluation Scale. Fortschr Neurol Psychiatr. 2006;74:714–22.
25. Lueken U, Seidl U, Völker L, Schweiger E, Kruse A, Schröder J. Development of a short version of the Apathy Evaluation Scale specifically adapted for demented nursing home residents. Am J Geriatr Psychiatry. 2007;15:376–85.
26. Caeiro L, Silva T, Ferro JM, Pais-Ribeiro J, Figueira ML. Metric Properties of the Portuguese Version of the Apathy Evaluation Scale. Psicologia, Saúde & Doenças. 2012;13:266–82.
27. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci. 1992;4:134–9.
28. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44:2308–14.

29. Habib M. Activity and motivational disorders in neurology: proposal for an evaluation scale. Encéphale. 1995;21:563–70.
30. Sockeel P, Dujardin K, Devos D, Denève C, Destée A, Defebvre L. The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2006;77:579–84.
31. Dujardin K, Sockeel P, Delliaux M, Destée A, Defebvre L. The Lille Apathy Rating Scale: validation of a caregiver-based version. Mov Disord. 2008;23:845–9.
32. Jorge RE, Starkstein SE, Robinson RG. Apathy following stroke. Can J Psychiatry. 2010; 55:350–4.
33. Hoffmann M, Cases LB. Etiology of frontal network syndromes in isolated subtentorial stroke. Behav Neurol. 2008;20:101–5.
34. Habib M. Disorders of motivation. In: Bogousslavsky J, Cummings JL, editors. Behaviour and mood disorders in focal brain lesions. Cambridge: Cambridge University Press; 2000. p. 261–684.
35. Bhatia KP, Marsden CD. The behavioural and motor consequences of focal lesions of the basal ganglia in man. Brain. 1994;117:859–76.
36. McGilchrist I, Goldstein LH, Jadresic D, Fenwick P. Thalamo-frontal psychosis. Br J Psychiatry. 1993;163:113–5.
37. Absher JR, Cummings JL. Neurobehavioral examination of frontal lobe functions. Aphasiology. 1995;9:181–92.
38. Starkstein SE, Fedoroff JP, Price TR, Leiguarda R, Robinson RG. Apathy following cerebrovascular lesions. Stroke. 1993;24:1625–30.
39. Krolak-Salmon P, Croisile B, Houzard C, Setiey A, Girard-Madoux P, Vighetto A. Total recovery after bilateral paramedian thalamic infarct. Eur Neurol. 2000;44:216–8.
40. Brown RG, Pluck G. Negative symptoms: the 'pathology' of motivation and goal-directed behaviour. Trends Neurosci. 2000;23:412–7.
41. Rauch SL, Savage CR. Neuroimaging and neuropsychology of the striatum. Bridging basic science and clinical practice. Psychiatr Clin North Am. 1997;20:741–68.
42. Chow TW, Cummings JL. Frontal-subcortical circuits. In: Miller BL, Cummings JL, editors. The human frontal lobes. New York: The Guilford Press; 1999.
43. Cummings JL. Frontal-subcortical circuits and human behavior. Arch Neurol. 1993;50: 873–80.
44. Caeiro L, Ferro JM, Costa J. Apathy secondary to stroke: a systematic review and meta-analysis. Cerebrovasc Dis. 2013;35:23–39.
45. Onoda K, Kuroda Y, Yamamoto Y, et al. Post-stroke apathy and hypoperfusion in basal ganglia: SPECT study. Cerebrovasc Dis. 2011;31:6–11.
46. Castellanos-Pinedo F, Hernández-Pérez JM, Zurdo M, et al. Influence of premorbid psychopathology and lesion location on affective and behavioral disorders after ischemic stroke. J Neuropsychiatry Clin Neurosci. 2011;23:340–7.
47. Mayo NE, Fellows LK, Scott SC, Cameron J, Wood-Dauphinee S. A longitudinal view of apathy and its impact after stroke. Stroke. 2009;40:3299–307.
48. Santa N, Sugimori H, Kusuda K, Yamashita Y, Ibayashi S, Iida M. Apathy and functional recovery following first-ever stroke. Int J Rehabil Res. 2008;31:321–6.
49. Hama S, Yamashita H, Shigenobu M, 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.
50. Hama S, Yamashita H, Shigenobu M, et al. Depression or apathy and functional recovery after stroke. Int J Geriatr Psychiatry. 2007;22:1046–51.
51. Brodaty H, Sachdev PS, Withall A, Altendorf A, Valenzuela MJ, Lorentz L. Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke – the Sydney Stroke Study. Psychol Med. 2005;35:1707–16.
52. Perren F, Clarke S, Bogousslavsky J. The syndrome of combined polar and paramedian thalamic infarction. Arch Neurol. 2005;62:1212–6.
53. Yamagata S, Yamaguchi S, Kobayashi S. Impaired novelty processing in apathy after subcortical stroke. Stroke. 2004;35:1935–40.

54. Okada K, Kobayashi S, Yamagata S, Takahashi K, Yamaguchi S. Poststroke apathy and regional cerebral blood flow. Stroke. 1997;28:2437–41.
55. Engelborghs S, Marien P, Pickut BA, Verstraeten S, De Deyn PP. Loss of psychic self-activation after paramedian bithalamic infarction. Stroke. 2000;31:1762–5.
56. Bogousslavsky J, Regli F, Delaloye B, Delaloye-Bischof A, Assal G, Uske A. Loss of psychic self-activation with bithalamic infarction. Neurobehavioural, CT, MRI and SPECT correlates. Acta Neurol Scand. 1991;83:309–16.
57. Kang SY, Kim JS. Anterior cerebral artery infarction: stroke mechanism and clinical-imaging study in 100 patients. Neurology. 2008;70:2386–93.
58. Glodzik-Sobanska L, Slowik A, Kieltyka A, Kozub J, Sobiecka B, Urbanik A, et al. Reduced prefrontal N-acetylaspartate in stroke patients with apathy. J Neurol Sci. 2005;238:19–24.
59. Heilman KM, Valenstein E, Watson RT. The neglect syndrome. In: Frederiks JAM, editor. Handbook of clinical neurology. New York: Elsevier; 1995. p. 153–83.
60. Davidson RJ. Cerebral asymmetry, emotion and affective style. In: Davidson RJ, Hugdahl K, editors. Brain asymmetry. Cambridge: MTI Press; 1995.
61. Habib M. Athymhormia and disorders of motivation in Basal Ganglia disease. J Neuropsychiatry Clin Neurosci. 2004;16:509–24.
62. Jouvent E, Reyes S, Mangin JF, et al. Apathy is related to cortex morphology in CADASIL. A sulcal-based morphometry study. Neurology. 2011;76:1472–7.
63. Reyes S, Viswanathan A, Godin O, et al. Apathy: a major symptom in CADASIL. Neurology. 2009;72:905–10.
64. Caeiro L, Santos CO, Ferro JM, Figueira ML. Neuropsychiatric disturbances in acute subarachnoid haemorrhage. Eur J Neurol. 2011;18:857–64.
65. Haug T, Sorteberg A, Sorteberg W, Lindegaard KF, Lundar T, Finset A. Cognitive functioning and health related quality of life after rupture of an aneurysm on the anterior communicating artery versus middle cerebral artery. Br J Neurosurg. 2009;23:507–15.
66. Haley EC, Brashear HR, Barth JT, Cail WS, Kassell NF. Deep cerebral venous thrombosis. Clinical, neuroradiological, and neuropsychological correlates. Arch Neurol. 1989;46: 337–40.
67. Oya Y, Sakurai Y, Takeda K, Iwata M, Kanazawa I. A neuropsychological study on a patient with the resection of the right lateral frontal lobe. Rinsho Shinkeigaku. 1997;37:829–33.
68. Ferro JM, Canhão P. Complications of cerebral vein and sinus thrombosis. Front Neurol Neurosci. 2008;23:161–71.
69. Jarzebska E. Stroke patients' apathy. Pol Merkur Lekarski. 2007;22:280–2.
70. Carota A, Berney A, Aybek S, et al. A prospective study of predictors of poststroke depression. Neurology. 2005;64:428–33.
71. Piamarta F, Iurlaro S, Isella V, et al. Unconventional affective symptoms and executive functions after stroke in the elderly. Arch Gerontol Geriatr Suppl. 2004;9:315–23.
72. Haring HP. Cognitive impairment after stroke. Curr Opin Neurol. 2002;15:79–84.
73. Kurz AF. What is vascular dementia? Int J Clin Pract Suppl. 2001;120:5–8.
74. Watanabe MD, Martin EM, DeLeon OA, Gaviria M, Pavel DG, Trepashko DW. Successful methylphenidate treatment of apathy after subcortical infarcts. J Neuropsychiatry Clin Neurosci. 1995;7:502–4.
75. Laplane D. The role of basal ganglia in mental life. Rev Prat. 1990;40:1304–11.
76. Withall A, Brodaty H, Altendorf A, Sachdev PS. A longitudinal study examining the independence of apathy and depression after stroke: the Sydney Stroke Study. Int Psychogeriatr. 2011;23:264–73.
77. Hama S, Yamashita H, Shigenobu M, et al. Sitting balance as an early predictor of functional improvement in association with depressive symptoms in stroke patients. Psychiatry Clin Neurosci. 2007;61:543–51.
78. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–98.
79. Hommel M, Trabucco-Miguel S, Joray S, Naegele B, Gonnet N, Jaillard A. Social dysfunctioning after mild to moderate first-ever stroke at vocational age. J Neurol Neurosurg Psychiatry. 2009;80:371–5.

80. Feil D, Razani J, Boone K, Lesser I. Apathy and cognitive performance in older adults with depression. Int J Geriatr Psychiatry. 2003;18:479–85.
81. Hazif-Thomas C, Chantoin-Merlet S, Thomas P, Bonneau V, Billon R. Loss of motivation and frontal dysfunctions in old patients. Encéphale. 2002;28:533–41.
82. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382–9.
83. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56–62.
84. Zung WW. A self-rating depression scale. Arch Gen Psychiatry. 1965;12:63–70.
85. Andersson S, Krogstad JM, Finset A. Apathy and depressed mood in acquired brain damage: relationship to lesion localization and psychophysiological reactivity. Psychol Med. 1999;29:447–56.
86. Harris Y, Gorelick PB, Cohen D, Dollear W, Forman H, Freels S. Psychiatric symptoms in dementia associated with stroke: a case–control analysis among predominantly African-American patients. J Natl Med Assoc. 1994;86:697–702.
87. Skidmore ER, Whyte EM, Holm MB, et al. Cognitive and affective predictors of rehabilitation participation after stroke. Arch Phys Med Rehabil. 2010;91:203–7.
88. Duffy JD, Campbell JJ. The regional prefrontal syndromes: a theoretical and clinical overview. J Neuropsychiatry Clin Neurosci. 1994;6:379–87.
89. Jaillard A, Naegele B, Trabucco-Miguel S, LeBas JF, Hommel M. Hidden dysfunctioning in subacute stroke. Stroke. 2009;40:2473–9.
90. Caeiro L, Ferro JM, Melo TP, Canhão P, Figueira ML. Post-stroke apathy: an exploratory longitudinal stud. Cerebrovasc Dis. 2013..
91. Withall A, Brodaty H, Altendorf A, Sachdev PS. Who does well after a stroke? The Sydney stroke study. Aging Ment Health. 2009;13:693–8.
92. Zawacki TM, Grace J, Paul R, et al. Behavioral problems as predictors of functional abilities of vascular dementia patients. J Neuropsychiatry Clin Neurosci. 2002;14:296–302.
93. Galynker I, Prikhojan A, Phillips E, Focseneanu M, Ieronimo C, Rosenthal R. Negative symptoms in stroke patients and length of hospital stay. J Nerv Ment Dis. 1997;185:616–21.
94. Owolabi MO. What are the consistent predictors of generic and specific post-stroke health-related quality of life? Cerebrovasc Dis. 2010;29:105–10.
95. Gainotti G, Azzoni A, Razzano C, Lanzillotta M, Marra C, Gasparini F. The Post-Stroke Depression Rating Scale: a test specifically devised to investigate affective disorders of stroke patients. J Clin Exp Neuropsychol. 1997;19:340–56.
96. Weber K, Meiler-Mititelu C, Herrmann FR, Delaloye C, Giannakopoulos P, Canuto A. Longitudinal assessment of psychotherapeutic day hospital treatment for neuropsychiatric symptoms in dementia. Aging Ment Health. 2009;13:92–8.
97. Landes AM, Sperry SD, Strauss ME, Geldmacher DS. Apathy in Alzheimer's disease. J Am Geriatr Soc. 2001;49:1700–7.
98. van Reekum R, Stuss DT, Ostrander L. Apathy: why care? J Neuropsychiatry Clin Neurosci. 2005;17:7–19.
99. Roth RM, Flashman LA, McAllister TW. Apathy and its treatment. Curr Treat Options Neurol. 2007;9:363–70.
100. Kohno N, Abe S, Toyoda G, Oguro H, Bokura H, Yamaguchi S. Successful treatment of post-stroke apathy by the dopamine receptor agonist ropinirole. J Clin Neurosci. 2010;17:804–6.
101. Spiegel DR, Kim J, Greene K, Conner C, Zamfir D. Apathy due to cerebrovascular accidents successfully treated with methylphenidate: a case series. J Neuropsychiatry Clin Neurosci. 2009;21:216–9.
102. Sugden SG, Bourgeois JA. Modafinil monotherapy in poststroke depression. Psychosomatics. 2004;45:80–1.
103. Whyte EM, Lenze EJ, Butters M, et al. An open-label pilot study of acetylcholinesterase inhibitors to promote functional recovery in elderly cognitively impaired stroke patients. Cerebrovasc Dis. 2008;26:317–21.
104. Robinson RG, Jorge RE, Clarence-Smith K, Starkstein S. Double-blind treatment of apathy in patients with poststroke depression using nefiracetam. J Neuropsychiatry Clin Neurosci. 2009;21:144–51.

Chapter 7
Disturbances in the Voluntary Control of Emotional Expression After Stroke

Jong S. Kim and Smi Choi-Kwon

Abstract Disturbances in the voluntary control of emotional expression after a stroke were first reported in the nineteenth century and extensively reviewed by Wilson in 1924. A variety of terms have since been used such as pathological laughing and crying, pseudobulbar affect, emotionalism, emotional lability, involuntary emotional expression disorder, and post-stroke emotional incontinence (PSEI). The prevalence of PSEI ranges 6–34 % (mostly 10–20 %) of stroke patients. It seems that PSEI is more often observed in the subacute stage than in the acute or chronic stage. However, there are patients who show abnormal emotional display before the onset of other major neurologic dysfunction (*fou rire prodromique*).

Recent advances in brain imaging technologies have shown that lesions affecting frontal-internal capsular-pontine base circuitry most often produce PSEI. Cerebellar, basal ganglionic, and thalamic lesions are also occasionally associated with PSEI. Wilson proposed that pathological crying and laughing is caused by disinhibition of a brainstem fasciorespiratory control center for emotional expression secondary to lesions of descending corticobulbar pathways from higher cortical brain centers. This disinhibition theory has been modified, and it is currently believed that deficits in any areas of brain network related to emotional expression (cortico-limbic subcortical-thalamic-ponto-cerebellar system) can lead to PSEI.

Lesion location studies, positron emission tomography studies, and clinical trial results have shown that serotonin dysfunction plays an important role in producing PSEI. Selective serotonin reuptake inhibitors (SSRIs) are recommended as first-line agents for the treatment of PSEI as they are promptly effective and tolerable and

J.S. Kim, MD, PhD (✉)
Department of Neurology, University of Ulsan College of Medicine,
Asan Medical Center, 145, Song-Pa, Seoul 138-600, South Korea
e-mail: jongskim@amc.seoul.kr

S. Choi-Kwon, PhD, RN
College of Nursing, Research Institute of Nursing Science,
Seoul National University, Seoul, Korea

J.M. Ferro (ed.), *Neuropsychiatric Symptoms of Cerebrovascular Diseases*,
Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-1-4471-2428-3_7, © Springer-Verlag London 2013

may also improve patients' quality of life. When SSRIs are ineffective or poorly tolerated, tricyclic antidepressants, selective adrenergic receptor inhibitors, or dopaminergic agents can be considered.

Keywords Emotion • Expression • Crying • Laughing • Depression • Stroke

Introduction

Disturbances in the voluntary control of emotional expression after a stroke were first reported in the nineteenth century. Since Wilson's description of the classic model of pathological laughing and crying [1], clinicians have paid increased attention to this issue. Abnormal emotional displays have been described using a variety of terms, including pseudobulbar affect, pathological laughing and crying, emotionalism, lability of mood, and emotional incontinence [2]. Patients typically present with uncontrollable outbursts of involuntary laughing or crying that are unrelated to the underlying emotional state [1]. However, a milder form of emotional lability, provoked by congruous emotional stimuli, is more prevalent in clinical practice [3]. Patients suffering from emotional expression disorders are not necessarily depressed or elated during their emotional displays [2]. Nevertheless, when the symptoms are frequent or severe, they can be embarrassing and distressing for both the patient and their caregivers.

Recent advances in imaging technologies such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography have increased our understanding of the lesion location and pathogenesis of this syndrome, and a number of randomized clinical trials (RTCs) have shown effective therapeutic strategies. In this chapter, we review the history, nomenclature, clinical features, lesion locations, pathogenesis, involved neurotransmitters, and therapeutic strategies associated with disturbed control of emotional expression after stroke.

History

Abnormal emotional displays in patients with brain pathology are described in medical literature as far back as 1837 [4]. In 1872, Charles Darwin wrote in his book "The Expression of the Emotions in Man and Animals" that "certain brain diseases have a special tendency to induce weeping" [5]. Years later, several European authors including Oppenheim and Siemerling [6], Brissaud [7], and Nothnagel [8] published clinical case reports that described pathological laughing and crying. In 1903, a French neurologist, Charles Féré [9], described a patient who showed pathological laughter heralding an apoplectic event and used the term "*fou rire prodromique*" to describe this phenomenon. The following year, Weisenberg [10] published the first case series of pathological laughing and crying in the USA and

Table 7.1 Terminologies describing abnormal emotional display after brain disease

	Pros	Cons
Pseudobulbar affect (laughing, crying)	Widely used, familiar to physicians	Not all the patients show bulbar symptoms Pathophysiologic mechanisms are beyond corticobulbar tracts involvement
Pathological affect (laughing, crying)	Familiar to physicians, easy to understand Correctly imply that the symptoms are related to brain pathology	Does not exclude ictal symptoms (gelastic epilepsy)
Emotional lability, affective lability	Can encompass a large number of patients showing emotional problems	Less specific, does not clearly covey the meaning of symptoms related to brain disorders
Emotionalism	Comprehensive, short	Less specific, does not clearly covey the meaning of symptoms related to brain disorders
Emotional incontinence	Correctly imply that the symptoms are due to neurological disorders	Some criticize it as distasteful
Involuntary emotional expression disorder	Clearly differentiates expression from formulation disorders of emotion	The term "involuntary" is confusing Gives patients unnecessary stigma as a "disorder"

described the essential features of this syndrome: impulsive laughing and crying that is beyond the control of the patient and brought on by the slightest irritation, or occasionally without any apparent cause, and crying that may terminate in laughing or vice versa. It was in 1924, however, when Wilson [1] wrote a comprehensive, landmark review on the important clinical and pathological features of this syndrome. The subsequent paper by Davison and Kelman [11] is another excellent and comprehensive description of this issue.

Nomenclature

Multiple terminologies have been used to describe these abnormal emotional displays in patients with brain disease, and they are summarized in Table 7.1. The term most familiar to physicians may be pseudobulbar affect, incorporating pseudobulbar crying, laughing, weeping, and pseudobulbar palsy. The term has been used because symptoms of pseudobulbar palsy (dysarthria, facial palsy, dysphagia, and increased jaw jerk) are frequently present in these patients. However, this term is inappropriate for several reasons. Firstly, episodes may occur without these neurologic signs [12]. Recent studies have found that mild emotional displays were often accompanied by unilateral brain lesions that did not produce significant bulbar symptoms [3, 13]. Furthermore, lesions that lead to abnormal emotional displays

are not necessarily limited to the corticobulbar circuitry and may involve the cortical, subcortical, and limbic structures [14]. Therefore, although this term has been used until recently [12, 15–17], it is clearly inappropriate.

Another widely used term is pathological crying or laughing. This was used by Wilson [1] to describe "exaggerated, forced, involuntary, uncontrollable laughing or weeping." Pathological crying or laughing is easy to understand, appropriately implicates the presence of underlying brain pathology, and therefore has been frequently used until recently [3, 18–23]. However, this term indicates any laughing and crying caused by brain pathology and does not exclude ictal symptoms in patients with gelastic epilepsy [24, 25]. In addition, milder symptoms, such as simple, excessive smiling, or weeping upon congruous emotive stimuli [13, 26, 27], are not readily incorporated by this term. Finally, the term does not differentiate between pathological expression and pathological formulation of primary feelings. In this sense, the term pathological affect [28] is also inappropriate, as it implies abnormal development of emotion in patients with hysteria or depression.

Emotional lability [27, 29] and affective lability [30] are also used to describe abnormal emotional displays in patients with neurologic disorders. These terms are occasionally used to indicate symptoms similar to pathological laughing and crying [26] or emotional incontinence [29], but they are also used to indicate excessive weeping due to depression or a sad situation. In addition, these are too mild to incorporate the severely abnormal emotional displays described in early reports [1, 31]. Emotional incontinence is another term frequently used [13, 32–34]. It encompasses a broad range of symptoms, from simple excessive emotional displays to severe pathological laughing or crying, and clearly indicates that they are related to neurologic disorders. Moreover, as "incontinence" is frequently used in clinical neurology, the term is familiar to us. The term emotionalism has also been used occasionally to imply similar meanings [26, 35, 36] but is less specific and does not clearly convey the meaning that this is a specific symptom secondary to a neurologic disorder.

Recently, "involuntary emotional expression disorder" has been proposed as a term to describe abnormal emotional displays in neurology patients [2]. Although we agree on its merits, this term is still confusing. There are patients with bilateral voluntary facial paresis who have no facial weakness during pathological laughing and crying [1]. Although Wilson hypothesized that lesions affecting the "voluntary" pathways from the cerebral motor cortex result in dysregulation of the brainstem emotion center [1], this theory has since been criticized [18]. Thus, using the term "involuntary" may lead to confusion. Furthermore, although it is generally agreed that the abnormal emotional displays are primarily a problem in the output of emotion, there are lingering arguments that patients may also have abnormalities on the perception side [37], and this possibility is not suitably encompassed by the term "expression disorder." Finally, using the term "disorder" may give patients unnecessary stigma; abnormal emotional displays are a simple neurologic symptom but are not a specific disorder. To avoid this confusion, some authors used simpler terms such as "excessive crying" [37] or "uncontrolled crying" [38, 39]. Although we appreciate the comprehensiveness and the simplicity of these terms, they do not sufficiently convey the meaning of medical symptoms caused by brain lesions.

With all this consideration, we will use the term post-stroke emotional incontinence (PSEI) in the text. Although some authors interpret this term as distasteful [15] or derogatory [40] to patients, we do not agree. In our view, emotional incontinence is simple, yet sufficiently indicates the dysregulation of emotional expression due to brain pathology. This can be used in medical settings alongside terms such as urinary and fecal incontinence.

Phenomenology

Illustrative Patient

A 72-year-old hypertensive woman developed sudden dysarthria and mild right hemiparesis. From then on, she showed frequent, excessive laughing and, less often, crying on trivial occasions. In addition, she gradually became more forgetful and had difficulty in gait. When she was admitted to our hospital 2 years later, she was alert and oriented. She had dysarthria, dysphagia, and increased deep tendon reflexes in both limbs. Her gait was clumsy and spastic. Her daughter reported that she occasionally fell down; she was once admitted to an orthopedic clinic due to spine fracture. Her mini-mental state examination score was 21/30, and cognitive function tests showed impaired attention, memory, visuospatial, word retrieval, and frontal executive functions. However, she did not have a particular difficulty in her daily life as a housewife. There was no personality change according to her relatives.

Of note was that she laughed frequently. During the interview of 5 min, she laughed approximately ten times. The laughter was sudden, explosive, uncontrollable, and lasted usually for 15–30 s (Fig. 7.1). Meeting and talking with somebody frequently triggered her laughing. According to her daughter, the laughing was especially frequent when the patient encountered her granddaughters. The patient reported that she also laughs while left alone. However, her daughter stated that she seems to laugh while she thinks about her family especially her granddaughters, upon which the patient agreed.

Although it was the laughter that was mainly observed, she also cried occasionally upon trivial events. During the interview, after one prolonged laugher, tears were observed in her eyes. When asked whether she was depressed, she denied but stated that she is stressed because of her gait difficulty and frequent laughing. She did not have major depression according to DSM-IV criteria. The frequent and excessive laughing prevented her from normal social life; she rarely went out for shopping because she was afraid of her laughing being watched by others. Occasionally, she had difficulty in falling asleep because she continuously laughed.

Brain MRI showed multiple, bilateral subcortical, and white matter ischemic lesions (Fig. 7.2). Magnetic resonance angiography showed mild stenosis on distal

Fig. 7.1 Patient showing excessive and uncontrollable laughing (Permission obtained from the patient)

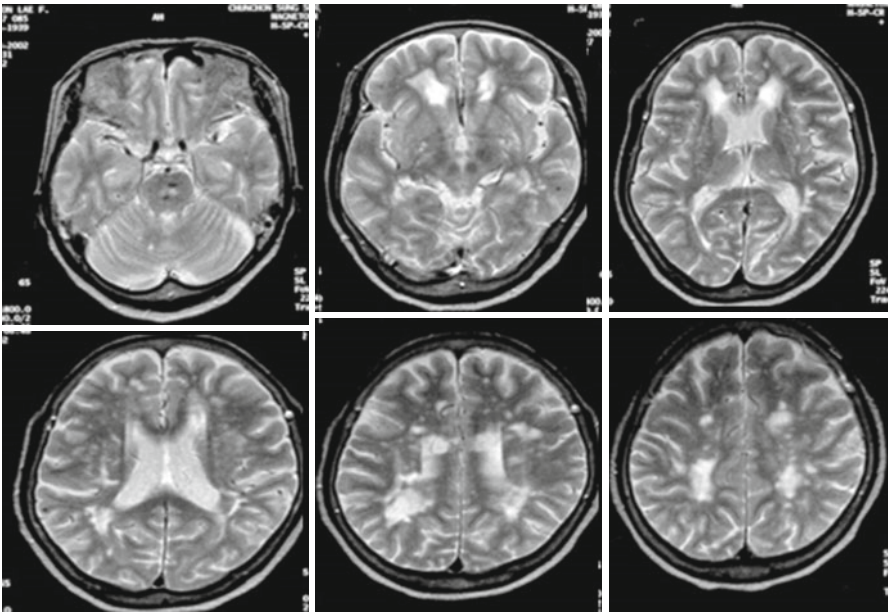


Fig. 7.2 T2-weighted MRI shows multiple periventricular and white matter ischemic lesions

basilar artery. Fluoxetine 20 mg/day was given, which significantly reduced the frequency and intensity of her laughing. Her excessive laughing persisted with some fluctuation in intensity during 5 years of follow-up. The excessive laughing recurred whenever the medication was discontinued.

Typically, PSEI patients show excessive and inappropriate crying or laughing without apparent motivating stimuli or in response to stimuli that would not normally have evoked such responses. The episodes are sudden, episodic, and uncontrollable, and the symptoms occur in a stereotypical way, resembling an automatism. The pathological facial expressions do not correspond with an analogous emotional change and do not serve to resolve inner tensions as they do in healthy individuals [1, 11, 31]. Unlike the patient described above, crying is generally more common than laughing, but many patients cry and laugh and can switch between the two during the course of one episode [1, 11].

Except for severe cases, episodes of PSEI rarely occur when the patient is left alone and are usually provoked by emotional or social stimuli [3, 26, 41]. The stimuli may be very trivial. For example, approaching the patient's bedside can trigger explosive laughing or crying. Although the stimuli appear to be emotionally incongruent, the severity of PSEI evoked may still be related to the degree of stimulation. For example, Wilson described a man who exhibited laughter whenever he read war news, and the more serious and anxious the news, the more he laughed [1]. Early reports emphasized the importance of these incongruent or contradictory emotional stimuli and the "unheralded," "uncontrollable" nature of symptoms [31]. For example, patients may laugh uncontrollably at the funeral ceremony of a relative. However, recent studies have found that symptoms are more often triggered by appropriate and congruent stimuli, although their responses are obviously excessive [13, 26]. Moreover, "unheralded" and "uncontrollable" crying and laughing are uncommon in clinical practice. Allman et al. [41] analyzed 30 stroke patients who cried on one or more occasions over 1 month period and found that only five patients had episodes of crying without warning and five had "uncontrollable" crying. Other authors have also discussed that the trigger is usually emotionally relevant. House et al. [26] interviewed patients with PSEI and categorized the provoking stimuli as (a) sad or depressing: thoughts of illness, dying from stroke, discussion of illness, pictures of famine or disaster; (b) sentimental: visits from grandchildren, conventional expression of greeting, enquiries about well-being; and (c) discussion of the symptom itself: asking about PSEI itself provoked tearfulness.

One of the most common stimuli for PSEI is conversation [3, 39], especially the initiation of speech. Other stimuli include apprehension, difficulty and suffering, situations characterized by a certain mood (e.g., amusing, festive, mourning) [39], and unfamiliar or awkward situations [3]. For example, patients are more likely to exhibit PSEI when they meet unfamiliar visitors or doctors than when they meet their spouses. Patients may laugh when they saw their wives wearing a new dress, but not an ordinary one [3]. In the hospital, watching dysfunctional neurological findings (e.g., hand tremor on finger to nose test), which is not familiar to ordinary persons, often triggers PSEI [3, 42]. We observed a patient who experienced severe laughter whenever he saw other patients receiving rehabilitation therapy. Another

patient laughed whenever he spoke the vowels (a, e, i, o, or u) during rehabilitation therapy for aphasia.

After being discharged to their home, it is common to see patients weep at television dramas that did not evoke crying before the onset of stroke [3]. Although crying in this situation may not be an abnormal response, PSEI patients cry longer and more frequently. Therefore, although the emotional valence is not incongruent, and the display is not uncontrollable, this behavior is considered abnormal by both the patient and their relatives and should be considered a part of PSEI.

Poeck [31] attempted to differentiate emotional lability from pathological laughing and crying, stating that the former occurs in an appropriate situation, is accompanied by an alteration of mood, and does not have the fixed sequential pattern seen in the latter. However, along with others [37, 41], we believe that differentiating between these two conditions is not always easy. According to our observations [3], patients symptoms may vary; they may show pathological laughing and crying but also weep easily at another time. Furthermore, although the severe, classical pathological laughing and crying may persist in some PSEI patients (as in the illustrative case), the intensity of the symptoms is often attenuated with time, becoming simple emotional lability [3, 43]. Finally, as discussed above, truly unheralded crying, without any warning signs, is uncommon in clinical practice and is difficult to rate especially when there was warning in some episodes but not others [41]. Thus, we consider the clinical spectrum of PSEI very diverse, with symptoms often lying between the extremes of emotional lability and pathological laughing and crying. The two extreme ends seem to differ in a quantitative rather than qualitative way.

Although PSEI is usually observed at the time of stroke, it may clinically manifest a few days, weeks, or even several months after the onset of stroke [3]. In some cases, this may be due to the failure of physicians to diagnose PSEI in the acute phase of stroke. However, it is also possible that PSEI is not manifest until sometime after stroke: patients with altered consciousness, aphasia, or decreased cognition may not be able to perceive social or emotional stimuli until some way into recovery. In some cases, PSEI may be detected only when patients are discharged from a hospital and when they are exposed to a wider variety of social and emotional stimuli. Persistent functional deficits or a lack of social support in the subacute stages of stroke may also evoke delayed-onset PSEI [44]. Finally, the delayed onset may be related with the complex pathophysiology of PSEI; it may develop due to asynchronous recovery during reorganization of the cortical-subcortical emotional circuitry after the acute phase [3].

In contrast, there are patients who show abnormal emotional display *before* the onset of other major neurologic dysfunction. This rare but interesting phenomenon was initially described by Féré in 1903 as *fou rire prodromique* (prodrome of crazy laughter). Coelho and Ferro [45] reviewed 18 published cases of *fou rire prodromique* and found that *fou rire* can last anywhere from a few seconds to several hours. The other neurologic deficits usually appeared immediately after the *fou rire*; however, there were cases where their appearance was delayed for days or even months. There is also one report of a patient with multiple vascular risk factors who showed recurrent spells of crying associated with left paresthesia and mild

weakness that resolved within 3 h [46], which suggests that a transient ischemic attack may manifest as transient laughing or crying.

The frequency of and the severity of PSEI episodes experienced by the patient vary greatly. When severe, these episodes produce significant distress and embarrassment and impair patients' social or occupational function as shown in the illustrative case. A recent study showed that patients with PSEI had significantly lower scores in the general and mental health, social function, and role-emotional dimensions of quality of life than those without [47].

Diagnostic Criteria

Wilson [1] described the abnormal emotional displays as exaggerated, forced, involuntary, uncontrollable laughing or weeping and stated that there is an unbalanced relation between stimulus and response and a disconnection between mood and affect and that the outbursts are of a stereotyped nature. Poeck [31] described four similar criteria for pathological laughing and crying: (1) a response to a nonspecific stimulus, (2) the absence of a corresponding change in affect or a lack of relation between the affective change and the observed expression, (3) the absence of voluntary control over the extent and duration of facial expressions, and (4) the absence of a corresponding change in mood lasting beyond the actual laughing or crying and a lack of relief after such an expression of mood. The third of these was considered to be the most important.

Twenty years later, House et al. [26] diagnosed PSEI using five simple questions: (1) Have you been more tearful since the stroke than you were beforehand? (2) Does the weepiness come suddenly at times when you aren't expecting it? (3) If you feel the tears coming on, or if they have started, can you control yourself to stop them? (4) Have you been unable to stop yourself crying in front of other people? (5) Is that a new experience to you? Thus, the crying or laughing associated with PSEI should be sudden, unheralded and uncontrollable. Nevertheless, the House criteria are more generous than those used previously [1, 31] as they include emotional displays secondary to stimuli congruent with mood.

However, as discussed above, we see more patients with mild yet excessive or inappropriate laughing or crying that does not fit with these criteria but is nevertheless considered abnormal by both the patient and relatives. For this reason, a less stringent set of criteria were developed by Kim and Choi-Kwon [13], where PSEI was diagnosed if both the patient and his/her relatives agree that excessive and/or inappropriate laughing and/or crying occurred on at least two occasions. The crying or laughing is not required to have been sudden, unheralded, or uncontrollable, as these characteristics are rare and difficult to assess in clinical practice [41]. This assessment is easy to perform and takes only a few minutes and can therefore be utilized conveniently by busy clinicians. The severity of the PSEI may be assessed with the concomitant use of a visual analogue scale. However, as confirmation of laughing and/or crying is required from relatives of the patient, these criteria cannot be used for patients who live alone.

There are more recent criteria that have not yet been used in the study of PSEI. The diagnostic criteria of Nieuwenhuis-Mark et al. [37] require that episodes are frequent and immediate, the patient is more likely to burst out laughing or crying than previously was the case, emotional reactions are linked with specific or (in some cases) nonspecific stimuli, the intensity of the emotional reaction is out of proportion to what would be expected, and the patient is not able to control his behavior in social situations. The criteria of Cummings et al. [2] are more complex. Diagnosis of PSEI requires episodes of involuntary or exaggerated emotional expression that result from a brain disorder, including episodes of laughing, crying, or related emotional displays. Episodes represent a change from the persons' usual emotional reactivity, may be incongruent with the person's mood or in excess of the corresponding mood states, and are independent or in excess of any preceding stimulus. They are sudden in onset, brief (lasting seconds to minutes), and stereotyped and may vary in severity between patients. Episodes may be, but are not required to be, accompanied by autonomic changes (e.g., flushing of the face), pseudobulbar palsy signs, and proneness to or episodes of anger.

In addition to tools for diagnosing the presence and absence of PSEI, there are tools for assessing the degree and severity of PSEI. The best known of these was the scale developed by Robinson et al. [48]. This scale assesses the frequency at which the patient has experienced sudden episodes of laughing or crying and asks questions to ascertain details of the triggers for, and severity and duration of, these episodes and the associated emotions. The inter-rater and test-retest reliability is good. There also are scales that were developed for patients with amyotrophic lateral sclerosis [30] or multiple sclerosis [49] that may be used in stroke patients as well.

Prevalence

Emotional incontinence is observed in a wide range of neurologic disorders, including amyotrophic lateral sclerosis [50, 51], Parkinson's disease [52], Alzheimer's disease [53], multiple system atrophy [54], multiple sclerosis [22, 55, 56], and traumatic brain injury [57–59]. The reported prevalence of emotional incontinence in these conditions ranges from 10 to 50 %. In the acute/subacute stage of stroke, PSEI prevalence has been reported to vary from 6 to 34 % [13, 26, 27, 29, 33, 35, 44, 60–62] (Table 7.2). The heterogeneous results are due to different diagnostic criteria of PSEI, the timing of assessment, and characteristics of study population. The most frequently used diagnostic criteria are those of House [26] followed by Kim [13]. As discussed above, the Kim criteria do not require uncontrollable or unheralded emotional displays and thus include milder cases. Indeed, Tang et al. [33] reported that 17.9 % of Chinese stroke patients were diagnosed with PSEI according to the Kim criteria but only 6.3 % according to the House criteria.

Unfortunately, patients with aphasia, cognitive dysfunction, or severe neurologic deficits are generally excluded from prevalence estimates. As patients with bilateral, diffuse brain lesions show more severe, frequent, and persistent PSEI [1], the

Table 7.2 List of study results showing the prevalence and related factors of post-stroke emotional incontinence

Author, year	Country	Number of patients	Time interval (post-stroke)	Notable inclusion criteria	Exclusion criteria	Criteria for PSEI	Prevalence	Related factors	Comments
House et al., 1989 [26]	United Kingdom	89, 119, 112, respectively	1, 6, 12 months	None	Aphasia, decreased consciousness	House criteria	15, 21, 11 %, respectively	Depression cognitive impairment, left frontal/temporal lesion	None
Morris et al., 1993 [27]	Australia	66	Approx. 2 months	First-ever, CT-identified stroke, single lesion, can interview reliably	None	Interview with "CIDI"	18 %	Anterior cortical lesion	Not related to PSD
MacHale et al., 1998 [60]	Scotland	145	6 months	None	Cognitive dysfunction, severe aphasia	House criteria	18 %	Right anterior lesion	Related to PSD
Calvert et al., 1998 [35]	United Kingdom	448	1 month	Fluent English to interview, nearby residents	Severe aphasia, cognitive impairment, concurrent major illness	House criteria	22 %	Young age	Related to PSD Irritability Idea of reference
Kim and Choi-Kwon, 2000 [13]	Korean	148	2–4 months	CT/MRI identified stroke, 40–80 years	Past history of stroke, multiple brain lesions, severe aphasia and cognitive dysfunction, past history of depression	Kim criteria	34 %	Female, Ischemic (vs. hemorrhagic), severe motor dysfunction, anterior cortical lesion	None

(continued)

Table 7.2 (continued)

Author, year	Country	Number of patients	Time interval (post-stroke)	Notable inclusion criteria	Exclusion criteria	Criteria for PSEI	Prevalence	Related factors	Comments
Tang et al., 2004 [33]	Chinese	127	3 months	Chinese ethnicity, ability to participate in the study	Any neurological disease other than stroke	House criteria, Kim criteria	6 % (House criteria) 18 % (Kim criteria)	Past history of depression, cortical lesion	None
Tang et al., 2009 [29]	Chinese	519	3 months	Chinese ethnicity, >18 years	TIA, hemorrhagic stroke, other neurologic condition	Kim criteria	14 %	Microbleeds, low MMSE, female	None
Kim et al., 2011 [62]	Korean	276	2 weeks	CT/MRI identified ischemic stroke, ability to participate in the study	Hemorrhagic stroke, other neurologic condition, MMSE <16, severe physical illness	Kim criteria	13 %	Previous stroke, high NIHSS, serotonin polymorphism (5-HTTLPRs allele)	None
Choi-Kwon et al., 2012 [44]	Korean	508	At admission, 3 months	CT/MRI identified stroke, admitted <7days after onset	Hemorrhagic stroke, MMSE<24, severe aphasia, severe medical illness, history of depression	Kim criteria	9 % (at adm) 12 % (3 months)	Lesion location (at adm), functional disability, serotonin polymorphism, low social support (at 3 months)	None

Abbreviations: *PSEI* post-stroke emotional incontinence, *CIDI* composite international diagnostic instrument, *PSD* post-stroke depression, *TIA* transient ischemic attack, *MMSE* mini-mental state examination, *NIHSS* national institutes of health stroke scale, *uni* unilateral analysis, *multi* multiple logistic regression analysis

prevalence is likely to be underestimated. Post-stroke emotional incontinence should therefore be considered one of the major emotional symptoms in stroke survivors.

There have been few studies that examined the longitudinal course of PSEI. Our observations are that the severity of PSEI generally diminishes with time [3] and often disappears after a period of several months or years [43, 63]. However, PSEI may newly appear in the subacute stage. One report indicates that the prevalence of PSEI was 15 % at 1 month post-stroke, 21 % at 6 months post-stroke, and 11 % at 12 months post-stroke [26], suggesting that PSEI may be most prevalent in the subacute stage. In a recent study of 508 stroke patients, we also showed that the prevalence of PSEI was increased from 9 % at admission to 12 % at 3 months post-stroke [44]. Of the 48 patients who were diagnosed with PSEI in the acute stage of stroke, 24 had recovered by 3 months post-stroke, and there were 40 new diagnoses. Functional deficits measured with the modified Rankin scale, and the serotonin polymorphism VNTR STin2, were related to the new development of PSEI at 3 months. These studies collectively indicate that PSEI should be considered an evolving symptom that may disappear or newly develop in the acute/subacute stage of stroke.

Factors Related to the Development of PSEI

Severe motor dysfunction [13] and neurologic dysfunction assessed by the National Institutes of Health Stroke Scale [33, 62] or the modified Rankin scale [33, 44] are related to the development of PSEI. A lack of social support is also related to the development of PSEI in the subacute stage [44]. The lesion location [13, 27, 44] and the presence of depression [13, 26, 35] are also closely related to PSEI and are discussed in more detail below. It has also been shown that age [33, 35], gender [13], and type of stroke (ischemic vs. hemorrhagic) [13] are associated with the development of PSEI. However, these results are from univariate analyses and have not been replicated by other studies (Table 7.2).

The factors related to PSEI may differ according to the timing of the investigation. In a recent study, we showed that lesion location (subcortical area) was the only factor that was associated with PSEI at the time of admission, whereas functional status, serotonin polymorphism, and low social support were related to PSEI at 3 months post-stroke [44].

Relation Between PSEI and Neuropsychiatric Symptoms

Generally, PSEI is considered to be the result of abnormalities in the expression of, rather than formulation of emotion. Thus, PSEI and depression are separate and independent constructs. Post-stroke emotional incontinence is differentiated from

Table 7.3 Difference between emotional incontinence and depression

	Emotional incontinence	Depression
Concept	Mainly expression disorder, affect (transient)	Content problem, mood (sustained)
Stimuli	Often with incongruent stimuli	Congruent situation
Emotional expression	Crying, laughing, or both	Crying
Duration	Brief (minutes)	Tonic mood lasting days or months
Voluntary control	Uncontrollable in classical cases	Can be modified
Stereotypy	Stereotypical	Variable features
Brain disorder	Yes	No except for post-brain disease depression
Bulbar symptoms	Usually present	None
Fatigue	Not related	Common
Sleep and appetite disorder	Not related	Maybe present
Anhedonia	Not related	Maybe present
Suicidal idea	Not related	Maybe present
Thought content	Not related	Decreased self-esteem

depression by duration, affect, behavior, insight, perception, and course (Table 7.3) [2, 37]. However, PSEI seems to be closely related to concurrent or past history of depression. There are reports that more than half of patients with pathological laughing and crying had depression [48, 60], and patients with the past history of depression had a 14-fold greater risk of developing PSEI [33]. In our recent study [44], post-stroke depression (PSD) was significantly correlated with PSEI both at admission and at 3 months post-stroke. Among the patients with PSEI at admission, 42 % had depression at admission, and 44 % had depression at 3 months post-stroke. The close relation between PSEI and PSD may, at least in part, be explained by the similar lesion location (fronto-basal ganglia-brainstem pathways), perhaps with similar neurochemical changes [13]. However, the lesion location [13] and underlying pathophysiological mechanisms (see below) are still different between PSD and PSEI; improvement of pathological laughing and crying by nortriptyline was independent of depression status [48], and selective serotonin reuptake inhibitors (SSRIs) improved PSEI more effectively than they did PSD [64].

Nevertheless, the close relation between PSEI and the past history of depression [33], severe neurological deficits [13], and the lack of social support [44] raises suspicion that PSEI may at least in part be related to reactive depression in premorbidly depressive patients. According to Nieuwenhuis-Mark et al. [37], although PSEI is mainly an emotional expression disorder, these patients may also differ from normal persons in their exposure to precipitating emotional stimuli. Calvert et al. [35] interviewed 448 stroke survivors and found that PSEI was closely associated with depression, irritability, and ideas of reference. Although ideas of reference may be related to the embarrassing nature of PSEI, the authors proposed that PSEI might be just one manifestation of a more general disorder of emotional control that occurs after a stroke.

In addition to depression, PSEI seems to be related to cognitive impairment [26, 29, 64]. This is understandable as anterior cortical lesions are closely associated with PSEI [13, 26, 33, 60] as discussed below. However, it should be noted that patients with severe cognitive dysfunction were generally excluded in previous studies (Table 7.2), and so the full extent of the relation between PSEI and cognitive impairment remains unknown.

Post-stroke emotional incontinence is also related to anger proneness. We found that PSEI was more closely associated with anger proneness than it was with PSD [65]. In addition, PSEI and anger proneness were related to similar lesion locations (preferably involving the striatocapsular and pontine base areas) and exhibited similar therapeutic responses to SSRIs [66]. These results suggest that PSEI and anger proneness may be part of a spectrum of wider emotional control disorders that are secondary to brain damage associated with neurochemical derangement. However, although a serotonin polymorphism is related to PSEI [44], anger proneness is more closely related to monoamine oxidase (MAO)-A polymorphism [67]. Therefore, although PSEI and anger proneness are closely related, there still are differences in the underlying pathophysiological mechanisms.

There is also evidence that PSEI may be related to sexual dysfunction. We examined non-depressed, sexually active patients 3 months and 2 years post-stroke [63] and found that the presence of PSEI was associated with decreased erectile function 3 months after the stroke. Two years after the stroke, the presence of PSEI at 3 months post-stroke was significantly related to decreased libido, coital frequency, and erectile function. We speculated that an alternation of the serotonergic system secondary to stroke might be related to both post-stroke emotional and sexual disturbances, although the role of serotonin in sexual function is quite complex [68].

Lesion Location Related to PSEI

As shown in the illustrative case, PSEI frequently occurs in patients with diffuse, multiple strokes associated with bulbar palsy, gait difficulty, or quadriparesis [1]. In these patients, it is difficult to locate the lesion that is responsible for PSEI. However, early reports [1, 6, 7] already stated that PSEI could be produced by focal, unilateral infarcts.

Brissaud [7] and Wilson [1] emphasized the lesions occurring in the genu or the anterior limb of the internal capsule as a responsible lesion for PSEI, which probably involve the corticobulbar tract that descends from the frontal operculum and the lower part of the precentral gyrus. Poeck [31] reviewed 30 cases of PSEI verified by autopsy and found single lesions in ten patients. Subcortical areas were damaged in all, and the anterior limb of the internal capsule was damaged in the majority of cases. The putamen was involved in four cases, the caudate nucleus in three, and the thalamus in two cases. He emphasized the role of subcortical lesions in producing PSEI and suggested that a single circumscribed cortical lesion cannot produce pathological laughing and crying [31]. However, Davison and Kelman [11] described

more diverse lesion locations that are involved in PSEI, including frontal, parietal, and temporal cortices and the hippocampus, and proposed that these cortical areas may act as centers for the integration of affective responses, perhaps through intimate connections with the hypothalamus.

Recently, with the advent of imaging techniques such as CT and MRI, thorough premortem examination of lesion location has become possible. Studies using these imaging tools have confirmed that lenticulocapsular lesions, particularly those involving the genu or the anterior portion of the posterior limb of the internal capsule, are closely associated with PSEI [3, 69]. In addition, MRI studies have revealed that the brainstem is another important region related to PSEI [3]. These studies have also shown that the frequency of PSEI does not differ between left and right lesions [27] but that anterior cortical strokes more often lead to PSEI than posteriorly located strokes do [26, 60]. We [13] studied 148 patients with unilateral strokes that were identified using CT/MRI and found that PSEI was frequent (>40 %) in patients with lesions in the anterior cortical area (anterior cerebral artery territory and superior division middle cerebral artery territory), the base of the brain stem (pontine base and medial medullary area) and lenticulocapsular areas, whereas none of the patients with lesions in the posterior cortical (parietal or occipital lobe) and dorsolateral brainstem (dorsal pontine or lateral medullary area) areas exhibited PSEI. Patients with lesions in the thalamus or cerebellum had an intermediate prevalence of PSEI. Taken together, these results suggest that anterior cortex-internal capsule/basal ganglia-ventral brainstem circuitry is closely related to PSEI. Although the lesion location is similar to that producing PSD, PSEI seems to be more closely related to subcortical (basal ganglia and pontine) lesions [13].

Limbic structures such as the medial temporal lobe, thalamus, and hypothalamus are related to formation and regulation of emotion, and, as discussed below, the cerebellum also plays a critical role in the regulation of emotional expression [18]. Indeed, strokes occurring in the thalamus [70] or the cerebellum [18, 42] do produce PSEI, and lesions affecting the limbic areas have been shown to produce gelastic seizures [24, 71, 72]. However, lesions in these locations are not as frequent as lenticulocapsular/ventral brainstem regions [13], in part because limbic areas are less often involved in cerebrovascular diseases.

It has been suggested that the right hemisphere is associated with negative emotion and the left hemisphere with positive emotions, and therefore, damage to the right hemisphere more often produces laughing, whereas left hemispheric lesions more often produce depression or crying [73]. However, this argument has not been supported by recent studies [67], probably because PSEI is related to dysfunction in the expression of, rather than formulation of, emotion [2, 24].

As diffuse, multiple cerebral ischemic lesions are closely related to PSEI [1], it may be expected that white matter signal intensities or microbleeds play a role in development of PSEI. Indeed, patients with PSEI had a higher incidence of periventricular white matter lesions than those without PSEI. However, the difference was not statistically significant [13]. More recently, Tang et al. [29] reported that microbleeds, especially those located in the thalamus, are closely related to PSEI.

However, this result has not been replicated [44] and further studies are required to clarify the relation between PSEI and diffuse cerebral small vessel diseases.

Finally, the lesion locations related to *fou rire prodromique*, laughing or crying heralding other symptoms of stroke [9], include the brainstem [20, 74–77]; subcortical areas including internal capsule, striatum, and the thalamus [45, 69, 78–80]; and the cortex of the middle cerebral artery territory [81]. Thus, the lesion locations associated with *fou rire prodromique* appear to be similar to those associated with usual PSEI.

Pathogenesis

Wilson proposed that pathological crying and laughing is caused by the release (or disinhibition) of a brainstem fasciorespiratory control center for emotional expression secondary to lesions of descending regulatory (corticobulbar) pathways from higher cortical brain centers [1]. Although the presence of a discrete structure representing the fasciorespiratory "center" has been questioned, the critical anatomic structures for laughing and crying, such as the seventh cranial nerve, the nucleus ambiguus, and the phrenic nuclei in the upper cervical cords, are in close proximity and are believed to be controlled by ventral paralimbic networks [82]. Moreover, frequent involvement of the anterior cortical region [27] and lenticulocapsular-brainstem pathway in PSEI patients [13] seems to supports this disinhibition hypothesis. Thus, this old hypothesis is still considered plausible [15, 31].

Davison and Kelman [11] proposed an expanded version of Wilson's theory in which frontal, premotor, motor, and temporal cortical areas act as centers for the integration of affective responses. The hypothalamus or other diencephalic nuclei, which are under cortical inhibitory influence, are considered to be the main centers for the release of affective responses, and a lesion of the cortico-hypothalamic tract would remove cortical control and thereby induce excessive affective responses.

However, there are certain clinical features of PSEI that are not readily explained by this simple, one-sided, disinhibition theory; not all patients show symptoms of bulbar palsy; laughing may change to crying or vice versa in response to the same stimulus; and the responses may be induced by entirely incongruent stimuli. Therefore, emotional expression seems to be regulated in a more complex manner, perhaps associated with structures outside of the cortico-capsular-brainstem circuitry.

Parvizi et al. [18] described patients presenting with PSEI due to lesions of the ponto-cerebellar pathway [54, 83–86] and hypothesized that the cerebellum may play a modulatory role and adjust the execution of laughing or crying to the cognitive and situational context. Dysfunction of circuitry involving the cerebellum may exert influence over the brainstem nuclei as well as the cerebral cortex itself. In this way, cerebellar lesions may result in the impairment of circuitry relevant for the adjustment of laugher and crying responses or in the inability of the brainstem regions to produce appropriate emotional display. Given the fact that thalamic, striatal, and pallidal lesions are involved in PSEI [13], these structures may also regulate

affective responses, perhaps by means of intimate association with the hypothalamus [11].

Recent studies have shown that higher cortical areas, particularly the prefrontal cortex, are involved in modulating and tuning human emotions [87, 88]. There seems to be two cortical paralimbic networks [23]. The ventral paralimbic network including the orbitofrontal, ventromedial frontal, anterior cingulate, and insular cortices incorporates the core functions of the limbic system and integrates social and motivational information to generate contextually relevant emotional responses [82]. The ventral network system receives regulatory input from a dorsal paralimbic network that is composed of the hippocampus, the dorsal region of the anterior cingulate gyrus, and the dorsomedial and dorsolateral prefrontal cortices. This dorsal network permits conscious awareness and voluntary regulation of emotion [82]. The cerebellum seems to modulate the functions of both the ventral and the dorsal systems [84, 89].

Considering this complex structures and pathways related to emotion, and the variety of lesion locations producing PSEI, Rabins and Archinegas [90] suggested that a complex cortico-limbic subcortical-thalamic-ponto-cerebellar system contributes to the expression of emotions. Deficits in any areas of this system may cause disruption of generalized network functions and thereby lead to disturbances in emotional expression.

Traditionally, the lesions affecting this network were considered to lower the threshold for emotional output [1, 31]. However, PSEI may also involve abnormalities on the perception side. There may be three factors that determine the nature and degree of abnormal crying: (1) the exposure to emotional stimuli, (2) the appraisal of these stimuli, and (3) the ability to control one's tears. According to Nieuwenhuis-Mark et al. [37], patients with stroke or other brain diseases differ from normal subjects in the appraisal of precipitating emotional stimuli, suggesting that PSEI may not solely be an emotional output disorder, as early authors emphasized [1, 31]. It, however, should be noted that even as early as 1939, Davison and Kelman [11] considered the psychodynamic problems associated with altered "feeling tone" as a possible component of pathological crying.

In patients with gelastic seizures, stimulation of the left superior mesial frontal region produced seizures that manifest as laughter without a subjective feeling of mirth, whereas stimulation of the fusiform gyrus and parahippocampal gyrus produced bursts of laughter accompanied by a feeling of mirth [24]. Therefore, the anterior cingulate region may be involved in the motor act of laughter and the basal temporal cortex in processing laughter's emotional content. This implies that strategic lesion location may influence the motor and sensory components of emotion differently, even though the final phenomena are equally expressed as excessive or inappropriate laughing and crying. In addition, the close association between PSEI and the past history of depression [33], severe neurological deficits, and perceived lack of social support [44] suggests that psychological difficulties in association with individual genetic predisposition [44, 62] may also play a role in altering the sensory part of the emotional regulation system. Further studies are required to explore this complex issue.

The pathogenic mechanism of *fou rire prodromique* seems to be identical with that of usual PSEI [79], as the clinical features of laughing and crying are similar except that they occur before the appearance of other neurologic symptoms. However, patients with *fou rire prodromique* differ from PSEI patients in that they are not neurologically disabled nor aware of their final neurologic outcome at the time of their emotional display. Therefore, the mechanism seems to be pure emotional output abnormality secondary to a release phenomenon [91]. Other explanations, not necessarily at odds with the aforementioned mechanism, include ephaptic stimulation and activation of the descending corticopontine/bulbar pathway secondary to early ischemic injury [77]. Finally, at least in some patients who had cortical lesions, the possibility of seizure after ischemic insult cannot be ruled out [81].

Neurotransmitters and Genetic Traits Involved in PSEI

Although the pathogenesis of PSEI remains unclear, neuroanatomical lesion studies suggest the involvement of serotonergic pathways [61, 63, 92]. The serotonergic pathway ascends from the brainstem raphe nuclei to the limbic forebrain structures and then projects through the basal ganglia to the frontal cortex. Lesions associated with PSEI generally correlate with the areas of the brain that have abundant serotonergic fibers and receptors [13, 61, 92–94], and previous studies have reported successful treatment of PSEI with SSRIs [66, 95]. Furthermore, serotonin transporter binding ratios in the midbrain and pons regions are lower in stroke patients with PSEI than in those without PSEI [96]. Finally, serotonin gene polymorphism was found to be related to the development of PSEI [44, 62]. However, the exact mechanism of serotonin dysfunction in PSEI remains uncertain. Perhaps damage to the serotonergic (raphe) nuclei in the ventral brainstem and their ascending projection may decrease the cerebral availability of serotonin, impairing the regulation of affect and leading to PSEI [23]. The therapeutic effect of SSRIs on PSEI may be due to the repletion of serotonin in this system and subsequent improvement in the operation of higher cortical areas. However, as serotonergic receptors are widespread throughout the brain, SSRIs may also exert direct action on the brainstem, cerebellum, and limbic systems.

Various other neurotransmitters have also been proposed to be involved in PSEI. Early studies [97, 98] reported the improvement of PSEI after administering levodopa or amantadine hydrochloride, suggesting that dopamine may have a positive role in stabilizing the influence of motor cortex on the brainstem laughing/crying centers. Dopamine is an important modulator of information processing circuits in the brain. There are dopaminergic connections between the ventral tegmental, substantia nigra, and cortico-limbic-striatal areas, and dopaminergic projections may modulate the signal-to-noise ratio in this circuitry [99]. However, there are no large-scale RTCs that have used dopaminergic agents, and the role of dopamine in PSEI requires further investigation.

Glutamine is another important neurotransmitter that is involved in emotion. Glutamine is the principal excitatory neurotransmitter, and gamma-aminobutyric

acid (GABA) is the primary inhibitory neurotransmitter in the glutaminergic system. The balance of excitation and inhibition is modulated by other neurotransmitter systems such as dopamine, serotonin, acetylcholine, and the sigma receptor system, and this regulation may be important in emotional regulation [90]. Noncompetitive glutamate receptor antagonists such as dextromethorphan stabilize glutamatergic neurotransmission and prevent excessive glutamate-mediated excitatory activity [100]. Dextromethorphan was found to be effective in the treatment of pathological laughing and crying in amyotrophic lateral sclerosis [101] and multiple sclerosis [102], perhaps due to its effect on sigma-1 receptors; the receptors are concentrated in the brainstem, cerebellum, and limbic structures [103] and may be closely related to PSEI. As activation of sigma-1 receptor agonists increases the serotonergic function of the dorsal raphe nucleus [104], dextromethorphan may also modulate the serotonergic system.

It remains unknown why some patients exhibit PSEI while others do not, even when the lesion location and the degree of neurologic deficits are apparently similar. This may be partially explained by the differential involvement of strategic areas that preferentially affect the neurotransmitter systems in patients with grossly similar lesion locations [61]. Alternatively, genetic polymorphism, particularly in the serotonin system, may play a role; Kim et al. [62] studied 276 Korean stroke patients and found that the 5-HTTLPRs allele was related to the susceptibility to develop PSEI at 2 weeks after stroke. However, another study of Korean stroke patients found that it was the number of tandem repeats within intron 2 (STin2 VNTR) that was associated with PSEI at 3 months post-stroke [44]. Although the difference in these results is difficult to explain, these results collectively suggest that, in addition to the location of brain lesion damaging serotonergic neuronal fibers, serotonin polymorphism in individual subjects may determine the susceptibility to PSEI.

Pharmacological and Non-pharmacological Treatments

Selective Serotonin Reuptake Inhibitors and Tricyclic Antidepressants

There were many case studies [52, 105–108] that reported positive outcomes of SSRIs and tricyclic antidepressants (TCAs) on the treatment of PSEI, and a recent Cochrane review confirmed that these drugs are effective in reducing the frequency and severity of PSE [109]. In five RCTs [66, 95, 110–112], SSRI administration was effective in alleviating PSEI, and two RCTs showed that TCAs were effective in treating PSEI [48, 113] (Table 7.4). The effective doses of SSRIs are at the low end of the therapeutic range used for treating depression. To date, the evidence suggests that SSRIs should be the first choice for PSEI treatment. They are preferred over TCAs because the time required to reduce PSEI symptoms is much shorter, they are better tolerated, and they have a lower potential for drug interaction and side effects.

Table 7.4 Randomized controlled trials on post-stroke emotional incontinence

Author, year	Agent/dose/duration	Country	Patient characteristics	No. of patients	Time from stroke	% of PSD	Effect	Outcome	Follow-up time
TCAs									
Ohkawa et al., 1989 [113]	Amitriptyline/50 mg/days/3 weeks	Japan	Patients admitted to a single hospital	7[a] 7[b]	1 month to 2 years	Not stated	+	Amitriptyline was useful in treating pathological laughing	3 weeks
Robinson et al., 1993 [48]	Nortriptyline/20, 50, 70, 100 mg/day/6 weeks	USA	Patients admitted to a single hospital	15[a] 14[b]	15.7 months	Major (50)	+	Nortriptyline effectively ameliorated emotional disorder	2/4/6 weeks
SSRIs									
Andersen et al., 1993 [95]	Citalopram/10, 20 mg/day/3 weeks	Denmark	Patients admitted to a single hospital	16[a] 16[b]	6–913 days	0	+	Significant reduction in crying episodes	1/24 week
Brown et al., 1998 [110]	Fluoxetine/20 mg/day/10 days	UK	Patients admitted to a single	9[a] 10[b]	Not stated	0	+	50 % or more reduction in frequency of	3 days 10 days
Burns et al., 1999 [111]	Sertraline/50 mg/day/8 weeks	UK	Patients admitted to three hospitals	14[a] 14[b]	1–156 months	0	+	Significant improvements in impression change, emotional lability, and tearfulness	4/8/10 weeks
Murray et al., 2005 [112]	Sertraline/50, 100 mg/day/26 weeks	Sweden	Outpatient clinic in four centers	62[a] 61[b]	3–375 days	Major(66.1) Minor(33.9)	+	Significant improvements in hostile feelings, perceived quality of life, and emotional distress	6 weeks 26 weeks

(continued)

Table 7.4 (continued)

Author, year	Agent/dose/duration	Country	Patient characteristics	No. of patients	Time from stroke	% of PSD	Effect	Outcome	Follow-up time
Choi-Kwon et al., 2006 [65]	Fluoxetine/20 mg/day/3 months	South Korea	Outpatient clinic in a single hospital	76[a]	3–28 months	42.1	+	Significant reduction in crying but not in laughing	1/3/6 months
				76[b]				Subjective reports of improvvement in both crying and laughing	

Abbreviations: *TCAs* tricyclic antidepressants, *SSRIs* selective serotonin reuptake inhibitors, *MMSE* mini-mental state examination, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, *MADRS* Montgomery-Åsberg Depression Rating Scale, *PSE* post-stroke emotionalism, *PSD* post-stroke depression

[a]Experience group

[b]Control group: matched placebo

Fluoxetine was reported to have a sustained effect on PSEI symptoms at 3 months after its discontinuation [66] and improve general health domains of quality of life at 9 months after the cessation of medication [114].

Despite the positive evidence for SSRIs in PSEI, there are a number of methodological limitations in these RCTs that should be kept in mind. First, the participants studied ranged from 6 days to more than 3 years post-stroke at the time of randomization [48, 66, 95, 112, 113]. The PSEI may spontaneously improve over the course of months [3], and the etiology and severity of PSEI may differ between patients early after stroke and those who survive in the long term [44]; therefore, recruiting patients at different stages after stroke makes it difficult to generalize the results. Trials that include homogeneous patient groups may be needed to fully determine the efficacy of SSRIs and TCAs. Second, the duration of treatment in the published RCTs varies from 10 days [110] to 26 weeks [112] for SSRIs but only from 3 weeks [113] to 6 weeks [48] for TCA. Therefore, longer treatment durations may be necessary, especially for TCAs. Third, the dose–response relations for pathological laughing and pathological crying have not been determined separately. We observed a significant reduction in pathological crying, but no change in laughing, with dose of 20 mg/day fluoxetine [66], suggesting that dose response may differ between the two affective states. Future studies are needed to determine appropriate doses for the treatment of pathological laughing and crying. Finally, many patients with PSEI also have PSD. The inclusion of participants with both PSEI and PSD limits the ability to interpret the therapeutic results. However, at least three studies [48, 66, 112] reported that patients with PSEI alone exhibited reduced symptoms after SSRI treatment, suggesting that SSRIs have a beneficial effect on PSEI regardless of the presence of depression.

Selective Adrenergic Receptor Inhibitors

In contrast to the RCTs using SSRIs [66, 95, 110–112] and TCAs [48, 113], there are only case studies addressing the pharmacological treatment of PSEI with the selective adrenergic receptor inhibitors (SNRIs), reboxetine [115], venlafaxine [116], mirtazapine [117], and lamotrigine [118]. The mechanism of action of these agents may be direct or indirect augmentation of the serotonergic function. With limited data, these SNRIs are currently reserved for patients who fail to respond to or cannot be treated with SSRIs [117].

Levodopa and Amantadine

Dopaminergic agents may also be used to treat PSEI. Although no RCTs are available at this time, case series suggest that levodopa or amantadine may be effective in treating PSEI [97, 98]. Amantadine inhibits the reuptake of dopamine in

postsynaptic receptors and therefore increases the activity of dopamine. Amantadine is also an agonist for the sigma-1 receptor, which is found in the limbic, motor, and brainstem areas, and modulates firing of dorsal raphe serotonergic neurons [119, 120]. However, because most patients with PSEI are elderly, the gastrointestinal side effects of levodopa and amantadine should be considered, and these medications are not currently considered the drug of choice for PSEI.

Dextromethorphan/Quinidine (Nuedexta)

Dextromethorphan/quinidine (Nuedexta®; Avanir) is another potentially useful drug for the treatment of PSEI [15]. Recent RTCs using this drug have shown decreased number of crying and laughing episodes in patients with either multiple sclerosis or amyotrophic lateral sclerosis [101, 102]. Dextromethorphan is an NMDA receptor antagonist and also a sigma-1 receptor agonist. As discussed above, sigma-1 receptors are heavily expressed in the limbic system, and the beneficial effect of dextromethorphan may be mediated by activation of sigma-1 receptor or enhancement of serotonergic activities. As dextromethorphan undergoes extensive first-pass metabolism in the liver by CYP2D6 after absorption from the gastrointestinal tract, a minimal dose (10 mg) of quinidine sulfate has been added to the drug to inhibit the metabolism and increase the bioavailability of dextromethorphan. Although quinidine may cause QT prolongation and immune-mediated thrombocytopenia, there were no significant side effects reported [121]. The efficacy of Nuedexta for treating PSEI has not been tested and has not been compared to TCAs or SSRIs. When used alone, it appears to be safe; however, concomitant use of this drug with other serotonergic agents could be problematic due to drug interaction; this might precipitate a life-threatening serotonin syndrome, particularly if the concomitant drugs are also metabolized by CYP2D6 (such as fluoxetine, paroxetine, and tricyclic antidepressants).

Non-pharmacological Management

There are no RCTs of non-pharmacological treatments for PSEI, although some RCTs address the positive effects of non-pharmacological treatment for PSD [122– 126]. Depressive symptoms occur in 25–50 % of PSEI patients; therefore, cognitive behavioral therapy (CBT) may also be useful for patients with PSEI. This therapy is designed to challenge dysfunctional thoughts or beliefs that are associated with low mood and may show a positive effect on the confidence and daily activities of patients with depression. The drawbacks of CBT are that cognitively impaired or aphasic patients may not benefit, it is not cost-effective, and several weeks of treatment are needed before improvements are seen. There also are conflicting reports as to the effectiveness of CBT [125–127]. Further studies are needed to verify the benefit of CBT in patients with PSEI.

Summary

In summary, once PSEI is recognized and diagnosed, it can, in most cases, be reduced by pharmacological interventions without or with only mild side effects. SSRIs are recommended as first-line agents for the treatment of PSEI as they are effective and tolerable and may also improve patients' quality of life. When SSRIs are ineffective or poorly tolerated, TCAs, SNRIs, and dopaminergic agents can be considered. Nuedexta may be another useful alternative drug, although its efficacy for PSEI requires further study. The education and support of PSEI patients and their family members with CBT may form an important part of treatment. There are, however, limited data to guide clinicians on how long patients should remain on treatment regimens and how soon to start treating the patients. The need for long-term treatment needs to be evaluated on an individual basis.

References

1. Wilson SA. Original papers: some problems in neurology. J Neurol Psychopathol. 1924;4(16): 299–333.
2. Cummings JL, Arciniegas DB, Brooks BR, Herndon RM, Lauterbach EC, Pioro EP, et al. Defining and diagnosing involuntary emotional expression disorder. CNS Spectr. 2006;11(6):1–7.
3. Kim JS. Pathologic laughter after unilateral stroke. J Neurol Sci. 1997;148(1):121–5.
4. Magnus A. Fall von Aufhebung des Willenseinflusses auf einige Hirnnerven. In: Müller J, editors. Mullers Archiv fur Anatomie, Physiologies und Wissenschaftliche Medicin. Leipzig: Veit et Comp; 1837. p. 258–66.
5. Darwin C. The expression of the emotions in man and animals. New York/London: D Appleton and Company; 1872.
6. Oppenheim H, Siemerling E. Mittheilungen uber Psueobulbarparalyse und acute Bulbarparalyse. Ber Klin Wochenschr. 1886;23:791–4.
7. Brissaud E. Lecons sur les Maladies Nerveuses. Paris: Masson; 1895.
8. Nothnagel H. Zur Diagnose der Schugelerkrakungen. Z Kin Med. 1889;16:424–30.
9. Fere MC. Le fou rire prodromique. Rev Neurol (Paris). 1903;7:353–8.
10. Weisenberg T. Report of three cases with necropsy and of three cases without necropsy. Univ Penn Med Bull. 1905;18:1–39.
11. Davison C, Kelman H. Pathologic laughing and crying. Arch Neurol Psychiat. 1939;42:595–643.
12. Asfora WT, DeSalles AA, Abe M, Kjellberg RN. Is the syndrome of pathological laughing and crying a manifestation of pseudobulbar palsy? J Neurol Neurosurg Psychiatry. 1989;52(4):523–5.
13. Kim JS, Choi-Kwon S. Poststroke depression and emotional incontinence: correlation with lesion location. Neurology. 2000;54(9):1805–10.
14. Mega MS, Cummings JL, Salloway S, Malloy P. The limbic system: an anatomic, phylogenetic, and clinical perspective. In: Salloway S, Malloy P, Cummings JL, editors. The neuropsychiatry of limbic and subcortical disorders. Washington DC: American Psychiatric Press; 1997. p. 3–18.
15. Rosen HJ, Cummings J. A real reason for patients with pseudobulbar affect to smile. Ann Neurol. 2007;61(2):92–6.
16. Schiffer R, Pope LE. Review of pseudobulbar affect including a novel and potential therapy. J Neuropsychiatry Clin Neurosci. 2005;17(4):447–54.

17. Arciniegas DB, Lauterbach EC, Anderson KE, Chow TW, Flashman LA, Hurley RA, et al. The differential diagnosis of pseudobulbar affect (PBA). Distinguishing PBA among disorders of mood and affect. Proceedings of a roundtable meeting. CNS Spectr. 2005;10(5):1–14, quiz 5–6.
18. Parvizi J, Anderson SW, Martin CO, Damasio H, Damasio AR. Pathological laughter and crying: a link to the cerebellum. Brain. 2001;124(Pt 9):1708–19.
19. Bhatjiwale MG, Nadkarni TD, Desai KI, Goel A. Pathological laughter as a presenting symptom of massive trigeminal neuromas: report of four cases. Neurosurgery. 2000;47(2):469–71; discussion 71–2.
20. Tei H, Sakamoto Y. Pontine infarction due to basilar artery stenosis presenting as pathological laughter. Neuroradiology. 1997;39(3):190–1.
21. Parvizi J, Arciniegas DB, Bernardini GL, Hoffmann MW, Mohr JP, Rapoport MJ, et al. Diagnosis and management of pathological laughter and crying. Mayo Clin Proc. 2006;81(11):1482–6.
22. Dark FL, McGrath JJ, Ron MA. Pathological laughing and crying. Aust N Z J Psychiatry. 1996;30(4):472–9.
23. Wortzel HS, Oster TJ, Anderson CA, Arciniegas DB. Pathological laughing and crying: epidemiology, pathophysiology and treatment. CNS Drugs. 2008;22(7):531–45.
24. Arroyo S, Lesser RP, Gordon B, Uematsu S, Hart J, Schwerdt P, et al. Mirth, laughter and gelastic seizures. Brain. 1993;116(Pt 4):757–80.
25. Berkovic SH, Andermann F. Pathologic laughter. In: Joseph AB, Young RR, editors. Movement disorders in neurology and neuropsychiatry. Boston: Blackwell Sci; 1992. p. 382–8.
26. House A, Dennis M, Molyneux A, Warlow C, Hawton K. Emotionalism after stroke. BMJ. 1989;298(6679):991–4.
27. Morris PL, Robinson RG, Raphael B. Emotional lability after stroke. Aust N Z J Psychiatry. 1993;27(4):601–5.
28. Arciniegas DB, Topkoff J. The neuropsychiatry of pathologic affect: an approach to evaluation and treatment. Semin Clin Neuropsychiatry. 2000;5(4):290–306.
29. Tang WK, Chen YK, Lu JY, Mok VC, Xiang YT, Ungvari GS, et al. Microbleeds and post-stroke emotional lability. J Neurol Neurosurg Psychiatry. 2009;80(10):1082–6.
30. Moore SR, Gresham LS, Bromberg MB, Kasarkis EJ, Smith RA. A self report measure of affective lability. J Neurol Neurosurg Psychiatry. 1997;63(1):89–93.
31. Poeck K. Pathophysiology of emotional disorders associated with brain damage. In: Vinken PJ, Bruyn GW, editors. Handbook of clinical neurology. New York: Elsevier; 1969. p. 343–67.
32. Nahas Z, Arlinghaus KA, Kotrla KJ, Clearman RR, George MS. Rapid response of emotional incontinence to selective serotonin reuptake inhibitors. J Neuropsychiatry Clin Neurosci. 1998;10(4):453–5.
33. Tang WK, Chan SS, Chiu HF, Ungvari GS, Wong KS, Kwok TC. Emotional incontinence in Chinese stroke patients – diagnosis, frequency, and clinical and radiological correlates. J Neurol. 2004;251(7):865–9.
34. Sandyk R, Gillman MA. Nomifensine for emotional incontinence in the elderly. Clin Neuropharmacol. 1985;8(4):377–8.
35. Calvert T, Knapp P, House A. Psychological associations with emotionalism after stroke. J Neurol Neurosurg Psychiatry. 1998;65(6):928–9.
36. Allman P, Hope RA, Fairburn CG. Emotionalism following brain damage: a complex phenomenon. Postgrad Med J. 1990;66(780):818–21.
37. Nieuwenhuis-Mark RE, van Hoek A, Vingerhoets A. Understanding excessive crying in neurologic disorders: nature, pathophysiology, assessment, consequences, and treatment. Cogn Behav Neurol. 2008;21(2):111–23.
38. van Gijn J. Treating uncontrolled crying after stroke. Lancet. 1993;342(8875):816–7.
39. Grinblat N, Grinblat E, Grinblat J. Uncontrolled crying: characteristics and differences from normative crying. Gerontology. 2004;50(5):322–9.

40. Duda JE. History and prevalence of involuntary emotional expression disorder. CNS Spectr. 2007;12(4 Suppl 5):6–10.
41. Allman P, Hope T, Fairburn CG. Crying following stroke. A report on 30 cases. Gen Hosp Psychiatry. 1992;14(5):315–21.
42. Doorenbos DI, Haerer AF, Payment M, Clifton ER. Stimulus-specific pathologic laughter: a case report with discrete unilateral localization. Neurology. 1993;43(1):229–30.
43. Kim JS, Lee JH, Im JH, Lee MC. Syndromes of Pontine base infarction. A clinical-radiological correlation study. Stroke. 1995;26(6):950–5.
44. Choi-Kwon S, Han K, Choi S, Suh M, Kim YJ, Song H, et al. Poststroke depression and emotional incontinence: factors related to acute and subacute stages. Neurology. 2012;78(15):1130–7.
45. Coelho M, Ferro JM. Fou rire prodromique. Case report and systematic review of literature. Cerebrovasc Dis. 2003;16(1):101–4.
46. Mendez MF. Crying spells as symptoms of a transient ischaemic attack. J Neurol Neurosurg Psychiatry. 1999;67(2):255.
47. Chen YK, Wong KS, Mok V, Ungvari GS, Tang WK. Health-related quality of life in patients with poststroke emotional incontinence. Arch Phys Med Rehabil. 2011;92(10):1659–62.
48. Robinson RG, Parikh RM, Lipsey JR, Starkstein SE, Price TR. Pathological laughing and crying following stroke: validation of a measurement scale and a double-blind treatment study. Am J Psychiatry. 1993;150(2):286–93.
49. Smith RA, Berg JE, Pope LE, Callahan JD, Wynn D, Thisted RA. Validation of the CNS emotional lability scale for pseudobulbar affect (pathological laughing and crying) in multiple sclerosis patients. Mult Scler. 2004;10(6):679–85.
50. Ironside R. Disorders of laughter due to brain lesions. Brain. 1956;79(4):589–609.
51. Gallagher JP. Pathologic laughter and crying in ALS: a search for their origin. Acta Neurol Scand. 1989;80(2):114–7.
52. Kaschka WP, Meyer A, Schier KR, Froscher W. Treatment of pathological crying with citalopram. Pharmacopsychiatry. 2001;34(6):254–8.
53. Starkstein SE, Migliorelli R, Teson A, Petracca G, Chemerinsky E, Manes F, et al. Prevalence and clinical correlates of pathological affective display in Alzheimer's disease. J Neurol Neurosurg Psychiatry. 1995;59(1):55–60.
54. Parvizi J, Joseph J, Press DZ, Schmahmann JD. Pathological laughter and crying in patients with multiple system atrophy-cerebellar type. Mov Disord. 2007;22(6):798–803.
55. Surridge D. An investigation into some psychiatric aspects of multiple sclerosis. Br J Psychiatry. 1969;115(524):749–64.
56. Feinstein A, Feinstein K, Gray T, O'Connor P. Prevalence and neurobehavioral correlates of pathological laughing and crying in multiple sclerosis. Arch Neurol. 1997;54(9):1116–21.
57. Zeilig G, Drubach DA, Katz-Zeilig M, Karatinos J. Pathological laughter and crying in patients with closed traumatic brain injury. Brain Inj. 1996;10(8):591–7.
58. McGrath J. A study of emotionalism in patients undergoing rehabilitation following severe acquired brain injury. Behav Neurol. 2000;12(4):201–7.
59. Tateno A, Jorge RE, Robinson RG. Pathological laughing and crying following traumatic brain injury. J Neuropsychiatry Clin Neurosci. 2004;16(4):426–34.
60. MacHale SM, Cavanagh JT, Bennie J, Carroll S, Goodwin GM, Lawrie SM. Diurnal variation of adrenocortical activity in chronic fatigue syndrome. Neuropsychobiology. 1998;38(4):213–7.
61. Kim JS. Post-stroke emotional incontinence after small lenticulocapsular stroke: correlation with lesion location. J Neurol. 2002;249(7):805–10.
62. Kim JM, Stewart R, Kang HJ, Bae KY, Kim SW, Shin IS, et al. Associations of serotonergic genes with poststroke emotional incontinence. Int J Geriatr Psychiatry. 2012;27(8):799–806.
63. Choi-Kwon S, Kim JS. Poststroke emotional incontinence and decreased sexual activity. Cerebrovasc Dis. 2002;13(1):31–7.
64. McCullagh S, Moore M, Gawel M, Feinstein A. Pathological laughing and crying in amyotrophic lateral sclerosis: an association with prefrontal cognitive dysfunction. J Neurol Sci. 1999;169(1–2):43–8.

65. Kim JS, Choi S, Kwon SU, Seo YS. Inability to control anger or aggression after stroke. Neurology. 2002;58(7):1106–8.
66. Choi-Kwon S, Han SW, Kwon SU, Kang DW, Choi JM, Kim JS. Fluoxetine treatment in poststroke depression, emotional incontinence, and anger proneness: a double-blind, placebo-controlled study. Stroke. 2006;37(1):156–61.
67. Choi-Kwon S, Han K, Cho K-H, Choi S, Suh M, Nah H-W, Kim JS. Factors associated with post-stroke anger proneness in ischemic stroke patients. Eur J Neurol, in press.
68. Gorzalka BB, Mendelson SD, Watson NV. Serotonin receptor subtypes and sexual behavior. Ann N Y Acad Sci. 1990;600:435–44; discussion 45–6.
69. Ceccaldi M, Milandre L. A transient fit of laughter as the inaugural symptom of capsular-thalamic infarction. Neurology. 1994;44(9):1762.
70. Lauterbach EC, Price ST, Spears TE, Jackson JG, Kirsh AD. Serotonin responsive and non-responsive diurnal depressive mood disorders and pathological affect in thalamic infarct associated with myoclonus and blepharospasm. Biol Psychiatry. 1994;35(7):488–90.
71. Tasch E, Cendes F, Li LM, Dubeau F, Montes J, Rosenblatt B, et al. Hypothalamic hamartomas and gelastic epilepsy: a spectroscopic study. Neurology. 1998;51(4):1046–50.
72. Dericioglu N, Cataltepe O, Tezel GG, Saygi S. Gelastic seizures due to right temporal cortical dysplasia. Epileptic Disord. 2005;7(2):137–41.
73. Sackeim HA, Greenberg MS, Weiman AL, Gur RC, Hungerbuhler JP, Geschwind N. Hemispheric asymmetry in the expression of positive and negative emotions. Neurologic evidence. Arch Neurol. 1982;39(4):210–8.
74. Wali GM. "Fou rire prodromique" heralding a brainstem stroke. J Neurol Neurosurg Psychiatry. 1993;56(2):209–10.
75. Assal F, Valenza N, Landis T, Hornung JP. Clinicoanatomical correlates of a Fou rire prodromique in a Pontine infarction. J Neurol Neurosurg Psychiatry. 2000;69(5):697–8.
76. Ertekin C, Ekmekci O, Celebisoy N. Le fou rire prodromique. J Neurol. 1997;244(4): 271–2.
77. Gondim FA, Parks BJ, Cruz-Flores S. "Fou rire prodromique" as the presentation of pontine ischaemia secondary to vertebrobasilar stenosis. J Neurol Neurosurg Psychiatry. 2001;71(6):802–4.
78. Uzunca I, Utku U, Asil T, Celik Y. "Fou rire prodromique" associated with simultaneous bilateral capsular genu infarction. J Clin Neurosci. 2005;12(2):174–5.
79. Carel C, Albucher JF, Manelfe C, Guiraud-Chaumeil B, Chollet F. Fou rire prodromique heralding a left internal carotid artery occlusion. Stroke. 1997;28(10):2081–3.
80. Osseby G, Manceau E, Huet F, Becker F, Chouchane W, Durand C, et al. 'Fou Rire prodromique' as the heralding symptom of lenticular infarction, caused by dissection of the internal carotid artery in a 12-year-old boy. Eur J Paediatr Neurol. 1999;3(3):133–6.
81. Garg RK, Misra S, Verma R. Pathological laughter as heralding manifestation of left middle cerebral artery territory infarct: case report and review of literature. Neurol India. 2000; 48(4):388–90.
82. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: the neural basis of normal emotion perception. Biol Psychiatry. 2003;54(5):504–14.
83. Pollack IF, Polinko P, Albright AL, Towbin R, Fitz C. Mutism and pseudobulbar symptoms after resection of posterior fossa tumors in children: incidence and pathophysiology. Neurosurgery. 1995;37(5):885–93.
84. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain. 1998;121(Pt 4):561–79.
85. Levisohn L, Cronin-Golomb A, Schmahmann JD. Neuropsychological consequences of cerebellar tumour resection in children: cerebellar cognitive affective syndrome in a paediatric population. Brain. 2000;123(Pt 5):1041–50.
86. Parvizi J, Schiffer R. Exaggerated crying and tremor with a cerebellar cyst. J Neuropsychiatry Clin Neurosci. 2007;19(2):187–90.
87. Sinha R, Lacadie C, Skudlarski P, Wexler BE. Neural circuits underlying emotional distress in humans. Ann N Y Acad Sci. 2004;1032:254–7.

88. Davidson RJ, Abercrombie H, Nitschke JB, Putnam K. Regional brain function, emotion and disorders of emotion. Curr Opin Neurobiol. 1999;9(2):228–34.
89. Schmahmann JD, Caplan D. Cognition, emotion and the cerebellum. Brain. 2006;129(Pt 2): 290–2.
90. Rabins PV, Arciniegas DB. Pathophysiology of involuntary emotional expression disorder. CNS Spectr. 2007;12(4 Suppl 5):17–22.
91. Swash M. Released involuntary laughter after temporal lobe infarction. J Neurol Neurosurg Psychiatry. 1972;35(1):108–13.
92. Andersen G, Ingeman-Nielsen M, Vestergaard K, Riis JO. Pathoanatomic correlation between poststroke pathological crying and damage to brain areas involved in serotonergic neurotransmission. Stroke. 1994;25(5):1050–2.
93. Lavoie B, Parent A. Immunohistochemical study of the serotoninergic innervation of the basal ganglia in the squirrel monkey. J Comp Neurol. 1990;299(1):1–16.
94. Palacios JM, Waeber C, Bruinvels AT, Hoyer D. Direct visualization of serotonin1D receptors in the human brain using a new iodinated radioligand. Brain Res Mol Brain Res. 1992;13(1–2):175–8.
95. Andersen G, Vestergaard K, Riis JO. Citalopram for post-stroke pathological crying. Lancet. 1993;342(8875):837–9.
96. Murai T, Barthel H, Berrouschot J, Sorger D, von Cramon DY, Muller U. Neuroimaging of serotonin transporters in post-stroke pathological crying. Psychiatry Res. 2003;123(3):207–11.
97. Wolf JK, Santana HB, Thorpy M. Treatment of "emotional incontinence" with levodopa. Neurology. 1979;29(10):1435–6.
98. Udaka F, Yamao S, Nagata H, Nakamura S, Kameyama M. Pathologic laughing and crying treated with levodopa. Arch Neurol. 1984;41(10):1095–6.
99. O'Donnell P. Dopamine gating of forebrain neural ensembles. Eur J Neurosci. 2003;17(3): 429–35.
100. Rogawski MA. Low affinity channel blocking (uncompetitive) NMDA receptor antagonists as therapeutic agents–toward an understanding of their favorable tolerability. Amino Acids. 2000;19(1):133–49.
101. Brooks BR, Thisted RA, Appel SH, Bradley WG, Olney RK, Berg JE, et al. Treatment of pseudobulbar affect in ALS with dextromethorphan/quinidine: a randomized trial. Neurology. 2004;63(8):1364–70.
102. Panitch HS, Thisted RA, Smith RA, Wynn DR, Wymer JP, Achiron A, et al. Randomized, controlled trial of dextromethorphan/quinidine for pseudobulbar affect in multiple sclerosis. Ann Neurol. 2006;59(5):780–7.
103. Klein M, Musacchio JM. High affinity dextromethorphan binding sites in guinea pig brain. Effect of sigma ligands and other agents. J Pharmacol Exp Ther. 1989;251(1):207–15.
104. Bermack JE, Debonnel G. The role of sigma receptors in depression. J Pharmacol Sci. 2005;97(3):317–36.
105. Muller U, Murai T, Bauer-Wittmund T, von Cramon DY. Paroxetine versus citalopram treatment of pathological crying after brain injury. Brain Inj. 1999;13(10):805–11.
106. Benedek DM, Peterson KA. Sertraline for treatment of pathological crying. Am J Psychiatry. 1995;152(6):953–4.
107. Mukand J, Kaplan M, Senno RG, Bishop DS. Pathological crying and laughing: treatment with sertraline. Arch Phys Med Rehabil. 1996;77(12):1309–11.
108. Okun MS, Riestra AR, Nadeau SE. Treatment of ballism and pseudobulbar affect with sertraline. Arch Neurol. 2001;58(10):1682–4.
109. Hackett ML, Yang M, Anderson CS, Horrocks JA, House A. Pharmaceutical interventions for emotionalism after stroke. Cochrane Database Syst Rev. 2010;(2), CD003690.
110. Brown KW, Sloan RL, Pentland B. Fluoxetine as a treatment for post-stroke emotionalism. Acta Psychiatr Scand. 1998;98(6):455–8.
111. Burns A, Russell E, Stratton-Powell H, Tyrell P, O'Neill P, Baldwin R. Sertraline in stroke-associated lability of mood. Int J Geriatr Psychiatry. 1999;14(8):681–5.

112. Murray V, von Arbin M, Bartfai A, Berggren AL, Landtblom AM, Lundmark J, 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):708–16.
113. Ohkawa S, Mori E, Yamadori A. Treatment of pathological laughing with amitriptyline. Rinsho Shinkeigaku. 1989;29(9):1183–5.
114. Choi-Kwon S, Choi J, Kwon SU, Kang DW, Kim JS. Fluoxetine improves the quality of life in patients with poststroke emotional disturbances. Cerebrovasc Dis. 2008;26(3):266–71.
115. Moller M, Andersen G. Inhibition of selective noradrenergic reuptake as treatment of pathological laughter. J Clin Psychopharmacol. 2007;27(1):108–10 [Case Reports Letter].
116. Smith AG, Montealegre-Orjuela M, Douglas JE, Jenkins EA. Venlafaxine for pathological crying after stroke. J Clin Psychiatry. 2003;64(6):731–2.
117. Kim SW, Shin IS, Kim JM, Lim SY, Yang SJ, Yoon JS. Mirtazapine treatment for pathological laughing and crying after stroke. Clin Neuropharmacol. 2005;28(5):249–51.
118. Ramasubbu R. Lamotrigine treatment for post-stroke pathological laughing and crying. Clin Neuropharmacol. 2003;26(5):233–5.
119. Peeters M, Maloteaux JM, Hermans E. Distinct effects of amantadine and memantine on dopaminergic transmission in the rat striatum. Neurosci Lett. 2003;343(3):205–9.
120. Peeters M, Romieu P, Maurice T, Su TP, Maloteaux JM, Hermans E. Involvement of the sigma 1 receptor in the modulation of dopaminergic transmission by amantadine. Eur J Neurosci. 2004;19(8):2212–20.
121. Pioro EP, Brooks BR, Cummings J, Schiffer R, Thisted RA, Wynn D, et al. Dextromethorphan plus ultra low-dose quinidine reduces pseudobulbar affect. Ann Neurol. 2010;68(5):693–702.
122. Scogin F, Welsh D, Hanson A, Stump J, Coates A. Evidence-based psychotherapies for depression in older adults. Clin Psychol Sci Pract. 2005;12(3):222–37.
123. Kemp BJ, Corgiat MD, Gill C. Effects of brief cognitive-behavioral group psychotherapy on older persons with and without disabling illness. Behav Health Aging. 1992;2:21–8.
124. Watkins CL, Auton MF, Deans CF, Dickinson HA, Jack CI, Lightbody CE, et al. Motivational interviewing early after acute stroke: a randomized, controlled trial. Stroke. 2007;38(3): 1004–9.
125. Lincoln NB, Flannaghan T. Cognitive behavioral psychotherapy for depression following stroke: a randomized controlled trial. Stroke. 2003;34(1):111–5.
126. Mitchell PH, Veith RC, Becker KJ, Buzaitis A, Cain KC, Fruin M, et al. Brief psychosocial-behavioral intervention with antidepressant reduces poststroke depression significantly more than usual care with antidepressant: living well with stroke: randomized, controlled trial. Stroke. 2009;40(9):3073–8.
127. Hackett ML, Anderson CS, House AO, Xia J. Interventions for treating depression after stroke. Stroke. 2009;40:e487–e488

Chapter 8
Poststroke Aggressiveness

A. Carota, J. Bogousslavsky, and P. Calabrese

Abstract Aggressiveness is not a medical diagnosis. It corresponds to behavioral changes that patients display often in the acute, subacute, and chronic phases of stroke. These changes are related to the emotion of anger and associate variably with the anger trait, hostility, impulsivity, disruptiveness, confusion, agitation, anxiety, depression, and some cognitive changes which could be specific or not to the localization of the vascular lesion. For assessment purposes, it is important that poststroke aggressiveness represents a significant change in comparison to the prestroke condition and that it has sufficient clinical severity to be considered distressing and producing significant interference with personal and social patterns of functioning.

The link between aggressiveness and regional brain dysfunction remains still poorly understood.

In order to achieve a better comprehension of aggressiveness-related states and to finalize effective interventions, we propose to organize them in categories which are specific to poststroke disorders taxonomies (such as the dysexecutive syndrome; catastrophic reactions, aphasia and other left hemisphere syndromes; misoplegia, somatoparaphrenia, misidentification disorders, and other right hemisphere syndromes; poststroke delirium, mania, psychosis, and mood disorders; poststroke pain and fatigue conditions; and vascular dementia).

A. Carota (✉)
Center for Brain and Nervous System Disorders, Genolier Swiss Medical Network
Neurocenter and Department of Neurology, Clinique Genolier,
Rte du Muids 3 - CP 100, Genolier CH-1272, Switzerland
e-mail: acarota@genolier.net

J. Bogousslavsky
Center for Brain and Nervous System Disorders, Genolier Swiss Medical Network
Neurocenter and Department of Neurology and Neurorehabilitation, Clinique Valmont,
Glion, Switzerland

P. Calabrese
Division of Molecular and Cognitive Neuroscience, Basel University, Basel, Switzerland

J.M. Ferro (ed.), *Neuropsychiatric Symptoms of Cerebrovascular Diseases*,
Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-1-4471-2428-3_8, © Springer-Verlag London 2013

Additional studies with clinically meaningful long-term outcomes are required to identify and support pharmacological and behavioral interventions. Drug therapy for poststroke agitation and aggression remains a significant research issue.

Keywords Aggressiveness • Anger • Irritability • Impulsivity • Stroke • Dysexecutive syndrome • Catastrophic reaction • Aphasia • Right hemisphere • Poststroke mood disorders

Case 1

A 66-year-old right-handed man had almost complete left middle cerebral artery territory ischemic stroke of cardioembolic etiology (atrial fibrillation), which occurred 16 years before.

Residual neurologic deficits were severe Wernicke aphasia (WA), right homonymous hemianopia, faciobrachial paresis, and hypoesthesia. Spontaneous language was hyperfluent and deeply uncommunicative because of continuous phonological and verbal paraphasias (neologisms, jargonophasia) intermingled with frequent swearing. Auditory and written comprehension was almost abolished. The patient was unable to process any kind of communicative inputs, even gestural. Semantic repetition, reading, and writing were severely affected in the same way as spontaneous language. However, he needed only minor help for most basic activities of daily living at home. He was able to walk alone with a cane. The patient's collaboration was only just sufficient in routine activities at home and out. He and his wife participated to few social events which seemed pleasurable to him.

Caregivers did not note depressive signs. However, he showed irritability and aggressiveness as he was prone to slander when he seemed to misunderstand the conversation. Aphasia therapy was withdrawn several years before due to the emergence of irritability and anger in coping with linguistic tasks.

Few days before Christmas, 16 years after the onset of stroke, he shot himself in the head with a pellet gun, which he had moved secretly from the storage basement into the house. The lead bullets pierced the temples (from the left to the right) throughout the orbits, sectioning the optic and the oculomotor nerves bilaterally, outside the cranial cavity. The patient became blind, but the brain remained otherwise uninjured, and he did not present new neurological deficits. No surgical intervention was conducted, and the patient spent 2 months in a psychiatric hospital, 1 month in a rehabilitation hospital, and 2 months in an institution before being discharged at home.

An antidepressant (citalopram) was introduced early and progressively increased to the highest recommended dose (60 mg/day) over a month. However, his general condition and behavior were considered to be similar to the status prior to the suicide attempt (Fig. 8.1).

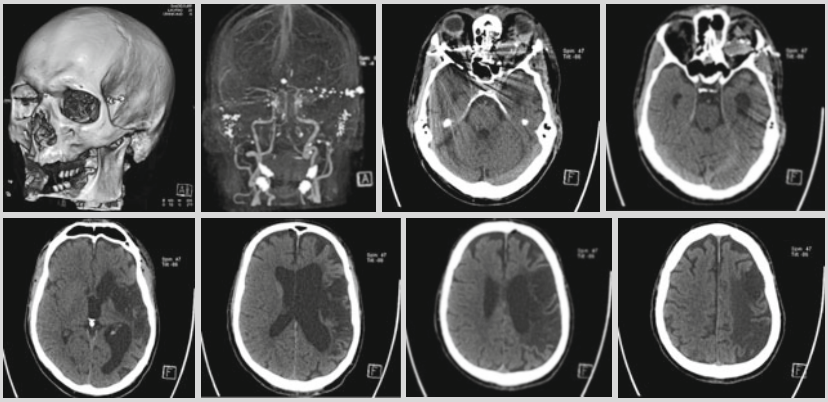


Fig. 8.1 From *left to right*, *up to down*: in the *first row*, note the bullet remnants in the orbits along the optic nerves with the evidence of an orbital hematoma on the left. Note the holes on the left (entrance) and right (outlet) temples, which let foresee the bullet trajectory. The images (*lower row*) show the residual malacic ischemic lesion located within the left MCA territory and including the perisylvian language areas

Discussion

Over 16 years after the stroke onset and before the suicide attempt, anger and irritability were the most prominent and persisting behavioral alterations of the patient. These symptoms usually appear among the ones which may follow Wernicke aphasia (WA). In fact, patients with WA seem to experience high frustration due to impaired verbal communication. Hence, they are particularly vulnerable to anger and aggressiveness. For this patient, it was not possible to perform standard clinical mood assessments as comprehension and verbal expression were severely affected. Neurologists, neuropsychiatrists, neuropsychologist, and speech-language therapists have an important role in identifying affective symptoms of patients with severe aphasia and making appropriate referrals for establishing medical, psychiatric, or pharmacological intervention. The access to harmful situations or to weapons should be carefully considered and prevented in patients with WA, especially when they display anger or frustration.

Case 2

A 70-year-old right-handed man, known for atrial fibrillation and arterial hypertension, was a victim of a cardioembolic multifocal stroke in the left middle cerebral artery territory with consecutive Broca's aphasia (BA), catastrophic reactions, dysexecutive syndrome, and right ataxic hemiparesis.

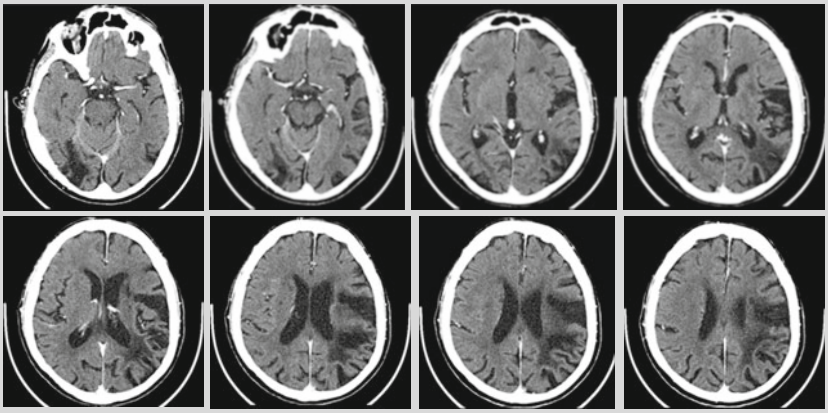


Fig. 8.2 Brain transverse CT sections Showing multifocal strokes (in the superficial posterior cerebral artery territory on the *right* and in the superficial middle cerebral artery territory on the *left*)

CT scan showed in addition an ancient stroke in the superficial territory of the right posterior cerebral artery. Since the admission to the rehabilitation hospital, fluoxetine was started. After 3 months of rehabilitation, he was able to communicate with phrases of moderate complexity, although considerable articulatory effort. Comprehension was sufficient for most complex sentences. At discharge, the Functional Independence Measure (FIM) was 90/126 (moderately severe deficit). He was able to walk and he needed mild supervision in basic activities of daily living.

After his discharge at home, anger, irritability, and frustration escalated to an overwhelming degree. He refused to continue aphasia therapy and physiotherapy, and his social contacts progressively diminished. His wife experienced an increased caregiver burden as, at home, she was the constant target of taunting, verbal, and physical attacks. Irritability was triggered by misunderstandings, by the need to repeat him words and sentences because of his linguistic utterances. His clinical condition corresponded to a multi-infarctual dementia, as supported by radiological images (Fig. 8.2).

At that point, aphasia, dysarthria, dysphagia, and hemiparesis suddenly worsened, and this was considered to be the consequence of a new subcortical stroke (in the deep middle cerebral artery territory). The patient was admitted again to the rehabilitation ward in the postacute phase. Despite the patient was assigned to the same therapists, his collaboration was severely reduced.

While performing linguistic tasks, he could show sudden frustration and hostility with gestures (knocking the pencil and the papers on the table, shouting to the therapist, and leaving). He showed the same oppositional behavior during the deglutition therapy. The videofluoroscopy study showed tracheal aspiration but the patient refused the PEG tube. He did not adapt to

the prescription of a modified diet (soft food) and thickened liquids. He rejected the use of both the cane and the walker and the risk of falling remained high.

The treatment with pregabalin, quetiapine, and citalopram only slightly improved the irritability and aggressiveness at the cost of mild sedation. He refused any sort of psychological support or behavioral intervention. As the intention of being discharged back home was not feasible, the length of the hospitalization considerably increased. The social insurance ceased to cover the costs of the rehabilitative therapies. Only after several meetings with the rehabilitative team and his family, he accepted to be transferred to a residential care institution at the condition to go home during the weekends. The functional independence score was 66/126 (severe deficit) after 3 months of the second period of rehabilitation.

Discussion

For this 70-year-old patient, with a multi-infarct dementia, aggressiveness and catastrophic reactions were significant behavioral changes that emerged early after the first stroke. The presence of nonfluent aphasia, catastrophic reactions in response to linguistic demands, irritability, anger, and hostility poorly responded to pharmacological interventions. These behavioral symptoms significantly reduced the participation to the rehabilitative programs, increased the burden of the caregivers and the rehabilitative team, extended the length of the hospitalization, and prevented his discharge. Although not considered among the items of most current stroke scales for deficit or outcome assessment, aggressiveness was, for this patient, the most important symptom to treat from a family, social, and rehabilitative point of view.

Aggressiveness had a negative effect on functional recovery and increased substantially the risk of morbidity (aspiration pneumonia and falls) and mortality.

Introduction

Aggressiveness (verbal and physical), aggression, and irritability are behavioral changes that patients display often in the acute [1, 2] subacute, and chronic phases of stroke [3, 4]. Nevertheless, the link between aggressiveness and regional brain dysfunction is poorly understood. Behavioral and pharmacological interventions for aggressiveness are often insufficient and the rehabilitative interventions and medical follow-up can be seriously compromised by aggressive behaviors (cf case 1 and case 2). Irritability increases the length of the hospitalization in rehabilitative settings. Aggressiveness reduces the stroke patients' quality of life and is a major source of burden and stress for them and their families. Aggressive behaviors endanger interpersonal relationships and occupational functioning and might cause legal problems [4]. Irritability and hostility are determinants for other aspects of

disease and morbidity such as treatment nonadherence, suicide attempts (cf. case 1), and violence. In elderly patients, aggressiveness is a common reason for referral to psychogeriatric services and for admission to a nursing home. In institutions, aggressive patients create serious management problems and deplete nursing resources. Furthermore, anger and aggressiveness could substantially limit the patient's competences in self-determination and self-agency (the ability to have a meaningful leadership role to make choices).

Therefore, it is important to support clinical research aimed to screen, to achieve a better comprehension of, and to treat poststroke aggressiveness.

The Multidimensionality of Poststroke Aggressiveness

Aggressiveness (intention and delivery to harm) and aggression are the overt behavioral translation of anger and do not correspond to specific medical diagnoses.

Anger is a basic emotion characterized by indignation, dislike, belligerence, rage, or wrath and refers to a dimension of feelings and attitudes. Anger represents the emotional or affective component of the aggressive behavior. Anger, as other emotions, tends to occur in relation to subjects or objects or to some external or internal stimuli, lasts for seconds or minutes, has unique facial expressions, and tends to elicit to adaptive behavior.

State anger is embedded in a specific situational context, and it fluctuates over time as a function of external events.

Trait anger (or anger proneness) is a personality trait, a general stable temperament of low threshold reactivity for angry feelings.

Irritability is the condition to be easily angered and corresponds to a mood state that predisposes toward certain emotions (anger), cognitive states (e.g., hostile appraisals), and certain actions (aggression). Irritability is subjectively unpleasant and displays by means of behaviors characterized by the expression of negative emotions generally in interpersonal relationships or social contexts.

Hostility is a cognitive dimension of anger and corresponds to a negative evaluation of persons and things accompanied with a desire to harm or aggress them. Hostility could manifest with cynicism, mistrust, and denigration.

Aggression corresponds to the translation of aggressiveness into its behavioral forms.

Aggressiveness and related states and behaviors are often associated with psychomotor agitation and appear disproportionate to the context.

For aggressive patients, the perception of the environment and interpersonal interactions are often distorted by states of threat, victimization, or disrespect, and in this context, provocation and retaliation are critical factors.

Aggressiveness can be further classified into the premeditated and impulsive subtypes, according to the degree of control that the patient can assume over the behavior [5]. This is an important aspect as impulsive and non-impulsive (i.e., planned or premeditated) aggression might have different mechanisms and responses

to pharmacological interventions [6] and might also be judged differently from a forensic point of view.

Impulsivity is a multidimensional concept that involves the tendency to act quickly without reflection, overthrowing normal control mechanisms on emotions, behaviors, and cognition. Impulsive individuals only insufficiently avoid or suppress acts that are potentially harmful. The psychological construct of impulsivity includes deficits in planning (inability to plan ahead), cognition (making up one's mind quickly), and regulation of motor acts (acting without thinking).

Disruptiveness corresponds to a subjective evaluation of the examiner on the intensity of the aggressiveness of the examined. Physical aggression is the most disruptive form of aggressiveness.

Aggressiveness and aggression can manifest with verbal or motor behaviors against objects, people, and toward self (i.e., self-injury, suicide).

Physical aggressive behaviors of stroke patients include biting, grabbing, hitting, hurting oneself or others, falling intentionally, kicking, and physical sexual advances, pushing, scratching, spitting, tearing, and throwing things. Aggressiveness can associate with other agitated behaviors (inappropriate dressing and/or disrobing, inappropriate eating or drinking, exit-seeking behaviors, handling and hiding things, hoarding, pacing, repetitious mannerisms, restlessness, attention-seeking behaviors, complaining, and negativism). Verbal aggressive behaviors manifest with cursing, making strange noises, screaming, shrieking, hostile muttering, taunting and verbal sexual advances, and repetition of sentences and questions. Aggression can be active (direct engagement to harm) and direct (face-to-face confrontation) or passive (causing harm by not doing something) and indirect (harming circuitously through another person or object), or undirected (unspecific discharge of negative affect).

In stroke patients, aggressiveness and cognitive changes are often associated. Cognitive deficits affect not only the reliability of patients' answers to standardized verbal assessments [7] but also the patients' insight into their own behavior. Many aggressive patients deny obstinately being aggressive, and for them, the experience and the expression of emotion might dissociate as it happens for depressive feelings and crying in patients with pseudobulbar palsy. Aphasia challenges the assessment of anger and irritability even with the use of analogical or observational scales. Independently from aphasia, aggressiveness impoverishes efforts and motivation toward behavioral and neuropsychological evaluations.

Aggressiveness could be subtle, fluctuating in time or strictly related to the context in which it manifests. It may also associate or alternate in stroke patients with opposite emotional behaviors such as apathy or placidity.

Sometimes, only detailed and repeated examinations can clarify whether there is a relationship between aggressiveness and cognitive changes. An example is the patient with WA or other fluent aphasia for whom a paranoid ideation manifests as a consequence of the verbal deafness-like deficits (cf. case 1).

A well-known example of disturbed social judgment, poor comprehension of deficits, and aggressiveness is that of William Douglas (former Supreme Court, Justice "the most doctrinaire and committed civil libertarian ever to sit on the

court" who, after a right hemisphere stroke, showed a deep anosognosia into his behavioral and cognitive changes [8]. He engaged into inappropriate social behaviors and outrages as he attempted to continue participating in the court cases for 2 years, as he believed to be able to plead at the bench despite of his obvious incapacity.

Other emotional or psychological factors that are strictly related to neurologic deficits should be considered in the assessment of aggressiveness such as the frustration due to the inability to communicate with aphasia [9], to move with hemiparesis, to filter out excessive stimulation, or to be aware about the loss of the social role. Aggressiveness could be heavily triggered by the experience of physical pain or discomfort, fatigue, anxiety, and depression.

For diagnostic purposes, it is also important that poststroke aggressiveness represents a significant change in comparison to the prestroke condition. Thus, "prestroke" aggressiveness should be systematically inquired. Prestroke personality traits could be implicated in the emergence of aggressiveness and other behavioral and psychological symptoms after stroke [10]. Social and familial issues, prior exposure to violence, psychotropic mediction, drug and alcohol addiction, and notion of prestroke depression and anxiety constitute other relevant factors.

Another issue that is relevant for diagnosis is that poststroke irritability, impulsivity, and aggressiveness should have sufficient clinical severity to be considered distressing and should produce significant interference with personal and social patterns of functioning. Furthermore, in understanding the impact of aggressive behaviors and successive changes to therapies, it is important to take into account both: the type of behavior and its frequency.

Although aggressiveness could be easily outlined and recognized by anyone, a major problem for clinical studies in stroke is that its underlying psychological, psychopathological, or psychiatric constructs are not yet easily translated or translatable into operational terms. For example, there are no DSM-IV diagnostic criteria that could apply to the diagnosis of poststroke aggressive behaviors.

Aggressiveness can manifest together with other psychiatric symptoms and be categorized into other several poststroke syndromes or disorders that do not fit with DSM-IV diagnosis.

Psychodinamic factors

Although anger, irritability, aggressiveness, and aggression could emerge directly from brain damage after stroke, it is noteworthy to understand and inquire the role of psychodynamic factors. Patients' irritability could be heavily related to the unexpected dramatic changes of body integrity and intimate life projects, hence a psychological assessment is here required.

Early after onset, there may be a profound sense of confusion (reflecting the effects of a life-threatening trauma), which mixes with cognitive impairments and other symptoms of which the person may even be only partially aware. This combination lead some patients to view the situation as unreal and themselves as no longer

being "a real person." The new emotional condition of a patient (or the caregiver) who thinks how brain stroke changed the previous life has been often compared (in terms of psychodynamic mechanisms) to a bereavement. As the person becomes aware of what has happened and, at least, of some of the consequences, he asks about: "Why me?" Loss of control over both physical and cognitive skills, combined with an apparent inability to recover as expected and with future uncertainties, provokes frustration and anger. Some patients experience generalized anxiety; others have specific fears (e.g., not to be able again to walk, to talk, to drive, to return to work).

These preliminary considerations on the multiplicity of the aspects related to poststroke anger and aggressiveness point out to the need of a multidisciplinary or holistic clinical approach, which includes neurologic, neuropsychiatric, behavioral, emotional, psychological or psychodynamic, pharmacological, rehabilitative, and social evaluations and interventions. That approach to diagnose, investigate, and treat aggressive behaviors would be necessarily complex. Unfortunately, at the moment, aggressiveness is not recorded among the items of the most current stroke and outcome assessment scales.

Poststroke Disorders That Might Manifest with Aggressiveness (Table 8.1)

The Dysexecutive Syndrome

The dysexecutive (or "frontal lobe") syndrome refers to the disruption of those human faculties that allow adapting behaviors according to environmental needs. This syndrome includes, besides aggressiveness, a broad range of behavioral changes that generally do not fit into both stroke and DSM-IV taxonomies.

According to the frontal-subcortical anatomo-functional systems classification [11], three prototypical variants of the dysexecutive syndrome have been proposed [12]. This classification reminds to the effects of the frontal lobe lesions previously described in the work of Luria [13].

Table 8.1 Poststroke disorders that might manifest with aggressiveness

Dysexecutive syndrome
Emotional dyscontrol and disinhibition
Loss of empathy
Catastrophic reactions and Wernicke aphasia
Personality changes
Mania
Psychosis, delusions, and misidentification syndromes
Delirium/confusion with agitated behaviors
Misoplegia and somatoparaphrenia
Depression and suicide
Anxiety
Pain and fatigue syndromes
Vascular dementia

The dorsolateral prefrontal circuit originates in Brodmann's areas 9 and 10 on the lateral surface of the anterior frontal lobe (superficial superior middle cerebral artery territory). Neurons in these regions project to the dorsolateral head of the caudate nucleus, which projects by direct and indirect routes to the internal globus pallidus (Gpi)-substantia nigra pars reticulata (SNr) complex. This complex outputs to the parvocellular pars of the ventral anterior and mediodorsal thalamus which closes the circuit by projecting back to Brodmann's areas 9 and 10 of the dorsolateral frontal lobe.

Stroke confined to the dorsolateral prefrontal region (after lobar hemorrhage or watershed infarcts) manifests with slowness in thinking, failure to recognize concepts and generate hypothesis, lack of flexibility, perseveration, stereotypical motor behavior (e.g., grasping), and acting on simple motivations [14]. In this context, aggressiveness might manifest as an impulsive behavior due to lack of cognitive control on emotions. The dorsal prefrontal cortex (PFC) systems explicitly conceptualize emotional stimuli and analyze how associations between stimuli and emotional responses can be changed.

The second circuit originates from neurons of the anterior cingulate cortex (ACC) (Brodmann's area 24, anterior cerebral artery territory), which provide input to the ventral or limbic striatum (the ventromedial caudate, ventral putamen, nucleus accumbens, and olfactory tubercle) that connects by direct and indirect routes to the ventral pallidum, which, by its turn, gives input to the magnocellular mediodorsal thalamus. The mediodorsal thalamus closes the circuit sending projections to the ACC. The anterior cingulate cortex is believed to have a prominent role in modulating arousal, which is a critical feature of negative emotions. The connectivity of the ACC and amygdala may provide a means by which emotional arousal is modulated. Patients with stroke involving the ACC (in the anterior cerebral artery territory) often show apathy and a low level of anger and irritability [15–17].

The orbitofrontal circuit (anterior communicant artery region) originates in the lateral orbital gyrus of Brodmann's area 11 and the medial inferior frontal gyrus of the areas 10 and 47. These areas send projections to the ventromedial caudate, which projects in turn by direct and indirect loops to the GPi and the SNr. Neurons are sent from the GP and SNr to the magnocellular division of the ventral anterior and mediodorsal thalamus. This division of the circuit then closes with projections from this thalamic region to the lateral orbitofrontal cortex.

The orbitofrontal cortex (OFC) is thought to mediate socially appropriate behaviors and empathy. Stroke (generally hemorrhagic) circumscribed to this cortical region is rare except as a complication of rupture and repair of anterior communicating artery aneurysms. This localization might produce marked personality changes such as impulsiveness, anger, irritability, explosiveness, tactlessness, affective ability, and lack of personal sensitivity [18]. Similar emotional changes have been reported with ventral caudate [19] and right thalamic lesions (limbic nuclei) [20]. With orbitofrontal damage, aggressiveness and antisocial behavior can be the resultant of lack of emotional appraisal of interpersonal relationships [21] or incompetence in following moral rules.

Patients with traumatic brain injury and lesions of the orbital frontal cortex have higher aggression/violence scores on questionnaires compared to normal controls and patients with lesions in other brain regions [22]. Studies of impulsive aggressors have found hypoactivation of the ACC and OFC regions of the medial prefrontal cortex [23]. The OFC carries out low-level appraisals of punishment/reward values of behavioral responses (in contrast to complex punishment/reward appraisals performed by lateral prefrontal cortical regions) and of the appropriateness of behaviors in accordance with social rules. Patients with OFC damage can lose the notion of sociobehavioral appropriateness.

The somatic marker hypothesis [8] argues that somatic states associated with previous stimuli/events provide an effective, automatic mechanism to facilitate choice of response options [8, 24]. It is further argued that lesions to the ventromedial PFC effectively deactivate this mechanism, resulting in poor decision-making and antisocial behavior [24, 25].

fMRI studies in healthy subjects provide robust evidence for the key role of the frontal lobes (especially the OFC) in anger, antisocial behavior [26], and general emotions recognition and control [27].

The ventral PFC and OFC areas seem engaged in processing the context-appropriate emotional value of stimuli (rewarding or unrewarding) and selecting actions on the basis of those evaluations. Maintaining cognitive representations of emotional situations might be the role of the ventral prefrontal areas that receive inputs from perceptual, memory, and limbic systems, especially from the amygdala.

However, despite this broad frontal-subcortical loops classification, the frontal systems are highly reciprocally interconnected and also relay, through subcortical nuclei, to the limbic system and to other cortical associative areas. Thus, the frontal-subcortical network extends widely over the brain and is particularly vulnerable to every stroke. In the majority of cases, the ischemic lesion involves more than one system and patients may present combined features of those dysexecutive syndromes.

Emotional Dyscontrol and Disinhibition

Emotional dyscontrol and defective emotional regulation may be critical factors for the emergence of aggressiveness and antisocial behavior. Anger, as the other emotions, is a multicomponential processes characterized by different latencies, magnitude, duration, and offset of multiple responses such as overt behaviors, internal experience, endocrine and peripheral autonomic changes. Each of these processes can be subjected to different control mechanisms. It is important to distinguish between behavioral (suppressing the overt expression of anger) and cognitive control on emotions (e.g., attending to or interpreting anger-eliciting situations in ways that limit emotional responding) as these regulatory processes might dissociate. Anger control also requires a feedback from the occurring behavior, feelings, and

autonomic changes and from the external world in general. Anger control might be unconscious (automated) or conscious (controlled).

Thus, the system of anger generation and regulation could be the sum of multiple, partially independent subsystems that go along with top-down and bottom-up and serial and parallel processing. The challenge is to investigate these subsystems separately.

The role of prefrontal areas in anger regulation is has been elucitated on the basis of neuroimaging studies on healthy individuals by means of specific paradigms fins with showing some evidence in structural MRI studies based on voxel-based morphometry [28]. The behaviors of patients with frontal lobe damage are a decisive argument for the role of the prefrontal region in emotional regulation and control. Such patients tend to be emotionally impulsive and poorly affectively regulated [3].

Their behaviors include decreased concern with social propriety, environmental dependency, utilization, imitation and stereotyped behaviors, restlessness, exuberance, euphoria, emotionalism, facetiousness, extroversion, lack of restraint, purposelessness, childish behavior, distractibility, egocentricity, grandiosity, capriciousness and instability, social and sexual disinhibition, poor judgment, diminished foresight, social withdrawal, absence of tact, concreteness, acting on simple motivations, impulsiveness, self-centeredness, and immorality but also inertia, lack of ambition, indifference to the environment, satisfaction with inferior performance, slowness in thinking, lack of emotional expression, decreased self-concern, shallow affect, depressed outwardly directed behavior, and social sense. Several of these behaviors might occur together even in the absence of severe cognitive deficits.

Thus, the primary disorder of aggressiveness due to the damage of frontal systems seems likely to resemble a personality disorder [29] dominated by lack of empathy, control, and self-reflection (vulnerability to interference, impoverished judgment, and inability to self-correct and self-monitor). However, the precise nature of prefrontal regulatory mechanisms on anger has still to be determined. Researchers have still to find a common frame about even such basic issues as whether the left or right PFC is preferentially charged with the regulation of negative versus positive emotion [30].

Loss of Empathy and Defective Theory of Mind (ToM)

Empathy is the sense of feeling and understanding the feelings and needs of others in reference to oneself. Loss of empathy has been repeatedly proposed as a core deficit in control disorders such as aggressiveness. Hence, anger regulation and conflict resolution could depend from the capacity of empathizing.

The theory of mind (ToM) and emotional intelligence (EI) are cognitive constructs that are tightly related to empathy.

ToM (or “mentalizing” or perspective taking) highlights the idea that we have insights, within a defined temporal window, of cognitive and affective aspects of our minds as well as a basic understanding of the ideas, thoughts, and feelings of others

with whom we interact or share situations. The somewhat shallow defined term of "emotional intelligence" has been used to describe the ability to understand emotions and express feelings, to understand how others feel and to relate with them, to manage and control emotions, to use emotions in adapting to one's environment and generate and use positive affects, and to be self-motivated in coping with daily demands and challenges.

Empathy, ToM, and EI could be essential factors inhibiting aggression and disrupting behaviors, as the propensity to be aggressive could reflect an insufficient empathic response to the distress of others.

Aggressive behaviors might arise from an abnormal processing of affective information, resulting in a deficiency in experiencing fear, empathy, and guilt, which normally take control on violent impulses and remind to moral or ethical rules. Empathy, ToM, or EI faculties act upon recognition of emotional states reflected in the tone of voice, facial expression, or body posture signaling, in order to anticipate the actions of others and adaptively guide response behaviors. Thus, some patients might lack empathy as they lose their ability to recognize actions in the social word. This condition has been otherwise defined as social-emotional agnosia, which is difficult to distinguish from, and could co-occur with alexithymia. Lack of empathy, ToM, and EI has been related to the spectrum of conduct disorders and of antisocial behaviors in healthy adolescents.

Functional neuroimaging data clearly support the role of the prefrontal lobe (together with its connections to the temporal cortex and the amygdala) in tasks demanding empathy and ToM. The prefrontal, insular, and temporal areas implicated in empathy and ToM might be part of the prefrontal "mirror" system [31].

However, only few studies explored deficits of empathy, TOM, and EI in patients with stroke [32–37]. These studies suggest a dominant role for the right prefrontal cortex.

Empathy and EI are crucial domains in planning clinical research on poststroke aggressiveness. Impaired ability to attribute mental states to others has implications for interventional or rehabilitative cognitive and behavioral programs and relevance for relatives and caregivers.

Catastrophic Reactions (CR) and Wernicke Aphasia (WA)

Patients with aphasia are often observed to display aggressiveness in both the acute and chronic phases of stroke. However, there have been few systematic studies that investigated the association of aphasia with anger and aggressiveness.

Aggressiveness is particularly manifest in patients with CR and with WA.

The German neurologist, neuropsychologist, and psychiatrist Kurt Goldstein (1878–1965) first coined the term "catastrophic reaction" referring to a state of confusion and anxiety which is caused by the patient's sudden inability to perform certain tasks. Clinically, CR is an outburst of frustration, depression, and anger suddenly building up to an overwhelming degree in overt behaviors (shouting, cursing, hitting, kicking, and biting). Within psychiatric taxonomies, this behavior seems to

remind to the intermittent explosive disorder (or episodic dyscontrol syndrome) in healthy adolescents. The DSM-IV indicates the salient features of the intermittent explosive disorder as several discrete episodes of failure to resist aggressive impulses that result in serious assaultive acts or destruction of property and the degree of aggressiveness expressed during the episodes being grossly out of proportion to any precipitating psychosocial stressors.

Starkstein et al. validated a specific scale to inquire the presence and to measure the severity of the CR and suggested a relationship between this behavior and post-stroke depression [38].

Through an observational scale, in a cohort of 326 consecutive patients with first ever stroke, Carota and colleagues [39] reported the occurrence of this behavior in relatively few patients (3.9 %), all with aphasia. Those patients shared a common lesion site next to the insular region. The authors concluded that CR might be the behavioral translation of a "paleological thinking," emerging from homologous areas of the right hemisphere when language and paralimbic areas are damaged in the dominant one. Hence, CR would correspond to a shift from a left to a right mode of limbic processing.

This hypothesis has been also proposed to explain the aggressiveness of patients with WA and finds some evidence in the fact that patients with anosognosia of the hemiplegia who are generally indifferent to their condition or its consequences have suffered stroke on the right hemisphere with lesions often on homologous sites (associative temporoparietal posterior areas) [40, 41] than WA patients.

WA is a severe form of fluent aphasia as verbal expression (fluent paraphasic speech), comprehension, and reading are extensively perturbed. The peculiar behavioral profile of WA patients has been relied to the damage of associative temporal areas next to Wernicke area [42, 43]. This profile includes abnormal affective displays such as paranoid agitation, frustration, anger, aggressiveness, psychosis, euphoric indifference, anxiety, and restlessness.

A psychological or psychodynamic hypothesis for the aggressiveness of WA patients is based on the assumption that they are deeply unaware of their own linguistic difficulties, are not able to monitor their own verbal output, and do not understand others' responses to their language. Thus, WA patients should experience a condition that inevitably engenders frustration, irritability, and feelings of isolation. Such a condition might be sometimes exacerbated by the others' demands of clarification by repeating what the patient says or by the "sound of silence" in conversation breaks [44].

With WA, there is no access to the patient's inner world. Interviews or questionnaires that screen or assess poststroke depression, other affective disorders (such as mania and schizotypic conditions), and suicide cannot be generally administered in patients with WA (cf. case 1).

The potential for depression, anxiety, alienation, behavioral dyscontrol, and, finally, suicide potentiality, should be seriously pondered for patients with WA by all health-care providers and discussed carefully with the family.

The assessment of patients with severe aphasia should employ measures of both verbal and nonverbal communication, possibly with supportive communicative partners in ecological contexts and daily life activities [45].

Personality Changes

Personality changes are frequent after stroke [46, 47]. Emergence of anger after stroke has been often classified in the DSM-IV category of personality changes and enduring personality changes. Personality disorders are the most frequent of all psychiatric diagnosis and they are defined by experiences and behaviors that differ from social norms and expectations. They include difficulties in cognition, emotiveness, interpersonal functioning, and control of impulses with the result of irritability, anxiety, distress, or depression. Patients experiencing poststroke anger and irritability and showing aggressiveness might behave as psychiatric patients diagnosed with antisocial, avoidant, obsessive-compulsive, paranoid, passive-aggressive, sadistic and schizoid personality disorder.

Mania

Aggressiveness is a common component of manic symptoms. Among the several manic syndromes that are categorized in the DSM-IV, only manic episodes have been investigated in stroke. Symptoms of manic episodes are agitation, inflated self-esteem, and decreased need for sleep, distraction, flight of ideas, impulsiveness, psychosis, and excessive involvement in pleasurable activities with potentially harmful consequences. However, these symptoms have been also described, in the case of stroke patients, in terms of disinhibition, acquired sociopathy, pseudopsychopathic syndrome, and frontal lobe syndrome, terms that may engender confusion when comparing different studies.

During the acute phase of stroke, manic behaviors generally emerge when strategic areas are involved (frontal and temporal lobe, caudate nucleus, thalamus [generally unilateral paramedian artery infarction]), mostly within the right hemisphere 20, 48–51], and are usually associated with significant memory disturbances, signs of the dysexecutive syndrome, or spatial neglect.

Psychosis, Delusions, and Misidentification Syndromes

The relationship between aggressiveness and psychotic symptoms has been widely described. Pure or florid psychosis has been reported to be an extremely rare complication of stroke and there have been only a few reports, all of which suggested, however, an association with strategic localizations, in the right hemisphere, that are similar to those of mania [52].

Delusions are false or absurd beliefs that are resistant to reason or confrontation and that the patient defends against all logical odds, without any credible evidence and often with irritability, agitation, and aggressiveness. They are a rare

complication of stroke in the acute phase [53] and might generally appear when the ischemic lesion includes the right temporal lobe.

In the absence of cognitive or perceptive visual changes or distortions, misidentification syndromes consist in specific delusions by which it is no more possible to match the real identities of persons, objects, and places with the subjective feelings normally related to those identities. This conflict engenders usually frustration, anger, and violent behaviors [54].

Patients with reduplicative paramnesia sustain that a place or location has been duplicated or transposed to another location, while patients with the Capgras syndrome affirm that one member of the family (usually the spouse) has been replaced by an identical-looking impostor. Patients with the Fregoli syndrome believe that all the people they meet are represented by a single person that changes appearance. Patients with intermetamorphosis believe that individuals exchange their reciprocal identities. These very rare syndromes occur with right hemisphere stroke [55–57] with frontal, parietal, temporal, or thalamic localization. Delusional misidentification syndromes are situated in the interface between neurology and psychiatry, as they can manifest with the same semiology for patients with stroke and for patients with schizophrenia without distinct brain damage.

Delirium/Confusion with Agitated Behaviors

Agitated delirium is a rare clinical manifestation in the acute phase of stroke and is predictive of unfavorable outcomes, particularly higher mortality, longer hospitalizations, and dementia [58–60]. Unfortunately, items for agitation and psychomotor behavior are included in some scales for delirium such as the Delirium Rating Scale [61] but not in other scales such as the Confusion Assessment Method [62].

Misoplegia and Somatoparaphrenia

The term misoplegia was coined by Critchley in 1955 and refers to a deep dislike mounting to wrath of rage or hatred against paralyzed limbs in patients with hemiplegia (generally the arm) [63]. Some manifestations of this condition may be restricted to verbal aggression toward a limb, but commonly, misoplegia includes physical acts such as striking and beating the hemiplegic extremity. One patient with this condition put out cigarettes on his paralyzed arm (personal observation of the authors). Unfortunately, misoplegia has not been the object of systematic clinical and cognitive studies.

Somatoparaphrenia consists in attributing the ownership of the affected limb to someone else (generally a close relative), usually along with anger. Misoplegia and somatoparaphrenia emerge after right hemisphere stroke (frontal, insular, or parietal localization) [64–67], are almost invariably associated with spatial neglect and frequently with anosognosia of hemiplegia, and belong to the category of abnormal attitudes toward the affected limb. This category includes also asomatognosia,

anosodiaphoria, personification, illusory limb movement, supernumerary limbs, and all behaviors which manifest with the above-reported stroke localizations.

Poststroke Depression and Suicide

Poststroke depression (PSD) is a condition with high prevalence (33 %) over all stroke phases and which has high negative impact on participation to rehabilitation, daily activities, quality of life, survival of patients, caregiver burden, and health-care costs. Irritability and aggressiveness are also frequent symptoms that manifest with depression. In depressive individuals (without stroke), impulsivity/aggression has been reported to be significantly related to suicidal behavior [68], while higher levels of aggression have been correlated to the increased lethality of suicide attempts [69].

Suicide is the most extreme form of aggressiveness and violence against his own body. Suicide rate among stroke patients is low but not negligible (up to 7 %) and suicidal intents are frequent, in both acute and chronic phases [70, 71]. However, the prevalence of suicidal ideations appears similar between patients with stroke and patients with other chronic medical conditions. Prestroke depression might be a risk factor for suicide in patients with PSD [72]. It is particularly difficult to assess suicidal thoughts or plans in patients with severe aphasia (cf. case 1); however, their presence should be accurately pondered for every aphasic patient, especially those ones with both severely impaired auditory and written comprehension.

Over the first 6 months after stroke, unexpected suicides have been related to the damage of the temporal and parietal cortex [73]. There are no data to affirm that antidepressants can substantially increase the risk of suicide after stroke.

Poststroke Anxiety

Anxiety has been conceptualized with aggressiveness and irritability along the same continuum of behavior.

Most studies investigated the prevalence of the generalized anxiety disorder after stroke and found a very high prevalence even in long term, although probably slightly inferior than depression. However, very often, the two disorders occur together.

An extraordinary example of behavioral changes consisting of irritability, depression, concentration difficulties, and anxiety has been provided by the Swiss writer C.F. Ramuz who reported in his diary the effects of a stroke on his life [74].

Poststroke anxiety shares many symptoms with the post-traumatic stress disorder.

Both disorders follow a sudden and unpredictable life-threatening event. Poststroke anxiety is assumed to have both biological and psychological foundations, but the relationship with stroke location remains to be disentangled. Frontal-subcortical loops are probably involved [75]. There is still insufficient evidence to guide the pharmacological treatment of anxiety after stroke [76].

Poststroke Pain and Fatigue Syndromes

Pain syndromes, physical discomfort, and fatigue are frequent after stroke [77, 78]. They are all causes of irritability and aggressiveness. The reported prevalence of chronic pain in stroke survivors varies considerably with figures ranging from 11 to 50 %. Pain syndromes and physical discomfort are due to poststroke central neurogenic pain; spasticity and muscular stiffness or spasms; joint, musculoskeletal, and tissue modifications (retraction, pseudoarthrosis, contractures); hemiplegic pain shoulder syndromes; headache; loss of conditioning; infections (pulmonary and urinary); pressure ulcers; falls; and fractures. Assessment of pain syndromes and their prevention and treatment are mandatory for treating irritability and aggressiveness. Medical and neurologic complications occur frequently after stroke in rehabilitative setting [79].

Vascular Dementia (VaD)

Agitation, irritability, taunting, screaming, catastrophic reactions, and aggressive behaviors are particularly frequent in patients with vascular dementia (cf. case 2) and correspond to the most prevalent neuropsychiatric symptoms.

Aggression and depression have a tendency to be more frequent in patients with VaD than in individuals with Alzheimer disease (AD) [80]. For AD patients, indeed, delusions, apathy, and aberrant motor behaviors prevail. In cohorts of patients with VaD, behavioral changes (including agitation/aggressiveness) have been more often assessed with the Neuropsychiatric Inventory (NPI) than with other scales. In patients with large-vessel VaD, a higher severity of agitation/aggression and euphoria is reported than in patients with small-vessel VaD, who exhibit more apathy [81]. Agitation, irritability, and aggression might be the signs of a personality change that could precede the cognitive decline and heralding the onset of small-vessel VaD. As different variants of VaD are traced (multi-infarct dementia, subcortical ischemic vascular dementia, vascular dementia after strategic stroke), it would be interesting to study in large groups of patients whether it would be possible to identify specific correlations between VaD variants and specific fronto-subcortical circuits for aggressiveness, anger, and irritability.

Diagnostic Instruments

Several questionnaires allow inquiring the presence of anger, irritability, aggressiveness, and aggression (Staxi-2; Spielberger Trait Anger Scale; Anger Self-Report; Anger Questionnaire; Buss-Perry Scale; Behavioral Anger Response Questionnaire; Irritability Questionnaire; Irritability, Depression, and Anxiety

Scale; Aggression Questionnaire; Novaco Anger Scale and Provocation Inventory; Symptom Checklist-90-Revised that includes a hostility subscale) and their multiple dimensions (anger expression out/in, anger control out/in, outward/inward irritability). These questionnaires have been extensively used in psychiatric fields, especially in adolescents, to investigate personality disorders and tendencies toward violent behaviors.

However, the applicability of these questionnaires to large cohorts of stroke patients would be difficult as many of them have aphasia or cognitive deficits [7]. Actually, up to 25–30 % of stroke patients may suffer of aphasia [82]. Patients with moderate-severe spatial neglect (35 % of the total stroke population in the first stroke phases) [83] might show altitudinal biases and prefer the top of self-report scales. Anosognosia (lack of awareness) and anosodiaphoria (indifference to the deficit), alexithymia (difficulty in identifying and reporting own feelings), unawareness of emotions, defective abstract thinking, and magnitude estimation deficits undermine introspection into emotional experiences. Observational scales specific to anger, irritability, hostility, and aggression (Overt Aggression Scale, Observational Scale for Aggressive Behavior, the Aberrant Behavior Checklist, the Uplift/Burden Scale), although easier to apply, do not permit sufficient insight into the different anger aspects.

The Neuropsychiatric Inventory (NPI) is a multidimensional proxy-based instrument, which has been mainly used in patients with neurodegenerative disorders [84]. NPI is a structured caregiver's interview, which assesses 10 behavioral disturbances, including agitation/aggression and irritability/lability, and quantifies their severity and frequency and the effects on caregivers. A similar scale is the Brief Psychiatric Rating Scale which, among its 24 items, includes suicidality, hostility, suspiciousness, hallucinations, tension, uncooperativeness, and motor hyperactivity.

The Frontal Behavioral Inventory, the Dysexecutive Questionnaire, the Frontal System Behavior Scale, the Brain Impairment Behavior Scale, the Cohen-Mansfield Agitation Inventory, and the Burns Irritability Apathy Scale are other scales employed for proxies or nursing staff to rate behavioral changes and include items of irritability and aggressiveness.

In systematic studies or when detailed clinical evaluations of aggressiveness are required for stroke patients, the combined use of self-reported or caregiver-based scales with observational methods should be encouraged.

Specific Studies on Poststroke Anger, Aggressiveness, and Irritability

In a study performed by Paradiso and coworkers, patients were asked whether they experienced episodes of anger and aggressive behaviors by means of a structured clinical interview [85]. The percentage of patients with cognitive impairment in the angry outburst group (66 %) were greater than the control group (22 %). Angered

patients had a higher frequency of anterior left hemisphere lesions (46.7 %) compared with controls (29.4 %).

Chan and colleagues [86] identified aggressiveness and violent behaviors (scored by nurse staff or proxies) in 25 % of 92 patients with recent stroke by means of at least 1 of the following 5 items of the present state examination (shouting or quarreling, hitting people or throwing or breaking things, episode of violent behavior with catastrophic impact on others, agitation during the interview, excitement or violence during the interview). In this study, aggressiveness showed to be associated with depression and anxiety and the aggressive patients had lesions that were located more frontal than in nonaggressive patients.

Using the 10-item Spielberger Trait Anger Scale, Kim and coworkers interviewed 145 patients, 3–12 months after stroke, to assess the inability to control anger or aggression [3]. This inability was present in 47 patients (32 %) and was closely related to motor dysfunction, dysarthria, emotional incontinence, and lesions affecting frontal-lenticulocapsular-pontine base areas.

Greenop and colleagues, by means of structured informant interview (NEO Personality Inventory revised, NPI), found that, 3 months after stroke, agitation and irritability were associated with high premorbid neuroticism personality trait [10].

Aybek and colleagues prospectively recruited and assessed 254 stroke patients in earliest phases after stroke with the Emotional Behavior Index (EBI), a 38-item scale designed to evaluate observed behavioral changes [2]. They found observed aggressiveness in 17 % of the patients and correlated it to personal history of depression but not with stroke severity and lesion localization.

Santos and coworkers [87] screened anger prospectively in 202 consecutive acute stroke patients in the earliest phases (≤4 days) using eight items from three psychiatric scales (Catastrophic Reaction Scale, Mania Rating Scale, and Comprehensive Psychopathological Rating Scale) by defining the presence of anger if the patient scored positive at least in one item. By using this cutoff, anger was detected in 35 % of patients but manifested in two dissociated components: emotional-cognitive (in-anger) and behavioral (out-anger), without significant correlation with lesion localization. In another study, important physical aggressiveness requiring neuroleptic treatment was found in 3/41 (7 %) of patients with acute posterior cerebral artery stroke [88].

The most important conclusion resulting from the above studies is that anger and aggressiveness are feelings that patients report or display very often after stroke in both the acute and chronic phases.

However, based on these findings, it is not possible yet to trace a specific structural or functional neuroanatomical localization of poststroke aggressiveness.

Treatment of Poststroke Aggressiveness

When all possible causative factors (pain, distress, medical complications, and misunderstandings) have been extensively evaluated and treated, persisting verbal and physical aggressiveness require pharmacologic or behavioral interventions.

Drugs should be used only when non-pharmacologic approaches have failed and when aggressiveness is severe, recurrent, or persistent. Unfortunately, there are no specific studies on the pharmacological treatment of poststroke aggressiveness. Actually, most recommendations derive from studies on traumatic brain injury and dementia (in particular, Alzheimer's disease) [89], studies which were not double blind, randomized, or placebo controlled. As most of those studies allowed the use of concomitant medications, it is unclear whether the efficacy of a drug is independent from the others.

As in older, medically fragile patients, there is a higher risk of side effects; the balance between harm and benefits of drugs depends upon an individual assessment.

When there is the need of a prompt treatment to limit harm (e.g., disruptive behaviors, interference with nursing care), atypical neuroleptics (quetiapine, olanzapine, risperidone, aripiprazole, clozapine) should be started with the lowest doses and titrated according to symptom severity and frequency. Once started, effectiveness and safety of these drugs need frequent monitoring. When physical aggressiveness requires the administration of i.v. drugs, it is necessary to apply a monitor and a surveillance, preferably in a continuous care setting. However, there is the evidence (for patients with dementia) that a specific anti-aggressive effect (separated from the sedative one) can be already achieved with the lowest doses of neuroleptics [89].

It is important to stress that stroke patients, at risk of aggressiveness and fugue, require strict surveillance to limit the risk to harm, and in rehabilitation settings, for example, at night, where nurse resources are diminished, this could require the use of contentions or the presence of relatives or external operators.

Tapering and withdrawing of neuroleptics should be thought after a short period of behavioral stability as there is not any evidence supporting a long-term use. For aggressiveness, only mild sedation should be envisioned.

Haloperidol, despite the possibility of extrapyramidal side effects, could be introduced as the first treatment over short periods, because of its high efficacy and manageability and low risks of hypotension.

Atypical neuroleptics show lower propensity for extrapyramidal symptoms and tardive dyskinesia than typical antipsychotics. Nevertheless, this assumption has been recently questionned [90].

Several side effects of neuroleptics should be pondered [91], especially for patients with strokes, such as sedation (associated with aspiration pneumonia), QTc interval prolongation (dose dependent), hyperlipidemia, weight gain (dose dependent), diabetes mellitus, sexual side effects, cataract, and extrapyramidal side effects. They increase the overall risk of cerebrovascular events and death, especially in the elderly patients. They are prone to age pharmacokinetic-related changes that determine higher and/or more variable drug concentrations. Neuroleptics (as well as SSRI and cholinomimetics) increase the seizure risk that is due to cortical stroke. Neuroleptics and benzodiazepines increase cognitive dysfunction and worsen recovery in rehabilitative settings. Anticonvulsants (valproate, carbamazepine, gabapentin, pregabalin) could be very useful for impulsive chronic aggressiveness associated with relevant affective and mood changes. Gabapentin and

pregabalin have the best tolerability profile, but their efficacity for aggressiveness has not been yet sufficiently investigated. Although selective serotonin reuptake inhibitors (SSRIs) are widely used clinically for the treatment of aggression, there are relatively few controlled trials on their efficacy. They show benefits of fluoxetine [92, 93] and citalopram [94, 95] in aggressive patients with personality disorders and dementia. Fluoxetine improves quality of life scores of stroke patients, particularly in the mental health subdomains, although no definite improvement has been noted in the anger proneness scale [96]. Fluoxetine and citalopram, known to be effective in the treatment of poststroke depression and emotional lability, might improve irritability and anger when they are associated symptoms of depression. Trazodone and mirtazapine could be useful when a sedative effect is required and when insomnia or the sleep/waking cycle is reversed.

Beta-adrenergic antagonists have been most extensively studied and show good effectiveness in patients with a history of traumatic brain injury [97]. However, elderly patients with stroke could be prone to the specific side effects of these agents.

Benzodiazepine appears to be efficacious and safe only for short-term use and for acute agitation. Because of potential adverse events (including falls, excessive sedation, dysphagia, development of tolerance, and increasing of cognitive deficits), these agents should be used only for behavioral emergencies or as sedatives for medical or surgical procedures.

Lamotrigine, gabapentin, and pregabalin might also be particularly useful as add-on drugs because they have a good safety profile and less hepatic interferences with other drugs. They also reduce neuronal excitability in case of seizures.

As for anticonvulsants, there is also some evidence for lithium to be effective for aggressiveness but side effects (tremor, sedation, nausea, polyuria) could be relevant even within recommended blood levels. Lithium neurotoxicity can increase with concomitant antipsychotic medication [98].

The use of cholinesterase inhibitors might be of some utility in patients with vascular dementia. However, some caution should be taken about the risk of epilepsy, especially in patients who already had seizures and are not treated by antiepileptics.

The role of psychological intervention (e.g., cognitive behavior therapy) for patients with stroke presenting irritability, anger, and aggressiveness remains to be demonstrated, although the organic basis of anger suggests that such patients would be perhaps less responsive to psychological or cognitive therapies. Patients with aggressiveness and irritability must be motivated to seek psychological treatments. However, those patients are often unaware of the inappropriateness of their behaviors and their effects on caregivers. Aggressiveness is often the behavioral equivalent of the dysexecutive syndrome. Thus, deficits of concrete thinking, lack of abstract reasoning, difficulties with cognitive flexibility, and problems in switching ideas can lead to complicated therapeutic encounter or simply to attending sessions at the designated time.

However, there is some data supporting the common experience that behavioral intervention can be helpful [99].

The Neuroscientific Perspective of Poststroke Aggressiveness

The definition and classification of poststroke aggressiveness and related conditions should be further elaborated, unified, and clinically rated by standardized and validated scales and other procedures. In other terms, it occurs to define the criteria which are significant for diagnosis, including characterization of intensity and frequency of behaviors. This could be achieved when different specialists and hospitals, involved actively in the management of stroke patients (from the stroke unit to the rehabilitation ward), constitute a common network and share similar protocols and registries to collect data.

In such a framework, the following dual attributes of anger, aggressiveness, and aggression should be taken into account: intentions versus behaviors, physical versus verbal, direct versus indirect, positive-constructive versus negative-destructive, overt versus covert, proactive versus reactive, impulsive versus premeditated, and predatory versus affective [5, 100].

Poststroke aggressiveness, in most cases, identifies with a dyscontrol syndrome and with the hostile-impulsive-uncontrolled-unplanned-reactive-hot blooded-overt-defensive-affective-negative-destructive-high aroused subtype of anger more than with the instrumental-premeditated-controlled-planned-proactive-coldblooded-hidden-offensive-predatory-positive-constructive-low aroused subtype.

Studies correlating loci of focal injury and patterns of altered aggressiveness might bring unique insights into the brain architecture responsible for mediating and inhibiting hostile behaviors. Indeed, the increased anger and irritability of stroke sufferers might be related to brain damage other than to distress about their condition or other, even if significant, psychodynamic aspects.

Neurophysiology, pharmacology, and clinical neuroscience researches suggest, as well as for the control of emotions, that the neural regulation of anger, aggressiveness, aggression, and irritability is controlled by a multiregional hierarchical model. For this reason, we believe that future studies on aggressiveness should not address to large and unspecific cohorts of stroke patients. Moreover, the object of such studies should be samples of patients which are enrolled according to those specific categories, within stroke taxonomies, which have previously described and summarized in Table 8.1.

These categories of poststroke aggressiveness could still fit in four further superordinate groups such as (1) frontal circuits related, (2) aphasia related, (3) right hemisphere related, and (4) poststroke mood disorders related.

Biological differences for groups of patients with aggressiveness within specific poststroke conditions might be detected with neurophysiology (differences in visceral/autonomic/somatic/muscular and brain activities), functional neuroimaging (differences in brain anatomy and activity), and neurochemical (differences in brain neurotransmitter levels and activity) techniques.

On the other side, cognitive and psychological studies, within the abovementioned stroke categories, should precise differences in mental and emotional dispositions and control mechanisms. In this context, it will be possible to detect

brain activation with functional neuroimaging (fMRI, PET) coupled with neurophysiological techniques (EEG/ERPs) by mean of an experimental paradigm that focuses on specific psychological processes.

This is might represent a useful conceptual frame in order to disentangle, as much as possible, neurobiological factors of aggressiveness from psychodynamic, psychosocial, or vulnerability issues.

Furthermore, the choice of adequate scales to assess the severity of behavioral displays within these categories which are specific to stroke taxonomies is straightforward.

This is mandatory for assessing treatment benefits as it is necessary to define the magnitude of change considered to be clinically meaningful. Additional studies with long-term outcomes, also including outcome measures, are required to identify and support pharmacological and behavioral interventions. Pharmacological studies as well as systematic behavioral approaches for poststroke agitation and aggression also deserve a significant research priority.

References

1. Ghika-Schmid F, van Melle G, Guex P, Bogousslavsky J. Subjective experience and behavior in acute stroke: the Lausanne Emotion in Acute Stroke Study. Neurology. 1999;52(1):22–8.
2. Aybek S, Carota A, Ghika-Schmid F, Berney A, Melle GV, Guex P, Bogousslavsky J. Emotional behavior in acute stroke: the Lausanne emotion in stroke study. Cogn Behav Neurol. 2005;18(1):37–44.
3. Kim JS, Choi S, Kwon SU, Seo YS. Inability to control anger or aggression after stroke. Neurology. 2002;58(7):1106–8.
4. Buijck BI, Zuidema SU, Spruit-van Eijk M, Geurts AC, Koopmans RT. Neuropsychiatric symptoms in geriatric patients admitted to skilled nursing facilities in nursing homes for rehabilitation after stroke: a longitudinal multicenter study. Int J Geriatr Psychiatry. 2012;27(7):734–41.
5. Barratt ES, Stanford MS, Dowdy L, Liebman MJ, Kent TA. Impulsive and premeditated aggression: a factor analysis of self-reported acts. Psychiatry Res. 1999;86(2):163–73.
6. Malone RP, Bennett DS, Luebbert JF, Rowan AB, Biesecker KA, Blaney BL, Delaney MA. Aggression classification and treatment response. Psychopharmacol Bull. 1998;34(1):41–5.
7. Barrett AM. Rose-colored answers: neuropsychological deficits and patient-reported outcomes after stroke. Behav Neurol. 2010;22(1–2):17–23.
8. Damasio AR. Descartes' error: emotion, reason, and the human brain. Harper Perennial; 1995.
9. Hussey M. I'm no longer silent. Top Stroke Rehabil. 2010;17(1):6–9.
10. Greenop KR, Almeida OP, Hankey GJ, van Bockxmeer F, Lautenschlager NT. Premorbid personality traits are associated with post-stroke behavioral and psychological symptoms: a three-month follow-up study in Perth, Western Australia. Int Psychogeriatr. 2009;21(6):1063–71.
11. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci. 1986;9:357–81.
12. Bonelli RM, Cummings JL. Frontal-subcortical circuitry and behavior. Dialogues Clin Neurosci. 2007;9(2):141–51.
13. Luria AR. Frontal lobe syndromes. In: Vinken PJ, Bruyn GW, editors. Handbook of clinical neurology II. New York: Elsevier; 1969.
14. Stuss DT, Benson DF. The frontal lobes. New York: Raven; 1986.

15. Bogousslavsky J, Regli F. Anterior cerebral artery territory infarction in the Lausanne Stroke Registry. Clinical and etiologic patterns. Arch Neurol. 1990;47(2):144–50.
16. Borggreve F, De Deyn PP, Mariën P, Cras P, Dierckx RA. Bilateral infarction in the anterior cerebral artery vascular territory due to an unusual anomaly of the circle of Willis. Stroke. 1994;25(6):1279–81.
17. Kang SY, Kim JS. Anterior cerebral artery infarction: stroke mechanism and clinical-imaging study in 100 patients. Neurology. 2008;70:2386–93.
18. Starkstein SE, Robinson RG. Mechanism of disinhibition after brain lesions. J Nerv Ment Dis. 1997;185(2):108–14.
19. Mendez MF, Adams NL, Lewandowski KS. Neurobehavioral changes associated with caudate lesions. Neurology. 1989;39(3):349–54.
20. Bogousslavsky J, Ferrazzini M, Regli F, Assal G, Tanabe H, Delaloye-Bischof A. Manic delirium and frontal-like syndrome with paramedian infarction of the right thalamus. J Neurol Neurosurg Psychiatry. 1988;51(1):116–9.
21. Beer JS, John OP, Scabini D, Knight RT. Orbitofrontal cortex and social behavior: integrating self-monitoring and emotion-cognition interactions. J Cogn Neurosci. 2006;18(6):871–9.
22. Grafman J, Schwab K, Warden D, Pridgen A, Brown HR, Salazar AM. Frontal lobe injuries, violence, and aggression: a report of the Vietnam head injury study. Neurology. 1996;46(5):1231–8.
23. Best M, Williams JM, Coccaro EF. Evidence for a dysfunctional prefrontal circuit in patients with an impulsive aggressive disorder. Proc Natl Acad Sci U S A. 2002;99(12):8448–53.
24. Damasio AR, Tranel D, Damasio H. Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. Behav Brain Res. 1990;41(2):81–94.
25. Bechara A, Damasio H, Tranel D, Damasio AR. Deciding advantageously before knowing the advantageous strategy. Science. 1997;275(5304):1293–5.
26. Raine A, Yang Y. Neural foundations to moral reasoning and antisocial behavior. Soc Cogn Affect Neurosci. 2006;1(3):203–13.
27. Roelofs K, Minelli A, Mars RB, van Peer J, Toni I. On the neural control of social emotional behavior. Soc Cogn Affect Neurosci. 2009;4(1):50–8.
28. Kühn S, Gallinat J, Brass M. "Keep calm and carry on": structural correlates of expressive suppression of emotions. PLoS One. 2011;6(1):e16569.
29. Stuss DT, Gow CA, Hetherington CR. "No longer Gage": frontal lobe dysfunction and emotional changes. J Consult Clin Psychol. 1992;60(3):349–59.
30. Harmon-Jones E. Early Career Award. Clarifying the emotive functions of asymmetrical frontal cortical activity. Psychophysiology. 2003;40(6):838–48.
31. Carr L, Iacoboni M, Dubeau M-C, Mazziotta JC, Lenzi GL. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. Proc Natl Acad Sci U S A. 2003;100(9):5497–502.
32. Happé F, Brownell H, Winner E. Acquired "theory of mind" impairments following stroke. Cognition. 1999;70(3):211–40.
33. Apperly IA, Samson D, Chiavarino C, Humphreys GW. Frontal and temporo-parietal lobe contributions to theory of mind: neuropsychological evidence from a false-belief task with reduced language and executive demands. J Cogn Neurosci. 2004;16(10):1773–84.
34. Apperly IA, Samson D, Chiavarino C, Bickerton W-L, Humphreys GW. Testing the domain-specificity of a theory of mind deficit in brain-injured patients: evidence for consistent performance on non-verbal, "reality-unknown" false belief and false photograph tasks. Cognition. 2007;103(2):300–21.
35. Samson D, Apperly IA, Humphreys GW. Error analyses reveal contrasting deficits in "theory of mind": neuropsychological evidence from a 3-option false belief task. Neuropsychologia. 2007;45(11):2561–9.
36. Weed E, McGregor W, Feldbaek Nielsen J, Roepstorff A, Frith U. Theory of mind in adults with right hemisphere damage: what's the story? Brain Lang. 2010;113(2):65–72.
37. Hoffmann M, Cases LB, Hoffmann B, Chen R. The impact of stroke on emotional intelligence. BMC Neurol. 2010;10:103.

38. Starkstein SE, Fedoroff JP, Price TR, Leiguarda R, Robinson RG. Catastrophic reaction after cerebrovascular lesions: frequency, correlates, and validation of a scale. J Neuropsychiatry Clin Neurosci. 1993;5(2):189–94.
39. Carota A, Rossetti AO, Karapanayiotides T, Bogousslavsky J. Catastrophic reaction in acute stroke: a reflex behavior in aphasic patients. Neurology. 2001;57(10):1902–5.
40. Pia L, Neppi-Modona M, Ricci R, Berti A. The anatomy of anosognosia for hemiplegia: a meta-analysis. Cortex. 2004;40(2):367–77.
41. Vocat R, Staub F, Stroppini T, Vuilleumier P. Anosognosia for hemiplegia: a clinical-anatomical prospective study. Brain. 2010;133:3578–97.
42. Yang Z-H, Zhao X-Q, Wang C-X, Chen H-Y, Zhang Y-M. Neuroanatomic correlation of the post-stroke aphasias studied with imaging. Neurol Res. 2008;30(4):356–60.
43. Ogar JM, Baldo JV, Wilson SM, Brambati SM, Miller BL, Dronkers NF, Gorno-Tempinii ML. Semantic dementia and persisting Wernicke's aphasia: linguistic and anatomical profiles. Brain Lang. 2011;117(1):28–33.
44. Liechty JA. The sounds of silence: relating to people with aphasia. J Psychosoc Nurs Ment Health Serv. 2006;44(8):53–5.
45. van der Meulen I, van de Sandt-Koenderman WME, Duivenvoorden HJ, Ribbers GM. Measuring verbal and non-verbal communication in aphasia: reliability, validity, and sensitivity to change of the Scenario Test. Int J Lang Commun Disord. 2010;45((4):424–35.
46. Stone J, Townend E, Kwan J, Haga K, Dennis MS, Sharpe M. Personality change after stroke: some preliminary observations. J Neurol Neurosurg Psychiatry. 2004;75(12):1708–13.
47. Ferro JM, Caeiro L, Santos C. Poststroke emotional and behavior impairment: a narrative review. Cerebrovasc Dis. 2009;27 Suppl 1:197–203.
48. Berthier ML, Kulisevsky J, Gironell A, Fernández Benitez JA. Poststroke bipolar affective disorder: clinical subtypes, concurrent movement disorders, and anatomical correlates. J Neuropsychiatry Clin Neurosci. 1996;8(2):160–7.
49. Mimura M, Nakagome K, Hirashima N, Ishiwata H, Kamijima K, Shinozuka A, Matsuda H. Left frontotemporal hyperperfusion in a patient with post-stroke mania. Psychiatry Res. 2005;139(3):263–7.
50. Hoffmann M. Isolated right temporal lobe stroke patients present with Geschwind Gastaut syndrome, frontal network syndrome and delusional misidentification syndromes. Behav Neurol. 2008;20(3):83–9.
51. Santos CO, Caeiro L, Ferro JM, Figueira ML. Mania and stroke: a systematic review. Cerebrovasc Dis. 2011;32(1):11–21. Available from: 21576938.
52. Chemerinski E, Robinson RG. The neuropsychiatry of stroke. Psychosomatics. 2000;41(1):5–14.
53. Kumral E, Oztürk O. Delusional state following acute stroke. Neurology. 2004;62(1):110–3.
54. Förstl H, Almeida OP, Owen AM, Burns A, Howard R. Psychiatric, neurological and medical aspects of misidentification syndromes: a review of 260 cases. Psychol Med. 1991;21(4):905–10.
55. Lee K, Shinbo M, Kanai H, Nagumo Y. Reduplicative paramnesia after a right frontal lesion. Cogn Behav Neurol. 2011;24(1):35–9.
56. Spiegel DR, Laroia R, Samuels D. A possible case of Capgras syndrome after a right anterior cerebral artery cerebrovascular accident treated successfully with mirtazapine. J Neuropsychiatry Clin Neurosci. 2008;20(4):494.
57. de Pauw KW, Szulecka TK, Poltock TL. Frégoli syndrome after cerebral infarction. J Nerv Ment Dis. 1987;175(7):433–8.
58. Shi Q, Presutti R, Selchen D, Saposnik G. Delirium in acute stroke: a systematic review and meta-analysis. Stroke. 2012;43(3):645–9.
59. Carin-Levy G, Mead GE, Nicol K, Rush R, van Wijck F. Delirium in acute stroke: screening tools, incidence rates and predictors: a systematic review. J Neurol. 2012;259(8):1590–9.
60. Melkas S, Laurila JV, Vataja R, Oksala N, Jokinen H, Pohjasvaara T, Leppävuori A, Kaste M, Karhunen PJ, Erkinjuntti T. Post-stroke delirium in relation to dementia and long-term mortality. Int J Geriatr Psychiatry. 2012;27(4):401–8.

61. Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. Psychiatry Res. 1988;23(1):89–97.
62. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113(12):941–8.
63. Critchley M. Misoplegia, or hatred of hemiplegia. Mt Sinai J Med. 1974;41(1):82–7.
64. Baier B, Karnath H-O. Tight link between our sense of limb ownership and self-awareness of actions. Stroke. 2008;39(2):486–8.
65. Pearce JMS. Misoplegia. Eur Neurol. 2007;57(1):62–4.
66. Feinberg TE, Venneri A, Simone AM, Fan Y, Northoff G. The neuroanatomy of asomatognosia and somatoparaphrenia. J Neurol Neurosurg Psychiatry. 2010;81(3):276–81.
67. Gandola M, Invernizzi P, Sedda A, Ferrè ER, Sterzi R, Sberna M, Paulesu E, Bottini G. An anatomical account of somatoparaphrenia. Cortex. 2012;48(9):1165–78.
68. Dumais A, Lesage AD, Alda M, Rouleau G, Dumont M, Chawky N, Roy M, Mann JJ, Benkelfat C, Turecki G. Risk factors for suicide completion in major depression: a case–control study of impulsive and aggressive behaviors in men. Am J Psychiatry. 2005;162(11):2116–24.
69. Baca-García E, Oquendo MA, Saiz-Ruiz J, Mann JJ, de Leon J. A pilot study on differences in aggression in New York City and Madrid, Spain, and their possible impact on suicidal behavior. J Clin Psychiatry. 2006;67(3):375–80.
70. Santos CO, Caeiro L, Ferro JM, Figueira ML. A study of suicidal thoughts in acute stroke patients. J Stroke Cerebrovasc Dis. 2012;21(8):749–54.
71. Fuller-Thomson E, Tulipano MJ, Song M. The association between depression, suicidal ideation, and stroke in a population-based sample. Int J Stroke. 2012;7(3):188–94.
72. Forsström E, Hakko H, Nordström T, Räsänen P, Mainio A. Suicide in patients with stroke: a population-based study of suicide victims during the years 1988–2007 in northern Finland. J Neuropsychiatry Clin Neurosci. 2010;22(2):182–7.
73. Katayama M, Naritomi H, Oomura M, Nukata M, Yamamoto S, Araki K, et al. Case reports of unexpected suicides in patients within six months after stroke. Kobe J Med Sci. 2011; 56(5):E184–94.
74. Bogousslavsky J. "The adventure": Charles-Ferdinand Ramuz's extraordinary stroke diary. Front Neurol Neurosci. 2010;27:207–15.
75. Tang WK, Chen Y, Lu J, Liang H, Chu WC, Tong Mok VC, Ungvari GS, Wong KS. Frontal infarcts and anxiety in stroke. Stroke. 2012;43(5):1426–8.
76. Campbell Burton CA, Holmes J, Murray J, Gillespie D, Lightbody CE, Watkins CL, Knapp P. Interventions for treating anxiety after stroke. Cochrane Database Syst Rev. 2012;3, CD008390.
77. Klit H, Finnerup NB, Overvad K, Andersen G, Jensen TS. Pain following stroke: a population-based follow-up study. PLoS One. 2011;6(11):e27607. Cited 2011 Nov 28.
78. Naess H, Lunde L, Brogger J. The triad of pain, fatigue and depression in ischemic stroke patients: the Bergen Stroke Study. Cerebrovasc Dis. 2012;33(5):461–5.
79. Dromerick A, Reding M. Medical and neurological complications during inpatient stroke rehabilitation. Stroke. 1994;25(2):358–61.
80. Wetzels RB, Zuidema SU, de Jonghe JFM, Verhey FRJ, Koopmans RTCM. Course of neuropsychiatric symptoms in residents with dementia in nursing homes over 2-year period. Am J Geriatr Psychiatry. 2010;18(12):1054–65.
81. Staekenborg SS, Su T, van Straaten EC, Lane R, Scheltens P, Barkhof F, van der Flier WM. Behavioural and psychological symptoms in vascular dementia; differences between small- and large-vessel disease. J Neurol Neurosurg Psychiatry. 2010;81(5):547–51.
82. Croquelois A, Bogousslavsky J. Stroke aphasia: 1,500 consecutive cases. Cerebrovasc Dis. 2011;31(4):392–9.
83. Azouvi P, Samuel C, Louis-Dreyfus A, Bernati T, Bartolomeo P, Beis JM, Chokron S, Leclercq M, Marchal F, Martin Y, De Montety G, Olivier S, Perennou D, Pradat-Diehl P, Prairial C, Rode G, Siéroff E, Wiart L, Rousseaux M, French Collaborative Study Group on Assessment of Unilateral Neglect (GEREN/GRECO). Sensitivity of clinical and behavioural

tests of spatial neglect after right hemisphere stroke. J Neurol Neurosurg Psychiatry. 2002;73(2):160–6.
84. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44(12):2308–14.
85. Paradiso S, Robinson RG, Arndt S. Self-reported aggressive behavior in patients with stroke. J Nerv Ment Dis. 1996;184(12):746–53.
86. Chan K-L, Campayo A, Moser DJ, Arndt S, Robinson RG. Aggressive behavior in patients with stroke: association with psychopathology and results of antidepressant treatment on aggression. Arch Phys Med Rehabil. 2006;87(6):793–8.
87. Santos CO, Caeiro L, Ferro JM, Albuquerque R, Luísa Figueira M. Anger, hostility and aggression in the first days of acute stroke. Eur J Neurol. 2006;13(4):351–8.
88. Botez SA, Carrera E, Maeder P, Bogousslavsky J. Aggressive behavior and posterior cerebral artery stroke. Arch Neurol. 2007;64(7):1029–33.
89. Ballard C, Corbett A. Management of neuropsychiatric symptoms in people with dementia. CNS Drugs. 2010;24(9):729–39.
90. Miller DD, Caroff SN, Davis SM, Rosenheck RA, McEvoy JP, Saltz BL, Riggio S, Chakos MH, Swartz MS, Keefe RS, Stroup TS, Lieberman JA, Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Extrapyramidal side-effects of antipsychotics in a randomised trial. Br J Psychiatry. 2008;193(4):279–88.
91. Uçok A, Gaebel W. Side effects of atypical antipsychotics: a brief overview. World Psychiatry. 2008;7(1):58–62.
92. Salzman C, Wolfson AN, Schatzberg A, Looper J, Henke R, Albanese M, Schwartz J, Miyawaki E. Effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. J Clin Psychopharmacol. 1995;15(1):23–9.
93. Coccaro EF, Kavoussi RJ. Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. Arch Gen Psychiatry. 1997;54(12):1081–8.
94. Pollock BG, Mulsant BH, Rosen J, Mazumdar S, Blakesley RE, Houck PR, Huber KA. A double-blind comparison of citalopram and risperidone for the treatment of behavioral and psychotic symptoms associated with dementia. Am J Geriatr Psychiatry. 2007;15(11):942–52.
95. Pollock BG, Mulsant BH, Rosen J, Sweet RA, Mazumdar S, Bharucha A, Marin R, Jacob NJ, Huber KA, Kastango KB, Chew ML. Comparison of citalopram, perphenazine, and placebo for the acute treatment of psychosis and behavioral disturbances in hospitalized, demented patients. Am J Psychiatry. 2002;159(3):460–5.
96. Choi-Kwon S, Han SW, Kwon SU, Kang D-W, Choi JM, Kim JS. Fluoxetine treatment in poststroke depression, emotional incontinence, and anger proneness: a double-blind, placebo-controlled study. Stroke. 2006;37(1):156–61.
97. Fleminger S, Greenwood RJ, Oliver DL. Pharmacological management for agitation and aggression in people with acquired brain injury. Cochrane Database Syst Rev. 2006;4, CD003299.
98. Glenn MB, Wroblewski B, Parziale J, Levine L, Whyte J, Rosenthal M. Lithium carbonate for aggressive behavior or affective instability in ten brain-injured patients. Am J Phys Med Rehabil. 1989;68(5):221–6.
99. Chang K, Zhang H, Xia Y, Chen C. Testing the effectiveness of knowledge and behavior therapy in patients of hemiplegic stroke. Top Stroke Rehabil. 2011;18(5):525–35.
100. Ramírez JM, Andreu JM. Aggression, and some related psychological constructs (anger, hostility, and impulsivity); some comments from a research project. Neurosci Biobehav Rev. 2006;30(3):276–91.

Chapter 9
Denial of Illness

Patrik Vuilleumier, Roland Vocat, and Arnaud Saj

Abstract Patients with stroke or other brain lesions may remain unaware and explicitly deny their neurological deficits, including paralysis, blindness, amnesia, and aphasia – a phenomenon called anosognosia. The neuropsychological disorders and neuroanatomical substrates underlying anosognosia are still poorly known. Whereas purely psychological defense mechanisms cannot account for it, no unique neuropsychological deficit in executive function, reasoning, or memory appears to be consistently linked to anosognosia. This chapter first reviews the most common forms of anosognosia for different domains of deficits and then focuses on denial of hemiplegia. Evidence from recent studies on the latter case suggests a role of multiple component deficits affecting not only motor control, attention, or proprioception but also emotional and self-monitoring systems implicated in error detection as well as belief formation and updating. These abilities are likely to rely on a distributed network of brain areas, possibly including limbic and subcortical circuits in insula, basal ganglia, and amygdala, in addition to premotor and executive control systems.

Keywords Anosognosia • Denial • Error monitoring • Stroke • Hemiplegia • Neglect • Proprioception

P. Vuilleumier (✉)
Department of Neurology, University Hospital of Geneva, Geneva, Switzerland

Department of Neurosciences, Medical Center, University of Geneva, Geneva, Switzerland

Département de Neurosciences Fondamentales, Centre Médical Universitaire,
Bâtiment AB, 7008, 1 rue Michel-Servet, 1211 Geneva 4, Switzerland
e-mail: patrik.vuilleumier@unige.ch

R. Vocat
Valais Hospital, Sion, Switzerland

University Hospital of Geneva, Geneva, Switzerland

A. Saj
Department of Neurosciences, University of Geneva, Geneva, Switzerland

Department of Neurology, University Hospital of Geneva, Geneva, Switzerland

J.M. Ferro (ed.), *Neuropsychiatric Symptoms of Cerebrovascular Diseases*,
Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-1-4471-2428-3_9,

Introduction

Stroke often results in severe and conspicuous deficits, such as paralysis, loss of speech, and blindness. Strikingly, however, some patients suffering from these deficits may deny their impairment and thus claim to have intact neurological or cognitive abilities despite a severe handicap. This striking dissociation between the presence and the subjective experience of deficits has been termed "anosognosia" by Babinski, who first reported this phenomenon in a patient with hemiplegia [1–3]. Anosognosia, broadly defined as a lack of awareness or denial of one's illness that is not fully explained by amnesia, confusion, or a more global mental disorder, may concern a wide range of neurological or psychiatric deficits [1, 4]. It occurs in several neurological conditions besides hemiplegia, for example, in cortical blindness after bilateral occipital lesions, in some forms of amnesia after frontotemporal lesions, in aphasic syndromes (particularly for Wernicke type), or in other disturbances such as neglect or apraxia (see [1, 5]). Anosognosia is also common in neurodegenerative disease, particularly in frontotemporal dementia and Alzheimer disease. In all these conditions, denial of illness has a profound impact on everyday life for both the patients and their caregivers. It can significantly affect medical care by delaying appropriate consultation and limiting the acceptance of reeducation and treatment. Hence, anosognosia is usually associated with worse prognosis for functional recovery.

The cognitive mechanisms and anatomical substrates associated with denial of neurological illness still remain poorly known. Despite a frequent occurrence and many clinical reports, the phenomenon has rarely been studied using systematic experimental approaches. The most common presentation of anosognosia concerns hemiplegia, usually affecting the left limbs after injury of the right hemisphere, and is therefore often associated with hemispatial neglect, but the two disorders can be dissociated in some cases. Spatial hemineglect itself is intimately linked to anosognosia manifestations since these patients typically fail to notice their loss in spatial awareness, although some form of declarative knowledge concerning the existence of neglect and its consequences may be verbally reported by the patient after being told and undergoing rehabilitation (even when they actually still remain unable to compensate their inattention in spontaneous behavior). The commonalities or specificities between different domains of anosognosia (e.g., paralysis, blindness) remain largely unknown. Besides denial of the illness, a partial form (or variant) of impaired awareness of deficits is "anosodiaphoria," which is defined as a lack of concern or affective responses commensurate to the severity of neurological handicap. Finally, denial can also be motivated by psychodynamic factors, such as threat to self-esteem, fear of impaired body integrity, and exaggerated optimistic biases (see Weinstein and Kahn [22]), although these factors are generally insufficient to explain most cases of anosognosia after brain lesions, in particular when denial can be dissociated between two deficits or even between two limbs [1]. Although denial, anosognosia, and unawareness of illness are terms often used interchangeably in clinical practice, it might be valuable to better define them in future studies and link

them to more specific mechanisms or behaviors. For instance, denial may be more appropriate to refer to explicit manifestations that can be of neurological or psychological origin, whereas anosognosia seems more appropriate to describe both implicit and explicit aspects of impaired awareness of neurological disorders [6].

In this chapter, we will mainly focus on anosognosia for left hemiplegia after a lesion of the right hemisphere, since it is common and has received greater attention in the neuropsychological literature. The cognitive and anatomical factors associated with AHP have been investigated less rarely than anosognosia in other domains. We will also briefly describe the other neurological and psychiatric conditions where manifestations of anosognosia have been observed.

Anosognosia for Hemiplegia

Anosognosia for hemiplegia (AHP) may occur with motor disorders of different degrees of severity and may affect the upper and/or lower limb to different extent in some cases. It is most common after acute stroke, but similar phenomena may occasionally be observed with other hemispheric lesions or dysfunctions such as tumors, demyelinating diseases, or post-seizure Todd's paralysis. Some rare forms have been reported for sensorimotor loss after brainstem strokes or peripheral neuropathies [7, 8], but related to severe concomitant disturbances in cognitive functions (such as dementia or confusion) which are not necessarily present in patients with focal hemispheric stroke. Although AHP is also sometimes observed for a right hemibody paralysis after left hemisphere damage, a much higher frequency of left-sided disorders has been clearly established, not only in studies of patients with focal brain lesions but also during investigations with the WADA test [9]. Therefore, AHP is often associated with left spatial hemineglect [114] which may contribute to the unknowing of left limbs and their impairment, although neglect alone seems insufficient to account for AHP [2]. AHP may occasionally be accompanied by other disturbances on the body schema such as kinetic illusion, supernumerary phantom limbs, or delusions concerning the affected limbs (e.g., patients may believe that the paralyzed limb is a grafted prosthetics).

Clinically, AHP is usually evaluated using a systematic interview developed by Bisiach, in which questions about the deficits are asked in a progressive fashion, reflecting the degree at which the motor deficit is verbally acknowledged by the patient: (1) spontaneously, (2) after a general question about health, (3) after a specific question about the limb, or (4) after confrontation with a requested motor action. The severity of AHP can be rated (from 0 to 3) based on the question level at which the patient does or does not report his/her deficit. AHP may also manifest in nonverbal behaviors, for example, when the patient attempts to go out of the bed despite hemiplegia or makes unrealistic plans for sport activities.

The neuropsychological and anatomical correlates of AHP have begun to be better defined in recent years (see below), but the exact brain circuits and cognitive mechanisms for awareness or unawareness of paralysis still remain little understood [10].

As already noted above, AHP is associated with a poor prognosis for recovery, presumably because of the lack of cooperation and motivation of the patients during their rehabilitation which is a "natural" consequence of their denial of deficit [11].

Anosognosia in Cortical Blindness

Besides the original description of AHP by Babinski, the first cases of denial of a neurological illness were reported in patients with complete blindness, typically following bilateral occipital lesions, due to vascular or traumatic injuries [12–14]. This form of denial is often termed Anton or Anton-Babinski syndrome. Angelergues et al. [15] distinguished several degrees of anosognosia for such deficits: (1) no denial of blindness, but no spontaneous complaint and indifference (i.e., anosodiaphoria); (2) explicit denial of visual loss and attribution of difficulties to external causes (lack of lighting, inappropriate glasses, etc.); (3) anosognosia associated with hallucinatory percepts and patient claiming to see objects or people, with more or less of fantasy; and (4) anosognosia of blindness accompanied by mental confusion. Anosognosia of blindness is often associated with an amnesic syndrome, for example, when a bilateral stroke in posterior temporal artery extends to the hippocampal regions (Dide-Botcazo syndrome [16]). In some cases, denial of blindness is favored by the appearance of visual hallucinations or confusion due to concomitant lesions [17]. Mental confusion or other cognitive disorders may also contribute to anosognosia for blindness in rare cases with peripheral ocular origin or in traumatic cases combining injuries to the optic nerves and frontal lobes. Anosognosia for visual loss is also observed in patients with hemianopia, frequently associated with spatial neglect and an extension of occipital lesions toward the parietal lobe.

Anosognosia in Aphasia

The assessment of awareness for the language deficits in aphasic patients is hampered by significant difficulties. It is difficult to obtain from an aphasic patient a detailed verbal description of his knowledge about his disorder, because of the limitations in expression or comprehension. Interestingly, awareness of aphasic symptoms is directly correlated to residual abilities for understanding, much more than to those for verbal expression. Anosognosia of speech disorders is therefore more common in Wernicke or conduction aphasia.

One method to quantify the degree of anosognosia is to assess the control exerted by the patient on language production, in particular by measuring self-corrections [18]. A scale of anosognosia and auto-correction for aphasia developed by Wepman [19] is always used in clinical assessment. An aphasic who does correct himself may still become aware of his mistakes by signals from interlocutors: this is the mechanism called "open loop" [20], while an aphasic with anosognosia is apparently

unable to use these cues nor to rely on an internal model of speech plans to compare them with actual output (closed loop). The latter problem might potentially be similar to an impaired monitoring of motor intentions as proposed for AHP [21].

Anosognosia for aphasia is typically associated with jargon, echolalia, or stereotypic speech, such as in transcortical sensory aphasia. Some patients are able to recognize their own productions as inappropriate when these are reported by another person or played back from audio recordings. Weinstein and Kahn [22] reported that jargon could sometimes occur specifically in response to questions about the disease (pure denial of disease) but this is rare. A milder form of anosognosia for specific language impairment may be seen when patients fail to continuously monitor the quality of their productions, even if they are aware of their language disorder. A careful consideration of these aspects is important for rehabilitation strategy.

Anosognosia in Amnesia

Anosognosia is present only in some forms of amnesic deficits, and its manifestations are directly related to the etiology and extent of brain lesions. Anosognosia is always present in Korsakoff's syndrome of alcoholic origin. In this case, its intensity is correlated with the existence of confabulations, with a parallel evolution over time after acute onset. The loss of confabulations during follow-up is usually associated with improving awareness of memory impairment. In amnesic syndromes following surgery on aneurysms of the anterior communicating artery, anosognosia is also frequent and often accompanied with confabulation. Van der Linden and Bruyer [23] reported a constant association of anosognosia with frontal dysexecutive signs. Schinder and colleagues also pointed to a frequent involvement of orbitofrontal damage in patients with spontaneous confabulation and severe denial of amnesia [24].

In contrast, amnesic patients with hippocampal injury are generally not or less anosognosic. For example, the patient HM was partially aware of his memory problems [25]. Many other examples of severe amnesic syndromes without anosognosia or confabulations with hippocampal lesions are given in the literature (see for review [26]). Likewise, patients with transient global amnesia (TGA) may exhibit high levels of anxiety and concerns for their memory loss despite very severe anterograde amnesia. This cannot be simply attributed to the patients "forgetting" about their problems. These findings indicate that anosognosia for amnesia is not a consequence of the severity of memory deficits and cannot be simply attributed to the patients "forgetting" their amnesic problems. However, a role for memory problems in anosognosia has been proposed in patients presenting Dide-Botcazo syndrome (anosognosia of blindness and amnesia after bilateral PCA stroke; see [16]). Thus, overall the mechanisms for anosognosia of amnesia remain poorly known, possibly caused by the disorganized retrieval of false memories in patients with confabulations or deficits in post-retrieval executive monitoring functions associated with the frontal lobes.

Anosognosia in Neurodegenerative Disease

Besides acute cerebrovascular lesions, progressive brain dysfunction associated with some forms of dementia may also cause anosognosia for various deficits. It is common in Alzheimer disease (AD), where it has been hypothesized that the particular pattern of memory impairment, with losses in recent memory but sparing of older (semantic) information [27, 28], may lead to an outdated sense of self (for review [29, 30]). Anosognosia is also constant in frontotemporal dementias (specifically in the compartmental variant). In contrast, it is absent in the initial stages of semantic dementia and primary progressive aphasia, as long as degeneration remains confined to cortical temporal areas. One might nevertheless qualify this view by considering separately the specific cognitive alterations that occur during the course of the disease. Patients may be aware of some but not other deficits.

The assessment of anosognosia in dementia is difficult, but important for adequate care. It can be measured globally as the difference between judgments made by the patient and his entourage on the intensity of difficulties in various activities, as well as between scores on specific neuropsychological tests and subjective ratings by the patient. In standardized tasks (Neuropsychological Assessment Battery, NAB [31]) that quantify real-world abilities, patients are also asked to predict their performance relative to a normal distribution graph [32]. Such self-appraisal is usually impaired in frontotemporal disease more than in AD.

A certain degree of anosognosia is common in the early stages of AD, even though patients may complain of memory problems, and it steadily increases as the disease progresses. Mangone et al. [33] found a correlation between anosognosia and the severity of dementia, particularly on tests probing functions of the prefrontal cortex such as the visual reproduction subtest of the Wechsler Intelligence Scale and the Continuous Performance Test. These results suggest a relationship between anosognosia and right hemispheric prefrontal damage. However, other authors [34] found a great heterogeneity of anosognosia in AD, without systematic correlation with the degree of deterioration in cognitive dysfunctions.

A few recent studies [35, 36] also investigated the neuroanatomy of anosognosia in neurodegenerative disorders by using voxel-based morphometry (VBM) and show a relationship between self-appraisal accuracy and atrophy in right ventromedial prefrontal cortex. Then together, these data accord with other studies indicating that right hemisphere damage is frequently present in patients with anosognosia behavior [26, 37–43].

Anosognosia in Schizophrenia

Denial or unawareness of disease is also commonly observed in schizophrenia, where it has been variably interpreted as a primary symptom of the illness or attributed to defensive mechanisms. However, there is substantial evidence that it is likely

to reflect a specific neuropsychological disturbance related to brain dysfunction. This "lack of insight" into one's own illness in patients with schizophrenia has long been known since Bleuler and can occur for both negative and positive symptoms [44]. Such poor insight may refer to variable aspects, however, concerning the overall manifestations of the disease, treatments, social consequences, or specific psychiatric symptoms. A discrepancy between the objective performance on neuropsychological tasks (e.g., executive or memory functions) and the self-evaluation made by the patient is frequently observed, suggesting a dysfunction in the "metacognitive" control abilities or in a more central reality monitoring system, as proposed by Frith [45]. Although results remain partly contradictory, it has been suggested that impaired frontal lobe functioning might provide a causal explanation for the poor insight as well as several other delusional aspects of schizophrenia.

A few anatomical studies (e.g., [44, 46]) systematically examined the relationship between different domains of poor insight and different subregions of the frontal lobe in 15 patients with chronic schizophrenia. The authors found that denial was associated with reduced volume in the bilateral middle frontal gyrus, rectus gyrus, and left anterior cingulate gyrus. One problem is that these studies were conducted in patients with chronic schizophrenia, which makes it difficult to identify the effects of chronic disease and exposure to antipsychotic medications. Another study in a sample of 35 patients without long-term effects of antipsychotic medication [47] reported that the lack of awareness of illness in schizophrenics was significantly correlated with a smaller volume in right DLPFC, relative to patients with preserved insight, regardless of global cognitive functioning and disease severity. Moreover, distinct aspects of impaired awareness, reflecting the ability to recognize different symptoms to different degrees [48], were related to distinct brain subregions [49], with atrophy in DLPFC being more specifically linked to denial itself, whereas atrophy in orbitofrontal cortex was linked to misattribution of symptoms.

Theories of Anosognosia

Many theories and speculations have been proposed since the initial description of this syndrome in 1914 by Babinski [50], but none is able to explain all aspects and variations of anosognosia [1, 51]. Many of these theories have been proposed based on hypothetical assumptions or observations of single cases, but systematic empirical approaches are still rare [52]. This lack of a universally accepted theory of anosognosia after one century of neuropsychological investigations suggests that a trivial mechanism for this deficit is unlikely and that anosognosia probably reflects a heterogeneous collection of deficits, i.e., with multifactorial origin and potential variability. Furthermore, it is not clear if common deficits are present across different domains of anosognosia (e.g., paralysis, blindness, memory) since dissociations can be observed between awareness and denial of different deficits within the same patient [1]. Although correlations with some forms of executive dysfunction and/or frontal lobe damage have been reported in different domains (see above), it is still

unclear which frontal lobe function or region would be critically linked to the emergence of anosognosia (when combined with brain lesions giving rise to the neurological deficit per se). A possible common theme, however, involves the role of "metacognitive" abilities allowing one to monitor performance and to compare the actual outcome of an action or response with some representation of the goals and desired outcome associated with that action [5, 52]. However, the exact cognitive processes mediating these abilities and their neural substrates remain poorly understood. Although cognitive neuroscience research has highlighted the role of specific areas in the brain (e.g., in anterior cingulate and insula as well as basal ganglia) in self-monitoring and error detection, there is little knowledge on the possible implication of these circuits in anosognosia (see [6]).

Below we will mainly review current views on AHP, since this is one of the most common domains of anosognosia after stroke, and several recent studies have begun to better characterize the possible components involved. While some of the mechanisms may be specific to motor paralysis, others might potentially be more general and thus also relevant in other domains.

Putative Mechanisms of Anosognosia for Hemiplegia

Babinski himself, during his first description of anosognosia, emphasized the role of sensory deficit, especially proprioception, depriving the patient from the sensation of the paralyzed limb. However, this explanation was insufficient, since many studies have reported patients presenting AHP and preserved proprioception. A similar but more sophisticated explanation was later proposed by Levine [53] who suggested that the combination of proprioceptive deficits with severe paralysis could make the patient unable to feel directly the lack of movement and that his paralysis has therefore to be deducted (or "discovered") by other cognitive processes of inference and reasoning, which are potentially deficient due to brain damage or confusion. Although this "discovery" theory is interesting by pointing to the role of different factors and provides an explanation for anosognosia in patients with peripheral paralysis and dementia [54], it does not account, however, for the vast majority of anosognosic patients who show no global cognitive decline as observed in dementia.

In contrast to this neurological explanation, another classic interpretation was put forward by Weinstein and Kahn [22] who emphasized the psychodynamic mechanisms of anosognosia. According to these authors, anosognosia is due to an active denial and motivational factors, favored by the brain injury but primarily reflecting a desire to preserve self-image and/or to avoid anxiety-related reactions. The authors showed that anosognosic patients frequently present with premorbid specific personality traits, characterized by a mental rigidity and perfectionism. However, this theory does not explain certain clinical dissociations in anosognosia (e.g., when the patient denies only one of its various symptoms), or the predominance of right hemispheric lesions, but has the merit of taking into account the affective mechanisms or motivational, which are often neglected by neuropsychological theories. Other explanations involving motivational repression have also been made more recently [55].

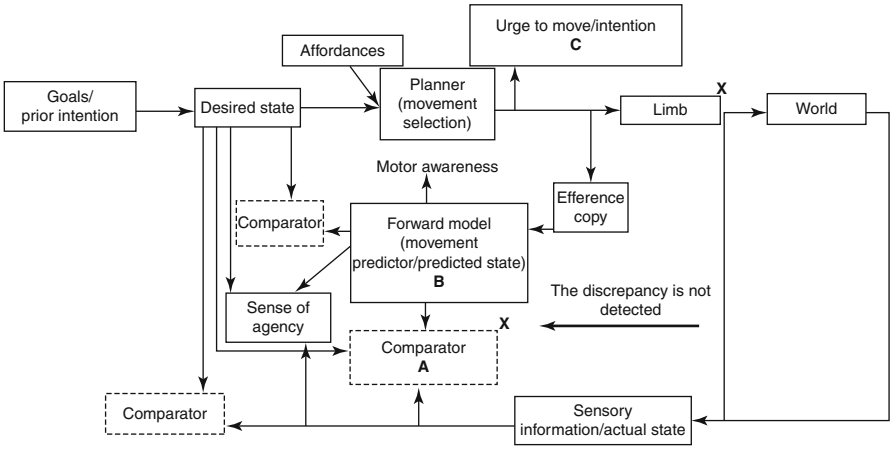


Fig. 9.1 Model of motor control according to [62]. The *'X'* indicates the locus of the lesion. In *A* is the comparator; in *B*, the predictor; in *C*, the locus of emergence of the intention to move

Other authors have reported that AHP might be linked with the production of confabulations [56], amnesic and dysexecutive symptoms [57], or a disconnection of frontal systems responsible for supervisory mechanisms and awareness [58]. But these associations are not found in all cases.

More recently, several researchers such Heilman and colleagues [59, 60] and Berti and colleagues [5, 21] have highlighted the role of impaired movement control mechanisms in AHP, derived from more general theories in normal [61]. The "feedforward" theory of Heilman postulates that the detection of paralysis requires the ability to detect a mismatch between the intention to move and the actual proprioceptive feedback corresponding to the desired movement. In this model, a deficit in the generation of motor commands (such as a motor intentional neglect) might cause anosognosia by depriving the patient of the possibility to detect the absence of movement, since no motor command would be generated. Berti and colleagues have further developed this hypothesis by highlighting, on the one hand, the existence of an "efferent copy" of the motor command that allows the generation of an internal model (feedforward) of the desired movement and, on the other hand, the existence of a "comparator" process evaluating the correspondence between this feedforward model and the ongoing feedback (proprioception, sensation). According to these authors [62], the disruption of the comparator would be the main cause of AHP. This theory has the merit of relying on a well-established model of motor control and experimental data but only applies to the field of motor deficits, without suggesting whether and how similar "comparator" mechanisms may be involved for anosognosia of other deficits (e.g., tactile anesthesia, blindness, amnesia) (Fig. 9.1)

In parallel, other data suggest that the AHP is not a unitary phenomenon, but may vary according to test procedures or patients [63]. For example, Marcel and colleagues developed a procedure to assess awareness of motor performance in which anosognosics were found to specifically overestimate themselves in a first-person

perspective but not in a third-person perspective (motor action imagined for another person). The authors attributed these difficulties to an impairment in multiple cognitive functions preventing an integration and updating of self body knowledge.

In recent years, several multifactorial hypotheses were also advanced [2, 51, 64–66]. In particular, an "ABC" model of anosognosia [2] was proposed to underscore that different combinations of deficits may explain the lack of awareness of neurological symptoms and lead to different forms of anosognosia in different patients. In this model, a first prerequisite is the difficulty in assessing the symptom (component A) which deprives the patient of a direct experience of it, due to elementary neurological disorders such as proprioceptive loss, neglect, and hemianopia [53]. The second factor is the difficulty of updating beliefs and knowledge (component B), which may reflect different cognitive disorders affecting mental flexibility, delusions, or amnesia [57]. Finally, a third factor implicates deficits in some monitoring or check operations (component C), necessary for adjusting to ambiguous cues or errors, making reasonable inferences in the presence of insufficient information, and searching for new information [67]. Critically, in this model, varying degrees of disruption in this chain of operations could lead to different behaviors: doubt and discovery, affording awareness of deficits, or, conversely, denial and delusion, causing anosognosia of different types (component D). In this perspective, some patients may show anosognosia despite relatively preserved motor commands or proprioceptive feedback when their abilities to adapt beliefs or checks are severely disrupted (or vice versa). Finally, various aspects of monitoring processes might potentially operate at explicit or implicit levels, leading to distinct declarative or behavioral manifestations of denial [6]. Similarly, Davies and Coltheart [64] proposed a two-factor theory of anosognosia, a first involving a delusional disorder and a second based on other cognitive disorders disrupting the discovery of the deficit. The latter proposals could potentially be extended beyond AHP since delusions as well as impairments in belief formation and check operations might contribute to denial in various domains of anosognosia.

Thus, overall, there is currently no general agreement on the cognitive and possibly emotional or motivational factors that determine poor awareness of movement disorder in patients with AHP [10], although it is increasingly recognized that it is likely to reflect a combination of neurological and neuropsychological deficits, rather than a unitary phenomenon. However, the exact nature of these deficits is still difficult to define and more research on AHP and other forms of denial of illness is required.

Clinical and Neuropsychological Study of AHP

To clarify the cognitive factors and cerebral substrates involved in anosognosia, we recently studied the clinical manifestations of AHP and lesion correlates in a large population of patients with motor weakness of the left hemibody after right hemisphere stroke [68]. For this study, we recruited a consecutive series of patients admitted with a first acute cerebrovascular accident and systematically investigated

anosognosia and other neurological symptoms using a battery of clinical and experimental tests shortly after admission (hyperacute phase: 0–3 days post stroke). All patients were then followed up during their hospitalization (post-acute: 4–10 days) and after 6 months (chronic stage). A similar neuropsychological and neurological assessment was performed in all three phases (hyperacute, post-acute, and chronic), with tests probing different components potentially implicated by existing theories of anosognosia (see above). Brain lesions were systematically recorded and analyzed using statistical methods for mapping voxel-based lesion [69, 70].

Over a period of 2 years, we examined 337 patients (all right handed) admitted for a first right hemisphere stroke, among whom 58 had a significant motor deficit (sufficient to disrupt activities of daily living) affecting 1 or 2 limbs (upper or lower) on the left side. These patients had a mean age of 65 years (standard deviation [SD] ± 14 years). The severity of motor deficit was assessed on a scale of 0–4 (0 = normal force, 1 = dropping of the limb when outstretched, 2 = complete fall of the limb, 3 = inability to raise the limb despite residual movement, 4 = complete absence of movement). The severity of deficits on this scale was distributed as follows: mean 2.84 (SD ± 1.21) in hyperacute phase, 2.55 (SD ± 1.8) in post-acute phase, and 1.16 (SD ± 1.50) in chronic phase.

The degree of awareness of the deficit was evaluated by several standardized instruments, including the scale of Bisiach [71] and the questionnaire of Feinberg [72]. In the scale of Bisiach, anosognosia is measured on a scale of 0–3 points: 0 if motor deficit is spontaneously reported, 1 if it is reported only after a specific question, 2 if it is acknowledged after confrontation (e.g., a failed attempt of movement at the request of the examiner), or 3 if it is still denied after confrontation. The Feinberg questionnaire includes 10 items, adapted from earlier clinical questionnaires [73, 74] which assess the ability to describe reasons for hospitalization, as well as sensations, movements, or opinions concerning the affected limb(s). For each patient, we computed a composite score of anosognosia by combining Bisiach and Feinberg scales [68]. Our results showed that AHP is extremely common in the hyperacute stage: apparent denial (e.g., Bisiach $\geq$ 2) was observed in more than one-third of patients on admission and remained high during the first week (one-quarter of patients), but then decreased significantly during reevaluation 6 months later (only 5 %).

Another test to measure anosognosia was adapted from the procedure of Marcel and colleagues [63]. This test requires comparing the evaluation (by the patient or the examiner) of the performance in a motor or a verbal fluency task (from 0 = normal, as usual, to 10 = totally impossible), before and after its actual execution. A discrepancy between the assessment by the patient and that by the examiner measures the degree of anosognosia, while a change in the evaluation by the patient before and after the test measures his/her ability to modify awareness and beliefs. Motor skills were tested with two unimanual tasks performed successively with each hand (a drink, drawing her hair) and two bimanual tasks (clap, open a bottle). In the hyperacute phase, 70 % of patients overestimated their motor performance with the affected limb at their first evaluation (before any attempt), and 50 % always overestimated it after the task (immediately or 15 min later) despite their actual

failure. In the post-acute phase, 50 % of patients still overestimated their motor performance both before and after a run. Furthermore, the degree of discordance between the assessment by the patient and the examiner was highly correlated with the severity of AHP measured with Bisiach and Feinberg scores ($r > 0.59$, $p < .001$). By contrast, in all phases, the prediction and evaluation of performance for verbal fluency tasks were relatively normal and did not correlate with the severity of AHP ($r < 0.17$). This dissociation suggests that denial of deficit in patients with AHP is specific to their motor skills but does not extend to the verbal domain.

In addition, the neurological examination of patients was completed by several other measures probing touch, proprioception, visual field, vigilance, spatial neglect, as well as basic executive functions, memory, and orientation, plus several personality scales measuring mood, anxiety, or optimism [75]. In all tests, patients with AHP generally showed more frequent and more severe deficits than patients without AHP. In particular, the severity of AHP (estimated by the composite score from Bisiach and Feinberg scales) correlated with the severity of tactile and proprioceptive deficits, the presence of hemianopia, the severity of visual and tactile extinction, and reduced alertness. Among neuropsychological deficits, the severity of the AHP also correlated with the severity of spatial neglect (estimated by different tests), as well as more weakly with the degree of spatial and temporal disorientation, memory impairment, and signs of global cognitive dysfunction in the MMSE. However, interestingly, the severity of the AHP did not correlate with impairment in simple frontal functions (evaluated at the bedside with verbal fluency and the categorization test of Weigl [76]) or in memory tests (short-term span or word list learning). Finally, no correlation was found with the personality scales. These results were broadly similar in the hyperacute (3 days) and post-acute phase (first week). These data indicate that AHP tends to occur in patients who have many other symptoms.

To further assess the contribution of each of these neurological and neuropsychological domains, we also performed a multiple regression analysis that showed that the factor most strongly related to the severity of AHP in the hyperacute phase was the severity of proprioceptive deficit (beta = 0.62, $p < .001$), whereas the severity of AHP in the post-acute phase was more closely related to the severity of spatial neglect (beta 0.38, $p < .013$). These findings accord with classical accounts for AHP by Babinksi [50] and Levine [53]. However, a number of double dissociations were also observed among our patients. On the one hand, eight of them had a complete proprioceptive deficit but no anosognosia (Bisiach score = 0), whereas a patient with anosognosia (Bisiach score = 2) showed no proprioceptive deficit. On the other hand, one patient had severe neglect (evident in all tests) but no signs of AHP, while conversely a patient with severe anosognosia (Bisiach score = 3) showed no signs of hemineglect in any of the four tests used. Taken together, these results suggest that the presence of proprioceptive disorder or spatial neglect can have an important role in the emergence of the AHP but only relative since these deficits are neither necessary nor sufficient. It seems therefore possible that the combination of different deficits is more important than the mere presence of a specific deficit.

In accord with the latter view, it was found that anosognosia scores were low (Bisiach <0.3 on average) in patients with only one or two neurological/neuropsychological deficits (hyperacute or post-acute phase), but significantly higher (>1.3 on average) when the patients had five or six deficits. In particular, the combination of severe proprioceptive loss (above the median of the whole group) and severe hemineglect (above the group median) was associated with a high incidence of AHP (14/18 patients in hyperacute phase and 11/15 in post-acute phase). Patients with one of these deficits alone exhibited AHP in less than half of the cases (8/16 hyperacute phase, 6/14 for post-acute phase), whereas patients with no proprioceptive deficit and no hemineglect only very rarely presented with anosognosia (2/14 and 4/15, respectively). This distribution is significantly different from chance (chi $2=6.74$, $p<.034$). Therefore, the simultaneous presence of different deficits, especially proprioceptive and hemineglect, may have additive or interactive effects favoring the emergence of AHP.

Furthermore, in our own study [68], we found a remarkable dissociation between AHP and anosognosia for hemineglect. The latter was evaluated using the scale of Catherine Bergego [77] that probes for symptoms of spatial neglect in everyday life as reported by the patients and by the nursing team. The discrepancy between these two reports measures the degree of anosognosia for hemineglect. Surprisingly, we found no correlation between the severity of anosognosia for hemiplegia and the severity of anosognosia for hemineglect in our population, in either the hyperacute or post-acute phase. This dissociation further suggests that awareness of hemiplegia and awareness of unilateral neglect involve at least partly distinct mechanisms, in accordance with a "modular" view of "metacognitive" mechanisms subserving awareness for different neurological functions [4, 78].

In summary, a systematic assessment of neurological and neuropsychological correlates of the AHP reveals that denial of illness may be relatively selective for the motor domain, even though it is strongly related to the presence and severity of other neurological deficits. A combination of deficits seems to favor the occurrence of the AHP, suggesting a multifactorial origin, consistent with the existence of large brain damage in most of these patients [2, 51, 68]. In particular, impaired proprioception and spatial attention, or any combination thereof, seem important but not sufficient for the emergence of an AHP. These associated deficits may thus constitute an essential permissive factor (but not unique) for the development of AHP as proposed in the "ABC model" [2] or other models [53].

Neuroanatomy of Anosognosia for Hemiplegia

Like neurological and neuropsychological mechanisms, the neuroanatomical substrates of AHP are still debated. Following the influential work of Bisiach [38] and Heilman [79], anosognosia has generally been attributed to lesions in the right parietal regions. In particular, a classic study of Bisiach et al. [39] compared lesions observed in 5 patients with AHP with 5 other patients without anosognosia and

revealed an overlap of damaged regions in the right temporoparietal junction in 4 out of 5 patients with anosognosia. However, the etiology of these lesions was mixed (vascular or tumoral), and the delay between symptom onset and anosognosia unclear. Similarly, Feinberg et al. [80] reported a strong association between lesion in the right inferior parietal lobe and asomatognosia.

More recently Berti and colleagues [81] conducted a systematic study of brain lesions in 17 patients with AHP and 12 without, all suffering from left spatial neglect. These authors observed a predominance of lesions in the right frontal regions (premotor cortex). In addition, one of their patients with AHP but without neglect suffered from an injury involving the same premotor regions. All these patients were examined during the first 2 months after an acute stroke, but with a variable delay. However, conflicting results have subsequently been reported by Karnath and Baier [82, 83], who studied brain lesions in 14 patients with AHP and 13 hemiplegic patients without (recruited on average between 3 and 7 days after stroke). A voxel-based analysis of brain damage in these patients revealed a predominance of lesions in the right insula, especially its posterior part, and in the white matter of the posterior internal capsule. The disagreement between these studies may have multiple reasons, including methods of assessment of anosognosia, time from onset of symptoms, and neuropsychological profile.

In our own study [68], we also performed a systematic investigation of lesions on brain MRIs in each patient (based on images T1, T2, and FLAIR). All lesions were reconstructed in 3D on the original image of each patient and then normalized into a standard anatomical volume (MNI: Montreal Neurological Institute). The comparisons between patient with and without anosognosia were made with standard anatomical subtraction methods (with the MRIcro software) and with voxel-based regression using neuropsychological scores obtained in various tests [69, 70]. First, to confirm the validity of these anatomic analyses, we showed that the severity of motor deficit correlated with lesions in regions of the precentral motor cortex and anterior internal capsule (in both the hyperacute and post-acute phases). Similarly, the severity of left unilateral neglect (estimated by the composite score of different visual tests) was correlated with lesions in the right posterior parietal cortex and dorsolateral prefrontal cortex (during both phases) and in the right temporoparietal region during the post-acute phase only. These results confirm previous studies on the anatomy of unilateral neglect obtained with similar methods [70, 84, 85] and thus validate the anatomical approach used for AHP [70].

The lesion mapping analysis of anosognosia was performed by using the composite scores of anosognosia severity (Bisiach and Feinberg scales), as a continuous variable in a linear voxel-based parametric regression analysis of brain lesions (VLSM: voxel-based lesion-symptom mapping) (cf. [69, 70]). This approach allowed us to weight the impact of injury in different regions depending on the severity of anosognosia in each individual, without making a dichotomous categorization of patients into two arbitrary groups (with anosognosia and without anosognosia). In the hyperacute phase (Fig. 9.2A), we found that the severity of AHP correlated with lesions in several anterior brain areas, including the insula, the anterior internal capsule, the basal ganglia and caudate nucleus head, as well as the anterior paraventricular white

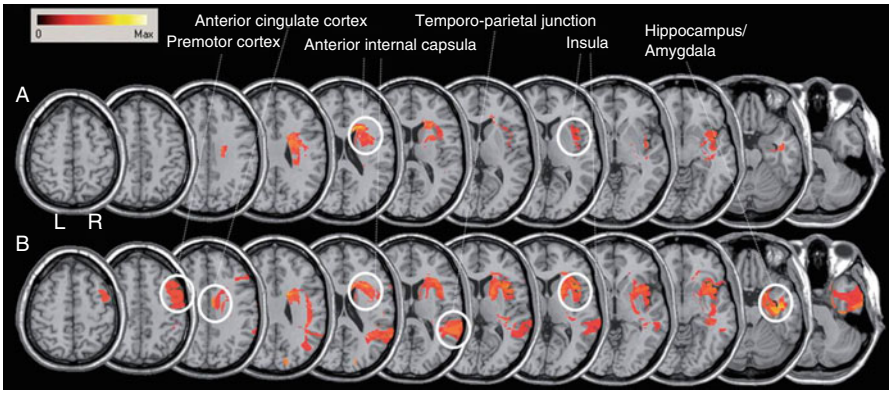


Fig. 9.2 Brain damage correlating with the severity of anosognosia for hemiplegia (Adapted from Vocat etal.[67])

matter of the right hemisphere. In post-acute phase (Fig. 9.2B), anosognosia severity correlated with the same areas, plus additional regions in the premotor cortex, dorsal anterior cingulate gyrus, temporoparietal junction, and medial temporal regions (hippocampus and amygdala). More generally, the total volume of lesions also correlated with the severity of anosognosia in the post-acute phase, but not in the subacute ($R=0.57$, $p=.001$, and $R=0.29$, $p=.08$, respectively) (Fig. 9.2)

In summary, voxel-based analyses of lesions associated with AHP point to partly distinct correlates for hyperacute and post-acute phases. In agreement with Baier and Karnath, lesions in the insula and anterior subcortical regions may be the most critical in the hyperacute and post-acute phases, but additional lesions in the parietal regions and frontal and/or medial temporal lobe appear to be necessary for the presence of persistent AHP beyond the hyperacute phase. These same regions are probably structurally intact but dysfunctional in the hyperacute phase (ischemic penumbra and diaschisis). Together, these lesions may result in different deficits in motor programming, spatial attention, and proprioception, but also error monitoring as well as memory and emotional processes. These anatomical data converge with behavioral outcomes in neuropsychological testing and reinforce the notion that anosognosia does probably not result from damage to a single brain system. In other words, the ability to assess and be aware of motor performance (or deficit) most likely involves a combination of several processes including sensory, motor, spatial, emotional, and monitoring systems, underpinned by different brain circuits.

On the one hand, these recent results confirm the classic work of Bisiach and colleagues showing the importance of the right temporoparietal junction, also implicated in asomatognosia and other disorders of the body schema [80, 86]. Our results (post-acute phase) are also compatible with a key role of premotor areas [81], possibly involved in the "feedforward" control of action [87]. It is likely that these regions are responsible for planning and initiating movement but also generating corollary motor signals (efference copy) used for monitoring and adjustment of

current movements, compared with proprioceptive sensory feedback. Finally, lesions in the insula are consistent with the results of Baier and Karnath [83]. However, while these authors pointed to a possible role of the insula in body perception and motor agency [82, 88], it is noteworthy that these regions are also strongly involved in emotional and monitoring processes, including risk estimation, error detection, decision making under uncertainty, and rejection of false beliefs [89–94]. The latter functions might also be relevant for promoting awareness of deficits in patients with brain damage. Some role for motivational or emotional factors is also suggested by the involvement of medial temporal structures [68], particularly the amygdala, whose function is closely associated with fear and detection of self-relevant events [3, 95, 96]. As suggested for neuropsychological deficits, the combination and variability of lesions within these brain systems may contribute to the emergence of AHP and its clinical heterogeneity in different patients.

Beliefs and Error Monitoring

Some of the regions implicated in AHP, such as the insula and anterior cingulate cortex [68], are known to be recruited during functional neuroimaging studies in normal subjects during error detection tasks [93], but also during tasks requiring to evaluate beliefs or knowledge about various facts [90]. For example, an interesting study by Harris and colleagues [90] examined brain activity in healthy volunteers while they judged various statements (concerning general semantics, maths, history, or autobiographical facts) and decided whether these statements were true, false, or uncertain (see Table 9.1). A selective activation of the insula and dorsal anterior cingulate gyrus was observed when the subjects rejected these statements as incorrect facts, consistent with the involvement of these regions in error detection [93] and performance monitoring [92]. Damage to these circuits or their connections may contribute to the behavior of patients with anosognosia who typically fail to call into question prior beliefs about their health and their motor or cognitive skills [97].

An inability to question past beliefs and detect their inaccuracy in uncertain conditions is not only consistent with the role of the insular and cingulate regions in normal brain and their frequent lesion in patients with anosognosia but also accord with the "ABC model" of anosognosia [2]. In this perspective, AHP can only result from a lack of appreciation of motor commands or proprioceptive feedback if it is accompanied at the same time by an inability to question beliefs or knowledge of the patient about his condition or an inability to trigger reactions of doubt or

Table 9.1 Examples of the belief verification task used by Harris et al. [89]

Mathematical facts	Semantic facts	Personal/autobiographical facts
$(2+6)+8=16$	Gigantic means "great"	You have two sisters
62 is divisible by 9	Devious means "friendly"	You were born in Paris
$1.2^{57}=32608.5153$	Acrasie means "weakness of will"	You had lunch at home on Dec. 8

Table 9.2 Test of riddles [96]

Clue n°1 :	My weight is about 300 g
Clue n°2 :	I produce a consistent sound
Clue n°3 :	The sport makes me excited
Clue n°4 :	I'm usually on the left side rather than the right side
Clue n°5 :	Lovers often draw me on the trees

verification in case of uncertainty. More research is needed to test for this hypothesis with patients with AHP by using error monitoring tasks related or unrelated to motor performance.

Thus, such hypothesis of an abnormal control of beliefs also implies that a deficit in motor control is not sufficient to explain the AHP (as proposed by "feedforward" models of action based on a comparison between motor intention and execution), but postulates the existence of other concomitant factors. In fact, this view converges with other recent neuropsychological investigations using monitoring tasks. For example, Jenkinson et al. [98] examined patients' ability to discriminate between information generated internally (by intention) or externally (by sensory experience), using a paradigm previously developed to test reality monitoring abilities in some psychiatric disorders (like schizophrenia). These abilities were estimated via a memory task for motor information (gestures) and visual information (drawings), which could be either real or imaginary. In the visual domain (perceived or imagined drawings), patients with AHP showed a greater difficulty in discriminating between these two types of memories (real or imagined) than hemiplegic patients without AHP or control subjects without paresis. In the motor domain (gestures performed, observed, or imagined), hemiplegic patients with and without AHP had greater difficulty to distinguish between the different memories than healthy subjects. These results suggest that reality monitoring deficits associated with anosognosia may extend beyond the motor domain and that more specific deficits in movement control may not be exclusively observed in anosognosic patients but also in those with motor impairments without anosognosia.

It therefore seems likely that some cognitive dysfunction related to performance monitoring and belief updating might contribute to anosognosia. This is supported by recent findings from a "riddles test" that was designed to be easily given at the bedside and examine the capabilities of belief flexibility and verification (cf. [97]). This test presents patients with successive verbal cues in order to discover a target word, initially unknown but indirectly described by the cues (see Table 9.2). After each new cue, the patient is asked to offer a word, new or identical to the previous word, and to indicate their level of confidence.

When this test was given to a group of patients with right brain damage, we found a striking difference between hemiplegic patients without anosognosia and those with persistent anosognosia (in subacute phase). Normal subjects and patients without AHP reported low confidence after the first cues (average ~ 2–3 on a scale of 8), which gradually increases with further clues. On the contrary, patients with AHP reported a high level of confidence with the first cue already (average ~5–6 on the scale of 8). Furthermore, patients without anosognosia and healthy subjects tended to change their response after the second, third, and fourth cues, whereas

patients with anosognosia frequently perseverated in their first response. Nevertheless, all patients including those with anosognosia gave the correct answer after the last cue, indicating that they did not show differential deficits in semantic knowledge. Rather, anosognosics exhibited selective difficulties to appraise the degree of uncertainty and doubt about uncertain beliefs, even when contradicted by experience. Note that this test does not involve any motor or sensory components. Furthermore, the perseverations of patients on incorrect answers in this test did not correlate with their performance in other tests of frontal functions, such as verbal fluency or flexible categorization of geometric shapes [76], or with scores on the MMSE. These findings therefore point to a particular deficit affecting cognitive flexibility and ability to update beliefs, which may contribute to the AHP in patients with motor weakness but impaired appreciation of this (e.g., due to proprioceptive deficit or hemineglect), as posited by the discovery and "ABC" framework [2, 53].

Implicit or Explicit Knowledge

Although patients with anosognosia deny the existence of their deficits, some aspects of their behavior have long suggested the possibility of unconscious or implicit knowledge of their disability. This was already described with the term of "Dunkle Erkenntnis" by Anton [12]. For example, the fact that the patients remain in bed or accept medical examinations, while denying the existence of paralysis or any illness, might suggest that patients have a latent or indirect knowledge of their deficits [1, 99]. Some authors have postulated that this knowledge was actually repressed by psychodynamic processes to protect the patient's psyche against a breach of physical integrity [100, 101]. Alternatively, it could reflect the existence of different neural pathways for detecting motor errors, with different access to conscious awareness [97].

An indirect test to probe such implicit knowledge has been described by Nardone and collaborators [55]. In their study, patients had to press as quickly as possible a button to the appearance of a dot in the middle of a screen, which was preceded by a word that could relate to their deficit (paralysis, arm, etc.) or was unrelated (house, sky). By comparing trials in which a word related to the disease was presented with those with a neutral word, the authors observed a slowing of reaction time in patients with AHP, and this slowing was proportional to the severity of anosognosia as measured by the Feinberg scale. These results were interpreted as evidence that patients had an implicit knowledge of their deficit, which was activated by the presentation of words related to their deficit but inhibited by repression processes (e.g., Freudian type), thus producing slower reaction times in the target detection task. A similar phenomenon suggesting an implicit knowledge of the deficit was also reported in a sentence completion task [101] where completion with words related to the disease was significantly reduced compared to the completion sentence of non-disease words [103].

To further study the implicit knowledge in patients with anosognosia, we also used a standard procedure of implicit association (IAT, Implicit Association Test), often applied in social psychology [103]. In this test, subjects must classify two categories of words related either to oneself (I, me, my, etc.) or to others (you, thou, etc.) and two categories of words related to good health (strength, vitality, well-being) or to illness (sickness, weakness, paralysis). In a condition called "congruent," the subject is asked to press the same button response to classify words referring to oneself and those relating to good health and to press the other button to categorize words referring to others and disease. In the second and critical condition, called "incongruent," the response mapping is changed so that the words referring to disease and self are classified with the same response button, while the words referring to others and health are categorized with the second button. This second condition typically leads to a time cost in reaction times because of the "natural" subjective incongruency between self and illness. According to the logic of IAT, if the subject considers himself/herself as healthy, the pairing between the concepts of good health and self is easy (hence leading to faster responses in the task), as compared with the pairing between self and illness words.

By testing a group of 12 hemiplegic patients with and without AHP in this test [97], we observed a significant increase in reaction time for the incongruent (self and illness) compared to congruent combination (self and health). Moreover, this cost correlated with individual scores in a scale of subjective health: in other words, the more a subject considers himself healthy, the more he has difficulty in classifying words referring to self and illness using the same response button (in terms of reaction time). However, in this test, patients with AHP were found to behave like healthy subjects, and their responses reflected their (incorrect) belief to be healthy, with no evidence of an implicit association with disease words. Further studies are needed to understand the discrepancy between results in this test and previous results of Nardone et al. [55] and Fotopoulou et al. [103].

Therapeutic Interventions

The presence of an AHP is associated with a relatively unfavorable prognosis for recovery. This is related to several factors, including the difficulty of the patient to become aware of its deficit, resulting in poor cooperation, lack of motivation, or even refusal for rehabilitation activities. Despite this pejorative significance of anosognosia, to date there are few specific treatment strategies to address this deficit [65]. Few studies, if any, have been conducted to address, in a systematic manner and/or in large groups of stroke patients, the potential benefit of therapeutic interventions aiming at increasing awareness of deficits.

However, several reports have shown a temporary remission of anosognosia and other symptoms after specific interventions, especially caloric vestibular

stimulation [105–107], but also prism adaptation [108]. More recently, a video feedback intervention was described and led to remarkable results [109]. In this study, patients were initially confronted with their motor deficits while they were filmed by the examiner. Subsequently, after having had the opportunity to observe their difficulties during this confrontation through video recording, these patients showed a significant reduction in anosognosia. These observations suggest that indirect experience of the motor deficit via the video enabled patients to better adjust their knowledge about their illness than a confrontation through direct experience. However, further studies are needed to confirm these effects and to evaluate systematic therapeutic interventions in these patients to improve awareness of deficits and promote recovery.

Emergence of a Multifactorial and Dynamic Model of Anosognosia

The review of neuropsychological and anatomical correlates of denial of illness after brain lesion converges to suggest a multifaceted phenomenon with a multifactorial origin, presumably reflecting the combined effect of different elementary deficits. Thus, AHP, the most common and most studied form of anosognosia, involves a disorder affecting not only the online control of motor action or intentions but appears to be associated with additional problems of monitoring and belief flexibility. Various combinations of critical deficits could lead to AHP by disrupting, on the one hand, the direct appreciation of motor losses (due to deficits in action controlled by internal "feedfoward" signals and/or "feedback" information conveyed by proprioception and spatial attention) and, on the other hand, by damaging the capacity to monitor and detect error in performance. Altogether, this could lead to inappropriate confidence in initial beliefs or partial information. This set of deficits is not only consistent with recent theories of anosognosia proposing a role for different mechanisms, such as the two-factor model [64] or ABC model [1, 68], but also plausible given the anatomical data obtained in AHP [5, 68, 81, 83]. Notably, AHP seems to correlate with lesions affecting the premotor cortex and the temporoparietal junction (both linked to motor control, proprioception, attention, or body schema) but also the insula, cingulate cortex, basal ganglia, and medial temporal regions including the amygdala (all related to motivational systems and executive control of the error).

Based on these results, we propose a general model of anosognosia [6, 10] in which the assessment of one's (e.g., motor) performance depends on access to different information sources (e.g., motor, proprioceptive, visual attention) and is performed in parallel at the conscious level (explicit) and unconscious level (implicit). Indeed, research on error detection and performance monitoring in healthy subjects shows that it is possible to record specific neurophysiological or behavioral responses in error (during motor tasks or others) even when the subject is not aware of having made such a mistake [93, 110–113]. Moreover, the existence of distinct

pathways (explicit and implicit) for motor control and self-monitoring makes it possible to consider different forms of anosognosia, involving different degrees of dysfunction in one or the other of these levels, or both. Thus, an explicit monitoring system may depend on the integrity of frontal and parietal cortical networks, whose damage could lead to a partial form of anosognosia where the patient verbally denies the existence of the deficit but nevertheless behaves appropriately to it. Conversely, dysfunction within the monitoring system could involve implicit networks in connection with the insula, cingulate cortex, and/or the amygdala, associated with a more "automatic" and preconscious detection of errors, whose damage may lead to implicit form of anosognosia – as observed in patients with anosodiaphoria or after head trauma (showing explicit knowledge of their deficits, but an absence of appropriate behavior given their situation). A combined deficiency of both systems could lead to a complete anosognosia, as observed after voluminous brain damage (Fig. 9.3).

AHP and other forms of anosognosia remain intriguing clinical disorders whose understanding needs to be improved, both because of the theoretical interest for mechanisms of self-awareness and because of the potential impact on therapeutic management in these patients. While many explanatory models have been proposed over the past century, none seems entirely satisfactory to date [1, 10, 51]. It seems important that clinical research in this area stands out from a single mechanistic framework and develops more detailed cognitive models based on empirical data [52]. We hope that recent findings described in this review provide a first step in this direction.

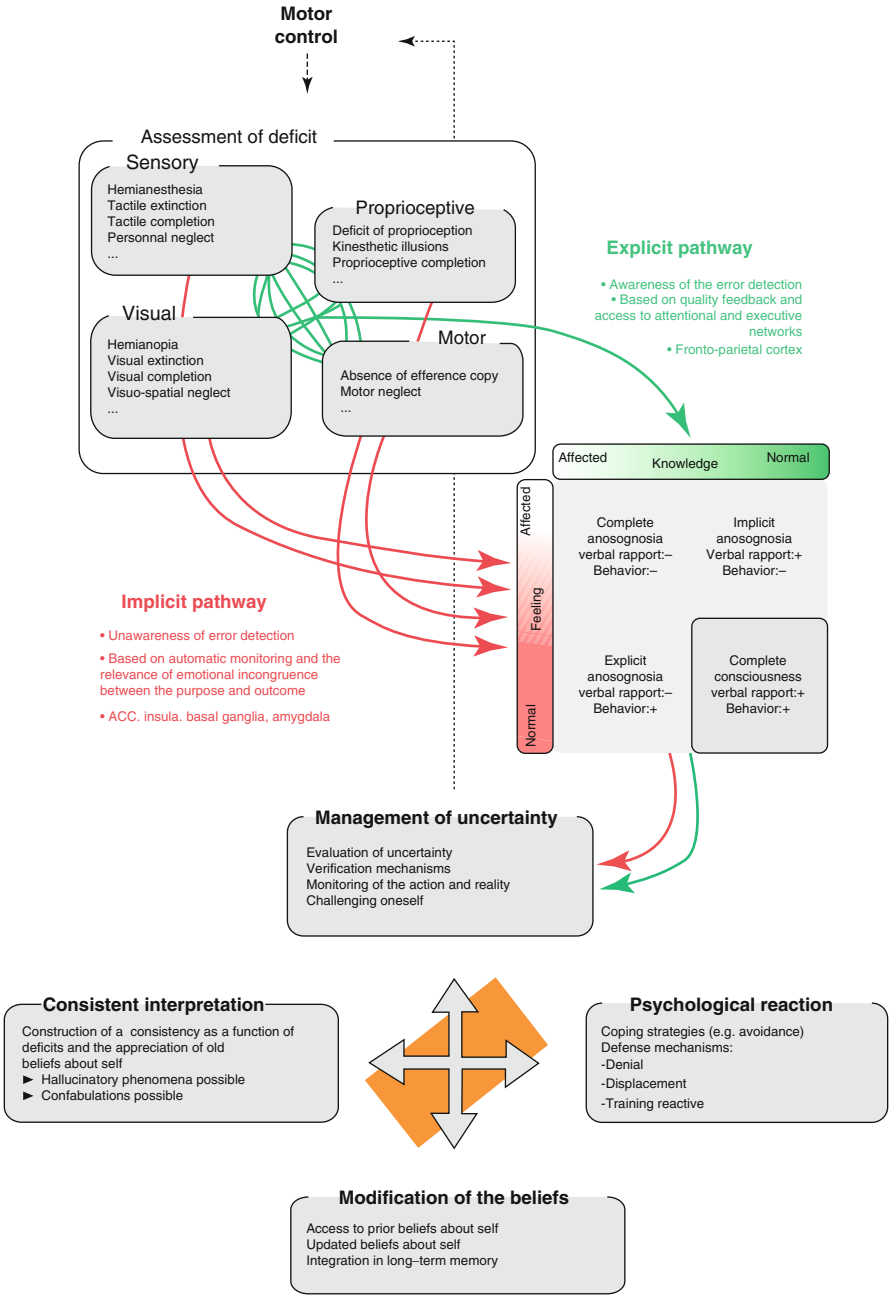


Fig. 9.3 Multifactorial model of anosognosia for hemiplegia (Adapted from Vocat and Vuilleumier [6])

References

1. Vuilleumier P. Anosognosia. In: Bogousslavsky J, Cummings JL, editors. Behavior and mood disorders in focal brain lesions. Cambridge: Cambridge University Press; 2000. p. 465–519.
2. Vuilleumier P. Anosognosia: the neurology of beliefs and uncertainties. Cortex. 2004;40(1):9–17.
3. Vuilleumier P. How brains beware: neural mechanisms of emotional attention. Trends Cogn Sci. 2005;9(12):585–94.
4. Prigatano G. The study of anosognosia. New York: Oxford University Press; 2010.
5. Pia L, Neppi-Modona M, Ricci R, Berti A. The anatomy of anosognosia for hemiplegia: a meta-analysis. Cortex. 2004;40(2):367–77.
6. Vocat R, Vuilleumier P. Neuroanatomy of impaired body awareness in anosognosia and hysteria: a multi-component account. In: Prigatano GP, editor. The study of anosognosia. New York: Oxford University Press; 2010. p. 357–403.
7. Bakchine S, Crassard I, Seilhan D. Anosognosia for hemiplegia after a brainstem haematoma: a pathological case. J Neurol Neurosurg Psychiatry. 1997;63(5):686–7.
8. Laplane D, Degos JD. Troubles inhabituels du schéma corporel par désafférentation périphérique. Rev Neurol. 1984;140(1):45–8.
9. Breier JI, Adair JC, Gold M, Fennell EB, Gilmore RL, Heilman KM. Dissociation of anosognosia for hemiplegia and aphasia during left-hemisphere anesthesia. Neurology. 1995;45(1):65–7.
10. Vocat R. L'anosognosie de l'hémiplégie, un siècle de recherches. Sarrebruck: Editions Universitaires Européennes; 2010.
11. Jenkinson PM, Preston C, Ellis SJ. Unawareness after stroke: a review and practical guide to understanding, assessing, and managing anosognosia for hemiplegia. J Clin Exp Neuropsychol. 2011;33(10):1079–93.
12. Anton G. Ueber Herderkrankungen des Gehirns, welche vom Patienten selbst nicht wahrgenommen werden. Wien Klin Wochenschr. 1898;11:227–9.
13. Anton G. Ueber die Selbstwahrnehmung der Herderkrankungen des Gehirns durch den Kranken bei Rindenbleiheit und Rindentaubheit. Arch Psychiatr Nervenkrankenheiten. 1899;32:86–127.
14. Von Monakow C. Experimentelle und pathologisch-anatomische Untersuchungen über die Beziehungen der sogenannten Sehphäre zu den infrakortikalen Opticuscentren und zum N. opticus. Arch Psychiatr Nervenkrankenheiten. 1885;16:151–99.
15. Angelergues R, de Ajuriaguerra J, Hécaen H. La négation de la cécité au cours des lésions cérébrales. Journal de Psycholgie Normale et Pathologique. 1960;57(4):381–404.
16. Cappellari M, Tomelleri G, Di Matteo A, et al. Dide-Botcazo syndrome due to bilateral occlusion of posterior cerebral artery. Neurol Sci. 2010;31(1):99–101.
17. Bergman PS. Cerebral blindness; an analysis of twelve cases, with especial reference to the electroencephalogram and patterns of recovery. AMA Arch Neurol Psychiatry. 1957;78(6):568–84.
18. Marshall RC, Tompkins CA. Verbal self-correction behaviors of fluent and nonfluent aphasic subjects. Brain Lang. 1982;15:292–306.
19. Wepman JM. The relationship between self-correction and recovery from aphasia. J Speech Hear Disord. 1958;23:302–5.
20. Seron X, van der Kaa MA, Remitz A, van der Linden M. Pantomime interpretation and aphasia. Neuropsychologia. 1979;17(6):661–8.
21. Spinazzola L, Pia L, Folegatti A, Marchetti C, Berti A. Modular structure of awareness for sensorimotor disorders: evidence from anosognosia for hemiplegia and anosognosia for hemianaesthesia. Neuropsychologia. 2008;46(3):915–26.

22. Weinstein EA, Kahn RL. The syndrome of anosognosia. AMA Arch Neurol Psychiatry (Chicago). 1950;64(6):772–91.
23. Van der Linden M, Bruyer R. Memory disorders and symptoms of frontal dysfunction in 29 patients operated on for an aneurysm of the anterior communicating artery. Acta Neurol Belg. 1992;92(5):255–77.
24. Schnider A, von Daniken C, Gutbrod K. The mechanisms of spontaneous and provoked confabulations. Brain. 1996;119(Pt 4):1365–75.
25. Milner B, Corkin S, Teuber HL. Further analysis of the hippocampal amnesic syndrome: 14 years follow-up study of HM. Neuropsychologia. 1968;6(3):215–34.
26. McGlynn SM, Schacter DL. Unawareness of deficits in neuropsychological syndromes. J Clin Exp Neuropsychol. 1989;11(2):143–205.
27. Kopelman MD, Wilson BA, Baddeley AD. The autobiographical memory interview: a new assessment of autobiographical and personal semantic memory in amnesic patients. J Clin Exp Neuropsychol. 1989;11(5):724–44.
28. Westmacott R, Freedman M, Black SE, Stokes KA, Moscovitch M. Temporally graded semantic memory loss in Alzheimer's disease: cross-sectional and longitudinal studies. Cogn Neuropsychol. 2004;21(2):353–78.
29. Mograbi DC, Brown RG, Morris RG. Anosognosia in Alzheimer's disease – the petrified self. Conscious Cogn. 2009;18(4):989–1003.
30. Rosen HJ. Anosognosia in neurodegenerative disease. Neurocase. 2011;17(3):231–41.
31. Stern RA, White T. Neuropsychological Assessment Battery (NAB). Lutz: Psychological Assessment Resources, Inc.; 2003.
32. Williamson C, Alcantar O, Rothlind J, Cahn-Weiner D, Miller BL, Rosen HJ. Standardised measurement of self-awareness deficits in FTD and AD. J Neurol Neurosurg Psychiatry. 2009;81(2):140–5.
33. Mangone CA, Hier DB, Gorelick PB, Ganellen RJ, et al. Impaired insight in Alzheimer's disease. J Geriatr Psychiatry Neurol. 1991;4(4):189–93.
34. Lopez OL, Becker JT, Somsak D, Dew MA, DeKosky ST. Awareness of cognitive deficits and anosognosia in probable Alzheimer's disease. Eur Neurol. 1994;34(5):277–82.
35. Hoefer M, Allison SC, Schauer GF, et al. Fear conditioning in frontotemporal lobar degeneration and Alzheimer's disease. Brain. 2008;131(Pt 6):1646–57.
36. Kim EJ, Rabinovici GD, Seeley WW, et al. Patterns of MRI atrophy in tau positive and ubiquitin positive frontotemporal lobar degeneration. J Neurol Neurosurg Psychiatry. 2007;78(12):1375–8.
37. Battersby WS, Bender MB, Pollack M, Kahn RL. Unilateral spatial agnosia (inattention) in patients with cerebral lesions. Brain. 1956;79(1):68–93.
38. Bisiach E, Geminiani G. Anosognosia related to hemiplegia and hemianopia. In: Prigatano GP, Schacter DL, editors. Awareness of deficit after brain injury: clinical and theoretical issues. New York: Oxford University Press; 1991. p. 17–39.
39. Bisiach E, Vallar G, Perani D, Papagno C, Berti A. Unawareness of disease following lesions of the right hemisphere: anosognosia for hemiplegia and anosognosia for hemianopia. Neuropsychologia. 1986;24(4):471–82.
40. Cobb S. Amnesia for the left limbs developing into anosognosia. Bull Los Angel Neuro Soc. 1947;12:48–52.
41. Von Hagen KO, Ives ER. Anosognosia (Babinski) imperception of hemiplegia: report of six cases, one with autopsy. Bull Los Angel Neuro Soc. 1937;2:95–103.
42. Waldenstrom J. On anosognosia. Acta Psychiatr Neurol (Kjobenhavn). 1939;14:215–20.
43. Warrington EK. The completion of visual forms across hemianopic field defects. J Neurol Neurosurg Psychiatry. 1962;25:208–17.
44. Flashman LA, Green MF. Review of cognition and brain structure in schizophrenia: profiles, longitudinal course, and effects of treatment. Psychiatr Clin North Am. 2004;27(1):1–18, vii.
45. Frith J, Knowlden S. Undifferentiated illness. Med J Aust. 1992;156(7):472–6.
46. Flashman LA, McAllister TW, Johnson SC, Rick JH, Green RL, Saykin AJ. Specific frontal lobe subregions correlated with unawareness of illness in schizophrenia: a preliminary study. J Neuropsychiatry Clin Neurosci. 2001;13(2):255–7.

47. Shad MU, Muddasani S, Prasad K, Sweeney JA, Keshavan MS. Insight and prefrontal cortex in first-episode Schizophrenia. Neuroimage. 2004;22(3):1315–20.
48. Amador XF, Strauss DH, Yale SA, Flaum MM, Endicott J, Gorman JM. Assessment of insight in psychosis [see comments]. Am J Psychiatry. 1993;150(6):873–9.
49. Shad MU, Tamminga CA, Cullum M, Haas GL, Keshavan MS. Insight and frontal cortical function in schizophrenia: a review. Schizophr Res. 2006;86(1–3):54–70.
50. Babinski J. Contribution a l'étude des troubles mentaux dans l'hémiplégie organique (anosognosie). Rev Neurol. 1914;27:845–8.
51. Orfei MD, Robinson RG, Prigatano GP, et al. Anosognosia for hemiplegia after stroke is a multifaceted phenomenon: a systematic review of the literature. Brain. 2007;130(Pt 12):3075–90.
52. Jenkinson PM, Fotopoulou A. Motor awareness in anosognosia for hemiplegia: experiments at last! Exp Brain Res. 2010;204(3):295–304.
53. Levine DN. Unawareness of visual and sensorimotor defects: a hypothesis. Brain Cogn. 1990;13(2):233–81.
54. Bakchine S, Crassard I, Seilhan D. Anosognosia for hemiplegia after a brainstem haematoma: a pathological case. J Neurol Neurosurg Psychiatry. 1998;63:686–7.
55. Nardone IB, Ward R, Fotopoulou A, Turnbull OH. Attention and emotion in anosognosia: evidence of implicit awareness and repression? Neurocase. 2007;13(5):438–45.
56. Feinberg TE. Anosognosia and confabulation. In: Feinberg TE, Farah MJ, editors. Behavioral neurology and neuropsychology. New York: McGraw-Hill; 1997. p. 369–90.
57. Starkstein SE, Fedoroff JP, Price TR, Leiguarda R, Robinson RG. Anosognosia in patients with cerebrovascular lesions: a study of causative factors. Stroke. 1992;23:1446–53.
58. Schacter DL. Unawareness of deficit and unawareness of knowledge in patients with memory disorders. In: Prigatano GP, Schacter DL, editors. Awareness of deficit after brain injury: clinical and theoretical issues. New York: Oxford University Press; 1991. p. 126–51.
59. Gold M, Adair JC, Jacobs DH, Heilman KM. Anosognosia for hemiplegia: an electrophysiologic investigation of the feed-forward hypothesis. Neurology. 1994;44(10):1804–8.
60. Heilman KM, Barrett AM, Adair JC. Possible mechanisms of anosognosia: a defect in self-awareness. Philos Trans R Soc Lond B Biol Sci. 1998;353(1377):1903–9.
61. Frith CD, Blakemore SJ, Wolpert DM. Abnormalities in the awareness and control of action. Philos Trans R Soc Lond B Biol Sci. 2000;355(1404):1771–88.
62. Spinazzola L, Pia L, Folegatti A, Marchetti C, Berti A. Modular structure of awareness for sensorimotor disorders: evidence from anosognosia for hemiplegia and anosognosia for hemianaesthesia. Neuropsychologia. 2008;46(3):915–26.
63. Marcel AJ, Tegner R, Nimmo-Smith I. Anosognosia for plegia: specificity, extension, partiality and disunity of bodily unawareness. Cortex. 2004;40(1):19–40.
64. Davies M, Davies AA, Coltheart M. Anosognosia and the two-factor theory of delusions. Mind Lang. 2005;20(2):209–36.
65. Prigatano GP. Anosognosia: clinical and ethical considerations. Curr Opin Neurol. 2009;22(6):606–11.
66. Starkstein SE, Jorge RE, Robinson RG. The frequency, clinical correlates, and mechanism of anosognosia after stroke. Can J Psychiatry. 2010;55(6):355–61.
67. Halligan PW, Marshall JC. The wise prophet makes sure of the event first: hallucinations, amnesia, and delusions. In: Halligan PW, Marshall JC, editors. Method in madness: cases studies in cognitive neuropsychiatry. Hove: Psychology Press; 1996. p. 237–66.
68. Vocat R, Staub F, Stroppini T, Vuilleumier P. Anosognosia for hemiplegia: a clinical-anatomical prospective study. Brain. 2010;133(Pt 12):3578–97.
69. Bates E, Wilson SM, Saygin AP, et al. Voxel-based lesion-symptom mapping. Nat Neurosci. 2003;6(5):448–50.
70. Verdon V, Schwartz S, Lovblad KO, Hauert CA, Vuilleumier P. Neuroanatomy of hemispatial neglect and its functional components: a study using voxel-based lesion-symptom mapping. Brain. 2010;133(Pt 3):880–94.

71. Bisiach E, Perani D, Vallar G, Berti A. Unilateral neglect: personal and extra-personal. Neuropsychologia. 1986;24(6):759–67.
72. Feinberg TE, Roane DM, Ali J. Illusory limb movements in anosognosia for hemiplegia. J Neurol Neurosurg Psychiatry. 2000;68(4):511–3.
73. Cutting J. Study of anosognosia. J Neurol Neurosurg Psychiatry. 1978;41(6):548–55.
74. Nathanson M, Bergman PS, Gordon CG. Denial of illness: its occurrence in one hundred consecutive cases of hemiplegia. Arch Neurol Psychiatry. 1952;68:380–7.
75. Herzberg PY, Glaesmer H, Hoyer J. Separating optimism and pessimism: a robust psychometric analysis of the revised Life Orientation Test (LOT-R). Psychol Assess. 2006;18(4):433–8.
76. Weigl E. Zur Psychologie sogenannter Abstraktionsprozesse. Z Psychol. 1927;103:2–45.
77. Azouvi P, Samuel C, Louis-Dreyfus A, et al. Sensitivity of clinical and behavioural tests of spatial neglect after right hemisphere stroke. J Neurol Neurosurg Psychiatry. 2002;73(2):160–6.
78. Berti A, Ladavas E, Della CM. Anosognosia for hemiplegia, neglect dyslexia, and drawing neglect: clinical findings and theoretical considerations. J Int Neuropsychol Soc. 1996;2(5):426–40.
79. Heilman KM. Anosognosia: possible neuropsychological mechanisms. In: Prigatano GP, Schacter DL, editors. Awareness of deficit after brain injury: clinical and theoretical issues. New York: Oxford University Press; 1991. p. 53–62.
80. Feinberg TE, Haber LD, Leeds NE. Verbal asomatognosia. Neurology. 1990;40:1391–4.
81. Berti A, Bottini G, Gandola M, et al. Shared cortical anatomy for motor awareness and motor control. Science. 2005;309(5733):488–91.
82. Karnath HO, Baier B. Right insula for our sense of limb ownership and self-awareness of actions. Brain Struct Funct. 2010;214(5–6):411–7.
83. Karnath HO, Baier B, Nagele T. Awareness of the functioning of one's own limbs mediated by the insular cortex? J Neurosci. 2005;25(31):7134–8.
84. Karnath HO, Fruhmann Berger M, Kuker W, Rorden C. The anatomy of spatial neglect based on voxelwise statistical analysis: a study of 140 patients. Cereb Cortex. 2004;14(10):1164–72.
85. Mort DJ, Malhotra P, Mannan SK, et al. The anatomy of visual neglect. Brain. 2003;126(Pt 9):1986–97.
86. Gerstmann J. Problems of imperception of disease and of impaired body territories with organic lesions: relation to body scheme and its disorders. Arch Neurol Psychiatry. 1942;48:890–913.
87. Fotopoulou A, Tsakiris M, Haggard P, Vagopoulou A, Rudd A, Kopelman M. The role of motor intention in motor awareness: an experimental study on anosognosia for hemiplegia. Brain. 2008;131(Pt 12):3432–42.
88. Farrer C, Frith CD. Experiencing oneself vs another person as being the cause of an action: the neural correlates of the experience of agency. Neuroimage. 2002;15(3):596–603.
89. Craig AD. How do you feel – now? The anterior insula and human awareness. Nat Rev Neurosci. 2009;10(1):59–70.
90. Harris S, Sheth SA, Cohen MS. Functional neuroimaging of belief, disbelief, and uncertainty. Ann Neurol. 2008;63(2):141–7.
91. Pourtois G, Vocat R, N'Diaye K, Spinelli L, Seeck M, Vuilleumier P. Errors recruit both cognitive and emotional monitoring systems: simultaneous intracranial recordings in the dorsal anterior cingulate gyrus and amygdala combined with fMRI. Neuropsychologia. 2010;48(4):1144–59.
92. Singer T, Critchley HD, Preuschoff K. A common role of insula in feelings, empathy and uncertainty. Trends Cogn Sci. 2009;13(8):334–40.
93. Ullsperger M, Harsay HA, Wessel JR, Ridderinkhof KR. Conscious perception of errors and its relation to the anterior insula. Brain Struct Funct. 2010;214(5–6):629–43.
94. Vocat R, Pourtois G, Vuilleumier P. Unavoidable errors: a spatio-temporal analysis of time-course and neural sources of evoked potentials associated with error processing in a speeded task. Neuropsychologia. 2008;46(10):2545–55.

95. Dolan RJ, Vuilleumier P. Amygdala automaticity in emotional processing. Ann N Y Acad Sci. 2003;985:348–55.
96. Sander D, Grafman J, Zalla T. The human amygdala: an evolved system for relevance detection. Rev Neurosci. 2003;14(4):303–16.
97. Vocat R, Saj A, Vuilleumier P. The riddle of anosognosia: does unawareness of hemiplegia involve a failure to update beliefs? Cortex. 2012.
98. Jenkinson PM, Edelstyn NM, Drakeford JL, Ellis SJ. Reality monitoring in anosognosia for hemiplegia. Conscious Cogn. 2009;18(2):458–70.
99. Cocchini G, Beschin N, Fotopoulou A, Della Sala S. Explicit and implicit anosognosia or upper limb motor impairment. Neuropsychologia. 2010;48(5):1489–94.
100. Ramachandran VS. The evolutionary biology of self-deception, laughter, dreaming and depression: some clues from anosognosia. Med Hypotheses. 1996;47(5):347–562.
101. Turnbull OH, Solms M. Awareness, desire, and false beliefs: Freud in the light of modern neuropsychology. Cortex. 2007;43(8):1083–90.
102. Nathaniel-James DA, Fletcher P, Frith CD. The functional anatomy of verbal initiation and suppression using the Hayling test. Neuropsychologia. 1997;35(4):559–66.
103. Fotopoulou A, Pernigo S, Maeda R, Rudd A, Kopelman MA. Implicit awareness in anosognosia for hemiplegia: unconscious interference without conscious re-representation. Brain. 2010;133(Pt 12):3564–77.
104. Greenwald AG, McGhee DE, Schwartz JL. Measuring individual differences in implicit cognition: the implicit association test. J Pers Soc Psychol. 1998;74(6):1464–80.
105. Cappa S, Sterzi R, Vallar G, Bisiach E. Remission of hemineglect and anosognosia during vestibular stimulation. Neuropsychologia. 1987;25(5):775–82.
106. Ramachandran VS. Anosognosia in parietal lobe syndrome. Conscious Cogn. 1995;4(1):22–51.
107. Vallar G, Sterzi R, Bottini G, Cappa S. Temporary remission of left hemianesthesia after vestibular stimulation: a sensory neglect phenomenon. Cortex. 1990;26(1):123–31.
108. Pisella L, Rode G, Farne A, Tilikete C, Rossetti Y. Prism adaptation in the rehabilitation of patients with visuo-spatial cognitive disorders. Curr Opin Neurol. 2006;19(6):534–42.
109. Fotopoulou A, Rudd A, Holmes P, Kopelman M. Self-observation reinstates motor awareness in anosognosia for hemiplegia. Neuropsychologia. 2009;47(5):1256–60.
110. Endrass T, Reuter B, Kathmann N. ERP correlates of conscious error recognition: aware and unaware errors in an antisaccade task. Eur J Neurosci. 2007;26(6):1714–20.
111. O'Connell RG, Dockree PM, Bellgrove MA, et al. The role of cingulate cortex in the detection of errors with and without awareness: a high-density electrical mapping study. Eur J Neurosci. 2007;25(8):2571–9.
112. Shalgi S, Barkan I, Deouell LY. On the positive side of error processing: error-awareness positivity revisited. Eur J Neurosci. 2009;29(7):1522–32.
113. Vocat R, Pourtois G, Vuilleumier P. Parametric modulation of error-related ERP components by the magnitude of visuo-motor mismatch. Neuropsychologia. 2011;49(3):360–7.
114. Vuilleumier P, Saj A. "Hemispatial neglect." In the behavioral and cognitive neurology of stroke. Godefroy O, (ed.), Cambridge: Cambridge University Press. 2013;126–157.

Part II
Psychiatry of Vascular Cognitive Impairment

Chapter 10
Neuropsychiatric Symptoms of CADASIL

Hugues Chabriat and Sonia Reyes

Abstract CADASIL is an inherited small artery disease caused by mutations of the NOTCH3 gene. The disease is responsible for migraine with aura at onset, for transient ischemic attacks and stroke during mid-adulthood, and can lead progressively to dementia. The neuropsychiatric manifestations of CADASIL include mood and behavior disturbances and various degrees of cognitive impairment. They are observed at all stages of the disorder. Episodes of mood disturbances (depression, manic episodes) are reported in 10–20 % of patients during the course of the disease; they are usually observed after the first ischemic events. Apathy is detected in more than one-third of patients several years after onset and alters the quality of life of patients. A marked decline of cognitive performances is detected in the vast majority of subjects with aging, particularly after age 50 years. However, executive dysfunction can be detected earlier, even after the third decade using dedicated cognitive tests. Dementia occurs after 60 years, usually after repeated ischemic event, and is nearly constant at the end stage of the disorder.

Keywords CADASIL • NOTCH3 • Apathy • Executive dysfunction • Cognitive decline • Mood disturbances • Depression • Vascular dementia

H. Chabriat (✉)
Department of Neurology, Hopital Lariboisière, APHP, Université Paris VII, Denis Diderot, 2 rue Ambroise Paré, Paris 75010, France

CERVCO, Université Paris VII, Denis Diderot, Paris, France

INSERM UMR740, Université Paris VII, Denis Diderot, Paris, France
e-mail: hugues.chabriat@lrb.aphp.fr

S. Reyes
Department of Neurology, Hopital Lariboisière, APHP, Université Paris VII, Denis Diderot, 2 rue Ambroise Paré, Paris, 75010, France

CERVCO, Université Paris VII, Denis Diderot, Paris, France

J.M. Ferro (ed.), *Neuropsychiatric Symptoms of Cerebrovascular Diseases*, Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-1-4471-2428-3_10,

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [1] is an inherited small artery disease of mid-adulthood. It is caused by mutations of the NOTCH3 gene on chromosome 19 [2]. The exact prevalence of CADASIL is unknown. The disease has been diagnosed in multiple countries on all continents. Based on a register for the disease in the west of Scotland, Ravzi et al. estimated that the prevalence of NOTCH3 gene mutation is about 4.14 per 100,000 adults in this population [3]. This frequency is probably underestimated.

CADASIL is still underdiagnosed but it appears as one of the most frequent hereditary cerebrovascular diseases. It is considered as a model of "pure" vascular dementia related to a small-vessel disease and as an archetype of the so-called subcortical ischemic vascular dementia [4]. CADASIL can be responsible for mood alterations, behavior disturbances, and cognitive impairment.

Pathophysiological Features

CADASIL is characterized by white-matter rarefaction and subcortical ischemic lesions easily detected in vivo by magnetic resonance imaging (MRI). Macroscopic examination of the cerebral tissue reveals a diffuse myelin pallor and rarefaction of hemispheric white matter usually sparing the U fibers [5]. Lesions predominate in the periventricular areas and centrum semiovale. They are associated with lacunar infarcts in the white matter and basal ganglia (lentiform nucleus, thalamus, caudate) [6, 7]. The most severe hemispheric lesions are the most profound [5, 8, 9]. In the brain stem, lesions predominate in the pons and correspond to the so-called pontine ischemic rarefaction of myelin previously reported by Pullicino et al. [10]. Small deep infarcts and dilated Virchow-Robin spaces are often associated with ischemic white-matter lesions.

In CADASIL, the wall of cerebral and leptomeningeal arterioles is thickened in association with a significant reduction of the lumen [5]. Penetrating arteries in the cortex and white matter are sometimes stenosed [11, 12]. Some inconstant features are close to those reported in patients with hypertensive encephalopathy [13] such as various degrees of duplication and splitting of internal elastic lamina, adventitial hyalinosis and fibrosis, and hypertrophy of the media. However, a distinctive feature is the presence of a granular material within the media extending into the adventitia [5, 8, 14–18]. The PAS-positive staining suggests the presence of glycoproteins within the media; the staining for amyloid substance and elastin is negative [6, 8]. By contrast, the endothelium is usually spared. Sometimes, the smooth muscle cells are not detectable and replaced by collagen fibers [13]. On electron microscopy, the smooth muscle cells appear swollen and often degenerated, some of them present with multiple nuclei. There is a granular, electron-dense, osmiophilic material

(GOM) within the media [19]. This material consists of granules of about 10–15 nm of diameter. It is localized close to the cell membrane of smooth muscle cells. The smooth muscle cells are often separated by large amounts of this material.

CADASIL is caused by stereotyped mutations of the NOTCH3 gene [2]. Unlike other members of the Notch gene family whose expression is ubiquitous, the NOTCH3 gene is expressed only in vascular smooth muscle cells [20] of arterial vessels [21]. It encodes a single pass transmembrane receptor of 2,321 amino acids protein, with an extracellular domain containing 34 EGF repeats (including 6 cysteine residues) and 3 Lin repeats associated with intracellular and transmembrane domains [2, 22]. This cell surface receptor is mediating signal transduction with receptor ligands such as Jagged (Jag) and Delta (D) on neighboring cells which are also type 1 transmembrane receptors [2, 23–25]. The NOTCH3 gene is required to generate functional arteries in mice and is involved in arterial differentiation and maturation of vascular smooth muscle cells [26]. The stereotyped missense mutations [2] or deletions [20] responsible for CADASIL are within epidermal-growth-factor-like (EGF-like) repeats and only located in the extracellular domain of the NOTCH3 protein [23, 27, 28]. All mutations responsible for the disease lead to an uneven number of cysteine residues.

The NOTCH3 protein usually undergoes complex proteolytic cleavages leading to an extracellular and a transmembrane fragment. These two fragments form a heterodimer at the cell surface of smooth muscle cells. In CADASIL, the ectodomain of the NOTCH3 receptor accumulates within the vessel wall of affected subjects [20]. This accumulation is found near but not within the characteristic granular osmiophilic material on electron microscopy. It is observed in all vascular smooth muscle cells and in pericytes within all organs (brain, heart, muscles, lungs, skin). An abnormal clearance of the NOTCH3 ectodomain from the smooth muscle cell surface is presumed to be responsible for this accumulation [20, 29].

Vascular abnormalities observed in the brain are also present in other organs [6, 8]. The GOM surrounding smooth muscle cells is also present in the media of arteries located in the spleen, liver, kidneys, muscle, and skin and also in the wall of carotid and aortic arteries [6, 8, 30]. These vascular lesions can be detected by nerve or muscle biopsy [31, 32]. The presence of the GOM in the skin vessels has been used to confirm the intravitam diagnosis of CADASIL using punch skin biopsies [8, 33–36].

Transgenic mice expressing mutant NOTCH3 develop vascular alterations characteristic of CADASIL [37]. Impaired autoregulation of cerebral blood flow has been detected in these mice with a decreased relaxation or increased resistance of cerebral vessels [38]. In addition, flow-induced dilation was significantly decreased and pressure-induced myogenic tone significantly increased in these arteries suggestive of impaired vascular mechanotransduction [39]. Recent data support that alterations of cerebrovascular autoregulation and of functional hyperemia occur parallel to a significant reduction of capillary density in the cerebral tissue early and before the appearance of visible structural changes within the vessel wall. These changes are presumably responsible for white-matter hypoperfusion detected at the onset of the disease [40].

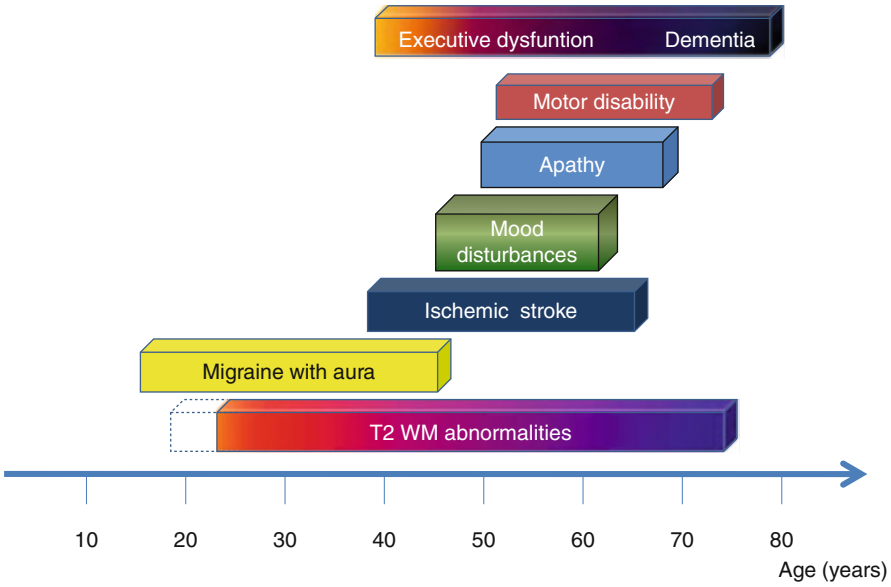


Fig. 10.1 Natural history with the main clinical manifestations of CADASIL

Neuropsychiatric Symptoms

Neuropsychiatric manifestations include mood and behavior disturbances and various degrees of cognitive impairment [41]. They can be observed at all stages of the disorder. Episodes of mood disturbances are reported in 10–20 % of patients during the course of the disease [42, 43]. Apathy is detected in more than one-third of patients. A marked decline of cognitive performances is detected in the vast majority of subjects with aging, particularly after age 50 years. Dementia is mostly observed after 60 years and appears nearly constant at the end stage of the disorder [34, 42, 44] (Fig. 10.1).

Mood Disturbances

About one-fifth of CADASIL patients experienced episodes of mood disturbances. Their frequency is widely variable among families [43, 45].

Episodes of major depression are reported by 10 % of 80 CADASIL patients investigated by Peters et al. [46]. In some cases, antidepressive drugs were found inefficient to relieve symptoms during the most severe episodes. Severe depression of the melancholic type alternating with typical manic episodes and suggesting bipolar mood disorder has been reported in few cases [47] although the NOTCH3 gene was not found involved in familial forms of bipolar disorder [48].

The location of ischemic lesions in basal ganglia and the frontal location of white-matter lesions may play a key role in the occurrence of such mood disturbances [49]. Recently, Brookes has shown that depression was a major predictor of quality of life in patients with small-vessel disease including patients with CADASIL [50].

Most often, psychiatric manifestations are observed in patients after diagnosis and with a history of ischemic symptoms and signal abnormalities at MRI examination. However, these episodes can be inaugural in some patients and may lead to misdiagnosis [43, 45, 51]. Leyhe et al. recently reported two cases admitted to a geronto-psychiatric hospital with psychopathological manifestations at the onset of the disorder [52]. The first case was a 66-year-old man who was described as a reserved, peaceful, and calm person and who became irritable, started to neglect himself and his duties, and presented a submanic episode mildly improved after a treatment with neuroleptic drugs. The patient started again to consume alcohol after years of abstinence. The second case was a 62-year-old woman with a 2-year episode of depressive symptoms who was initially successfully treated by amitriptyline. She was admitted to the hospital because she deteriorated despite medication with paranoid ideas and became melancholic. The psychopathological symptoms slowly improved under a combination of antidepressive, anxiolytic drugs and neuroleptics. In both cases, MRI results and the family history were essential for diagnosis.

Apathy and Other Psychiatric Manifestations

Apathy is defined as a lack of motivation [53, 54], but it can be also defined as a quantitative reduction of voluntary (or goal-directed) behavior [55]. Apathetic patients may also present with reduced interest in their environment, indifference, flattening of affect, or lack of emotional reactivity [56, 57]. Apathy is frequent and detected in 40 % of CADASIL patients [58]. This frequency is close to that reported in other subcortical disorders also involving basal ganglia such as Parkinson's or Huntington's disease. Reyes et al. observed that the presence of apathy can result in a reduction of quality of life independently of cognitive status and depression during the course of the disease [58].

Apathy is frequently associated with other neuropsychiatric symptoms in CADASIL. In a recent study, 94 % of apathetic patients had at least one other behavioral disturbance [58]. Irritability and depression were detected using NPI in two-thirds of apathetic patients; agitation or aggressive behavior is observed in half of them. This association may be explained by the fact that apathy is also considered as a potential manifestation of depression. Depressed patients can also show a loss of motivation, lack of goals and perspectives, and may even have anhedonia. However, nearly 40 % of apathetic patients with CADASIL are also found without depression, in agreement with distinct mechanisms underlying depression and apathy.

Apathy is also detected more frequently in presence of cognitive impairment and dementia in CADASIL. Men, older patients, and those with abnormal gait are also more likely to be apathetic than the others. The burden of subcortical MRI lesions seems involved in the occurrence of this symptom as reported for cognitive impairment.

Apathy has been reported in neurodegenerative diseases affecting the gray matter of basal ganglia [35]. In CADASIL, lacunar lesions most commonly occur in basal ganglia, thalamus, brain stem, and frontal and parietal white-matter regions [22]. Thus, damage of striato-cortical circuits linking such gray-matter areas to frontal cortical regions can result from white-matter tract damage or to ischemic infarctions in this disorder [36]. In CADASIL, although apathy was found associated with a large burden of subcortical ischemic lesions, it can be also detected in the presence of only few subcortical lesions and at an early stage of the disease in few cases. Therefore, the location of subcortical lesions may actually play a key role in the occurrence of this symptom. Jouvent et al. recently observed that apathy is related to the depth of the posterior cingulate cortical sulcus as well as with the depth and width of cortical sulci in mediofrontal and orbitofrontal areas in CADASIL [59]. These morphological changes presumably result from secondary degenerative processes occurring after the accumulation of subcortical lesions.

A large variety of other psychiatric manifestations can occur in CADASIL patients. Agoraphobia, addiction to alcohol, and psychotic pictures have been reported in affected individuals [42, 43, 60]. In the analysis performed by Reyes et al. in 132 CADASIL patients, the most frequent neuropsychiatric manifestations included irritability reported in 43 % of patients, anxiety in 37 %, and disinhibition and/or euphoria in about 10 %. Sleep difficulties are also frequently reported in CADASIL patients (40 %). In contrast, delusions and hallucinations appear exceptional [61]. The observation of schizophrenia in association with CADASIL is only anecdotal [62].

Cognitive Impairment

Symptomatic patients can remain several years without any neuropsychological decline [63]. However, cognitive impairment and dementia represent the second commonest clinical manifestation in CADASIL after acute ischemic symptoms.

The onset of cognitive deficit is usually mild and insidious and its exact time is often difficult to ascertain [41]. The cognitive changes may appear a long time before TIAs or stroke [64]. Cross-sectional studies [65–68] have shown that cognitive functions may be impaired early, most frequently attention and executive functions. In 42 patients, attention and executive functions were found to be affected in nearly 90 % of patients of age between 35 and 50 [68]. These disturbances are often associated with alterations in attention and memory suggestive of dysfunction within the subcortical-frontal network [46, 68, 69]. In contrast, others functions

such as verbal episodic memory and visuospatial abilities are usually preserved and may remain spared till late stages of the disease.

Some tests are particularly sensitive to the detection of early cognitive changes. They include the digit span backwards and forwards, the Trail-Making Test B, the Stroop test, and the Wisconsin Card Sorting Test. The errors of CADASIL patients often affect time measures in timed tasks (Stroop, Trail-Making Test, symbol digit, digit cancellation) though errors in monitoring can be also detected [67]. Patients may also show poor strategy and planning when completing tasks such as the Wisconsin Card Sorting Test and the Rey-Osterrieth memory test. Memory deficit may be associated with executive dysfunction, but its profile is usually distinct from dementia primarily involving the mesiotemporal cortex such as Alzheimer's disease. The Free and Cued Selective Reminding Test allowing differentiating different phases of memory processes can be used to show the preservation of the encoding process even though the retrieval is impaired. It is composed of (1) an encoding phase where 16 words belonging to 16 different semantic categories have to be retrieved, (2) three phases of free recall and cued recall (the last being delayed), and (3) a recognition test. In CADASIL, this test distinguishes a typical "subcortical" pattern characterized by low scores in immediate and delayed free recall, improving with cues and associated with relatively intact recognition. Intrusions may occur in the free recall task. This profile, still observed in two-thirds of demented patients, supports a usual preservation of the encoding process and anatomically of the mesiotemporal cortex in CADASIL [68]. Among 140 patients, Epelbaum et al. observed that one-third of CADASIL patients presented with various degrees of memory impairment, most of them with a typical "subcortical" profile. However, one-fifth of patients with memory impairment in their series presented with a typical amnestic syndrome of hippocampal type [70]. While alterations in spontaneous recall were found to be related to the severity of subcortical ischemic lesions, the profile of memory impairment, particularly the sensitivity to cueing, was found related to hippocampal atrophy that may occur in CADASIL [70].

With aging, the cognitive decline becomes more homogenous with significant changes in all cognitive domains. This extension cannot be ascribed to only the sole deterioration of executive performances but appears actually related to additional alterations in instrumental activities, language, and visuospatial abilities and suggests a diffuse cortical dysfunction well beyond the subcortical-frontal circuits [68]. The development of cognitive impairment appears sometimes associated with the occurrence of stroke. Nevertheless, a cognitive deficit and even dementia may also occur in patients without any clinical history of stroke. The cognitive profile of CADASIL patients was analyzed before and after the occurrence of strokes in two cross-sectional studies and showed some discrepant results. Amberla et al. [66] reported that executive functions were more widely affected with a significant mental slowing in CADASIL patients having a positive history of stroke. Conversely, Buffon et al. observed that visuospatial abilities were mostly impaired in patients with a positive history of stroke [68]. The cognitive deficit most often progresses in the total absence of ischemic events, mimicking in some cases a degenerative dementia [71, 72]. The temporal progression of cognitive symptoms varies among

subjects from rapid and marked deterioration to stable or even slightly improving performances [73].

Dementia is reported in one-third of symptomatic patients at the late phase of the disorder. The frequency of dementia increases considerably with age. Thus, about 60 % of patients older than 60 years are demented and more than 80 % of deceased subjects were reported to be demented before death. When dementia is present, the neuropsychological deficit is usually extensive [68]. Dementia is often associated with apathy. Conversely, severe aphasia, apraxia, and agnosia are rare [46, 68]. In addition, demented individuals have a relative preservation of recognition and semantic memory [68]. Noteworthily, as previously stated, two-thirds of them present improvement of memory with cues which suggests that the encoding process is preserved in most cases even at the late stage of the disease in contrast with the pattern of memory impairment in Alzheimer's disease . Dementia is observed in the absence of any other clinical manifestations in 10 % of cases [68]. The frequency and severity of cognitive decline are variable in different members of a given family. The variable location and severity of cerebral tissue damage may play a key role in this variability [74, 75].

Dementia is always associated with pyramidal signs. Gait difficulties are present in 90 %, urinary incontinence in 80–90 %, and pseudobulbar palsy in half of demented individuals. At the end stage of the disorder, CADASIL patients become bedridden. In a large retrospective study of 411 patients, Opherk et al. found that the median age at onset for inability to walk without assistance was 59 years in men and 62 in women, and for bedriddenness, 62 years in men and 66.5 years in women. The gender effect on disability has been confirmed recently in a large population of patients [76]. Together with aging and the evolution of the disease, after the sixth decade, two-thirds of patients older are demented [42] and more than 80 % of deceased subjects were reported to be demented before death [43].

Correlations with Cerebral Tissue Lesions

MRI is always abnormal in CADASIL patients with neurological symptoms other than migraine attacks [41]. MRI signal abnormalities can also be detected during a presymptomatic period of variable duration. They are observed as early as 20 years of age. After age 35, all subjects having the affected gene have an abnormal MRI [41]. The frequency of asymptomatic subjects with abnormal MRI decreases progressively with aging and becomes less than 5 % after 60 years [69].

MRI shows on T2-weighted images widespread areas of increased signal in the white matter (Fig. 10.2) associated with focal hyperintensities in basal ganglia, thalamus, and brain stem [69, 77]. The extent of white-matter signal abnormalities is highly variable. It increases dramatically with age. In subjects of age under 40 years, T2 hypersignals are usually punctate or nodular with a symmetrical distribution and predominate in periventricular areas and within the centrum semiovale. Later in life, white-matter lesions are diffuse and can involve the whole of white

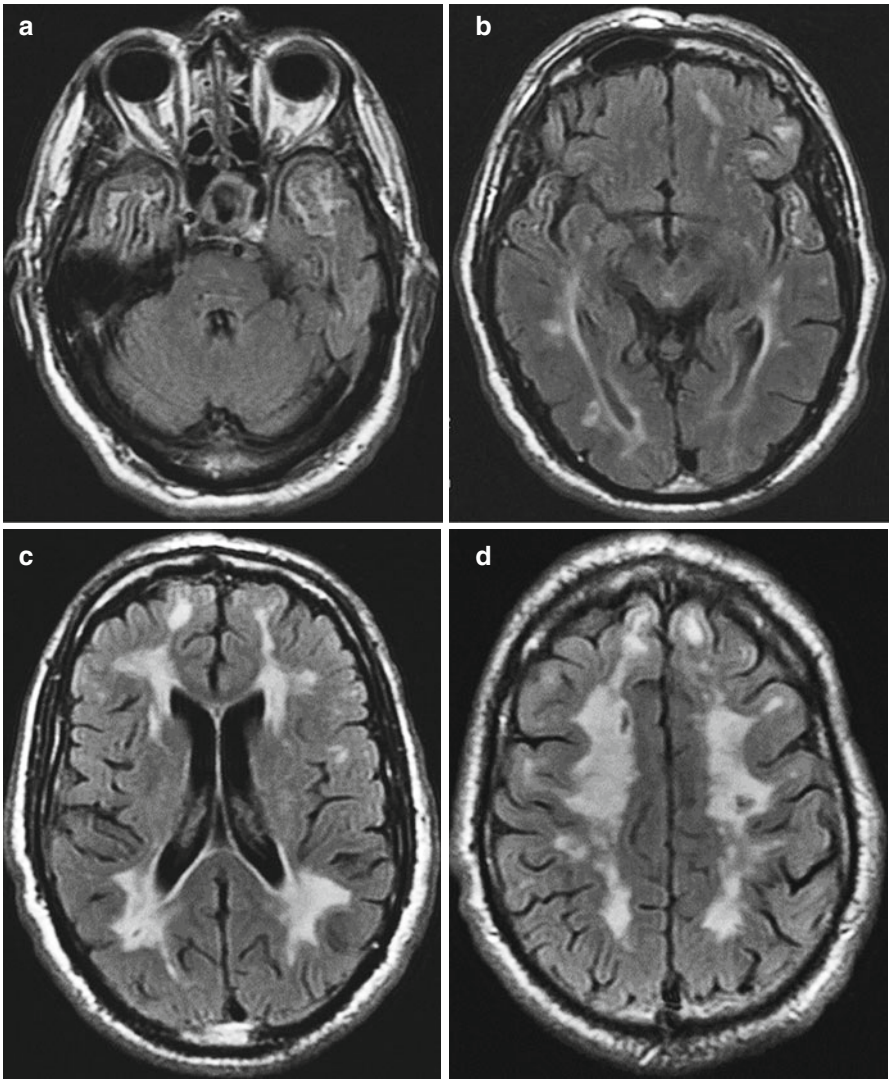


Fig. 10.2 Magnetic resonance flair images showing widespread T2 hyperintensities in the white matter in a CADASIL patient (from cerebellar level (**a**) to the level of centrum semiovale (**d**)). Note the involvement of the white matter of both temporal lobes in their anterior part with multiple punctiform juxtacortical hypointensities related to dilated perivascular spaces. Note also the involvement of the anterior frontal white matter at the highest level often detected in CADASIL

matter including the U fibers under the cortex [69, 77–79]. Scores of severity based on semiquantitative rating scales significantly increase with age not only in the white matter but also in basal ganglia and brain stem. Frontal and occipital periventricular lesions are constant when MRI is abnormal. The frequency of signal abnormalities in the external capsule (two-thirds of the cases) and in the anterior part of

the temporal lobes (60 %) is noteworthy and particularly useful for differential diagnosis with other small-vessel diseases [80–82]. T2 hyperintensities can be detected in the corpus callosum [79, 83]. Brain stem lesions predominate in the pons in areas irrigated by perforating arteries and can involve the mesencephalon [78]. In contrast, the medulla is usually spared.

On T1-weighted images, punctiform or larger focal hypointensities are frequent in the same areas and detected in about two-thirds of individuals with T2 hyperintensities [69]. They are observed both in the white matter and basal ganglia but also in the brain stem and correspond mostly to lacunar infarctions. Numerous hypointensities on T1-weighted images may also correspond to Virchow-Robin spaces which are more frequent and extensive in CADASIL than in healthy subjects. MRI signal abnormalities within the temporal white matter in CADASIL and particularly within the subcortical white matter are considered as a characteristic feature of the disease. They are also caused by a distension of the perivascular space of perforating arteries at the level of the junction of gray and white matter and by spongiosis in the surrounding parenchyma [84].

In contrast with the extent of white-matter hyperintensities weakly associated with the clinical severity [67], the degree of white-matter microstructural damage measured with diffusion tensor imaging appears strongly related to the clinical status in CADASIL [78]. This is in agreement with the correlations observed between the clinical status and the load of T1 lesions within the white matter which suggests that the degree of tissue destruction or neuronal loss is crucial for the appearance of disability in CADASIL [74, 78, 85].

The exact mechanisms of cognitive dysfunction in CADASIL remain unknown. The main hypothesis is that accumulation of subcortical lesions may damage particularly the striato-cortical circuits linking basal ganglia to frontal cortical areas with possible secondary cortical degeneration [74]. This hypothesis is supported by evidence of strong correlations between cortical atrophy and cognitive decline in the disease in both imaging and neuropathological studies. As described previously, severe cortical metabolic depression has indeed been observed by PET study in association with basal ganglia and thalamic infarcts [86]. The postmortem brain examination of a CADASIL case previously showed evidence of a diffuse loss of cortical neurons associated with cholinergic denervation [87]. Viswanathan et al. reported the presence of widespread neuronal apoptosis in the cerebral cortex of 4 CADASIL patients. Semiquantitative analysis suggested that the degree of cortical neuronal apoptosis was related to the extent of white-matter lesions and to the intensity of axonal damage in subcortical areas [88] and was associated with the severity of cognitive impairment. Therefore, subcortical axonal damage may induce cortical apoptosis through deafferentation and/or retrograde neuronal degeneration in CADASIL [89].

Disruption of cortical connections may affect striato-cortical circuits relaying in the thalamus and basal ganglia as well as cortical networks. This is supported by DTI findings showing a strong correlation between mean diffusivity measured in the thalamus and executive dysfunction [90] and between executive performances and mean diffusivity in the anteroposterior fasciculus of the cingulum bundle which

connects the dorsolateral prefrontal lobe with more posterior cortical regions including the hippocampal formation [91]. There is now accumulating evidence showing that the location of subcortical lesions and the corresponding remote consequences at the cortex level are of key importance in the pathophysiology of cognitive symptoms in CADASIL. Duering recently illustrated the impact of lesions in the anterior thalamic radiation on processing speed in CADASIL patients using a voxel-based lesion-symptom mapping approach [92]. Morphological cortical changes were also found to progress parallel to clinical worsening with the accumulation of subcortical lesions in line with this hypothesis [93].

Other Neurological Symptoms

The earliest clinical manifestations in CADASIL are attacks of migraine with aura occurring between age 20 and 40 years [34, 42, 44]. They are reported by 20–30 % of patients. In contrast with migraine without aura whose frequency is identical to that estimated in the general population, migraine with aura is reported in 20–40 % of CADASIL patients, a frequency 4–5-fold higher than in the general population. Among pedigrees, this frequency appears extremely variable. The mean age at onset is between 28 and 30 years [44, 94] with a large range from 6 to 48 years. In the largest series of Vahedi et al., the frequency of attacks appears extremely variable among affected individuals, from 2 per week to one to every 3–4 years [94]. Triggering factors of migraine with aura are similar to those of migraine in the general population (stress, flashing lights, fatigue, physical exercise, head trauma, strong smells…) [94] The most frequent symptoms are visual, sensory, or aphasic. Motor symptoms are reported in one-fifth of CADASIL patients who have attacks of migraine with aura. In contrast with the aura symptoms reported in the general population, more than half of patients have a history of atypical aura such as basilar, hemiplegic, or prolonged aura. A few patients even suffer from severe attacks with unusual symptoms such as confusion, fever, meningitis, or coma, exceptionally reported in migraine with aura [95–97].

Ischemic manifestations are the most frequent clinical manifestations: 60–85 % of patients have had transient ischemic attacks (TIAs) or completed strokes [42, 43, 98, 99]. They occur at a mean age of 45–50 years (extreme limits from 20 to 70 years) [17, 34, 42, 43]. Age of onset does not differ between men and women. In a follow-up study, Peters et al. estimated the incidence rate of stroke at 10.4 per 100 person-years [73]. Two-thirds of them are classical lacunar syndromes: pure motor stroke, ataxic hemiparesis, pure sensory stroke, sensorimotor stroke [43]. Other focal neurologic deficits of abrupt onset are less frequent: dysarthria either isolated or associated with motor or sensory deficit, monoparesis, paresthesia of one limb, isolated ataxia, nonfluent aphasia, hemianopia [43].

Five to 10 % of CADASIL patients experienced seizures, either focal or generalized [17, 42, 100]. They are usually reported in patients with a positive history of stroke. Epilepsy is usually well controlled by

Other neurological manifestations have occasionally been reported in CADASIL. Parkinsonism was diagnosed in few patients whose clinical presentation can mimic, in rare cases, progressive supranuclear palsy [101]. Deafness of acute or rapid onset has been reported in few subjects, but its exact frequency remains unknown [41]. Rufa et al. reported an acute unilateral visual loss secondary to a non-arteritic ischemic optic neuropathy in a single 60-year-old case who was demented, but this occurred 33 years earlier at age 27 [102].

The lack of cranial nerve palsy, spinal cord disease, and of symptoms of muscular origin is noteworthy in CADASIL [41]. The exact cause of the radiculopathy reported in one case by Ragno et al. remains undetermined [103]. Recently, several cases belonging to Italian and Chinese families with clinical and electrophysiological signs of peripheral sensorimotor neuropathy were described [104, 105].

Conclusion

Neuropsychiatric manifestations are common in CADASIL, a genetic small-vessel disease leading to "subcortical ischemic vascular dementia." Mood disturbances and various manifestations such as anxiety, sleep difficulties, irritability, as well as disinhibition or euphoria are reported in CADASIL patients. These manifestations may occur during the course of the disorder, rarely before 40 years and most frequently after the occurrence of ischemic events during the fifth or sixth decade. Apathy is one of the most frequent clinical features of the disorder. Episodes of mood disturbances are rarely isolated and often associated with executive dysfunction. When they are inaugural, different features of psychiatric manifestations such as their atypical clinical presentation, late age at onset or unusual response to treatment such as their resistance to antidepressive drug, the association with neurological signs (pyramidal symptoms, cognitive alterations), the detection of white-matter MRI abnormalities, as well as a positive familial history of stroke and dementia are helpful to raise the diagnosis of CADASIL.

Cognitive alterations are common in CADASIL but they are more or less severe. They can be detected at the early stage of the disorder, as soon as the third decade. They remain often insidious for several years mainly involving executive functions and attention. Alterations in processing speed tasks are also frequent at the early stage. A decline in cognitive performances is usually observed after the fifth decade and is most often progressive. Some acute worsening of cognitive performances can be observed after the occurrence of ischemic events. Cognitive decline leads progressively to dementia associated with pseudobulbar palsy, gait disturbances, and motor impairment.

Finally, CADASIL should be considered as a unique model to investigate the relationships between subcortical ischemic lesions and the cognitive and psychiatric status in small-vessel diseases. Further studies are needed to better understand the exact impact of cerebral tissue lesions and the role of their distribution or of their severity on the occurrence of neuropsychiatric symptoms in this disorder.

References

1. Tournier-Lasserve E, Joutel A, Melki J, Weissenbach J, Lathrop GM, Chabriat H, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy maps to chromosome 19q12. Nat Genet. 1993;3(3):256–9.
2. Joutel A, Ducros A, Alamowitch S, Cruaud C, Domenga V, Marechal E, et al. A human homolog of bacterial acetolactate synthase genes maps within the CADASIL critical region. Genomics. 1996;38(2):192–8.
3. Razvi SS, Davidson R, Bone I, Muir KW. The prevalence of cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) in the west of Scotland. J Neurol Neurosurg Psychiatry. 2005;76(5):739–41.
4. Erkinjuntti T. Subcortical ischemic vascular disease and dementia. Int Psychogeriatr. 2003;15 Suppl 1:23–6. Epub 2005/09/30.
5. Baudrimont M, Dubas F, Joutel A, Tournier-Lasserve E, Bousser MG. Autosomal dominant leukoencephalopathy and subcortical ischemic stroke. A clinicopathological study. Stroke. 1993;24(1):122–5. Epub 1993/01/01.
6. Ruchoux MM, Maurage CA. CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. J Neuropathol Exp Neurol. 1997;56(9):947–64.
7. Ruchoux MM, Brulin P, Brillault J, Dehouck MP, Cecchelli R, Bataillard M. Lessons from CADASIL. Ann N Y Acad Sci. 2002;977:224–31.
8. Ruchoux MM, Guerouaou D, Vandenhaute B, Pruvo JP, Vermersch P, Leys D. Systemic vascular smooth muscle cell impairment in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Acta Neuropathol. 1995;89(6):500–12.
9. Davous P, Fallet-Bianco C. Familial subcortical dementia with arteriopathic leukoencephalopathy. A clinico-pathological case. Revue neurologique. 1991;147(5):376–84. Epub 1991/01/01. Demence sous-corticale familiale avec leucoencephalopathie arteriopathique. Observation clinico-pathologique.
10. Pullicino PM, Miller LL, Alexandrov AV, Ostrow PT. Infraputaminal 'lacunes'. Clinical and pathological correlations. Stroke. 1995;26(9):1598–602. Epub 1995/09/01.
11. Okeda R, Arima K, Kawai M. Arterial changes in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in relation to pathogenesis of diffuse myelin loss of cerebral white matter: examination of cerebral medullary arteries by reconstruction of serial sections of an autopsy case. Stroke. 2002;33(11):2565–9.
12. Miao Q, Paloneva T, Tuominen S, Poyhonen M, Tuisku S, Viitanen M, et al. Fibrosis and stenosis of the long penetrating cerebral arteries: the cause of the white matter pathology in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Brain Pathol (Zurich, Switzerland). 2004;14(4):358–64.
13. Zhang WW, Badonic T, Hoog A, Jiang MH, Ma KC, Nie JX, et al. Structural and vasoactive factors influencing intracerebral arterioles in cases of vascular dementia and other cerebrovascular disease: a review. Immunohistochemical studies on expression of collagens, basal lamina components and endothelin-1. Dementia. 1994;5(3–4):153–62. Epub 1994/05/01.
14. Gray F, Robert F, Labrecque R, Chretien F, Baudrimont M, Fallet-Bianco C, et al. Autosomal dominant arteriopathic leuko-encephalopathy and Alzheimer's disease. Neuropathol Appl Neurobiol. 1994;20(1):22–30.
15. Mikol J, Henin D, Baudrimont M, Gaulier A, Bacri D, Tillier JN, et al. Atypical CADASIL phenotypes and pathological findings in two new French families. Revue neurologique. 2001;157(6–7):655–67. CADASIL: aspects phenotypiques inhabituels et observations anatomo-pathologiques dans deux nouvelles familles francaises.
16. Bergmann M, Ebke M, Yuan Y, Bruck W, Mugler M, Schwendemann G. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL): a morphological study of a German family. Acta Neuropathol. 1996;92(4):341–50.
17. Desmond DW, Moroney JT, Lynch T, Chan S, Chin SS, Shungu DC, et al. CADASIL in a North American family: clinical, pathologic, and radiologic findings. Neurology. 1998;51(3):844–9.

18. Filley CM, Thompson LL, Sze CI, Simon JA, Paskavitz JF, Kleinschmidt-DeMasters BK. White matter dementia in CADASIL. J Neurol Sci. 1999;163(2):163–7.
19. Gutierrez-Molina M, Caminero Rodriguez A, Martinez Garcia C, Arpa Gutierrez J, Morales Bastos C, Amer G. Small arterial granular degeneration in familial Binswanger's syndrome. Acta Neuropathol. 1994;87(1):98–105. Epub 1994/01/01.
20. Joutel A, Andreux F, Gaulis S, Domenga V, Cecillon M, Battail N, et al. The ectodomain of the Notch3 receptor accumulates within the cerebrovasculature of CADASIL patients. J Clin Invest. 2000;105(5):597–605.
21. Villa N, Walker L, Lindsell CE, Gasson J, Iruela-Arispe ML, Weinmaster G. Vascular expression of Notch pathway receptors and ligands is restricted to arterial vessels. Mech Dev. 2001;108(1–2):161–4.
22. Joutel A, Vahedi K, Corpechot C, Troesch A, Chabriat H, Vayssiere C, et al. Strong clustering and stereotyped nature of Notch3 mutations in CADASIL patients. Lancet. 1997; 350(9090):1511–5.
23. Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, et al. Notch3 mutations in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a mendelian condition causing stroke and vascular dementia. Ann N Y Acad Sci. 1997;826:213–7.
24. Joutel A, Tournier-Lasserve E. Notch signalling pathway and human diseases. Semin Cell Dev Biol. 1998;9(6):619–25.
25. Gray GE, Mann RS, Mitsiadis E, Henrique D, Carcangiu ML, Banks A, et al. Human ligands of the Notch receptor. Am J Pathol. 1999;154(3):785–94.
26. Joutel A, Monet M, Domenga V, Riant F, Tournier-Lasserve E. Pathogenic mutations associated with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy differently affect Jagged1 binding and Notch3 activity via the RBP/JK signaling Pathway. Am J Hum Genet. 2004;74(2):338–47.
27. Dotti MT, Federico A, Mazzei R, Bianchi S, Scali O, Conforti FL, et al. The spectrum of Notch3 mutations in 28 Italian CADASIL families. J Neurol Neurosurg Psychiatry. 2005; 76(5):736–8.
28. Peters N, Opherk C, Bergmann T, Castro M, Herzog J, Dichgans M. Spectrum of mutations in biopsy-proven CADASIL: implications for diagnostic strategies. Arch Neurol. 2005;62(7): 1091–4.
29. Joutel A, Tournier-Lasserve E. Molecular basis and physiopathogenic mechanisms of CADASIL: a model of small vessel diseases of the brain. Journal de la Societe de biologie. 2002;196(1):109–15. Bases moleculaires et mecanismes physiopathogeniques de CADASIL: un modele de maladie des petites arteres cerebrales.
30. Robinson W, Galetta SL, McCluskey L, Forman MS, Balcer LJ. Retinal findings in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (cadasil). Surv Ophthalmol. 2001;45(5):445–8.
31. Schroder JM, Sellhaus B, Jorg J. Identification of the characteristic vascular changes in a sural nerve biopsy of a case with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Acta Neuropathol. 1995;89(2):116–21.
32. Goebel HH, Meyermann R, Rosin R, Schlote W. Characteristic morphologic manifestation of CADASIL, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy, in skeletal muscle and skin. Muscle Nerve. 1997;20(5):625–7.
33. Ruchoux MM, Chabriat H, Bousser MG, Baudrimont M, Tournier-Lasserve E. Presence of ultrastructural arterial lesions in muscle and skin vessels of patients with CADASIL. Stroke. 1994;25(11):2291–2.
34. Chabriat H, Joutel A, Vahedi K, Iba-Zizen MT, Tournier-Lasserve E, Bousser MG. CADASIS. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalophathy. Revue neurologique. 1997;153(6–7):376–85. CADASIS. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalophathy.
35. Ebke M, Dichgans M, Bergmann M, Voelter HU, Rieger P, Gasser T, et al. CADASIL: skin biopsy allows diagnosis in early stages. Acta Neurol Scand. 1997;95(6):351–7.

36. Jen J, Cohen AH, Yue Q, Stout JT, Vinters HV, Nelson S, et al. Hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS). Neurology. 1997;49(5):1322–30.
37. Ruchoux MM, Domenga V, Brulin P, Maciazek J, Limol S, Tournier-Lasserve E, et al. Transgenic mice expressing mutant Notch3 develop vascular alterations characteristic of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Am J Pathol. 2003;162(1):329–42.
38. Lacombe P, Oligo C, Domenga V, Tournier-Lasserve E, Joutel A. Impaired cerebral vasoreactivity in a transgenic mouse model of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy arteriopathy. Stroke. 2005;36(5):1053–8.
39. Dubroca C, Lacombe P, Domenga V, Maciazek J, Levy B, Tournier-Lasserve E, et al. Impaired vascular mechanotransduction in a transgenic mouse model of CADASIL arteriopathy. Stroke. 2005;36(1):113–7.
40. Joutel A, Monet-Lepretre M, Gosele C, Baron-Menguy C, Hammes A, Schmidt S, et al. Cerebrovascular dysfunction and microcirculation rarefaction precede white matter lesions in a mouse genetic model of cerebral ischemic small vessel disease. J Clin Invest. 2010;120(2): 433–45. Epub 2010/01/15.
41. Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser MG. Cadasil. Lancet Neurol. 2009;8(7):643–53. Epub 2009/06/23.
42. Dichgans M, Mayer M, Uttner I, Bruning R, Muller-Hocker J, Rungger G, et al. The phenotypic spectrum of CADASIL: clinical findings in 102 cases. Ann Neurol. 1998;44(5): 731–9.
43. Chabriat H, Vahedi K, Iba-Zizen MT, Joutel A, Nibbio A, Nagy TG, et al. Clinical spectrum of CADASIL: a study of 7 families. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Lancet. 1995;346(8980):934–9.
44. Desmond DW, Moroney JT, Lynch T, Chan S, Chin SS, Mohr JP. The natural history of CADASIL: a pooled analysis of previously published cases. Stroke. 1999;30(6):1230–3.
45. Chabriat H, Bousser MG. CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy): a new genetic disease of the cerebral arteries associated with vascular leukoencephalopathies. La Revue du praticien. 2000;50(6):585–8. CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy): une nouvelle maladie genetique des arteres cerebrales au sein des leucoencephalopathies d'origine vasculaire.
46. Peters N, Opherk C, Danek A, Ballard C, Herzog J, Dichgans M. The pattern of cognitive performance in CADASIL: a monogenic condition leading to subcortical ischemic vascular dementia. Am J Psychiatry. 2005;162(11):2078–85.
47. Kumar SK, Mahr G. CADASIL presenting as bipolar disorder. Psychosomatics. 1997; 38(4):397–8.
48. Ahearn EP, Speer MC, Chen YT, Steffens DC, Cassidy F, Van Meter S, et al. Investigation of Notch3 as a candidate gene for bipolar disorder using brain hyperintensities as an endophenotype. Am J Med Genet. 2002;114(6):652–8.
49. Aylward EH, Roberts-Twillie JV, Barta PE, Kumar AJ, Harris GJ, Geer M, et al. Basal ganglia volumes and white matter hyperintensities in patients with bipolar disorder. Am J Psychiatry. 1994;151(5):687–93. Epub 1994/05/01.
50. Brookes RL, Willis TA, Patel B, Morris RG, Markus HS. Depressive symptoms as a predictor of quality of life in cerebral small vessel disease, acting independently of disability; a study in both sporadic small vessel disease and CADASIL. Int J Stroke. 2012. Epub 2012/03/01.
51. Thomas N, Mathews T, Loganathan A. Cadasil: presenting as a mood disorder. Scott Med J. 2002;47(2):36–7.
52. Leyhe T, Wiendl H, Buchkremer G, Wormstall H. CADASIL: underdiagnosed in psychiatric patients? Acta Psychiatr Scand. 2005;111(5):392–6; discussion 6–7.
53. Marin RS. Apathy: concept, syndrome, neural mechanisms, and treatment. Semin Clin Neuropsychiatry. 1996;1(4):304–14. Epub 1996/10/01.
54. Marin RS. Apathy: a neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci. 1991;3(3):243–54. Epub 1991/01/01.

55. Levy E, Jaskolski M, Grubb A. The role of cystatin C in cerebral amyloid angiopathy and stroke: cell biology and animal models. Brain Pathol. 2006;16(1):60–70. Epub 2006/04/15.
56. Starkstein SE, Leentjens AF. The nosological position of apathy in clinical practice. J Neurol Neurosurg Psychiatry. 2008;79(10):1088–92. Epub 2008/01/12.
57. Starkstein SE, Fedoroff JP, Price TR, Leiguarda R, Robinson RG. Apathy following cerebrovascular lesions. Stroke. 1993;24(11):1625–30. Epub 1993/11/01.
58. Reyes S, Kurtz A, Herve D, Tournier-Lasserve E, Chabriat H. Presymptomatic genetic testing in CADASIL. J Neurol. 2012;259:2131–6.
59. Jouvent E, Reyes S, Mangin JF, Roca P, Perrot M, Thyreau B, et al. Apathy is related to cortex morphology in CADASIL. A sulcal-based morphometry study. Neurology. 2011; 76(17):1472–7. Epub 2011/04/27.
60. Verin M, Rolland Y, Landgraf F, Chabriat H, Bompais B, Michel A, et al. New phenotype of the cerebral autosomal dominant arteriopathy mapped to chromosome 19: migraine as the prominent clinical feature. J Neurol Neurosurg Psychiatry. 1995;59(6):579–85.
61. Reyes S, Viswanathan A, Godin O, Dufouil C, Benisty S, Hernandez K, et al. Apathy: a major symptom in CADASIL. Neurology. 2009;72(10):905–10. Epub 2009/03/11.
62. Lagas PA, Juvonen V. Schizophrenia in a patient with cerebral autosomally dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL disease). Nord J Psychiatry. 2001;55(1):41–2.
63. Trojano L, Ragno M, Manca A, Caruso G. A kindred affected by cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). A 2-year neuropsychological follow-up. J Neurol. 1998;245(4):217–22.
64. Lesnik Oberstein SA, van den Boom R, Middelkoop HA, Ferrari MD, Knaap YM, van Houwelingen HC, et al. Incipient CADASIL. Arch Neurol. 2003;60(5):707–12.
65. Taillia H, Chabriat H, Kurtz A, Verin M, Levy C, Vahedi K, et al. Cognitive alterations in non-demented CADASIL patients. Cerebrovasc Dis. 1998;8(2):97–101.
66. Amberla K, Waljas M, Tuominen S, Almkvist O, Poyhonen M, Tuisku S, et al. Insidious cognitive decline in CADASIL. Stroke. 2004;35(7):1598–602.
67. Holtmannspotter M, Peters N, Opherk C, Martin D, Herzog J, Bruckmann H, et al. Diffusion magnetic resonance histograms as a surrogate marker and predictor of disease progression in CADASIL: a two-year follow-up study. Stroke. 2005;36(12):2559–65.
68. Buffon F, Porcher R, Hernandez K, Kurtz A, Pointeau S, Vahedi K, et al. Cognitive profile in CADASIL. J Neurol Neurosurg Psychiatry. 2006;77(2):175–80.
69. Chabriat H, Levy C, Taillia H, Iba-Zizen MT, Vahedi K, Joutel A, et al. Patterns of MRI lesions in CADASIL. Neurology. 1998;51(2):452–7.
70. Epelbaum S, Benisty S, Reyes S, O'Sullivan M, Jouvent E, During M, et al. Verbal memory impairment in subcortical ischemic vascular disease: a descriptive analysis in CADASIL. Neurobiol Aging. 2011;32(12):2172–82. Epub 2010/02/13.
71. Hedera P, Friedland RP. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: study of two American families with predominant dementia. J Neurol Sci. 1997;146(1):27–33.
72. Chabriat H, Tournier-Lasserve E, Vahedi K, Leys D, Joutel A, Nibbio A, et al. Autosomal dominant migraine with MRI white-matter abnormalities mapping to the CADASIL locus. Neurology. 1995;45(6):1086–91.
73. Peters N, Herzog J, Opherk C, Dichgans M. A two-year clinical follow-up study in 80 CADASIL subjects: progression patterns and implications for clinical trials. Stroke. 2004; 35(7):1603–8.
74. Molko N, Pappata S, Mangin JF, Poupon C, Vahedi K, Jobert A, et al. Diffusion tensor imaging study of subcortical gray matter in cadasil. Stroke. 2001;32(9):2049–54.
75. Zekry D, Duyckaerts C, Belmin J, Geoffre C, Moulias R, Hauw JJ. Cerebral amyloid angiopathy in the elderly: vessel walls changes and relationship with dementia. Acta Neuropathol. 2003;106(4):367–73. Epub 2003/08/05.
76. Gunda B, Herve D, Godin O, Bruno M, Reyes S, Alili N, et al. Effects of gender on the phenotype of CADASIL. Stroke. 2012;43(1):137–41. Epub 2011/10/29.

77. Dichgans M, Filippi M, Bruning R, Iannucci G, Berchtenbreiter C, Minicucci L, et al. Quantitative MRI in CADASIL: correlation with disability and cognitive performance. Neurology. 1999;52(7):1361–7.
78. Chabriat H, Mrissa R, Levy C, Vahedi K, Taillia H, Iba-Zizen MT, et al. Brain stem MRI signal abnormalities in CADASIL. Stroke. 1999;30(2):457–9.
79. Coulthard A, Blank SC, Bushby K, Kalaria RN, Burn DJ. Distribution of cranial MRI abnormalities in patients with symptomatic and subclinical CADASIL. Br J Radiol. 2000; 73(867):256–65.
80. Auer DP, Putz B, Gossl C, Elbel G, Gasser T, Dichgans M. Differential lesion patterns in CADASIL and sporadic subcortical arteriosclerotic encephalopathy: MR imaging study with statistical parametric group comparison. Radiology. 2001;218(2):443–51.
81. O'Sullivan M, Jarosz JM, Martin RJ, Deasy N, Powell JF, Markus HS. MRI hyperintensities of the temporal lobe and external capsule in patients with CADASIL. Neurology. 2001; 56(5):628–34.
82. Markus HS, Martin RJ, Simpson MA, Dong YB, Ali N, Crosby AH, et al. Diagnostic strategies in CADASIL. Neurology. 2002;59(8):1134–8.
83. Iwatsuki K, Murakami T, Manabe Y, Narai H, Warita H, Hayashi T, et al. Two cases of Japanese CADASIL with corpus callosum lesion. Tohoku J Exp Med. 2001;195(2):135–40.
84. van Den Boom R, Lesnik Oberstein SA, van Duinen SG, Bornebroek M, Ferrari MD, Haan J, et al. Subcortical lacunar lesions: an MR imaging finding in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Radiology. 2002;224(3):791–6.
85. Chabriat H. Diffusion histograms in CADASIL. Stroke. 2005;36(12):2526.
86. Tatsch K, Koch W, Linke R, Poepperl G, Peters N, Holtmannspoetter M, et al. Cortical hypometabolism and crossed cerebellar diaschisis suggest subcortically induced disconnection in CADASIL: an 18F-FDG PET study. J Nucl Med. 2003;44(6):862–9.
87. Mesulam M, Siddique T, Cohen B. Cholinergic denervation in a pure multi-infarct state: observations on CADASIL. Neurology. 2003;60(7):1183–5.
88. Viswanathan A, Gray F, Bousser MG, Baudrimont M, Chabriat H. Cortical neuronal apoptosis in CADASIL. Stroke. 2006;37(11):2690–5.
89. Gray F, Polivka M, Viswanathan A, Baudrimont M, Bousser MG, Chabriat H. Apoptosis in cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy. J Neuropathol Exp Neurol. 2007;66(7):597–607.
90. O'Sullivan M. Diffusion tensor MRI correlates with executive dysfunction in patients with ischaemic leukoaraiosis. J Neurol Neurosurg Psychiatry. 2004;75(3):441–7.
91. O'Sullivan M, Barrick TR, Morris RG, Clark CA, Markus HS. Damage within a network of white matter regions underlies executive dysfunction in CADASIL. Neurology. 2005;65(10): 1584–90.
92. Duering M, Zieren N, Herve D, Jouvent E, Reyes S, Peters N, et al. Strategic role of frontal white matter tracts in vascular cognitive impairment: a voxel-based lesion-symptom mapping study in CADASIL. Brain. 2011;134(Pt 8):2366–75. Epub 2011/07/19.
93. Jouvent E, Mangin JF, Duchesnay E, Porcher R, During M, Mewald Y, et al. Longitudinal changes of cortical morphology in CADASIL. Neurobiol Aging. 2012;33(5):1002.e29–36.
94. Vahedi K, Chabriat H, Levy C, Joutel A, Tournier-Lasserve E, Bousser MG. Migraine with aura and brain magnetic resonance imaging abnormalities in patients with CADASIL. Arch Neurol. 2004;61(8):1237–40.
95. Schon F, Martin RJ, Prevett M, Clough C, Enevoldson TP, Markus HS. "CADASIL coma": an underdiagnosed acute encephalopathy. J Neurol Neurosurg Psychiatry. 2003;74(2): 249–52.
96. Le Ber I, Carluer L, Derache N, Lalevee C, Ledoze F, Defer GL. Unusual presentation of CADASIL with reversible coma and confusion. Neurology. 2002;59(7):1115–6.
97. Feuerhake F, Volk B, Ostertag CB, Jungling FD, Kassubek J, Orszagh M, et al. Reversible coma with raised intracranial pressure: an unusual clinical manifestation of CADASIL. Acta Neuropathol. 2002;103(2):188–92.

98. Bousser MG, Tournier-Lasserve E. Summary of the proceedings of the First International Workshop on CADASIL. Paris, May 19–21, 1993. Stroke. 1994;25(3):704–7.
99. Singhal S, Bevan S, Barrick T, Rich P, Markus HS. The influence of genetic and cardiovascular risk factors on the CADASIL phenotype. Brain. 2004;127(Pt 9):2031–8.
100. Malandrini A, Carrera P, Ciacci G, Gonnelli S, Villanova M, Palmeri S, et al. Unusual clinical features and early brain MRI lesions in a family with cerebral autosomal dominant arteriopathy. Neurology. 1997;48(5):1200–3.
101. Van Gerpen JA, Ahlskog JE, Petty GW. Progressive supranuclear palsy phenotype secondary to CADASIL. Parkinsonism Relat Disord. 2003;9(6):367–9.
102. Rufa A, De Stefano N, Dotti MT, Bianchi S, Sicurelli F, Stromillo ML, et al. Acute unilateral visual loss as the first symptom of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Arch Neurol. 2004;61(4):577–80.
103. Ragno M, Tournier-Lasserve E, Fiori MG, Manca A, Patrosso MC, Ferlini A, et al. An Italian kindred with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Ann Neurol. 1995;38(2):231–6.
104. Lv H, Yao S, Zhang W, Wang ZX, Huang YN, Niu XY, et al. Clinical features in 4 Chinese families with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Beijing Da Xue Xue Bao. 2004;36(5):496–500.
105. Sicurelli F, Dotti MT, De Stefano N, Malandrini A, Mondelli M, Bianchi S, et al. Peripheral neuropathy in CADASIL. J Neurol. 2005;252(10):1206–9.

Chapter 11
Neuropsychiatric Aspects of Vascular Cognitive Impairment

Anna Poggesi and Leonardo Pantoni

Abstract Vascular cognitive impairment (VCI) is a term that describes all the forms of cognitive decline deriving from, or associated with, vascular diseases. The brain changes of vascular origin that may cause deficits in cognitive functions are various in terms of underlying pathology and territorial distribution. For this reason, the cognitive profile in VCI is not homogeneous and strongly depends on the pathological subtype. In addition to cognitive deficits, brain vascular diseases may cause also several psychiatric disturbances that may or may not coexist with the cognitive disturbances.

In the first part of this chapter, we discuss the concept of VCI, while in the second part, the cognitive and psychiatric manifestations of VCI are illustrated. This overview emphasizes the need of additional research to better understand the exact impact of cerebral vascular lesions, and the role of their distribution and severity, on the occurrence of cognitive and psychiatric symptoms in VCI. This approach might require tools more specifically developed for cerebrovascular diseases.

Keywords Vascular cognitive impairment • Cognitive profile • Behavioral and psychological symptoms • Cerebrovascular diseases • Cognitive and psychiatric assessment

Introduction

The term vascular cognitive impairment (VCI) refers to all forms of cognitive impairment, from mild to severe, associated with and presumably caused by cerebrovascular diseases [1]. Describing neuropsychiatric aspects in VCI is not an easy

A. Poggesi, MD, PhD • L. Pantoni, MD, PhD (✉)
NEUROFARBA Department, Neuroscience Section,
University of Florence, Largo Brambilla 3, 50134 Florence, Italy
e-mail: pantoni@unifi.it

J.M. Ferro (ed.), *Neuropsychiatric Symptoms of Cerebrovascular Diseases*,
Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-1-4471-2428-3_11,

task because a wide range of brain changes that may affect the clinical picture in different ways constitute the neuropathological basis of VCI. This is the main reason why the neuropsychiatric profile in VCI is not homogeneous and strongly depends on the pathophysiological subtype. In addition, neurodegenerative processes, expressed as brain atrophy and atrophy of the medial temporal lobe on neuroimaging, due to coexisting Alzheimer disease (AD) pathology, may influence and contribute to the final clinical picture. Neuropsychiatric manifestations in VCI include various degrees of cognitive impairment affecting various domains and several psychiatric disturbances. The first part of this chapter will deal with the concept of VCI, with some historical notes and the evolution of the concept; this will help in understanding the clinical aspects of the syndrome. The second part of the chapter will cover the neuropsychiatric aspects of VCI, distinguished in cognitive and psychiatric manifestations.

The Concept of Vascular Cognitive Impairment

Historical View and Definitions

The relationship between cerebrovascular diseases and cognitive decline is very complex, and this complexity has led over the years to radical views and strong debates [2, 3]. It is nowadays accepted that the earliest term vascular dementia (VaD) encompasses a heterogeneous group of diseases rather than representing a unique pathological process, with different causes and a wide spectrum of cognitive impairment, with only part of the patients being definable as overtly demented [4]. The broader concept of VCI was thus introduced 20 years ago in order to include all the possible aspects of the relationship between cerebrovascular diseases and cognition [1, 5]. In 1991, the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) promoted an international workshop to encourage research in the field of VaD. The purposes of the workshop were to reach a consensus on the definition of VaD and to set suitable diagnostic criteria that were then published in 1993 [6]. Hachinski and Bowler reacted to the publication of these criteria and strongly criticized the concept of VaD [5]. These authors proposed a radical modification of the concept and introduced the new term "vascular cognitive impairment" to describe the large spectrum of the cognitive consequences of vascular diseases, thus including also the early stages when dementia is not yet present. With the introduction of the VCI term, Hachinski and Bowler underlined the need for diagnosing cognitive disorders caused by vascular diseases as early as possible and, definitely, before the occurrence of dementia. They also stressed the fact that vascular diseases may cause cognitive impairment with different pathophysiological mechanisms resulting in different clinical profiles, thus stressing the limits of unifying sets of

criteria. One final relevant point emphasized the need of drawing more attention towards patients with a high vascular risk factor profile in order to prevent dementia [5]. Hachinski and Bowler introduced the concept of "brain-at-risk," a stage where patients with cerebrovascular diseases and vascular risk factors have no cognitive decline but are at increased risk thereof. This latter condition would therefore be the best time for preventive strategies to be applied.

In spite of this initial noteworthy conceptual proposal, operational criteria for VCI have never been developed and the term has been used over the years with different meanings. In a broader interpretation, VCI include cognitive impairment without dementia as well as VaD. The concept of VCI covers subjects with cognitive impairment related to stroke; multiple cortical infarcts, multiple subcortical infarcts, or both; silent infarcts; strategic infarcts; small-vessel disease with white matter lesions; and lacunes. Under the term VCI, some authors also include AD patients who have evidence of vascular lesions. In a consensus paper published in 2003, the following expressions of VCI were listed: poststroke dementia, VaD with all its subtypes, mixed and vascular mild cognitive impairment (MCI), and AD plus VaD (so-called mixed dementia) [1]. In the seminal experience of the Canadian Health and Aging Study instead, VCI encompasses three subtypes: (1) VaD, (2) mixed AD with a vascular component, and (3) vascular cognitive impairment no dementia [7].

VCI thus remains a quite generic term whose main merit is to recognize that vascular diseases may cause cognitive impairment and do so in different ways. However, it currently does not appear to have immediate practical applications. Despite this, most epidemiological studies are consistent in finding that VaD and VCI are highly prevalent diseases, being VaD the second most common cause of dementia after AD.

Pathophysiology

The common causal element in VCI is the cerebrovascular lesion which results from vascular pathology, being the primary lesion either hemorrhagic or, more commonly, ischemic. Schematically, the ischemic forms of VaD are broadly divided into large-vessel and small-vessel diseases. Patients in whom obvious cognitive decline is associated with the neuroimaging or pathological demonstration of multiple large (territorial) cerebral infarcts represent examples of so-called multi-infarct dementia in the strictest sense. In this VaD subtype, poststroke dementia is the most common form of acute-onset dementia. Another form of acute-onset poststroke dementia includes strategic infarct VaD, caused by a single strategically located cortico-subcortical lesion affecting a large-vessel arterial territory (usually the right posterior cerebral artery, the anterior cerebral artery, or the left gyrus angularis).

The term cerebral small-vessel disease refers to a group of pathological processes with various etiologies that affect the small arteries, arterioles, venules, and

capillaries of the brain [8]. Age-related and hypertension-related small-vessel diseases and cerebral amyloid angiopathy are the most common forms in this group. The consequences of small-vessel disease on the brain parenchyma are mainly lesions located in the subcortical structures such as lacunar infarcts, white matter lesions, large hemorrhages, and microbleeds. From a clinical point of view, small-vessel diseases are usually related to a progressive course, rather than to an acute onset, thus with a clinical course more similar to that of AD. In case of a single lacunar infarct in strategic zones (such as capsular genu, thalamus, or head of the caudate nucleus), the onset of dementia may be acute also if related to small-vessel disease. Finally, VCI may be related to other causes, such as mixed cortical and subcortical damage, single or multiple hemorrhage, vascular malformations, hypoperfusion, and genetic disorders.

From what reported above, it is well understandable that, given the many different subtypes of VCI, the clinical picture might also be very different.

Neuropsychiatric Aspects of Vascular Cognitive Impairment

Neuropsychiatric manifestations of VCI include various degrees of cognitive impairment and psychiatric disturbances. The definition, characterization, and the individuation of the possible treatment strategies of the disturbances associated with stroke and cerebrovascular diseases are important from a clinical point of view, not only for researchers and doctors but especially for patients and their families. In this relation, one first reflection concerns the need of a structured approach to the problem. Services dedicated to patients with neuropsychiatric consequences of cerebrovascular diseases might represent an important step for a better understanding of the phenomenon and for the implementation of the best screening, diagnostic, and treatment options for these patients [9].

Cognitive Profile

Available evidence suggests that in general, in the case of a vascular origin of the cognitive decline, there is a greater impairment in executive functions than in memory performances that are typically affected in AD patients. Executive functions, mostly depending on integrity of frontal lobe functions, include shifting, i.e., the ability to shift between tasks and mental sets; updating, i.e., the ability to update and monitor information; and inhibition, i.e., the ability to inhibit dominant responses [10]. In patients with VaD, the executive functions that tend to be disproportionately impaired include planning and sequencing, speed of mental processing, performance on unstructured tasks, and attention [11]. In addition, compared to patients with AD, those with VaD exhibit greater deficits on measures of verbal fluency and

more perseverations. Memory impairment is usually evident when vascular lesions coexist with Alzheimer pathology, but may also be present as a direct consequence of cerebrovascular disease [12–14].

Despite what reported above, cognitive profile in VaD is variable depending on the pathogenesis of the cognitive deficit, and also on the single patient's characteristics, mainly on coexisting lesions. Many VaD cases occur in relation to stroke, but even the stroke-related forms of VaD are heterogeneous from the clinical and pathogenic points of view. Infarcts may occur both in cortical and subcortical regions, although multi-infarct dementia is generally considered primarily a result of a cortical damage [11]. In this sense, the cognitive profile is characterized by a variable pattern of cognitive deficits, reflecting the size, location, and number of brain lesions [4]. These patients can present with aphasia, hemineglect, visual field deficits, difficulty in calculation, ideomotor apraxia, frontal lobe syndromes, and combination thereof. These are all disturbances that will significantly affect their functional capacities and make them cognitively disabled in a broad sense. Single-strategic infarct dementia defines a clinical picture characterized by the abrupt onset of cognitive impairment and behavioral changes in relation to the occurrence of a single infarct in specific regions of the brain such as the thalamus, the caudate nucleus, the angular gyrus, and the genu of the internal capsule [15]. The clinical picture is that of a frontal lobe syndrome with inattention, apathy, and psychomotor retardation and has been interpreted as a thalamocortical disconnection syndrome [16].

Small-vessel disease is today thought to be among the main causes of VCI. The question of whether structural damage related to small-vessel diseases has a causal role in cognitive deficits has been the object of debate during the past years. The effect of lacunar infarcts on cognitive function is nowadays accepted. Lacunar infarcts are in fact associated with cognitive decline and dementia during follow-up, with number and location of infarcts thought to be the main determining factors [8]. For example, in one study, the presence of lacunes in the thalamus was associated with low scores on the Mini-Mental State Examination and poor compound scores for speed and motor control and executive functions; there was also a significant negative association between the presence of lacunes in the putamen or pallidum and memory performance [17]. Silent infarcts, i.e., those not related to clinically obvious stroke and found incidentally on neuroimaging, CT, or MRI, are, by far, more frequent than those associated with stroke [8]. Also silent lacunar infarcts are associated with cognitive decline [18].

White matter lesions were once thought to be a neuroimaging finding of unclear and even doubtful clinical significance, but convincing evidence exists supporting the association between these lesions and cognitive impairment [19]. The evidence derives from both cross-sectional and longitudinal studies, and nowadays there should be little doubt about the role of white matter lesions in cognition. White matter lesions are not associated with global cognitive decline unless other lesions are also present, but with specific cognitive deficits such as psychomotor retardation; deficits of attention, planning, and set shifting; and dysexecutive syndrome [20, 21].

Severity of white matter lesions and their progression are also recognized as important predictors of cognitive decline and dementia [22, 23]. The conclusion that lacunar infarcts and white matter lesions are an important substrate for cognitive impairment, based on neuroimaging studies, has also been confirmed by a large pathological study evaluating 456 brains in which the presence of small-vessel disease was associated with a more than two-time increased risk of dementia at the age of 75 years [24].

Microbleeds, another neuroimaging expression of small-vessel disease, are currently receiving attention as they might be an additional factor in determining cognitive decline and dementia [25]. Cerebral microbleeds are increasingly detected in normal elderly populations, in all types of cerebrovascular disease, and are highly prevalent in both VCI and AD. Some studies in VCI, AD and normal individuals have shown a relationship between microbleeds and cognition, although their impact on cognitive function and the underlying mechanisms need to be further investigated [26].

The full clinical picture associated with cerebral small-vessel disease not only is limited to cognitive impairment but also includes gait, mood, behavioral, and urinary disturbances. The natural course is progressive, starting with mild and loosely associated disturbances and ending up with a final stage, which might be characterized by cognitive impairment severe enough to impair functional status, and thus fulfilling the criteria for dementia [8]. Disability has recently been demonstrated as one of the clinical correlates of white matter changes [27]. Moreover, gait might become very impaired with many patients almost unable to walk; mood might be depressed, with apathy; and urinary incontinence might be present [8]. It is however important to note that available evidence shows that the clinical and functional status in subjects with the same grade of brain lesion burden, especially when dealing with white matter changes, may be variable, suggesting the presence of "hidden" factors in determining the final clinical picture [28]. For example, it is known that some patients with similar visible small-vessel disease burden on conventional MRI have different clinical outcomes, hinting at the presence of additional, uncovered aspects that may contribute to symptoms and disturbances. The morphological alterations identified on conventional neuroimaging might not be sufficient to explain the clinical-functional phenotype which is frequently variable for typology and severity also in presence of overlapping neuroimaging findings. Researchers are now dedicating their efforts in disentangling this aspect. Preliminary studies using advanced neuroimaging techniques such as magnetization transfer, diffusion, and spectroscopy have suggested the possibility to acquire more in-depth information about the microstructural tissue damage and underlying metabolic alterations and the association with the cognitive performances evaluating both white matter lesions revealed by conventional neuroimaging and normal-appearing white matter [29]. Such data need to be confirmed by other studies taking into consideration the influence of other frequently coexisting lesions such as lacunar infarcts and cortical atrophy. In fact, part of the variance in cognitive function and other clinical disturbances can be explained if multiple lesion types, rather than just white matter changes, are taken into account.

Psychiatric Disturbances

Psychiatric disturbances, also referred to as behavioral and psychological symptoms of dementia, are common in cognitive impairment and are nowadays recognized as important aspects that may influence the quality of life of both patients and their caregivers. These disturbances are associated with referral to specialist services and increased rate of institutionalization, thus contributing to the financial costs of dementia [30].

Psychiatric disturbances have received less attention than cognitive symptoms of dementia over the past years, as they were not always seen as manifestations of a brain disease requiring treatment, nor was there sufficient awareness of treatment opportunities. The growing number of elderly people suffering from dementia worldwide and the awareness that this kind of disturbances are very frequent among demented patients, during the course of the disease, have then brought the research and medical community to address this issue as an essential step in the management of dementia. It is with these thoughts that in 1996, a consensus conference on the knowledge and implications for research and treatment of behavioral and psychological signs and symptoms of dementia was held [31].

Behavioral and psychological signs and symptoms are defined as "signs and symptoms of disturbed perception, thought content, mood, or behaviour that frequently occur in patients with dementia" [31]. A way of classifying these disturbances is to distinguish the following: (1) symptoms usually and mainly assessed on the basis of interviews with patients and relatives, including anxiety, depressive mood, sleep disturbances, hallucinations, and delusions, and (2) symptoms usually identified on the basis of observation of patient behavior, including aggression, screaming, restlessness, agitation, wandering, culturally inappropriate behaviors, sexual disinhibition, hoarding, cursing, and shadowing. Table 11.1 reports the range of the main behaviors that can be encountered in dementia. Signs and symptoms may cluster into syndromes [32]. Some authors suggest the presence of three clearly delineated subsyndromes/clusters: "mood/apathy" (including depression, apathy, sleep disturbances, and changes in appetite), "hyperactivity" (agitation, euphoria, irritability, disinhibition, and aberrant motor behavior), and "psychosis" (hallucinations and

Table 11.1 Behavioral and psychological signs and symptoms of dementia

Behavioral	Psychological
Agitation	Personality change
Aggression	Irritability
Aberrant motor behavior	Apathy
Wandering	Depression
Cursing	Anxiety
Screaming	Hallucinations
Hoarding	Delusions
Sexual disinhibition	Dysphoria
Shadowing	
Disinhibition	

delusions). Other authors have preferred to describe four subsyndromes: "hyperactive behaviors," "psychosis," "affective behaviors," and "apathy" [32].

Several studies have evaluated the prevalence of the neuropsychiatric symptoms of dementia. Depending on the method used, it has been estimated that they affect 50–90 % of persons with dementia in the course of the disease [33]. The prevalence is higher when patients in nursing home or clinical settings are considered. The few available population-based studies have confirmed the high prevalence of these disturbances in community-dwelling patients with dementia. The first population-based study was conducted in England in the 1980s and focused only on Alzheimer-type dementia [34–37], finding mood disorders as the most frequent (around 60 % of patients). A US study (Cache County, Utah) estimated that 61 % of participants with dementia exhibited one or more of the symptoms, with apathy, depression, and agitation as the most common ones [38]. Finally, data from the Cardiovascular Health Study Cognition study [33] have confirmed that neuropsychiatric symptoms occur in the majority of persons with dementia over the course of the disease. Among participants with dementia, 62 % suffered from a clinically significant neuropsychiatric symptom. There seems to be an association between the overall frequency of psychiatric disturbances and dementia severity, so that the more advanced stages of the disease are characterized by more psychiatric disturbances [38–40], although the findings has not been confirmed in all studies [41–43].

There is controversy about the possible relationship between neuropsychiatric disturbances and dementia subtypes. For example, some studies suggest that depression is specifically more common in VaD than in AD, while others disagree. Much of the literature available on neuropsychiatric disturbances relates to patients affected by AD, while for VaD, the available literature is rather small. In the Cardiovascular Health Study Cognition study [33], when comparing patients with AD to other types of dementia (mainly VaD), no differences were found in the frequency of neuropsychiatric symptoms except for aberrant motor behavior, which was more frequent in AD patients. In the US Cache County study [38], only modest differences were observed in the prevalence of psychological or behavioral disturbances in different types of dementia or at different stages of illness: participants with AD were more likely to have delusions and less likely to have depression.

Other studies have analyzed the comparison between VaD and other dementia subtypes (mostly AD) in respect to neuropsychiatric disturbances. The main methodological aspects and results of these studies are reported in Table 11.2. From this overview, it is clear that no definitive conclusion can be derived from available data, as some studies point out that VaD and AD have an equal clinical picture, some indicate that psychiatric disturbances are more frequent in VaD than AD, and some the opposite. A few considerations can be made. Studies addressing this issue vary according to cohort of subjects assessed and to type of instruments used. One of the scales most commonly used to assess behavioral and psychological symptoms in dementia is the Neuropsychiatric Inventory (NPI) [50]. This scale measures the severity and frequency of 12 noncognitive symptoms of dementia: agitation/aggression, irritability, disinhibition, delusions, hallucinations, depression, anxiety, euphoria, apathy, aberrant motor behavior, sleep disturbances, and changes in appetite and

Table 11.2 Cross-sectional studies assessing psychiatric disturbances in patients with vascular dementia (VaD) in comparison with other dementia subtypes

Author, year	Patients	Dementia type	Psychiatric disturbances assessed	Instruments	Results (differences between VaD and other dementia)
Starkstein, 1996 [44]	Outpatient	VaD = 20 pts AD = 40 pts Matched for age, sex and MMSE	Depression, dysthymia anxiety, psychosis, pathological laughing and crying, anosognosia, personality disorders	Structured psychiatric interview with dedicated instruments	VaD > AD for severe anosognosia and pathological crying For other disturbances VaD = AD
Lyketsos, 2000 [38]	Community-dwelling individuals	AD = 214 pts VaD = 62 pts Other dementias = 53	According to NPI[a]	NPI	AD higher frequency of delusions VaD higher frequency of depression No differences for the rest
Aharon-Peretz, 2000 [41]	Outpatients	Small-vessel VaD = 30 pts AD = 30 pts Matched for age and dementia severity	According to NPI[a]	NPI	Small-vessel VaD = AD
Ballard, 2000 [39]	Dementia clinic	AD 92 VaD 92 Clinical or postmortem criteria	Depression Anxiety Psychotic symptoms	Cornell Scale DSMIV checklist CUSPAD	VaD > AD for depression and anxiety
Kim, 2003 [42]	Out- and inpatient geriatric clinic	AD = 99 pts VaD = 36 pts	Global psychiatric symptomatology Depression Anxiety	Brief Psychiatric Rating Scale Hamilton-D Hamilton-A	VaD more severe disturbances
Ikeda, 2004 [45]	Community-dwelling individuals	VaD = 28 pts AD = 21 pts	According to NPI[a]	NPI	AD > VaD for delusions and aberrant motor behavior For other disturbances, VaD = AD
Srikanth, 2005 [40]	Outpatient neurology clinic	AD = 44 pts VaD = 31 pts FTD = 23 pts	According to NPI[a]	NPI	VaD = AD FTD > VaD and AD for disinhibition, aberrant motor behavior,

(continued)

Table 11.2 (continued)

Author, year	Patients	Dementia type	Psychiatric disturbances assessed	Instruments	Results (differences between VaD and other dementia)
Fuh, 2005 [46]	Outpatient	AD = 320 pts	According to NPI[a]	NPI	Cortical VaD higher NPI composite scores
		VaD = 212 pts (*subcortical VaD = 161 cortical VaD = 35*)			Cortical VaD > AD for agitation and sleep disturbances
Pinto, 2006 [47]	Outpatient psychiatric clinic	AD = 30 pts VaD = 29 pts	Delusions, hallucinations, activity disturbances, aggressiveness, sleep disturbances, depression, phobias, and anxiety	Behavioral Pathology in AD Scale	AD > VaD for delusions, hallucinations, anxieties, phobias, and caregiver distress
Chiu, 2007 [48]	Dementia clinic	VCI = 157 pts (*no dementia = 41 VaD = 95 AD with vascular component = 21*)	According to NPI[a]	NPI	VaD = *AD with vascular component*
Fernandez-Martinez, 2008 [49]	Outpatient	AD = 37 pts	According to NPI[a]	NPI	AD > VaD for sleep disturbances, appetite changes and aberrant motor behavior.
		VaD = 28 pts (*subcortical VaD = 22 pts*)			For other disturbances VaD = AD
Johnson, 2011 [43]	Outpatient neurology clinic	AD = 2,474 pts DLB = 151 pts VaD = 85 pts PDD = 74 pts Mixed dementias = 179 pts	According to NPI[a] A 3-factor model of psychiatric symptoms: mood, psychotic, and frontal	NPI	VaD exhibited the highest levels of mood, psychotic, and frontal symptoms. Depressed mood predominant feature in all dementia subtypes

AD Alzheimer disease, *CUSPAD* Columbia University Scale for the Assessment of Psychopathology in AD, *DLB* dementia with Lewy bodies, *FTD* frontotemporal dementia, *NPI* Neuropsychiatric Inventory, *PDD* Parkinson disease dementia, *pts* patients, *SVD* small-vessel dementia, *VaD* vascular dementia

[a]NPI assesses the following disturbances: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, and aberrant motor behavior

eating behaviors. Another consideration relates to the relative small number of patients assessed, especially when VaD groups are considered. Overall VaD groups have never reached 100 patients.

The main pitfall of these studies remains the fact that nearly all of them have considered VaD as a whole, thus not distinguishing the different pathogenetic subtypes. If the literature exploring neuropsychiatric disturbances in VaD is limited, even scarcer is thus that dealing with the different subtypes of VaD. Available data are based on few studies and suggest that neuropsychiatric disturbances have a different profile according to the subtype of vascular cognitive impairment. In this regard, data from the VantagE study have offered the opportunity to compare neuropsychiatric symptoms between small- and large-vessel VaD patients [51]. The VantagE study was a multicenter, phase III, prospective, randomized, double-blind, placebo-controlled clinical trial of the effects of rivastigmine in patients with mild to moderate VaD. At least one of the behavioral and psychological symptoms considered was reported in 92 % of the 484 enrolled patients. Apathy was the most prevalent (65 %), followed by depressive symptoms (45 %), irritability (42 %), and agitation/aggression (40 %). Apathy, aberrant motor behavior, and hallucinations were more frequently reported by patients with small-vessel VaD when compared to patients with large-vessel VaD, while agitation, aggression, and euphoria were more common in large-vessel VaD. Another study, the Lund Longitudinal Dementia Study, aimed at investigating clinical features in 175 neuropathologically defined VaD subgroups, including pure small-vessel dementia, pure large-vessel dementia, and combined small-vessel dementia with AD pathology [52]. Neuropsychiatric disturbances were assessed retrospectively using the medical records. They were more frequent in the combined small-vessel dementia with AD pathology. Hallucinations and delusions turned out to be more prevalent in the large-vessel group compared to the small-vessel one. None of the differences reached the level of statistical significance.

Aggressive behavior has been described as a possible and, if present, important clinical feature after hemispheric infarction in territories of the anterior, middle, or posterior cerebral arteries [53, 54].

The few available data summarized above relate to dementia. Only few studies have addressed neuropsychiatric disturbances in the prodromal stages of VaD (vascular MCI). In the Cardiovascular Health Study, this issue was addressed for the first time [33]. Neuropsychiatric symptoms were present in 43 % of MCI patients, and depression, apathy, and irritability resulted to be the most common. In the study by Chiu et al. [48] (Table 11.2), among the 157 patients globally affected by vascular cognitive impairment, 41 did not fulfil criteria of dementia and were thus considered as affected by MCI. These patients were compared to those affected by VaD or AD with vascular component. As expected, frequency and severity of disturbances were lower in the MCI group compared to the demented patients, but the overall frequency of neuropsychiatric symptoms did not differ among the three groups (nearly 90 %). In the MCI group, sleep disturbances, depression, and irritability were the most frequent. In the Consortium to Investigate Vascular Impairment of Cognition (CIVIC) study, behavioral outcomes were compared among patients with vascular cognitive impairment (thus including MCI) to patients cognitively normal or affected by AD.

VCI, and each of its subtypes, including VaD, showed readily detectable clinical evidence of disease progression, in terms of cognitive, functional, and behavioral performances. Progression was least in people with vascular MCI and greatest in those with VaD; people with mixed VaD/AD tended to have outcomes similar to those with AD. Depressive symptoms were both more common in VCI, and more likely to progress, than in AD, without significant differences in VCI subtype.

Conclusive Remarks

Neuropsychiatric manifestations are common in VCI. The many types of vascular brain changes responsible of the cognitive impairment and of the behavioral and psychological disturbances have been reported in the first part of this chapter. Neuropsychiatric disturbances have been divided in cognitive impairment and psychiatric symptoms. Although vascular lesions are related to executive dysfunction, the cognitive profile in VCI is very variable depending on the characteristics of the subsiding brain lesions, such as number, size, and location. Moreover, the coexistence of other brain pathological processes, mainly of the AD type, represents a major contributor of the final clinical picture.

In addition to cognitive impairment, behavioral and psychological symptoms are also very common in VCI and are associated with worse prognosis, higher costs of care, earlier institutionalization, and increased caregiver burden. Some data point to the fact that these disturbances might be different according to dementia subtype although, up to now, no clear conclusion can be derived concerning this statement. While it is less problematic to understand the importance of the different neuroimaging or pathological substrates in the determination of cognitive decline, little is known about the structural correlates underpinning behavioral and psychological symptoms. A possible explanation could be that psychiatric disturbances depend on other determinants (genetic? environment?). For example, in a cohort of AD patients, no clear relation between behavioral and psychological profile and medial temporal lobe atrophy or white matter changes burden could be demonstrated [55].

Further studies are needed to better understand the exact impact of cerebral tissue lesions, and the role of their distribution and their severity, on the occurrence of cognitive and psychiatric symptoms in VCI. This might require tools more specifically developed for the field of cerebrovascular diseases.

References

1. O'Brien JT, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L, Bowler JV, Ballard C, DeCarli C, Gorelick PB, Rockwood K, Burns A, Gauthier S, DeKosky ST. Vascular cognitive impairment. Lancet Neurol. 2003;2:89–98.
2. Hachinski VC. The decline and resurgence of vascular dementia. Can Med Assoc J. 1990;142:107–11.

3. Román GC. Facts, myths, and controversies in vascular dementia. J Neurol Sci. 2004; 226:49–52.
4. Pantoni L. Subtypes of vascular dementia and their pathogenesis: a critical overview. In: Bowler J, Hachinski V, editors. Vascular cognitive impairment: preventable dementia. Oxford: Oxford University Press; 2003. p. 217–29.
5. Hachinski VC, Bowler JV. Vascular dementia. Neurology. 1993;43:2159–60.
6. Romàn GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research study. Report of the NINDS-AIREN International Workshop. Neurology. 1993; 43:250–60.
7. Rockwood K, Wentzel C, Hachinski V, Hogan DB, MacKnight C, McDowell I. Prevalence and outcomes of vascular cognitive impairment. Vascular Cognitive Impairment investigators of the Canadian Study of Health and Aging. Neurology. 2000;54:447–51.
8. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010;9:689–701.
9. Ciolli L, Poggesi A, Salvadori E, Valenti R, Nannucci S, Pasi M, Pescini F, Inzitari D, Pantoni L. The VAS-COG clinic: an out-patient service for patients with cognitive and behavioral consequences of cerebrovascular diseases. Neurol Sci. 2012;33:1277–83.
10. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. Cogn Psychol. 2000;41:49–100.
11. Desmond DW. The neuropsychology of vascular cognitive impairment: is there a specific cognitive deficit? J Neurol Sci. 2004;226:3–7.
12. van de Pol L, Gertz H-J, Scheltens P, Wolf H. Hippocampal atrophy in subcortical vascular dementia. Neurodegener Dis. 2011;8:465–9.
13. Qiu C, Zhang Y, Bronge L, Herlitz A, Aspelin P, Bäckman L, Fratiglioni L, Wahlund LO. Medial temporal lobe is vulnerable to vascular risk factors in men: a population-based study. Eur J Neurol. 2012;19:876–83.
14. Gemmell E, Bosomworth H, Allan L, Hall R, Khundakar A, Oakley AE, Deramecourt V, Polvikoski TM, O'Brien JT, Kalaria RN. Hippocampal neuronal atrophy and cognitive function in delayed poststroke and aging-related dementias. Stroke. 2012;43:808–14.
15. Pantoni L, Basile AM, Romanelli M, Piccini C, Sarti C, Nencini P, Inzitari D. Abulia and cognitive impairment in two patients with capsular genu infarct. Acta Neurol Scand. 2001; 104:185–90.
16. Tatemichi TK, Desmond DW, Prohovnik I, Cross DT, Gropen TI, Mohr JP, Stern Y. Confusion and memory loss from capsular genu infarction: a thalamocortical disconnection syndrome? Neurology. 1992;42:1966–79.
17. Benisty S, Gouw AA, Porcher R, Madureira S, Hernandez K, Poggesi A, van der Flier WM, Van Straaten EC, Verdelho A, Ferro J, Pantoni L, Inzitari D, Barkhof F, Fazekas F, Chabriat H, LADIS Study Group. Location of lacunar infarcts correlates with cognition in a sample of non-disabled subjects with age-related white-matter changes: the LADIS study. J Neurol Neurosurg Psychiatry. 2009;80:478–83.
18. Vermeer SE, Longstreth Jr WT, Koudstaal PJ. Silent brain infarcts: a systematic review. Lancet Neurol. 2007;6:611–9.
19. Pantoni L, Poggesi A, Inzitari D. The relation between white-matter lesions and cognition. Curr Opin Neurol. 2007;20:390–7.
20. Gunning-Dixon FM, Raz N. The cognitive correlates of white matter abnormalities in normal aging: a quantitative review. Neuropsychology. 2000;14:224–32.
21. Ferro JM, Madureira S. Age-related white matter changes and cognitive impairment. J Neurol Sci. 2002;203–204:221–5.
22. Prins ND, van Dijk EJ, den Heijer T, Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Cerebral white matter lesions and the risk of dementia. Arch Neurol. 2004;61:1531–4.
23. Schmidt R, Petrovic K, Ropele S, Enzinger C, Fazekas F. Progression of leukoaraiosis and cognition. Stroke. 2007;38:2619–25.

24. Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C, Medical Research Council Cognitive Function and Ageing Study. Age, neuropathology, and dementia. N Engl J Med. 2009;360:2302–9.
25. Poels MM, Ikram MA, van der Lugt A, Hofman A, Niessen WJ, Krestin GP, Breteler MM, Vernooij MW. Cerebral microbleeds are associated with worse cognitive function: the Rotterdam Scan Study. Neurology. 2012;78:326–33.
26. Werring DJ, Gregoire SM, Cipolotti L. Cerebral microbleeds and vascular cognitive impairment. J Neurol Sci. 2010;299:131–5.
27. Inzitari D, Pracucci G, Poggesi A, Carlucci G, Barkhof F, Chabriat H, Erkinjuntti T, Fazekas F, Ferro JM, Hennerici M, Langhorne P, O'Brien J, Scheltens P, Visser MC, Wahlund LO, Waldemar G, Wallin A, Pantoni L, LADIS Study Group. Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort. BMJ. 2009;339:b2477. doi:10.1136/bmj.b2477.
28. Gouw AA, Seewann A, van der Flier WM, Barkhof F, Rozemuller AM, Scheltens P, Geurts JJ. Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations. J Neurol Neurosurg Psychiatry. 2011;82:126–35.
29. Schmidt R, Ropele S, Ferro J, Madureira S, Verdelho A, Petrovic K, Gouw A, van der Flier WM, Enzinger C, Pantoni L, Inzitari D, Erkinjuntti T, Scheltens P, Wahlund LO, Waldemar G, Rostrup E, Wallin A, Barkhof F, Fazekas F, LADIS Study Group. Diffusion-weighted imaging and cognition in the leukoaraiosis and disability in the elderly study. Stroke. 2010;41:e402–8.
30. Azermai M, Petrovic M, Elseviers MM, Bourgeois J, Van Bortel LM, Vander Stichele RH. Systematic appraisal of dementia guidelines for the management of behavioural and psychological symptoms. Ageing Res Rev. 2012;11:78–86.
31. Finkel SI, Costa e Silva J, Cohen G, Miller S, Sartorius N. Behavioral and psychological signs and symptoms of dementia: a consensus statement on current knowledge and implications for research and treatment. Int Psychogeriatr. 1996;8(Suppl3):497–500.
32. Bettney L, Butt S, Morris J, Connolly A, McCollum C, Burns A, Purandare N. Investigating the stability of neuropsychiatric sub-syndromes with progression of dementia: a 2-year prospective study. Int J Geriatr Psychiatry. 2012;27:1118–23.
33. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. JAMA. 2002;288:1475–83.
34. Burns A, Jacoby R, Levy R. Psychiatric phenomena in Alzheimer's disease I: disorders of thought content. Br J Psychiatry. 1990;157:72–6.
35. Burns A, Jacoby R, Levy R. Psychiatric phenomena in Alzheimer's disease II: disorders of perception. Br J Psychiatry. 1990;157:76–81.
36. Burns A, Jacoby R, Levy R. Psychiatric phenomena in Alzheimer's disease. III: disorders of mood. Br J Psychiatry. 1990;157:81–6.
37. Burns A, Jacoby R, Levy R. Psychiatric phenomena in Alzheimer's disease. IV: disorders of behaviour. Br J Psychiatry. 1990;157:86–94.
38. Lyketsos CG, Steinberg M, Tschanz JT, Norton MC, Steffens DC, Breitner JC. Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. Am J Psychiatry. 2000;157:708–14.
39. Ballard C, Neill D, O'Brien J, McKeith IG, Ince P, Perry R. Anxiety, depression and psychosis in vascular dementia: prevalence and associations. J Affect Disord. 2000;59:97–106.
40. Srikanth S, Nagaraja AV, Ratnavalli E. Neuropsychiatric symptoms in dementia-frequency, relationship to dementia severity and comparison in Alzheimer's disease, vascular dementia and frontotemporal dementia. J Neurol Sci. 2005;236:43–8.
41. Aharon-Peretz J, Kliot D, Tomer R. Behavioral differences between white matter lacunar dementia and Alzheimer's disease: a comparison on the neuropsychiatric inventory. Dement Geriatr Cogn Disord. 2000;11:294–8.
42. Kim JM, Lyons D, Shin IS, Yoon JS. Differences in the behavioral and psychological symptoms between Alzheimer's disease and vascular dementia: are the different pharmacologic treatment strategies justifiable? Hum Psychopharmacol. 2003;18:215–20.

43. Johnson DK, Watts AS, Chapin BA, Anderson R, Burns JM. Neuropsychiatric profiles in dementia. Alzheimer Dis Assoc Disord. 2011;25:326–32.
44. Starkstein SE, Sabe L, Vazquez S, Teson A, Petracca G, Chemerinski E, Di Lorenzo G, Leiguarda R. Neuropsychological, psychiatric, and cerebral blood flow findings in vascular dementia and Alzheimer's disease. Stroke. 1996;27:408–14.
45. Ikeda M, Fukuhara R, Shigenobu K, Hokoishi K, Maki N, Nebu A, et al. Dementia associated mental and behavioural disturbances in elderly people in the community: findings from the first Nakayama study. J Neurol Neurosurg Psychiatry. 2004;75:146–8.
46. Fuh JL, Wang SJ, Cummings JL. Neuropsychiatric profiles in patients with Alzheimer's disease and vascular dementia. J Neurol Neurosurg Psychiatry. 2005;76:1337–41.
47. Pinto C, Seethalakshmi R. Behavioral and psychological symptoms of dementia in an Indian population: comparison between Alzheimer's disease and vascular dementia. Int Psychogeriatr. 2006;18:87–93.
48. Chiu PY, Liu CH, Tsai CH. Neuropsychiatric manifestations in vascular cognitive impairment patients with and without dementia. Acta Neurol Taiwan. 2007;16:86–91.
49. Fernández-Martínez M, Castro J, Molano A, Zarranz JJ, Rodrigo RM, Ortega R. Prevalence of neuropsychiatric symptoms in Alzheimer's disease and vascular dementia. Curr Alzheimer Res. 2008;5:61–9.
50. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44:2308–14.
51. Staekenborg SS, Su T, van Straaten EC, Lane R, Scheltens P, Barkhof F, van der Flier WM. Behavioural and psychological symptoms in vascular dementia; differences between small- and large-vessel disease. J Neurol Neurosurg Psychiatry. 2010;81:547–51.
52. Andin U, Gustafson L, Brun A, Passant U. Clinical manifestations in neuropathologically defined subgroups of vascular dementia. Int J Geriatr Psychiatry. 2006;21:688–97.
53. Botez SA, Carrera E, Maeder P, et al. Aggressive behavior and posterior cerebral artery stroke. Arch Neurol. 2007;64:1029–33.
54. Kim JS, Choi S, Kwon SU, et al. Inability to control anger or aggression after stroke. Neurology. 2002;58:1106–8.
55. Staekenborg SS, Gillissen F, Romkes R, Pijnenburg YA, Barkhof F, Scheltens P, van der Flier WM. Behavioural and psychological symptoms are not related to white matter hyperintensities and medial temporal lobe atrophy in Alzheimer's disease. Int J Geriatr Psychiatry. 2008;23:387–92.

Part III
Cerebrovascular Disease and Psychiatric Disturbances

Chapter 12
Psychological and Psychiatric Triggers and Risk Factors for Stroke

Vincent Guiraud and Emmanuel Touzé

Abstract Recent evidence suggests that psychiatric and/or psychological factors could be independent risk factors for stroke. Some of these factors may act as stroke triggers producing short-term physiological changes that may directly lead to stroke onset. Most data is related to four distinct domains: (1) depression and/or anxiety and related syndromes, (2) personality and character traits, (3) psychological stress, and (4) psychotropic medication. Some factors (e.g., depression) are closely related to stroke risk, and there is some evidence that psychological stress could be an important risk factor. However, many studies have methodological limitations (small sample size, lack of adjustment for stroke risk factors, or residual confounding) and lack of standardized definition and/or measurement. Data about stroke triggers is scarce but epidemiological studies suggest a triggering effect of acute or subacute life stress exposure. The potential pathophysiological ways by which psychiatric and/or psychological factors may promote stroke include a higher frequency of unhealthy behaviors and direct biological effects on the cardiovascular system, notably through activation of the sympathetic nervous system. More research is still needed to improve measurement and to better investigate the impact of psychiatric and/or psychological factors. The clarification of pathophysiological mechanisms could help to consider preventive strategies.

Keywords Stroke • Risk factor • Trigger • Depression • Psychological stress • Life events • Etiology

V. Guiraud (✉) • E. Touzé
Université Paris Descartes, Sorbonne Paris Cité,
INSERM UMR S894, Service de Neurologie et Unité Neurovasculaire,
Pôle Raymond Garcin, Hôpital Sainte-Anne,
1, rue Cabanis, Paris 75674, France
e-mail: v.guiraud@ch-sainte-anne.fr

J.M. Ferro (ed.), *Neuropsychiatric Symptoms of Cerebrovascular Diseases*,
Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-1-4471-2428-3_12, © Springer-Verlag London 2013

Introduction

Over the past few decades, important progress has been made in our understanding of pathophysiological pathways responsible for stroke. The role of traditional risk factors (e.g., hypertension, diabetes, dyslipidemia) is now well established [1], and it has recently been shown that ten risk factors account for 90 % of the attributable risk of ischemic stroke [2]. In 1971, from a series of 32 stroke patients, Adler et al. [3] reported that "stroke typically occurred during a period of sustained or intermittent and often severe emotional disturbance which had been going on for weeks or months and which sometimes had become intensified shortly before the stroke occurred." More recently, results of several epidemiological studies have suggested that psychiatric and/or psychological factors could be independent risk factors for stroke [4].

Compared to traditional risk factors, psychiatric and/or psychological factors have been far less investigated for many reasons, including a lack of awareness of the potential link, the lack of obvious preventive strategy, potentially smaller effects, and most importantly a lack of consensus on definition and/or measurement of the vast majority of these factors. For example, psychological stress is difficult to define objectively as it encompasses several complex notions ranging from external stressors, such as job stress, life events, and financial problems, to potential reactions to stress such as depression, vital exhaustion, anxiety, and psychological distress [5]. Moreover, psychiatric and/or psychological factors are often considered as individual entities, although it is widely recognized that they tend to cluster. Thus, unless a range of potential psychiatric and psychological risk factors is examined concurrently, it is difficult to identify the independent contribution of each of them.

Likewise, it has been suggested that transient exposure to some factors or activities, better known as triggers, could also play a role in precipitating stroke [6, 7]. Although, several case-crossover studies have already demonstrated triggering effects of several psychiatric and/or psychological factors (e.g., life events, emotional distress, anger, negative emotions) on myocardial infarction onset [8, 9], the role of these transient factors as potential stroke triggers is less well established [7].

A better knowledge of psychological and/or psychiatric risk factors for cerebrovascular disease may have therapeutic implications for stroke prevention, because some of these factors (e.g., depression) are treatable and may improve our knowledge in the pathophysiology of stroke. This chapter reviews the relationships between psychiatric and/or psychological risk factors or triggers and stroke, focusing on mood disorders, personality and character traits, psychological stress, and psychotropic medication.

Psychiatric and Psychological Risk Factors

Mood Disorders and Related Syndromes

Depression

Depression is a broad and highly prevalent psychiatric disorder in the general population. The World Health Organization ranks depression as the fourth leading cause of disability worldwide [10]. In the United States, a survey showed that about 5 % of

adults experienced major depressive disorders in the prior 12 months and about 13 % a major depressive disorders during their lifetime [11]. Depression is twice as common in women as in men [12]. The consequences of depression are severe in terms of reduced well-being and quality of life [13]. Moreover, depression is associated with substantial impairment (e.g., social, work domains) [12, 14], comorbidity (e.g., anxiety, substance use) [12], poor health [15], and mortality mainly by suicide [16].

Based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria [17], the diagnosis for major depressive episode requires a period of at least 2 weeks during which there is depressed mood and/or loss of interest or pleasure in nearly all activities and at least four additional symptoms (e.g., changes in appetite or weight, decreased energy) (Table 12.1). The symptoms must persist for most of the day, nearly every day, for at least 2 consecutive weeks and be accompanied by clinically significant distress or impairment in social, occupational, or other important areas of functioning [17]. The severity of the disorder is determined by both the number and severity of symptoms, as well as the degree of functional impairment [17].

A strong body of evidence demonstrates the coexistence of depression in many chronic medical illnesses [18]. Onset of a disabling medical illness is, understandably, a risk factor for a depressive episode in vulnerable persons. However, depression might also be a causal factor in different illnesses, such as ischemic heart disease and stroke [19, 20]. Several meta-analyses have shown that depression is associated with an increased risk of coronary heart disease [19, 21, 22]. Two further recent prospective studies have suggested that depressive symptoms are associated with an increased short-term risk of coronary heart disease and long-term risk of stroke [23, 24]. However, most of the studies that have assessed the association between depression and stroke have methodological limitations including small sample size, restriction to specific subgroups, lack of adjustment for stroke risk

Table 12.1 Diagnostic criteria for major depressive episode [10]

A.	Five or more of the following symptoms during the same 2-week period with a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure
	1. Depressed mood
	2. Markedly diminished interest or pleasure in all or almost all activities
	3. Significant weight loss or decrease or increase in appetite
	4. Insomnia or hypersomnia
	5. Psychomotor agitation or retardation
	6. Loss of energy or fatigue
	7. Feeling of worthlessness or excessive or inappropriate guilt
	8. Diminished ability to think or concentrate or indecisiveness
	9. Recurrent thoughts of death, 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 (i.e., major depressive episode and manic 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., drug of abuse, medication) or a general medical condition
E.	The symptoms are not better accounted for by bereavement

Table 12.2 Characteristics of studies assessing the association between depression and the risk of incident stroke [25]

Source	No. of participants	No. of stroke cases	Follow-up (years)	Male (%)	Baseline mean age (years)	Depression measures	End point definition	Stroke ascertainment	Hazard ratios (95 % CI)	Prior stroke excluded
Vogt et al.(United States) [26]	2,573	NA	15	46	<65	A depression index, top vs. bottom tertile	Nonfatal ischemic or hemorrhagic stroke	Medical records and death certificates	0.84 (0.57–1.22)	Yes
Wassertheil-Smoller et al. (United States) [27]	4,367	204	Mean 4.5	44	72	20-item CES-D ≥16	Nonfatal and fatal ischemic or hemorrhagic stroke	Medical records	1.21 (1.08–1.35)	No
Everson et al. (United States) [28]	6,676	169	29	46	43	18-item HPLDS ≥5	Fatal ischemic or hemorrhagic stroke	Death certificates	1.55 (0.97–2.47)	Yes
Simons et al. (Australia) [29]	2,805	306	Median 8.2	44	65	CES-D, top tertile vs. bottom tertile	Nonfatal or fatal ischemic stroke	Medical records	1.41 (1.01–1.96)	No
Whooley et al. (United States) [30]	7,518	94	Mean 6	0	72	15-item GDS ≥6	Fatal ischemic or hemorrhagic stroke	Medical records	1.70 (0.80–3.50)	No
Jonas and Mussolino (United States) [31]	6,095	483	Mean 16	40–50	49	GWB-D, score 0–12	Nonfatal and fatal ischemic or hemor-rhagic stroke	Hospital records and death certificates	1.73 (1.30–2.31)	Yes
Larson et al. (United States) [32]	1,703	95	Mean 13	38	<65	DIS-diagnosed MDD	Nonfatal and fatal ischemic or hemorrhagic stroke	Self-report and death certificates	2.67 (1.08–6.63)	Yes

Ohira et al. (Japan) [33]	879	69	Mean 10.3	35	Mean between 56 and 62	20-item Zung SDS, top vs. bottom tertile	Nonfatal and fatal ischemic or hemorrhagic stroke	Register database and death certificates	1.90 (1.10–3.50)	Yes
Ostir et al. (United States) [34]	2,478	340	6	31	≥65	Modified 20-item CES-D ≥9	Nonfatal and fatal ischemic or hemorrhagic stroke	Self-report and death certificates		Yes
May et al. (United Kingdom) [35]	2,124	130	14	100	57	30-item GHQ ≥5	Nonfatal and fatal ischemic stroke	Medical records	1.26 (0.85–1.85)	Yes
Yasuda et al. (Japan) [36]	817	20	7.5	39	72	30-item GHQ, depression subscale, ≥1 standard score	Fatal ischemic or hemorrhagic stroke	Death certificates	3.62 (1.12–11.70)	No
Wassertheil-Smoller et al. (United States) [37]	93,676	751	Mean 4.1	0	Range 50–79	6-item CES-D ≥5, self-reported depression history	Nonfatal and fatal ischemic or hemorrhagic stroke	Self-report and medical records	1.01 (0.78–1.30)	No
Gump et al. (United States) [38]	11,216	167	Median 18.4	100	46	20-item CES-D ≥16	Fatal ischemic or hemorrhagic stroke	Death certificates	1.48 (0.93–2.36)	Yes

(continued)

Table 12.2 (continued)

Source	No. of participants	No. of stroke cases	Follow-up (years)	Male (%)	Baseline mean age (years)	Depression measures	End point definition	Stroke ascertainment	Hazard ratios (95 % CI)	Prior stroke excluded
Avendano et al. (United States) [39]	2,812	270	12	42	≥65	20-item CES-D ≥21	Nonfatal and fatal ischemic or hemorrhagic stroke	Self-report and medical records	Age ≤74 3.05 (1.63–5.70) Age >75 0.95 (0.46–1.98)	Yes
Stümer et al. (Germany) [40]	3,920	62	Median 8.5	48	53	Standardized personality questionnaires, top vs. medium tertile	Nonfatal and fatal ischemic or hemorrhagic stroke	Medical records and death certificates	1.53 (0.83–2.80)	Yes
Arbelaez et al. (United States) [41]	5,525	611	Median 11	42	73	10-item CES-D ≥9	Nonfatal and fatal ischemic stroke	Self-report and medical records	1.25 (1.02–1.53)	Yes
Kawamura et al. (Japan) [42]	535	103	Mean 6.3	40	≥65	SDS or modified version, and physician diagnosis	Fatal ischemic or hemorrhagic stroke	Death certificates	1.25 (0.82–1.90)	Yes
Salaycik et al. (United States) [43]	4,120	228	Mean 8	46	64	20-item CES-D ≥16; or ADM use	Nonfatal ischemic or hemorrhagic stroke	Medical records	Age <65 3.59 (1.76–7.33) Age ≥65 0.93 (0.59–1.47)	Yes
Bos et al. (the Netherlands) [44]	4,424	291	Mean 5.8	40	72	20-item CES-D ≥16	Nonfatal ischemic or hemorrhagic stroke	Medical records	1.21 (0.80–1.83)	Yes

Lee et al. (Taiwan, China) [45]	4,962	98	Mean 5	44	Range 18–44	Physician diagnosis	Nonfatal ischemic or hemorrhagic stroke	Medical records	5.43 (3.47–8.41)	Yes
Liebetrau et al. (Sweden) [46]	401	56	Mean 3	30	All 85 only	*DSM-III* diagnosed MDD and other types of depression	Nonfatal and fatal ischemic or hemorrhagic stroke	Self-report and medical records	2.60 (1.50–4.60)	Yes
Surtees et al. (United Kingdom) [47]	20,627	595	Median 8.5	43	Range 41–80	HLEQ related to *DSM-IV* MDD	Nonfatal and fatal ischemic or hemorrhagic stroke	Medical records	1.08 (0.67–1.75)	Yes
Whooley et al. (United States) [48]	1,017	47	Mean 4.8	80	67	9-item PHQ ≥10	Nonfatal and fatal ischemic or hemorrhagic stroke	Self-report and medical records	1.47 (0.70–3.11)	No
Wouts et al. (the Netherlands) [49]	2,965	176	Mean 7.7	48	71	CES-D ≥16; or DIS-diagnosed MDD	Nonfatal and fatal ischemic or hemorrhagic stroke	Self-report and medical records	No cardiac disease 0.44 (0.06–3.22) Cardiac disease 2.66 (0.61–11.56)	Yes
Glymour et al. (United States) [50]	19,087	1,864	Mean 8.1	41	66	8-item CES-D ≥3	Nonfatal and fatal ischemic or hemorrhagic stroke	Self-report	1.25 (1.12–1.39)	Yes

(continued)

Table 12.2 (continued)

Source	No. of participants	No. of stroke cases	Follow-up (years)	Male (%)	Baseline mean age (years)	Depression measures	End point definition	Stroke ascertainment	Hazard ratios (95 % CI)	Prior stroke excluded
Nabi et al. (Finland) [24]	23,282	129	7	41	Range 20–54	21-item BDI ≥10	Nonfatal and fatal ischemic or hemorrhagic stroke	Medical records	0.87 (0.57–1.32)	Yes
Peters et al. (International) [51]	2,656	97	Mean 2.1	39	83	15-item GDS ≥6	Nonfatal and fatal ischemic or hemorrhagic stroke	Self-report and medical records	1.82 (1.19–2.78)	No
Pan et al. (United States) [25]	80,574	1,033	Mean 6	0	66	MHI-5 ≤52 or self-reported diagnosis or ADM use	Nonfatal and fatal ischemic or hemorrhagic stroke	Self-report and medical records and death certificates	1.29 (1.13–1.48)	Yes

Abbreviations: *ADM* antidepressant medication, *BDI* Beck Depression Inventory, *CES-D* Center for Epidemiologic Studies Depression Scale, Diagnostic Interview Schedule, DSM *Diagnostic and Statistical Manual of Mental Disorders*, *GDS* Geriatric Depression Scale, *GHQ* General Health Questionnaire, *GWB-D* General Well-Being Schedule-Depressed Mood Scale, *HLEQ* Health and Life Experiences Questionnaire, *HPLDS* Human Population Laboratory Depression Scale, *LMHI* Langner Mental Health Index, *MDD* major depressive disorder, *MHI-5* 5-item Mental Health Index, *NA* not applicable, *PHQ* Patient Health Questionnaire, *SDS* Zung Self-Rating Depression Scale

factors or residual confounding, and lack of standardized definition and/or measurement of depression (Table 12.2) [24, 41, 43–45, 47, 50]. There is indeed a great heterogeneity across studies regarding assessment of depression (scales vs. interviews, different cutoff points for the same scale, the use of cutoff points vs. continuous scores) (Table 12.2). Furthermore, the evidence linking depression to stroke is mainly confined to first-ever stroke as post-stroke depression could not be easily differentiated clinically from endogenous depression [52, 53], Finally, in order to limit the risk of reverse causality (i.e., depression being the consequence rather than the cause of stroke), studies have generally been prospective, but in the absence of brain imaging at baseline, it cannot be excluded that undiagnosed strokes (e.g., silent stroke) may have caused depression (vascular depression hypothesis) [54]. Despite these potential limitations, two meta-analyses of prospective studies have recently shown that depressive symptoms at baseline are associated with a subsequent risk of stroke [25, 54]. Pan et al. [25] showed that depression increased the risk of any stroke (HR = 1.45; 95 % CI, 1.29–1.63) and fatal stroke (HR = 1.55; 1.25–1.93) (meta-analysis including 317,540 individuals and 8,478 incident stroke events).

Some evidence indicates that depression has both behavioral and direct pathophysiological effects. Thus, depression can induce neuroendocrine dysregulations (e.g., sympathetic nervous system activation, dysregulation of the hypothalamic–pituitary–adrenocortical axis) [55], hematologic (platelet aggregation dysfunction) [55] and immunological/inflammation (C-reactive protein, interleukin-1, and interleukin-6) effects [56, 57]. Depression has also been associated with hypertension and diabetes through increased adrenergic activity [58–60], related to poor health lifestyle, such as smoking [61], low physical activity [62], obesity [63], and reduced medication compliance, which themselves increase the risk of stroke. Depression is also associated with an elevated risk of cardiac arrhythmia [64]. Finally, antidepressant medications may also increase the risk of stroke (see section “Psychotropic Medication”) [65].

Depression-Related Syndromes

Psychological distress is a nonspecific term that encompasses sadness, frustration, anxiety, and a number of other negative mood states [66]. It also refers to symptoms of psychiatric disorders and normal emotional responses to adversity [66]. Only two studies, with conflicting results, have specifically investigated the role of psychological distress as a risk factor for stroke (Table 12.2) [35, 47]. Psychological distress was measured either with the General Health Questionnaire [67], or the Mental Heath Inventory [68], both comprising one or more items representing anxiety and depression but without distinguishing the specific nature of the distress [67]. Surtees et al. [47] found an association between psychological distress and stroke, whereas there was no association between major depressive disorder and stroke suggesting that psychological distress is a distinct entity from depression. This finding is also supported by a recent prospective study (6,576 healthy participants) showing an

association between psychological distress and a combined cardiovascular outcome including stroke [69].

Apart from psychological distress, there is also evidence that other depressive-related syndromes such as emotional well-being, or vital exhaustion, might be independent risk factors for stroke. Although these factors have been considered as distinct entities from depression in several prospective studies, there is undoubtedly an overlap with depression. Emotional well-being has been investigated using the Center for Epidemiologic Study-Depression Scale [70]. Although this scale usually assessed the presence of depression, Ostir et al. [34] used it to explore negative and positive affects. Positive affect is not simply the lack of depressive symptoms as persons in a positive mood are more likely to engage in social relationships, to be optimistic about their future, to cope successfully with stressful situations, and to feel in control of their live [34]. Vital exhaustion is characterized by unusual fatigue, loss of energy, increased irritability, and feelings of demoralization [71]. This factor has been examined with the Maastricht Interview Vital Exhaustion Scale. Studies that assessed the association between emotional well-being or vital exhaustion and stroke are summarized in Table 12.3.

Anxiety and Related Disorders

Generalized anxiety is a chronic and impairing disorder defined in the DSM-IV as the association between excessive anxiety and worry, with difficulties in controlling the worry, and at least three other symptoms (e.g., being easily fatigued, muscle tension) (Table 12.4) [17]. Although there is a high degree of overlap between anxiety and depression symptoms, anxiety can be distinguished from depressive disorders [76]. A few large-scale community studies have reported significant association between anxiety disorders and cardiac events [77–79], whereas no study specifically assessed the association between anxiety disorders and stroke. However, three prospective studies examined the association between anxiety and/or depression and a combined cardiovascular outcome including stroke [75, 80, 81]. Two studies found a significant association between anxiety and/or depression and incident cardiovascular events [80, 81]. Rothenbacher et al. [80] have compared anxiety and depression alone versus jointly in predicting cardiovascular disease outcomes and showed an association with anxiety alone. It is however interesting to note that all patients included in these studies had a recent history of cardiac events (e.g., coronary artery revascularization, angina pectoris, or congestive heart failure), suggesting that anxiety disorders could be the consequence rather than the cause (i.e., reverse causal hypothesis) [82].

A few studies have also investigated the association between panic disorders and stroke [83–85]. The diagnosis of panic disorder is based on recurrent unexpected panic attacks, which consist of sudden onset of intense fear or discomfort associated with at least four or more cognitive and somatic symptoms [17]. Weissman et al. [85] found that the risk of stroke was more than doubled among 60 individuals with panic disorder compared with 3,778 healthy individuals. Smoller et al. [84] showed

Table 12.3 Characteristics of studies assessing the association between emotional well-being or vital exhaustion and the risk of stroke

Source	Study design	No. of participants	No. of stroke cases	Follow-up, years or recruitment phase	Male (%)	Baseline age (years)	Psychological factor measures	Stroke ascertainment	Risk estimates (95 % CI)	Prior stroke excluded
Emotional well-being										
Ostir et al. (United States) [34]	Cohort	2,478	340	6 (1986–1992)	31	Age ≥65	Modified 20-item CES-D ≥9	Self-report and death certificates	RR_a = 1,04 (1.01–1.09)	Yes
Vital exhaustion										
Schuitemaker et al. (the Netherlands) [72]	Cohort	2,432	14	Median 4.25	50	Mean 51	Maastricht Interview Vital Exhaustion Scale	Register database	$p<0.002$	Yes
Schwartz et al. (United States) [73]	Cohort	13,066	202	6.3 (1987–1990 and 1992)	44	Mean 57	Maastricht Interview Vital Exhaustion Scale	Medical records	HR_a = 1.76 (1.23–2.51)	Yes
Purebl et al. (Hungary) [74]	Cross-sectional	11,122	501	2002	NR	Age ≥35	Maastricht Interview Vital Exhaustion Scale	Self-report	NR (no association)	NA
Kornerup et al. (Denmark) [75]	Cohort	9,186	409	6–9 (1991 and 1994–2000)	43	Mean 59 (women), 57 (men)	Maastricht Interview Vital Exhaustion Scale	Register database and medical records	Women HR_a = 2.19 (1.31–3.66) Men HR_a = 0.83 (0.35–1.96)	Yes

Abbreviations: RR_a adjusted relative risk, HR_a adjusted hazard ratio, *CES-D* Center for Epidemiologic Studies Depression Scale, *NR* not reported, *NA* not applicable

Table 12.4 Diagnostic criteria for generalized anxiety disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not and for at least 6 months, about a number of events or activities (such as work or school performance)
B. The person finds it difficult to control the worry
C. The anxiety and worry are associated with three (or more) of the following six symptoms:
1. Restlessness of feeling keyed up or on edge
2. Being easily fatigued
3. Difficulty concentrating or mind going blank
4. Irritability
5. Muscle tension
6. Sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)
D. The focus of the anxiety is not confined to features of an Axis I disorder
E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
F. The disturbance is not due to the direct physiological effects of a substance (e.g., drug abuse, medication) or general medical condition (e.g., hyperthyroidism) and does not occur exclusively during a mood disorder, a psychotic disorder, or a pervasive developmental disorder

Adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [17]

that women who had experienced panic attacks in the 6-month period before interview had a threefold higher risk of heart attack or stroke during a 5-year follow-up period than those who did not experience such attacks. Finally, Chen et al. [83] found that one in six patients with panic disorder experienced a stroke during a 3-year follow-up period corresponding to a twofold higher risk of stroke compared to people without panic disorder.

Individuals with anxiety disorders have impaired heart rate variability or increased sympathetic stimulation which could facilitate arrhythmias [86]. Anxiety could also induce behavioral effects since subjects with anxiety are prone to unhealthy lifestyle behaviors [87].

Other Psychiatric Disorders

Among other psychiatric disorders, schizophrenia has been associated with high medical morbidity or mortality rates [88]. Several prospective studies have shown an association between schizophrenia and mortality from cardiovascular diseases [89, 90], but little is known about the risk of stroke. In a retrospective study, Curkendall et al. [91] reported that people with schizophrenia were at a higher risk for stroke, but the most convincing evidence arises from two recent prospective studies [92, 93]. Lin et al. [92] showed that young schizophrenia patients have a twofold higher risk of stroke within 5 years of their hospitalization for acute exacerbation of schizophrenia as compared with a control group of patients hospitalized for an appendectomy (HR = 2.02, 1.53–2.54). Tsai et al. [93] have found that the likelihood of developing stroke was greater among patients with schizophrenia as compared with controls over a 5-year follow-up period (HR = 1.13, 1.06–1.22). These results are also supported by a large community retrospective cohort study

showing that people with severe mental illnesses (e.g., schizophrenia, psychoses) have an increased risk of death from stroke and coronary heart disease [94]. However, it is interesting to note that in most of these studies, traditional vascular risk factors were insufficiently considered as potential confounders.

Patients with schizophrenia have a high burden of risk factors, notably because of unhealthy lifestyle choices, lack of physical activity, poor compliance to drugs, inequity for the access to specialized medical care, and metabolic syndrome induced by antipsychotic drugs [88, 93, 95–97].

Personality and Character Traits

The first description of the type A behavior [98] has raised further interest in the relationship between personality patterns or individuals character traits and cardiovascular diseases.

Anger

Anger is conceptualized in the literature in terms of the degree to which people have this emotion and the means by which they express it [99]. The predisposition for frequent, intense, long-lasting anger is a relatively enduring and stable personality attribute known as *trait anger*. On the other hand, anger expression refers to how anger is managed, that is, whether it is expressed outwardly, held in, or controlled [99]. Spielberger et al. [99] consider that the opposite of expressing anger (*anger out*) was not its suppression (*anger in*) but its control (*anger control*). *Anger in* is defined as a tendency to experience angry affect and stay aroused, whereas *anger control* should be seen as a tendency to engage in calming activities that lower arousal and emotions [100].

High levels of anger have been associated with cardiac diseases [101], whereas less is known about the relationship between anger and the risk of stroke. In most studies, anger was investigated with the Spielberger Anger Scale, a questionnaire that measures a trait rather than a state (i.e., the frequency at which a person outwardly expresses anger towards other persons or objects when provoked in daily life) [99]. *Trait anger* has been modestly associated with an increased risk of stroke, especially with younger participants (<60 years) having nearly three times greater risk for ischemic stroke than those who reported having low *trait anger* (Table 12.5) [103]. Everson et al. [102] have found an association between high levels of *anger out* and incident stroke (Table 12.5). Moreover, in a subgroup of patients with prevalent coronary heart disease, those who were most prone to *anger out* had almost six times greater risk for stroke as compared to those who were less prone (Table 12.5). This finding was not replicated by Eng et al. [104] who found that moderate levels of *anger out* were protective against stroke (Table 12.5). Furthermore *anger in* [102] and *anger control* [40, 102] have not been associated with stroke (Table 12.5). To clarify the effects of anger on the risk of stroke, future studies should simultaneously assess different aspects of anger, including frequency, intensity, duration,

Table 12.5 Characteristics of studies assessing the association between personality and character traits and the risk of stroke

Source	Study design	No. of participants	No. of stroke cases	Follow-up years or recruitment phase	Male (%)	Baseline age (years)	Personality or character trait measures	Stroke ascertainment	Risk estimates (95 % CI)	Prior stroke excluded
Anger										
Everson et al. (Finland) [102]	Cohort	2,074	64[a]	Mean 8.3 (1984 and 1989–1996)	100	Mean 53	Spielberger Anger Expression Scale	Register database and hospital records	Anger out $RR_a = 2.03$ (1.05–3.94) Anger in $RR_a = 0.98$ (0.56–1.72)	Yes
Williams et al. (United States) [103]	Cohort	13,851	257[a]	Median 6.4 (1987 and 1989–1997)	44	Mean 57	Spielberger Trait Anger Scale	Self-report and hospital records	Trait anger (≤60 years) $HR_a = 1.96$ (1.06–3.62) Trait anger (>60 years) $HR_a = 0.60$ (0.27–1.34)	Yes
Eng et al. (United States) [104]	Cohort	23,522	57[c]	2 (1996–1998)	100	Range 50–85	Spielberger Trait Anger Scale	Medical records and death certificates	Anger out $RR_a = 0.42$ (0.20–0.88)	Yes
Stürmer et al. (Germany) [40]	Cohort	4,267	62[c]	Median 8.5 (1992 and 1995–2002 and 2003)	49	Mean 53	Standardized personality question-naires	Medical records and death certificates	Anger control $RR_a = 0.99$ (0.53–1.86)	No
Type A behavior										
Gentry et al. (United States) [105]	Case control	28 (14 controls)	28[b]	1972–1973	100	Range 39–65	Jenkins Activity Survey	NA	NR (no associa-tion)	No

Goetz et al. (Switzerland) [106]	Case control	19 (38 controls)	19[b]	1996	0	Mean 57	Bortner Personality Inventory	NA	$p<0.01$	No
Mann et al. (United Kingdom) [107]	Cohort	7,219	73[c]	5 (1977–1982)	NR	Range 35–64	Bortner Personality Inventory	Medical records	NR (no association)	No
Kim et al. (South Korea) [108]	Case control	224 (100 controls)	224[a]	1990–1995	67	Mean 57	Eysenck Personality Inventory	NA	Tenseness $OR_a = 1.1$ (1.02–1.20)	No
Zodpey et al. (India) [109]	Case control	166 (166 controls)	166[a]	NR	59	NR	NR	NA	OR = 3.0 (0.31–28.84)	No
Fernández-Concepcion et al. (Cuba) [110]	Case control	88 (99 controls)	88[a]	2000–2001	NR	NR	Jenkins Activity Survey	NA	$p<0.01$	No
Stürmer et al. (Germany) [40]	Cohort	4,267	62[c]	Median 8.5 (1992 and 1995–2002 and 2003)	49	Mean 53	Standardized personality questionnaires	Medical records and death certificates	Time urgency $RR_a = 1.68$ (0.86–3.25)	No
Pessimism										
Nabi et al. (Finland) [24]	Cohort	23,216	105[c]	Mean 7 (1998–2005)	41	Range 20–54	Life Orientation Test-Revised	Register database	Low pessimism $HR_a = 0.52$ (0.29–0.93)	Yes

(continued)

Table 12.5 (continued)

Source	Study design	No. of participants	No. of stroke cases	Follow-up years or recruitment phase	Male (%)	Baseline age (years)	Personality or character trait measures	Stroke ascertainment	Risk estimates (95 % CI)	Prior stroke excluded
Neuroticism or extraversion										
Nakaya et al. (Japan) [111]	Cohort	41,442	131[c]	11 (1990–2011)	NR	Mean 51	Eysenck Personality Inventory	Register database and death certificates	Neuroticism $RR_a = 1.0$ (0.7–1.4) Extraversion $RR_a = 0.9$ (0.6–1.2)	Yes
Shipley et al. (United Kingdom) [112]	Cohort	5,424	147[c]	21 (1984 and 1985–2005)	55	Mean 45	Eysenck Personality Inventory	Register database and death certificates	Neuroticism $HR_a = 1.05$ (0.99–1.11) Extraversion $HR_a = 0.98$ (0.92–1.04)	No
Personality disorders										
Moran et al. (United Kingdom) [113]	Cross-sectional	8,580	51[a]	2000	50	Mean 43	Structured Clinical Interview for Axis II Personality Disorders	Self-report	Any personality disorder $OR_a = 1.9$ (1.1–3.5)	NA
McCarron et al. (Ireland) [114]	Cohort	9,239	87[c]	Median 41 (1948–1968)	100	Mean 21	Physician diagnosis	Register database	Any personality disorder $HR_a = 1.95$ (1.06–3.59)	No

Abbreviations: RR_a adjusted relative risk, HR_a adjusted hazard ratio, OR_a adjusted odds ratio, *NR* not reported, *NA* not applicable

[a]The outcome for this study is ischemic and/or hemorrhagic stroke

[b]The outcome for this study is ischemic stroke

[c]The outcome for this study is nonfatal and fatal stroke

coping styles, and the potential for effect modification by socioeconomic status should also be considered [104].

Anger is associated with excessive sympathetic arousal and neuroendocrine activation, especially under conditions of stress, and in individuals who experienced frequent episodes of anger [115–117]. In addition, these changes could also induce endothelial damages because of increased blood pressure and flow velocity in response to an exaggerated discharge of catecholamines [118–120]. Furthermore, catecholamines can increase platelet adhesion and aggregation [121], vascular lipid uptake [122], and activation of macrophages [123]. Persons who have high levels of anger may also be more likely to engage in unhealthy behaviors [103]. Finally, Anger may also trigger stroke [124], and this triggering hypothesis may be an important conceptual framework (see section "Psychiatric and Psychological Triggers"). Persons who have high levels of anger may also be more likely to engage in adverse health behaviors [103].

Type A Behavior/Hostility

Type A behavior is characterized by aggressiveness (or hostility), ambition, competitiveness, time urgency, impatience, need for control, tenseness, behavioral alertness, and intense commitment to vocational goals [125]. This pattern has been associated with an increased risk of stroke in several studies [106, 110]; however, the association is not unequivocal and has cast doubt on the potential robustness of this pattern (Table 12.5) [105, 107, 109]. Suspecting that not all components of the type A behavior are pathogenic, this pattern has been deconstructed and it is currently admitted that, rather than whole type A behavior characteristics, only some particular dimensions (e.g., hostility, time urgency) may increase the risk of cardiovascular diseases [126]. Hostility, a broad psychological construct that encompasses various traits, such as cynicism, anger, and aggression, has been examined as a risk factor for cardiovascular events, including stroke. Only two prospective studies found conflicting results (Table 12.5) [126, 127]. Regarding other type A behavior dimensions, tenseness and need for control have been significantly associated with an elevated risk of stroke, whereas there was only a borderline significant increase with time urgency (Table 12.5) [40, 106, 108].

Type A behavior is related to hyperlipidemia [128], high daytime catecholamines excretion [129] and activation of the autonomic nervous system and the hypothalamic–pituitary axis and subsequent cardiovascular reactivity to stress [130], increased intima–media thickness [131], hypertension, vascular rigidity, and alteration of vascular smooth muscle morphology [126, 132]. Type A behavior might also have adverse effects through adverse health behaviors [133].

Personality Disorders and Temperament

Individuals with personality disorders (e.g., paranoid, borderline, schizoid) are known to be vulnerable to other psychiatric disorders such as depression and anxiety [134], but little is known about the risk of physical illnesses, especially stroke. A cross-sectional

study has reported an association between any avoidant, obsessive–compulsive, or borderline personality disorders and stroke (Table 12.5) [113]. McCarron et al. [114] investigated the relationship between some personality disorders (e.g., obsessive, paranoid, schizoid) in students and mortality (Table 12.5). Although the authors found that students with at least one personality disorders were almost twice as likely to die from stroke than healthy individuals, the association between each of these personality disorders and stroke mortality did not reach statistical significance (Table 12.5) [114]. By contrast, Stürmer et al. [40] did not find any association between some personality traits (e.g., psychoticism, internal locus of control over disease) and stroke (Table 12.5). Two prospective studies examined the influence *of neuroticism or extraversion* on all-cause mortality and stroke mortality but neither *neuroticism* nor *extraversion* was related to the risk of stroke death (Table 12.5) [111, 112]. Finally, Nabi et al. [24] have found an association between *pessimism*, defined as a general tendency to exhibit negative expectancies about the future and health outcome, and the risk of stroke (Table 12.5).

Chronic Psychological Stress

In population surveys on knowledge of stroke risk factors, stress is one of the most frequently mentioned factors, often before smoking and hypertension [135]. Many stroke patients report that they have recently endured much "stress." Whatever their own personal definition of this term, it is often connected to stressful life events. Psychological stress is often defined as an internal state of a person who perceives threats to his or her physical and psychological well-being [136]. However, in the absence of academic consensus on how stress should be defined and measured and of "gold standard" test [137], clinical studies have examined the relationship between psychological stress and stroke using various definitions and methods.

Psychological Stress

While awaiting the development of an accurate instrument, self-reported psychological stress has often been assessed in clinical studies by a single question defining "stress" as feeling tense, irritable or filled with anxiety, or as having sleeping difficulties as a result of conditions at work or at home [5, 138–140]. Using such an approach, there is evidence that psychological stress contributes to vascular diseases [4, 141]. In the INTERHEART study, the subjective perception of psychological stress, measured by a single question in the past year, was a strong and independent predictor of myocardial infarction [5]. Several prospective studies have also shown that self-perceived psychological stress was an independent risk factor for stroke [2, 138, 139, 141, 142] and stroke mortality (Table 12.6) [143]. However, these results were not replicated in two prospective studies (Table 12.6) [140, 144], and the use of a single question to assess

Table 12.6 Characteristics of studies assessing the association between chronic psychological stress and the risk of stroke

Source	Study design	No. of subjects	No. of stroke cases	Follow-up years or recruitment phase	Male (%)	Baseline age (years)	Stress measures	Stroke ascertainment	Risk estimates (95 % CI)	Prior stroke excluded
Self-reported psychological stress										
Rosengren et al. (Sweden) [141]	Cohort	6,935	112[a]	Mean 11.8 (1970 and 1973–1983)	100	Range 47–55	Feeling tense, irritable or filled with anxiety, or having sleeping difficulties	Register database and death certificates	OR_a = 1.8 (1.1–2.8)	No
Iso et al. (Japan) [143]	Cohort	73,424	657[b]	7.9 (1988 and 1990–1997)	41	Range 40–79	Level of stress in daily life	Register database and death certificates	Women OR_a = 2.24 (1.52–3.31) Men OR_a = 1.12 (0.78–1.61)	Yes
Truelsen et al. (Denmark) [140]	Cohort	12,574	929[a]	Mean 13 (1976, 1981 and 1983, 1991, and 1994–1997)	45	Range 29–53	Feeling tense, irritable or filled with anxiety, or having sleeping difficulties	Register database and medical records	OR_a = 1.13 (0.85–1.50)	Yes
Öhlin et al. (Sweden) [142]	Cohort	13,609	643[a]	Median 21 (1974 and 1980–1992)	80	Mean 45	Permanent stress	Register database	OR_a = 1.29 (1.04–1.60)	Yes
Harmsen et al. (Sweden) [138]	Cohort	7,457	1019[a]	28 (1970 and 1973–1998)	100	Range 47–55	Feeling tense, irritable or filled with anxiety, or having sleeping difficulties	Register database and medical records	OR_a = 1.25 (1.03–1.51)	Yes

(continued)

Table 12.6 (continued)

Source	Study design	No. of subjects	No. of stroke cases	Follow-up years or recruitment phase	Male (%)	Baseline age (years)	Stress measures	Stroke ascertainment	Risk estimates (95 % CI)	Prior stroke excluded
Strodl and Kenardy (Australia) [144]	Cohort	7,839	174[c]	3 (1996–1999)	0	Range 70–75	Level of stress in several issues (e.g., own health, money).	Self-report	OR_a = 1.46 (0.86–2.49)	Yes
Jood et al. (Sweden) [139]	Case control	600 (600 controls)	600[c]	1999–2003	64	Range 18–70; mean 56	Feeling tense, irritable or filled with anxiety, or having sleeping difficulties	NA	OR_a = 2.51 (1.42–4.44)	No
O'Donnel et al. (International) [2]	Case control	3,000 (3,000 controls)	3,000[a]	2007–2010	63	Range 18–70; mean 61	Combined measure of general stress at home and at work	NA	OR_a = 1.30 (1.06–1.60)	Yes
Work stress										
Virtanen et al. (Finland) [145]	Cohort	507,000	2,428[b]	14 (1980 and 1981–1994)	100	Range 25–64	Low job control	Register database	Rate $ratio_a$ = 1.19 (1.05–1.36)	NR
Gallo et al. (United States) [146]	Cohort	4,301	140[c]	10 (1992–2002)	50	Range 51–61; mean 55	Involuntary job loss	Self-report	HR_a = 2.43 (1.18–4.98)	No
André-Petersson et al. (Sweden) [147]	Cohort	7,770	134[a]	7,8 (1992 and 1996–2001)	39	Mean 55	Iso strain: high psychological demands and low decision latitude and low social support	Register database	Women HR_a = 1.51 (0.70–3.27) Men HR_a = 1.11 (0.60–2.06)	Yes

Kuper et al. (Sweden) [148]	Cohort	47,942	200[a]	Mean 11.2 (1991 and 1992–2002)	0	Range 30–50; mean 40	Job strain: high psychological demands and low decision latitude	Register database	$HR_a = 1.2$ (0.8–1.9)	Yes
							Low job control		$HR_a = 1.0$ (0.7–1.5)	
Toivanen et al. (Sweden) [149]	Cohort	3,438,502	2,147[b]	5 (1990–1995)	NR	Range 25–64	Low job control	Register database	Women Rate $ratio_a = 1.5$ (1.1–2.0) Men Rate $ratio_a = 0.9$ (0.7–1.1)	No
Tsutsumi et al. (Japan) [150]	Cohort	6,553	147[a]	Mean 11 (1992 and 1995–2005)	49	Range 18–65	Job strain	Self-report and medical records	Women $HR_a = 1.46$ (0.63–3.38) Men $HR_a = 2.53$ (1.08–5.94)	Yes
Other chronic stress										
Tanne et al. (Israel) [151]	Cohort	10,059	364[b]	23 (1963, 1965, and 1968, 1986, 1988 and 1991	100	Age ≥40	Serious or very serious family difficulties	Register database, medical records, and death certificates	$HR_a = 1.34$ (1.04–1.72)	NR
Sørensen et al. (Denmark) [152]	Cohort	51,485	1,881[a]	Mean 6 (1993 and 1997–2006)	47	Range 18–65; mean 56	Road traffic noise (10 dB higher level)	Register database	Rate $ratio_a = 1.14$ (1.03–1.25)	Yes

(continued)

Table 12.6 (continued)

Source	Study design	No. of subjects	No. of stroke cases	Follow-up years or recruitment phase	Male (%)	Baseline age (years)	Stress measures	Stroke ascertainment	Risk estimates (95 % CI)	Prior stroke excluded
Stress adaptive behavior										
André-Petersson et al. (Sweden) [153]	Cohort	238	43[a]	Mean 9.9 (1982 and 1983–1996)	100	Range 47–54	Poor adaptive profile (Stroop test)	Register database and medical records	$RR_a = 3.00$ (1.32–6.81)	No
Everson et al. (Finland) [154]	Cohort	2,303	113[a]	Mean 11.2 (1984 and 1989–1997)	100	Mean 53	Exaggerated stress-induced blood pressure reactivity	Register database	$HR_a = 1.58$ (1.07–2.33)	Yes
Surtees et al. (United Kingdom) [155]	Cohort	20,629	452[a]	Mean 7 (1996 and 2000–2005)	43	Range 41–80	Strong sense of coherence	Register database	Rate $\text{ratio}_a = 0.76$ (0.60–0.96)	Yes

Abbreviations: *NR* not reported, *NA* not applicable, OR_a adjusted odds ratio, RR_a adjusted relative risk, HR_a adjusted hazard ratio

[a]The outcome for this study is nonfatal and fatal stroke

[b]The outcome for this study is fatal stroke

[c]The outcome for this study is nonfatal stroke

self-reported psychological stress has several limitations. First, this question-combining measure of exposure, ability to cope with, and report psychological stress does not give insight into the subcomponents of psychological stress, and the association between self-perceived psychological stress and stroke may be confounded by psychological distress and emotional reactions (i.e., depression, anxiety, or sleep difficulties) [139]. Second, the validity of self-reported psychological stress is also questionable as "stress" could refer to both physical and psychological stress and there is no information of how the study participants understood the "stress" question, even though it is believed that the majority would interpret it as referring to psychological and not physical stress [140]. Third, the effect of psychological stress on stroke could be altered by coping strategies used by subjects. Thus, psychological stress in individuals who do not feel in control could be more harmful than stress that is self-inflicted or of which the person feels in control [140]. Finally, since there were no follow-up investigations of psychological stress after baseline in most studies, we do not know anything about the subjects' "stress status" after baseline and repeated measurements of psychological stress over time are necessary to give more reliable estimates of the effects of chronic psychological stress [142].

Work Stress

The job strain model of psychosocial work characteristics postulates that high psychological demands in combination with low decision latitude will result in the highest strain on the individuals [156]. Several studies have shown that high strain jobs are associated with an increased risk of coronary heart disease [157, 158]. Evidence on work stress as a risk factor for stroke is limited, and results are conflicting (Table 12.6) [145–147, 149, 150, 158]. However, these conflicting results could partly be explained by differences in work stress measures (e.g., iso strain, job strain, job control), study populations, and study durations.

Chronic Life Stress

In most studies, life stress has been defined as the numerical accumulation of major life events [159]. This method offers a clear advantage compared to other stress measures, in that measurement of life events that are easily identifiable and minimize the chance of subjective variation in responses [160]. In the INTERHEART study, exposure to major stressful life events in the past year was significantly more frequent in cases than in controls [5]. Regarding stroke risk, there is no definite conclusion from epidemiological studies because of conflicting results. Some studies found an association between chronic life events exposure and stroke [110, 161– 168], whereas others did not detect any association (Table 12.7) [144, 176–179].

Table 12.7 Characteristics of studies assessing the association between life stress and the risk of stroke

Source	Study design	No. of subjects	No. of stroke cases	Follow-up years, recruitment phase	Male (%)	Baseline age (years)	Stress ascertainment	Hazard period (control period)	Risk estimates (95 % CI)
Acute and subacute life stress									
Witte et al. (The Netherlands) [169]	Cohort	9,800,000	41[a]	17–27 June 1995, 1996, and 1997	NR	NR	European football championship (22 June 1996)	22 June 1996 (vs. 2 control periods: same period in 1995 and 1997)	Men $RR_a = 1.51$ (1.08–2.09) Women $RR_a = 1.11$ (0.80–1.56)
Antić et al. (Serbia) [170]	Case control	230 (230 controls)	230[b]	2005–2007	45	69	IRLE	24 h	OR = 1.92 (1.21–3.04)
Saposnik et al. (Canada) [171]	Cohort	NR	87[b]	2002–2004	50	72	Birthday	24 h	OR = 1.3 (1.1–1.5)
Guiraud et al. (France) [159]	Case crossover	247	247[c]	2007–2008	58	61	IRLE	1 week (vs. 3 weeks) and 1 month (vs. 5 months)	1 week $OR_a = 2.10$ (1.40–2.17) 1 month $OR_a = 2.96$ (2.19–4.00)
Antonio et al. (Italy) [172]	Cohort	135	36[c]	11 September–7 October 1998, 1999, 2000, and 2001	45	NR	Terrorist attack (11 September 2001)	11 September–7 October 2001 (vs. 3 control periods: same period in 1998, 1999, and 2000)	NR
Macko et al. (United States) [173]	Case control	34 (77 controls)	34[c]	NR	32	58	5 major life events	1 month	OR = 0.5 (0.2–1.4)

Tsuchida et al. (Japan) [174]	Cohort	34,000	8[b]	25 March–29 April 2004, 2005, 2006, and 2007	38	Mean 72	Noto Peninsula earthquake (25 March 2007)	25 March–29 April 2007 (vs. 3 control periods: same period in 2004, 2005, and 2006)	$p<0.01$
Chronic life stress									
House et al. (United Kingdom) [163]	Case control	113 (109 controls)	113[b]	1986	48	70	LEDS	6 and 12 months	6 months OR = 2.2 (0.9–5.7) 12 months OR = 2.3 (1.1–4.9)
Paschalis (Greece) [165]	Case control	84 (84 controls)	84[b]	January–June 1989	61	Mean 71	SRRS	Lifetime	$p=0.00003$
Kleinman et al. (Israel) [175]	Cohort	NR	10[b]	August 1989–March 1992	NR	NR	Persian gulf war	December 1990–March 1991 (vs. 7 control periods of 4 months)	$p<0.05$
Peris et al. (Spain) [176]	Case control	151 (151 controls)	151[b]	1994–1995 and 1996	54	Mean 72	SRRS	24 months	OR = 1.00 (0.99–1.00)
Abel et al. (United States) [177]	Case control	655 (1,087 controls)	655[c]	1993–1997	45	Mean 70	GSRRS	6 months	OR = 1.01 (0.99–1.01)
Fernández-Concepcion et al. (Cuba) [110]	Case control	88 (99 controls)	88[c]	2000–2001	NR	NR	SRRS	6 months	$p=0.02$
Tao (China) [168]	Case control	137 (137 controls)	137[c]	2000–2002	61	NR	LES	12 months	$p<0.001$

(continued)

Table 12.7 (continued)

Source	Study design	No. of subjects	No. of stroke cases	Follow-up years recruitment phase	Male (%)	Baseline age (years)	Stress ascertainmen	Hazard period (control period)	Risk estimates (95 % CI)
Sokejima et al. (Japan) [167]	Cohort	8,893	72[b]	17 January 1994–16 January 1996	NR	NR	Hanshin-Awaji earthquake (17 Jan 1995)	12 months (vs. 12 months before)	RR_a=2.4 (1.1–5.0)
Medin et al. (Sweden) [178]	Case control	65 (103 controls)	65[b]	2000–2002	62	Range 30–65	Change in working conditions	12 months	OR_a=3.08 (0.93–10.2)
Savadi-Oskouei et al. (Iran) [166]	Case control	150 (150 controls)	150[b]	2003–2004	48	NR	SRE	24 months	OR=2.7 (1.5–4.8)
Brass and Page (United States) [161]	Cohort	475 (81 controls)	44[b]	6 (1986–1992)	100	NR	Prisoner of war	NR	RR=7.50 (1.05–53.7)
Li et al. (Denmark) [179]	Cohort	314,807	1,836[b]	10.5 (1980–1997)	46	33	Death of child	NR	RR_a=1.00 (0.83–1.20)
Engström et al. (Sweden) [162]	Cohort	118,134	6,184[b]	Mean 10	45	Range 40–89	Marital dissolution (divorce or death of spouse)	NR	Divorced RR_a=1.23 (1.10–1.39) M RR_a=1.26 (1.12–1.41) W Widowed RR_a=1.13 (0.99–1.28) M RR_a=1.13 (1.02–1.24) W

Strodl and Kenardy (Australia) [144]	Cohort	7,839	174[c]	3 (1996–1999)	0	Range 70–75	24 life events	NR	OR = 0.74 (0.48–1.13)
Kornerup et al. (Denmark) [164]	Cohort	9,542	350[c]	6–9 (1991–1994 and 2001)	43	Mean 58	11 major life events	Lifetime (childhood)	HR_a = 1.41 (1.06–1.90)
								Lifetime (adulthood)	HR_a = 1.49 (1.09–2.04)

Abbreviations: OR_a adjusted odds ratio, HR_a adjusted hazard ratio, RR_a adjusted relative risk, *NR* not reported, *NA* not applicable, IRLE Interview for Recent Life Events Geriatric Social Readjustment Rating Scale, *LEDS* Life Events and Difficulties Schedule, *LES* Live Event Scale, *SRRS* Social Readjustment Rating Scale, SRE Schedule of Recent Experiences

[a]The outcome for this study is fatal myocardial infarction or stroke

[b]The outcome for this study is ischemic and/or hemorrhagic stroke

[c]The outcome for this study is ischemic stroke

Stress Adaptive Behavior

The effect of stress on the risk of stroke could be moderated by the coping possibilities and strategies used by subjects [155]. Thus, another way to assess the effects of psychological stress is to analyze patients' stress adaptive behavior. It can be speculated that individuals who chronically fail to find successful strategies in stressful situations are vulnerable to stress and thereby at higher risk of stroke. A large prospective study has found that fast adaptation to social stress was associated with a reduced risk of stroke (Table 12.6) [155]. Likewise, another prospective study has showed that poor adaptation to stress, measured by a color–word test, was associated with a threefold increase in the risk of stroke (Table 12.6) [153]. Finally, Everson et al. [154] have provided convincing evidence that stress-induced blood pressure reactivity, reflecting excessive sympathetic reactivity to stress, contributes to increased long-term risk of stroke (Table 12.6) [180, 181].

Other Type of Stress

Two single prospective studies have assessed the association between specific stressors and the risk of stroke (Table 12.6). Tanne et al. [151] have showed an association between perceived family problems, and some indicators of family support and coping style, and an increased risk of fatal stroke. Based on the hypothesis that exposure to noise from traffic activates the sympathetic and endocrine systems [182], Sørensen et al. [152] have found that road traffic noise also was an independent predictor of stroke.

Activation of the hypothalamic–pituitary–adrenal axis and the autonomic nervous system through catecholamines release [183] could increase blood pressure and pulse rates [184], platelet aggregation and inflammation [185], reduce insulin sensitivity [186, 187], and induce disturbances in hemostasis [188] and endothelial dysfunction [189]. Stressed subjects are also more likely than nonstressed subjects to have an adverse risk factor profile [140]. Moreover, chronic stress may induce exaggerated elevation in blood pressure in response to acute stress (cardiovascular reactivity hypothesis), and this reactivity is known to contribute to carotid atherosclerosis and coronary artery disease [180, 181]. Finally, it has also been suggested that stress may induce coronary vasoconstriction in areas of atherosclerotic plaques after mental stress [190], favor progression of atherosclerotic changes [191], and intima–media thickening [192]. In animal models, it has been shown that sympathetic stimulation in reaction to stress could cause cerebral vasoconstriction and reduce cerebral blood flow [193].

Psychotropic Medication

Some psychiatric disorders, such as schizophrenia or depression, have been associated with an increased risk of stroke in several prospective and case-control studies [25, 80, 93]. However, the chronic use of psychotropic medications in these

conditions could also have deleterious effects and increase the risk of cardiovascular diseases.

Antipsychotic Drugs

A meta-analysis of placebo-controlled trials has shown a significant increase in the risk of cerebrovascular events and a small but significant increase in overall mortality [194], associated with the use of atypical antipsychotic drugs in demented patients [195]. These findings are also supported by a recent systematic review including observational studies [97]. This systematic review has also shown that conventional antipsychotics seem to be associated with a higher risk compared to atypical antipsychotics [196], and the risk of stroke is not confined to patients with dementia [97]. Regarding the effects of antipsychotics in psychiatric populations, few studies are available. Jerrell and McIntyre [197] found no association between antipsychotic use and cerebrovascular disorders in a retrospective cohort study. This negative result was also supported by those of two retrospective studies conducted in children and adolecents [198], and in elderly psychiatric inpatients [199]. Only one study has suggested an increased risk of fatal stroke in patients with severe mental illnesses receiving antipsychotics [94].

Potential pathophysiological mechanisms include immunohematologic changes (e.g., increased coagulation factors, homocysteine, abnormal phospholipid metabolism), cardiovascular effects (e.g., enhancement of atrial fibrillation, orthostatic hypotension), inflammatory disturbances (e.g., increase in interleukin-6, pro-inflammatory cytokines), and underlying illnesses known to increase by themselves the risk of stroke (e.g., dementia, mental illness) [97].

Antidepressant Drugs

Selective serotonin reuptake inhibitors (SSRIs) are usually considered as the first line therapy for depression, notably in elderly patients [200]. There is a growing number of case reports attributing cerebral bleeding events to SSRI use, although pathophysiological mechanisms are still unclear. Among studies (mostly case-control studies) that examined the association between SSRI use and the risk of hemorrhagic stroke [65, 201–207], only two have found a significant association [65, 206]. However, the main unanswered question is whether the association between antidepressant use and cerebrovascular morbidity and mortality is truly related to drug exposure or to underlying differences in other vascular risk factors, including depression, among the exposed groups [65, 202, 204, 206]. The main potential pathophysiological hypothesis is that SSRIs block serotonin reuptake in platelets resulting in a depletion of platelet serotonin after several weeks of treatment, thus increasing the risk of bleeding [208, 209].

SSRIs use has also been associated with ischemic stroke [65, 201, 202, 206, 207]. SSRIs and serotonin/norepinephrine reuptake inhibitors appear to have effects on

cardiac conduction and negative inotropic effects [210], may increase C-reactive protein and serum cholesterol levels [211, 212], have vasoconstrictive effects on cerebral arteries (Call–Fleming syndrome), and have proserotonergic effects that increase platelet activation [213].

A few studies found that tricyclic antidepressants was associated with an increased risk of cerebrovascular events [65], fatal stroke [206], and vascular events including stroke [214]. Potential mechanisms linking tricyclic antidepressant use and stroke include orthostatic hypotension, reduced heart rate variability, and QT interval prolongation [215].

Psychiatric and Psychological Triggers

Apart from traditional risk factors, it has been hypothesized and demonstrated that acute vascular events (e.g., myocardial infarction or stroke) could be triggered by exposure to transient factors such as heavy physical exertion, negative and positive emotions, and anger [7, 124, 216]. These acute factors, called triggers, correspond to activities that produce short-term physiological changes that may directly lead to the onset of acute vascular diseases [217]. The definition of a trigger is however rather vague. In particular no agreement exists on how long before the onset of an acute vascular event an activity can be considered as a trigger rather than a more traditional risk factor [7]. Some triggers may exert a single, sharp, and short transient effect on the pathophysiological process, whereas others may exert more varied and pervasive effects, probably amplifying risk at multiple points and over a longer period [218]. Thus, the period of time associated with an increased risk, called hazard period, starts more or less quickly after trigger initiation, and its duration may vary according to the type of trigger [217]. The hazard period associated with an increased risk of acute event is defined as the average time that is relevant for the acute effect of the event. Thus, the hazard period onset and offset times may be sharply defined, as in heavy physical exertion, or less well defined, as with infection or life events [217]. Typically, trigger studies assessed activities in the period ranging from a few minutes to 24 h before the onset of stroke or, in some cases (e.g., infections), a few days or weeks before stroke onset [7]. The case-crossover design, in which participants are their own control, is currently the most powerful approach to study triggers avoiding some bias inherent to case-control studies [219], in particular selection bias and confounding effects [220]. However, even if this method is best suited to study triggers, identification of the exact timing of factor exposure remains crucial (because of possible recall bias), and accurate data from interviews are needed to establish the exact time of onset of the event [221].

Several case-crossover studies have already demonstrated triggering effects of various psychiatric and/or psychological factors (e.g., life events, emotional distress, anger, negative emotions) on myocardial infarction onset; [8, 9] however, the role of these transient factors as potential stroke triggers is still not well established [7].

Acute and Subacute Life Stress

As opposed to chronic life stress and in accordance with trigger definition, we will only consider in this section studies that assessed life stressors that occurred within the month preceding stroke onset, although there is no consensus on the maximal hazard period duration to define a trigger. Recent exposure to some population life stressors (e.g., earthquake or football match) has been significantly associated with nonfatal or fatal stroke [169, 174], whereas one study assessing the short-term effects of 2001, September 11th terrorist attack found no significant increased in ischemic stroke risk (Table 12.7) [172]. Literature on stressful life events and stroke is inconclusive as some studies have shown a positive association [159, 170, 171], whereas others have found no association (Table 12.7) [173]. In a recent case-crossover study, Guiraud et al. [159] have found an association between recent exposure to stressful life events (measured by the Interview for Recent Life Events [222]) and ischemic stroke onset. Stroke patients more often reported stressful life event exposures within hazard periods prior to stroke onset (first week or month) than during respective control periods leading to a two- to threefold increase in the risk of ischemic stroke within the week or month following exposure (Fig. 12.1) [159]. The most prevalent stressful life event categories corresponded to "hard" negative events (e.g., bereavement, health problems); however, the risk of stroke was not higher when only considering major life events.

Other Triggers

Other psychiatric and/or psychological stroke triggers have only been investigated in very few studies. Using a case-crossover approach, Koton et al. [124] investigated the association between a recent exposure to seven physical and psychological potential triggers and ischemic stroke. The short-term 2-h period relative risk estimates were significantly elevated for exposure to negative emotions (OR = 14.0; 4.4–89.7), anger (OR = 14.0; 2.8–253.6), and sudden posture changes as response to a startling event (OR = 24.0; 5.1–428.9), while the odds ratio for exposure to positive emotions was increased but did not reach statistical significance [124]. Likewise, Yoo et al. [223] found a significant association between exposure to psychological distress within 3 days prior to stroke onset compared to ten control periods, and this excess of risk was significantly greater for hemorrhagic than ischemic strokes.

In contrast to chronic stress, acute stress is easier to model and can be studied under laboratory conditions in both humans and animals. Psychological stress stimuli (e.g., complex mental task) have been reported as the best approximations to real-life stressors [183] and could induce through hypothalamic–pituitary–adrenal

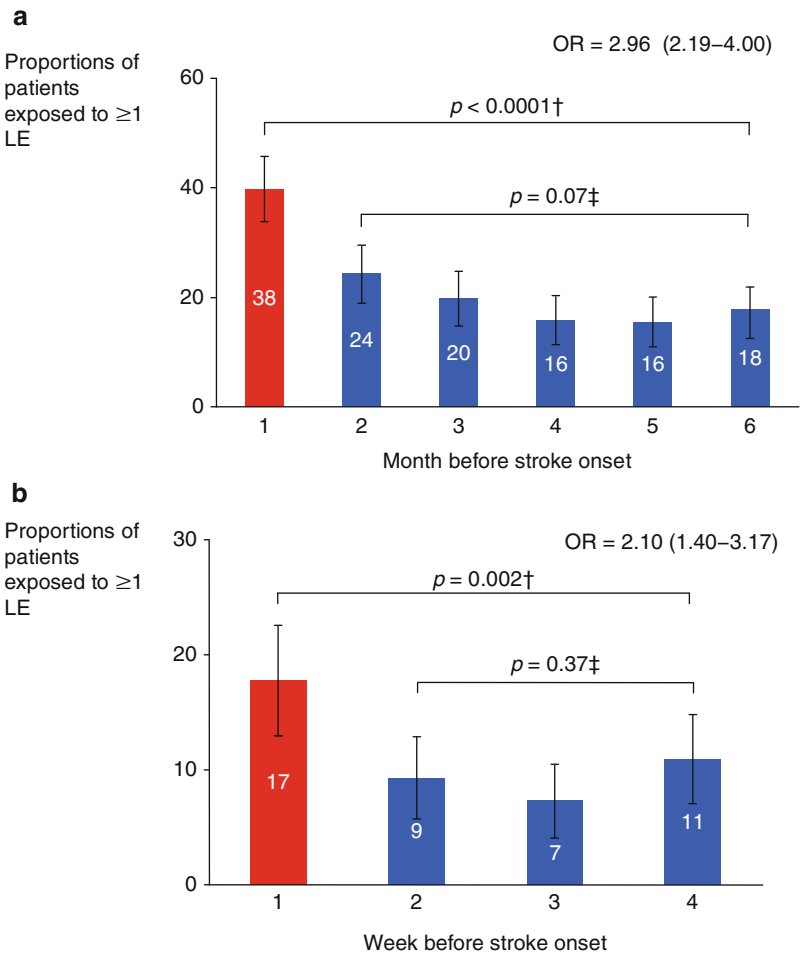


Fig. 12.1 Association between recent life event exposure and stroke risk (case-crossover study) (**a**) Proportion of exposed patients within 6 months before stroke onset and (**b**) proportion of exposed patients within 4 weeks before stroke onset. †Comparison of the proportion of exposed patients across all periods (hazard and control). ‡Comparison of the proportion of exposed patients across periods control only (Adapted from Guiraud et al. [159])

axis and sympathetic nervous system activations (1) increase in blood pressure, pulse rate [154, 224], serum lipid level, haemostatic factors, blood viscosity [225, 226], platelet-secreted proteins, epinephrine, and norepinephrine [227]; (2) transient and prolonged endothelial dysfunction [189, 228]; and (3) cardiac wall motion abnormalities, fall in ejection fraction, left ventricular dysfunction, epicardial coronary vasoconstriction in patients with coronary heart disease, and arrhythmias [224, 229–231].

Psychotropic Medications

In line with previous reports showing an association between chronic use of psychotropic medications and stroke, several studies have also investigated the triggering effects of these medications. Several studies have suggested that elevation in stroke risk related to psychiatric drugs is time dependent, increasing soon after drug initiation and then declining to baseline levels after a few months [97]. Three studies, all using different methodological approaches (i.e., nested case-control study, self-controlled case series, case–case–time-control design), have found a significant association between initiation of antipsychotic drugs (within the preceding week or month) and an increased risk of stroke [232–234]. Likewise, using a case-crossover design, Wu et al. [235] have shown that a recent antidepressant initiation (within the preceding 2 weeks) was associated with an elevated risk of stroke onset.

Conclusion

There is epidemiological and biological evidence suggesting that psychiatric and/or psychological factors, notably depression, may contribute to the pathogenesis of stroke. However, the causality of the relationships remains unproven because of methodological limitations of existing studies, and difficulties to have objective definition and measurement of psychological and psychiatric factors and to perform experimental studies. It remains also unknown whether therapeutic interventions (drugs or behavioral approaches) could reduce the risk of stroke.

References

1. Goldstein LB, Adams R, Alberts MJ, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2006;113(24):e873–923.
2. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010;376(9735):112–23.
3. Adler R, MacRitchie K, Engel GL. Psychologic processes and ischemic stroke (occlusive cerebrovascular disease). I. Observations on 32 men with 35 strokes. Psychosom Med. 1971;33(1):1–29.
4. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation. 1999;99(16):2192–217.

5. Rosengren A, Hawken S, Ounpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):953–62.
6. Elkind MS. Why now? Moving from stroke risk factors to stroke triggers. Curr Opin Neurol. 2007;20(1):51–7.
7. Guiraud V, Amor MB, Mas JL, Touze E. Triggers of ischemic stroke: a systematic review. Stroke. 2010;41(11):2669–77.
8. Nawrot TS, Perez L, Kunzli N, Munters E, Nemery B. Public health importance of triggers of myocardial infarction: a comparative risk assessment. Lancet. 2011;377(9767):732–40.
9. Strike PC, Perkins-Porras L, Whitehead DL, McEwan J, Steptoe A. Triggering of acute coronary syndromes by physical exertion and anger: clinical and sociodemographic characteristics. Heart. 2006;92(8):1035–40.
10. Murray CJ, Lopez AD. Evidence-based health policy – lessons from the Global Burden of Disease Study. Science. 1996;274(5288):740–3.
11. Hasin DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. Arch Gen Psychiatry. 2005;62(10):1097–106.
12. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003;289(23):3095–105.
13. Hays RD, Wells KB, Sherbourne CD, Rogers W, Spritzer K. Functioning and well-being outcomes of patients with depression compared with chronic general medical illnesses. Arch Gen Psychiatry. 1995;52(1):11–9.
14. Spijker J, Graaf R, Bijl RV, Beekman AT, Ormel J, Nolen WA. Functional disability and depression in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Acta Psychiatr Scand. 2004;110(3):208–14.
15. Dentino AN, Pieper CF, Rao MK, et al. Association of interleukin-6 and other biologic variables with depression in older people living in the community. J Am Geriatr Soc. 1999;47(1):6–11.
16. Insel TR, Charney DS. Research on major depression: strategies and priorities. JAMA. 2003;289(23):3167–8.
17. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington, D.C.: American Psychiatric Association; 2000.
18. Evans DL, Charney DS, Lewis L, et al. Mood disorders in the medically ill: scientific review and recommendations. Biol Psychiatry. 2005;58(3):175–89.
19. Frasure-Smith N, Lesperance F. Reflections on depression as a cardiac risk factor. Psychosom Med. 2005;67 Suppl 1:S19–25.
20. Krishnan KR. Depression as a contributing factor in cerebrovascular disease. Am Heart J. 2000;140(4 Suppl):70–6.
21. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. Int J Geriatr Psychiatry. 2007;22(7):613–26.
22. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. Psychosom Med. 2003;65(2):201–10.
23. Majed B, Arveiler D, Bingham A, et al. Depressive symptoms, a time-dependent risk factor for coronary heart disease and stroke in middle-aged men: The PRIME Study. Stroke. 2012;43(7):1761–7.
24. Nabi H, Kivimaki M, Suominen S, Koskenvuo M, Singh-Manoux A, Vahtera J. Does depression predict coronary heart disease and cerebrovascular disease equally well? The Health and Social Support Prospective Cohort Study. Int J Epidemiol. 2010;39(4):1016–24.
25. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. JAMA. 2011;306(11):1241–9.
26. Vogt T, Pope C, Mullooly J, Hollis J. Mental health status as a predictor of morbidity and mortality: a 15-year follow-up of members of a health maintenance organization. Am J Public Health. 1994;84(2):227–31.

27. Wassertheil-Smoller S, Applegate WB, Berge K, et al. Change in depression as a precursor of cardiovascular events. SHEP Cooperative Research Group (Systoloc Hypertension in the elderly). Arch Intern Med. 1996;156(5):553–61.
28. 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(10):1133–8.
29. Simons LA, McCallum J, Friedlander Y, Simons J. Risk factors for ischemic stroke: Dubbo Study of the elderly. Stroke. 1998;29(7):1341–6.
30. Whooley MA, Browner WS. Association between depressive symptoms and mortality in older women. Study of Osteoporotic Fractures Research Group. Arch Intern Med. 1998;158(19):2129–35.
31. Jonas BS, Mussolino ME. Symptoms of depression as a prospective risk factor for stroke. Psychosom Med. 2000;62(4):463–71.
32. Larson SL, Owens PL, Ford D, Eaton W. Depressive disorder, dysthymia, and risk of stroke: thirteen-year follow-up from the Baltimore epidemiologic catchment area study. Stroke. 2001;32(9):1979–83.
33. Ohira T, Iso H, Satoh S, et al. Prospective study of depressive symptoms and risk of stroke among Japanese. Stroke. 2001;32(4):903–8.
34. Ostir GV, Markides KS, Peek MK, Goodwin JS. The association between emotional well-being and the incidence of stroke in older adults. Psychosom Med. 2001;63(2):210–5.
35. May M, McCarron P, Stansfeld S, et al. Does psychological distress predict the risk of ischemic stroke and transient ischemic attack? The Caerphilly Study. Stroke. 2002;33(1):7–12.
36. Yasuda N, Mino Y, Koda S, Ohara H. The differential influence of distinct clusters of psychiatric symptoms, as assessed by the general health questionnaire, on cause of death in older persons living in a rural community of Japan. J Am Geriatr Soc. 2002;50(2):313–20.
37. Wassertheil-Smoller S, Shumaker S, Ockene J, et al. Depression and cardiovascular sequelae in postmenopausal women. The Women's Health Initiative (WHI). Arch Intern Med. 2004;164(3):289–98.
38. Gump BB, Matthews KA, Eberly LE, Chang YF. Depressive symptoms and mortality in men: results from the Multiple Risk Factor Intervention Trial. Stroke. 2005;36(1):98–102.
39. Avendano M, Kawachi I, Van Lenthe F, et al. Socioeconomic status and stroke incidence in the US elderly: the role of risk factors in the EPESE study. Stroke. 2006;37(6):1368–73.
40. Stürmer T, Hasselbach P, Amelang M. Personality, lifestyle, and risk of cardiovascular disease and cancer: follow-up of population based cohort. BMJ. 2006;332(7554):1359.
41. Arbelaez JJ, Ariyo AA, Crum RM, Fried LP, Ford DE. Depressive symptoms, inflammation, and ischemic stroke in older adults: a prospective analysis in the cardiovascular health study. J Am Geriatr Soc. 2007;55(11):1825–30.
42. Kawamura T, Shioiri T, Takahashi K, Ozdemir V, Someya T. Survival rate and causes of mortality in the elderly with depression: a 15-year prospective study of a Japanese community sample, the Matsunoyama-Niigata suicide prevention project. J Investig Med. 2007;55(3):106–14.
43. Salaycik KJ, Kelly-Hayes M, Beiser A, et al. Depressive symptoms and risk of stroke: the Framingham Study. Stroke. 2007;38(1):16–21.
44. Bos MJ, Linden T, Koudstaal PJ, et al. Depressive symptoms and risk of stroke: the Rotterdam Study. J Neurol Neurosurg Psychiatry. 2008;79(9):997–1001.
45. Lee HC, Lin HC, Tsai SY. Severely depressed young patients have over five times increased risk for stroke: a 5-year follow-up study. Biol Psychiatry. 2008;64(10):912–5.
46. Liebetrau M, Steen B, Skoog I. Depression as a risk factor for the incidence of first-ever stroke in 85-year-olds. Stroke. 2008;39(7):1960–5.
47. Surtees PG, Wainwright NW, Luben RN, Wareham NJ, Bingham SA, Khaw KT. Psychological distress, major depressive disorder, and risk of stroke. Neurology. 2008;70(10):788–94.
48. Whooley MA, de Jonge P, Vittinghoff E, et al. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. JAMA. 2008;300(20):2379–88.
49. Wouts L, Oude Voshaar RC, Bremmer MA, Buitelaar JK, Penninx BW, Beekman AT. Cardiac disease, depressive symptoms, and incident stroke in an elderly population. Arch Gen Psychiatry. 2008;65(5):596–602.

50. Glymour MM, Maselko J, Gilman SE, Patton KK, Avendano M. Depressive symptoms predict incident stroke independently of memory impairments. Neurology. 2010;75(23):2063–70.
51. Peters R, Pinto E, Beckett N, et al. Association of depression with subsequent mortality, cardiovascular morbidity and incident dementia in people aged 80 and over and suffering from hypertension. Data from the Hypertension in the Very Elderly Trial (HYVET). Age Ageing. 2010;39(4):439–45.
52. Spalletta G, Ripa A, Caltagirone C. Symptom profile of DSM-IV major and minor depressive disorders in first-ever stroke patients. Am J Geriatr Psychiatry. 2005;13(2):108–15.
53. Whyte EM, Mulsant BH. Post stroke depression: epidemiology, pathophysiology, and biological treatment. Biol Psychiatry. 2002;52(3):253–64.
54. Dong JY, Zhang YH, Tong J, Qin LQ. Depression and risk of stroke: a meta-analysis of prospective studies. Stroke. 2012;43(1):32–7.
55. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. Arch Gen Psychiatry. 1998;55(7):580–92.
56. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med. 2009;71(2):171–86.
57. Shimbo D, Chaplin W, Crossman D, Haas D, Davidson KW. Role of depression and inflammation in incident coronary heart disease events. Am J Cardiol. 2005;96(7):1016–21.
58. Davidson K, Jonas BS, Dixon KE, Markovitz JH. Do depression symptoms predict early hypertension incidence in young adults in the CARDIA study? Coronary Artery Risk Development in Young Adults. Arch Intern Med. 2000;160(10):1495–500.
59. Jonas BS, Franks P, Ingram DD. Are symptoms of anxiety and depression risk factors for hypertension? Longitudinal evidence from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. Arch Fam Med. 1997;6(1):43–9.
60. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. Diabetes Care. 2008;31(12):2383–90.
61. Anda RF, Williamson DF, Escobedo LG, Mast EE, Giovino GA, Remington PL. Depression and the dynamics of smoking. A national perspective. JAMA. 1990;264(12):1541–5.
62. Camacho TC, Roberts RE, Lazarus NB, Kaplan GA, Cohen RD. Physical activity and depression: evidence from the Alameda County Study. Am J Epidemiol. 1991;134(2):220–31.
63. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry. 2010;67(3):220–9.
64. Gorman JM, Sloan RP. Heart rate variability in depressive and anxiety disorders. Am Heart J. 2000;140(4 Suppl):77–83.
65. Chen Y, Guo JJ, Li H, Wulsin L, Patel NC. Risk of cerebrovascular events associated with antidepressant use in patients with depression: a population-based, nested case-control study. Ann Pharmacother. 2008;42(2):177–84.
66. Carney RM, Freedland KE. Psychological distress as a risk factor for stroke-related mortality. Stroke. 2002;33(1):5–6.
67. Goldberg DP, Gater R, Sartorius N, et al. The validity of two versions of the GHQ in the WHO study of mental illness in general health care. Psychol Med. 1997;27(1):191–7.
68. Veit CT, Ware Jr JE. The structure of psychological distress and well-being in general populations. J Consult Clin Psychol. 1983;51(5):730–42.
69. Hamer M, Molloy GJ, Stamatakis E. Psychological distress as a risk factor for cardiovascular events: pathophysiological and behavioral mechanisms. J Am Coll Cardiol. 2008;52(25):2156–62.
70. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas. 1977;1:385–401.
71. Appels A. Psychological prodromata of myocardial infarction and sudden death. Psychother Psychosom. 1980;34(2–3):187–95.
72. Schuitemaker GE, Dinant GJ, Van Der Pol GA, Verhelst AF, Appels A. Vital exhaustion as a risk indicator for first stroke. Psychosomatics. 2004;45(2):114–8.
73. Schwartz SW, Carlucci C, Chambless LE, Rosamond WD. Synergism between smoking and vital exhaustion in the risk of ischemic stroke: evidence from the ARIC study. Ann Epidemiol. 2004;14(6):416–24.

74. Purebl G, Birkas E, Csoboth C, Szumska I, Kopp MS. The relationship of biological and psychological risk factors of cardiovascular disorders in a large-scale national representative community survey. Behav Med. 2006;31(4):133–9.
75. Kornerup H, Marott JL, Schnohr P, Boysen G, Barefoot J, Prescott E. Vital exhaustion increases the risk of ischemic stroke in women but not in men: results from the Copenhagen City Heart Study. J Psychosom Res. 2010;68(2):131–7.
76. Kessler RC, Berglund PA, Dewit DJ, Ustun TB, Wang PS, Wittchen HU. Distinguishing generalized anxiety disorder from major depression: prevalence and impairment from current pure and comorbid disorders in the US and Ontario. Int J Methods Psychiatr Res. 2002; 11(3):99–111.
77. Eaker ED, Pinsky J, Castelli WP. Myocardial infarction and coronary death among women: psychosocial predictors from a 20-year follow-up of women in the Framingham Study. Am J Epidemiol. 1992;135(8):854–64.
78. Frasure-Smith N, Lesperance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. Arch Gen Psychiatry. 2008;65(1):62–71.
79. Kawachi I, Colditz GA, Ascherio A, et al. Prospective study of phobic anxiety and risk of coronary heart disease in men. Circulation. 1994;89(5):1992–7.
80. Rothenbacher D, Hahmann H, Wusten B, Koenig W, Brenner H. Symptoms of anxiety and depression in patients with stable coronary heart disease: prognostic value and consideration of pathogenetic links. Eur J Cardiovasc Prev Rehabil. 2007;14(4):547–54.
81. Rutledge T, Linke SE, Krantz DS, et al. Comorbid depression and anxiety symptoms as predictors of cardiovascular events: results from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. Psychosom Med. 2009;71(9):958–64.
82. Hanssen TA, Nordrehaug JE, Eide GE, Bjelland I, Rokne B. Anxiety and depression after acute myocardial infarction: an 18-month follow-up study with repeated measures and comparison with a reference population. Eur J Cardiovasc Prev Rehabil. 2009;16(6):651–9.
83. Chen YH, Hu CJ, Lee HC, Lin HC. An increased risk of stroke among panic disorder patients: a 3-year follow-up study. Can J Psychiatry. 2010;55(1):43–9.
84. Smoller JW, Pollack MH, Wassertheil-Smoller S, et al. Panic attacks and risk of incident cardiovascular events among postmenopausal women in the Women's Health Initiative Observational Study. Arch Gen Psychiatry. 2007;64(10):1153–60.
85. Weissman MM, Markowitz JS, Ouellette R, Greenwald S, Kahn JP. Panic disorder and cardiovascular/cerebrovascular problems: results from a community survey. Am J Psychiatry. 1990;147(11):1504–8.
86. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Decreased heart rate variability in men with phobic anxiety (data from the Normative Aging Study). Am J Cardiol. 1995;75(14):882–5.
87. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Symptoms of anxiety and risk of coronary heart disease. The Normative Aging Study. Circulation. 1994;90(5):2225–9.
88. Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. Br J Psychiatry. 2000;177:212–7.
89. Davidson M. Risk of cardiovascular disease and sudden death in schizophrenia. J Clin Psychiatry. 2002;63 Suppl 9:5–11.
90. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. Am Heart J. 2005;150(6):1115–21.
91. Curkendall SM, Mo J, Glasser DB, Rose Stang M, Jones JK. Cardiovascular disease in patients with schizophrenia in Saskatchewan, Canada. J Clin Psychiatry. 2004;65(5):715–20.
92. Lin HC, Hsiao FH, Pfeiffer S, Hwang YT, Lee HC. An increased risk of stroke among young schizophrenia patients. Schizophr Res. 2008;101(1–3):234–41.
93. Tsai KY, Lee CC, Chou YM, Su CY, Chou FH. The incidence and relative risk of stroke in patients with schizophrenia: a five-year follow-up study. Schizophr Res. 2012;138(1):41–7.
94. Osborn DP, Levy G, Nazareth I, Petersen I, Islam A, King MB. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Research Database. Arch Gen Psychiatry. 2007;64(2):242–9.
95. Kisely S, Campbell LA, Wang Y. Treatment of ischaemic heart disease and stroke in individuals with psychosis under universal healthcare. Br J Psychiatry. 2009;195(6):545–50.

96. Ryan MC, Thakore JH. Physical consequences of schizophrenia and its treatment: the metabolic syndrome. Life Sci. 2002;71(3):239–57.
97. Sacchetti E, Turrina C, Valsecchi P. Cerebrovascular accidents in elderly people treated with antipsychotic drugs: a systematic review. Drug Saf. 2010;33(4):273–88.
98. Friedman M, Rosenman RH. Association of specific overt behavior pattern with blood and cardiovascular findings; blood cholesterol level, blood clotting time, incidence of arcus senilis, and clinical coronary artery disease. J Am Med Assoc. 1959;169(12):1286–96.
99. Spielberger CD, Krasner SS, Solomon EP. The experience, expression, and control of anger. New York: Springer; 1988.
100. Deffenbacher JL, Oetting ER, Lynch RS, Morris CD. The expression of anger and its consequences. Behav Res Ther. 1996;34(7):575–90.
101. Everson SA, Kauhanen J, Kaplan GA, et al. Hostility and increased risk of mortality and acute myocardial infarction: the mediating role of behavioral risk factors. Am J Epidemiol. 1997;146(2):142–52.
102. Everson SA, Kaplan GA, Goldberg DE, Lakka TA, Sivenius J, Salonen JT. Anger expression and incident stroke: prospective evidence from the Kuopio ischemic heart disease study. Stroke. 1999;30(3):523–8.
103. Williams JE, Nieto FJ, Sanford CP, Couper DJ, Tyroler HA. The association between trait anger and incident stroke risk: the Atherosclerosis Risk in Communities (ARIC) Study. Stroke. 2002;33(1):13–9.
104. Eng PM, Fitzmaurice G, Kubzansky LD, Rimm EB, Kawachi I. Anger expression and risk of stroke and coronary heart disease among male health professionals. Psychosom Med. 2003;65(1):100–10.
105. Gentry WD, Jenkins CD, Kaplan BH, Heyman A, Breslin MS, Gianturco DT. The A behavior pattern and ischemic cerebrovascular disease. Heart Lung. 1979;8(6):1113–6.
106. Goetz S, Adler RH, Weber R. High "need for control" as a psychological risk in women suffering from ischemic stroke: a controlled retrospective exploratory study. Int J Psychiatry Med. 1992;22(2):119–29.
107. Mann AH, Brennan PJ. Type A behaviour score and the incidence of cardiovascular disease: a failure to replicate the claimed associations. J Psychosom Res. 1987;31(6):685–92.
108. Kim JS, Yoon SS, Lee SI, et al. Type A behavior and stroke: high tenseness dimension may be a risk factor for cerebral infarction. Eur Neurol. 1998;39(3):168–73.
109. Zodpey SP, Tiwari RR, Kulkarni HR. Risk factors for haemorrhagic stroke: a case-control study. Public Health. 2000;114(3):177–82.
110. Fernández-Concepcion O, Verdecie-Feria O, Chavez-Rodriguez L, Alvarez-Gonzalez MA, Fiallo-Sanchez MC. Type A behaviour and life events as risk factors for cerebral infarct. Rev Neurol. 2002;34(7):622–7.
111. Nakaya N, Tsubono Y, Hosokawa T, et al. Personality and mortality from ischemic heart disease and stroke. Clin Exp Hypertens. 2005;27(2–3):297–305.
112. Shipley BA, Weiss A, Der G, Taylor MD, Deary IJ. Neuroticism, extraversion, and mortality in the UK Health and Lifestyle Survey: a 21-year prospective cohort study. Psychosom Med. 2007;69(9):923–31.
113. Moran P, Stewart R, Brugha T, et al. Personality disorder and cardiovascular disease: results from a national household survey. J Clin Psychiatry. 2007;68(1):69–74.
114. McCarron P, Gunnell D, Harrison GL, Okasha M, Davey Smith G. Temperament in young adulthood and later mortality: prospective observational study. J Epidemiol Community Health. 2003;57(11):888–92.
115. Everson SA, McKey BS, Lovallo WR. Effect of trait hostility on cardiovascular responses to harassment in young men. Int J Behav Med. 1995;2(2):172–91.
116. Laude D, Girard A, Consoli S, Mounier-Vehier C, Elghozi JL. Anger expression and cardiovascular reactivity to mental stress: a spectral analysis approach. Clin Exp Hypertens. 1997;19(5–6):901–11.
117. Sloan RP, Shapiro PA, Bigger Jr JT, Bagiella E, Steinman RC, Gorman JM. Cardiac autonomic control and hostility in healthy subjects. Am J Cardiol. 1994;74(3):298–300.

118. Kaplan JR, Pettersson K, Manuck SB, Olsson G. Role of sympathoadrenal medullary activation in the initiation and progression of atherosclerosis. Circulation. 1991;84(6 Suppl):VI23–32.
119. Krantz DS, Manuck SB. Acute psychophysiologic reactivity and risk of cardiovascular disease: a review and methodologic critique. Psychol Bull. 1984;96(3):435–64.
120. Pauletto P, Scannapieco G, Pessina AC. Sympathetic drive and vascular damage in hypertension and atherosclerosis. Hypertension. 1991;17(4 Suppl):III75–81.
121. Anfossi G, Trovati M. Role of catecholamines in platelet function: pathophysiological and clinical significance. Eur J Clin Invest. 1996;26(5):353–70.
122. Born GV. Recent evidence for the involvement of catecholamines and of macrophages in atherosclerotic processes. Ann Med. 1991;23(5):569–72.
123. Adams DO. Molecular biology of macrophage activation: a pathway whereby psychosocial factors can potentially affect health. Psychosom Med. 1994;56(4):316–27.
124. Koton S, Tanne D, Bornstein NM, Green MS. Triggering risk factors for ischemic stroke: a case-crossover study. Neurology. 2004;63(11):2006–10.
125. Steptoe A. Psychological factors in cardiovascular disorders. London: Academic; 1981.
126. Haukkala A, Konttinen H, Laatikainen T, Kawachi I, Uutela A. Hostility, anger control, and anger expression as predictors of cardiovascular disease. Psychosom Med. 2010; 72(6):556–62.
127. Olson MB, Krantz DS, Kelsey SF, et al. Hostility scores are associated with increased risk of cardiovascular events in women undergoing coronary angiography: a report from the NHLBI-Sponsored WISE Study. Psychosom Med. 2005;67(4):546–52.
128. Friedman M, Rosenman RH, Byers S. Serum lipids and conjunctival circulation after fat ingestion in men exhibiting type-A behavior pattern. Circulation. 1964;29:874–86.
129. Friedman M, St George S, Byers SO, Rosenman RH. Excretion of catecholamines, 17-ketosteroids, 17-hydroxycorticoids and 5-hydroxyindole in men exhibiting a particular behavior pattern (A) associated with high incidence of clinical coronary artery disease. J Clin Invest. 1960;39:758–64.
130. Markovitz JH. Hostility is associated with increased platelet activation in coronary heart disease. Psychosom Med. 1998;60(5):586–91.
131. Matthews KA, Owens JF, Kuller LH, Sutton-Tyrrell K, Jansen-McWilliams L. Are hostility and anxiety associated with carotid atherosclerosis in healthy postmenopausal women? Psychosom Med. 1998;60(5):633–8.
132. Cinciripini PM. Cognitive stress and cardiovascular reactivity. I. Relationship to hypertension. Am Heart J. 1986;112(5):1044–50.
133. Oyefeso AO, Odeyale MA. Smoking and type A Behaviour. Scand J Psychol. 1991;32(1):79–81.
134. Longato-Stadler E, von Knorring L, Hallman J. Mental and personality disorders as well as personality traits in a Swedish male criminal population. Nord J Psychiatry. 2002;56(2):137–44.
135. Yoon SS, Byles J. Perceptions of stroke in the general public and patients with stroke: a qualitative study. BMJ. 2002;324(7345):1065–8.
136. Krantz DS, Contrada RJ, Hill DR, Friedler E. Environmental stress and biobehavioral antecedents of coronary heart disease. J Consult Clin Psychol. 1988;56(3):333–41.
137. Schneck MJ. Is psychological stress a risk factor for cerebrovascular disease? Neuroepidemiology. 1997;16(4):174–9.
138. Harmsen P, Lappas G, Rosengren A, Wilhelmsen L. Long-term risk factors for stroke: twenty-eight years of follow-up of 7457 middle-aged men in Goteborg, Sweden. Stroke. 2006;37(7):1663–7.
139. Jood K, Redfors P, Rosengren A, Blomstrand C, Jern C. Self-perceived psychological stress and ischemic stroke: a case-control study. BMC Med. 2009;7:53.
140. Truelsen T, Nielsen N, Boysen G, Gronbaek M. Self-reported stress and risk of stroke: the Copenhagen City Heart Study. Stroke. 2003;34(4):856–62.
141. Rosengren A, Tibblin G, Wilhelmsen L. Self-perceived psychological stress and incidence of coronary artery disease in middle-aged men. Am J Cardiol. 1991;68(11):1171–5.

142. Öhlin B, Nilsson PM, Nilsson JA, Berglund G. Chronic psychosocial stress predicts long-term cardiovascular morbidity and mortality in middle-aged men. Eur Heart J. 2004;25(10):867–73.
143. Iso H, Date C, Yamamoto A, et al. Perceived mental stress and mortality from cardiovascular disease among Japanese men and women: the Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (JACC Study). Circulation. 2002;106(10):1229–36.
144. Strodl E, Kenardy J. The 5-item mental health index predicts the initial diagnosis of nonfatal stroke in older women. J Womens Health (Larchmt). 2008;17(6):979–86.
145. Virtanen SV, Notkola V. Socioeconomic inequalities in cardiovascular mortality and the role of work: a register study of Finnish men. Int J Epidemiol. 2002;31(3):614–21.
146. Gallo WT, Teng HM, Falba TA, Kasl SV, Krumholz HM, Bradley EH. The impact of late career job loss on myocardial infarction and stroke: a 10 year follow up using the health and retirement survey. Occup Environ Med. 2006;63(10):683–7.
147. André-Petersson L, Engström G, Hedblad B, Janzon L, Rosvall M. Social support at work and the risk of myocardial infarction and stroke in women and men. Soc Sci Med. 2007;64(4):830–41.
148. Kuper H, Adami HO, Theorell T, Weiderpass E. The socioeconomic gradient in the incidence of stroke: a prospective study in middle-aged women in Sweden. Stroke. 2007;38(1):27–33.
149. Toivanen S, Hemstrom O. Is the impact of job control on stroke independent from socioeconomic status?: a large-scale study of the Swedish working population. Stroke. 2008;39(4):1321–3.
150. Tsutsumi A, Kayaba K, Kario K, Ishikawa S. Prospective study on occupational stress and risk of stroke. Arch Intern Med. 2009;169(1):56–61.
151. Tanne D, Goldbourt U, Medalie JH. Perceived family difficulties and prediction of 23-year stroke mortality among middle-aged men. Cerebrovasc Dis. 2004;18(4):277–82.
152. Sørensen M, Hvidberg M, Andersen ZJ, et al. Road traffic noise and stroke: a prospective cohort study. Eur Heart J. 2011;32(6):737–44.
153. André-Petersson L, Engström G, Hagberg B, Janzon L, Steen G. Adaptive behavior in stressful situations and stroke incidence in hypertensive men: results from prospective cohort study "men born in 1914" in Malmo, Sweden. Stroke. 2001;32(8):1712–20.
154. Everson SA, Lynch JW, Kaplan GA, Lakka TA, Sivenius J, Salonen JT. Stress-induced blood pressure reactivity and incident stroke in middle-aged men. Stroke. 2001;32(6):1263–70.
155. Surtees PG, Wainwright NW, Luben RL, Wareham NJ, Bingham SA, Khaw KT. Adaptation to social adversity is associated with stroke incidence: evidence from the EPIC-Norfolk prospective cohort study. Stroke. 2007;38(5):1447–53.
156. Karasek RA. Job demands, job decision latitude, and mental strain: implications for job redesign. Adm Sci Q. 1979;24:285–308.
157. Hammar N, Alfredsson L, Johnson JV. Job strain, social support at work, and incidence of myocardial infarction. Occup Environ Med. 1998;55(8):548–53.
158. Kuper H, Marmot M, Hemingway H. Systematic review of prospective cohort studies of psychosocial factors in the etiology and prognosis of coronary heart disease. Semin Vasc Med. 2002;2(3):267–314.
159. Guiraud V, Touze E, Rouillon F, Godefroy O, Mas JL. Stressful life events as triggers of ischemic stroke: a case-crossover study. Int J Stroke. 2012 May 9. doi: 10.1111/j.1747-4949.2012.00810.x. [Epub ahead of print].
160. Theorell TG. Review of research on life events and cardiovascular illness. Adv Cardiol. 1982;29:140–9.
161. Brass LM, Page WF. Stroke in former prisoners of war. J Stroke Cerebrovasc Dis. 1996;6(2):72–8.
162. Engström G, Khan FA, Zia E, et al. Marital dissolution is followed by an increased incidence of stroke. Cerebrovasc Dis. 2004;18(4):318–24.
163. House A, Dennis M, Mogridge L, Hawton K, Warlow C. Life events and difficulties preceding stroke. J Neurol Neurosurg Psychiatry. 1990;53(12):1024–8.

164. Kornerup H, Osler M, Boysen G, Barefoot J, Schnohr P, Prescott E. Major life events increase the risk of stroke but not of myocardial infarction: results from the Copenhagen City Heart Study. Eur J Cardiovasc Prev Rehabil. 2010;17(1):113–8.
165. Paschalis C. The association of stroke with life events. Cerebrovasc Dis. 1991;1:223–6.
166. Savadi-Oskouei DS, Sadeghi-bazargani H, Mohammadzadeh L. Can experiencing stressful life events be a risk factor of stroke? J Med Sci. 2009;9(6):280–3.
167. Sokejima S, Nakatani Y, Kario K, Kayaba K, Minowa M, Kagamimori S. Seismic intensity and risk of cerebrovascular stroke: 1995 Hanshin-Awaji earthquake. Prehosp Disaster Med. 2004;19(4):297–306.
168. Tao JS. Correlation of cerebral ischemic stroke with life events. Chin J Clin Rehabil. 2004;8(4):606–7.
169. Witte DR, Bots ML, Hoes AW, Grobbee DE. Cardiovascular mortality in Dutch men during 1996 European football championship: longitudinal population study. BMJ. 2000;321(7276): 1552–4.
170. Antić I, Petrovic B, Rancic N. Stress as a risk factor in the development of brain stroke. Med Pregl. 2011;64(3–4):161–7.
171. Saposnik G, Baibergenova A, Dang J, Hachinski V. Does a birthday predispose to vascular events? Neurology. 2006;67(2):300–4.
172. Antonio V, Olivia M, Stefania L. Stress reactions and ischemic CVAs after the September 11, 2001 terrorist attacks. Am J Emerg Med. 2004;22(3):226–7.
173. Macko RF, Ameriso SF, Barndt R, Clough W, Weiner JM, Fisher M. Precipitants of brain infarction. Roles of preceding infection/inflammation and recent psychological stress. Stroke. 1996;27(11):1999–2004.
174. Tsuchida M, Kawashiri MA, Teramoto R, et al. Impact of severe earthquake on the occurrence of acute coronary syndrome and stroke in a rural area of Japan. Circ J. 2009;73(7):1243–7.
175. Kleinman Y, Korn-Lubetzki I, Eliashiv S, Abramsky O, Eliakim M. High frequency of hemorrhagic strokes in Jerusalem during the Persian Gulf War. Neurology. 1992;42(11):2225–6.
176. Peris A, Martin-Gonzalez R, Valiente E, Ruiz A, Vioque J. Stressful life events as risk factors in acute cerebrovascular disease. Rev Neurol. 1997;25(148):1871–5.
177. Abel GA, Chen X, Boden-Albala B, Sacco RL. Social readjustment and ischemic stroke: lack of an association in a multiethnic population. Neuroepidemiology. 1999;18(1):22–31.
178. Medin J, Ekberg K, Nordlund A, Eklund J. Organisational change, job strain and increased risk of stroke? A pilot study. Work. 2008;31(4):443–9.
179. Li J, Johnsen SP, Olsen J. Stroke in parents who lost a child: a nationwide follow-up study in Denmark. Neuroepidemiology. 2003;22(3):211–6.
180. Everson SA, Kaplan GA, Goldberg DE, Salonen JT. Anticipatory blood pressure response to exercise predicts future high blood pressure in middle-aged men. Hypertension. 1996;27(5):1059–64.
181. Kamarck TW, Everson SA, Kaplan GA, et al. Exaggerated blood pressure responses during mental stress are associated with enhanced carotid atherosclerosis in middle-aged Finnish men: findings from the Kuopio Ischemic Heart Disease Study. Circulation. 1997; 96(11):3842–8.
182. Lusk SL, Gillespie B, Hagerty BM, Ziemba RA. Acute effects of noise on blood pressure and heart rate. Arch Environ Health. 2004;59(8):392–9.
183. Kajantie E, Phillips DI. The effects of sex and hormonal status on the physiological response to acute psychosocial stress. Psychoneuroendocrinology. 2006;31(2):151–78.
184. Kelsey RM, Blascovich J, Tomaka J, Leitten CL, Schneider TR, Wiens S. Cardiovascular reactivity and adaptation to recurrent psychological stress: effects of prior task exposure. Psychophysiology. 1999;36(6):818–31.
185. Black PH. The inflammatory response is an integral part of the stress response: implications for atherosclerosis, insulin resistance, type II diabetes and metabolic syndrome X. Brain Behav Immun. 2003;17(5):350–64.
186. Grignani G, Pacchiarini L, Zucchella M, et al. Effect of mental stress on platelet function in normal subjects and in patients with coronary artery disease. Haemostasis. 1992;22(3):138–46.

187. Moberg E, Kollind M, Lins PE, Adamson U. Acute mental stress impairs insulin sensitivity in IDDM patients. Diabetologia. 1994;37(3):247–51.
188. von Kanel R, Mills PJ, Fainman C, Dimsdale JE. Effects of psychological stress and psychiatric disorders on blood coagulation and fibrinolysis: a biobehavioral pathway to coronary artery disease? Psychosom Med. 2001;63(4):531–44.
189. Ghiadoni L, Donald AE, Cropley M, et al. Mental stress induces transient endothelial dysfunction in humans. Circulation. 2000;102(20):2473–8.
190. Yeung AC, Vekshtein VI, Krantz DS, et al. The effect of atherosclerosis on the vasomotor response of coronary arteries to mental stress. N Engl J Med. 1991;325(22):1551–6.
191. Barnett PA, Spence JD, Manuck SB, Jennings JR. Psychological stress and the progression of carotid artery disease. J Hypertens. 1997;15(1):49–55.
192. Everson SA, Lynch JW, Chesney MA, et al. Interaction of workplace demands and cardiovascular reactivity in progression of carotid atherosclerosis: population based study. BMJ. 1997;314(7080):553–8.
193. Kobayashi S, Waltz AG, Rhoton Jr AL. Effects of stimulation of cervical sympathetic nerves on cortical blood flow and vascular reactivity. Neurology. 1971;21(3):297–302.
194. Schneider LS, Dagerman KS, Insel PS. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA. 2005;294(15):1934–43.
195. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry. 2006;14(3):191–210.
196. Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med. 2005;353(22):2335–41.
197. Jerrell JM, McIntyre RS. Cerebro- and cardiovascular conditions in adults with schizophrenia treated with antipsychotic medications. Hum Psychopharmacol. 2007;22(6):361–4.
198. McIntyre RS, Jerrell JM. Metabolic and cardiovascular adverse events associated with antipsychotic treatment in children and adolescents. Arch Pediatr Adolesc Med. 2008;162(10):929–35.
199. Barak Y, Baruch Y, Mazeh D, Paleacu D, Aizenberg D. Cardiac and cerebrovascular morbidity and mortality associated with antipsychotic medications in elderly psychiatric inpatients. Am J Geriatr Psychiatry. 2007;15(4):354–6.
200. Mendlewicz J, Lecrubier Y. Antidepressant selection: proceedings from a TCA/SSRI Concensus Conference. Acta Psychiatr Scand Suppl. 2000;403:5–8.
201. Bak S, Tsiropoulos I, Kjaersgaard JO, et al. Selective serotonin reuptake inhibitors and the risk of stroke: a population-based case-control study. Stroke. 2002;33(6):1465–73.
202. Chen Y, Guo JJ, Patel NC. Hemorrhagic stroke associated with antidepressant use in patients with depression: does degree of serotonin reuptake inhibition matter? Pharmacoepidemiol Drug Saf. 2009;18(3):196–202.
203. de Abajo FJ, Jick H, Derby L, Jick S, Schmitz S. Intracranial haemorrhage and use of selective serotonin reuptake inhibitors. Br J Clin Pharmacol. 2000;50(1):43–7.
204. Douglas I, Smeeth L, Irvine D. The use of antidepressants and the risk of haemorrhagic stroke: a nested case control study. Br J Clin Pharmacol. 2011;71(1):116–20.
205. Kharofa J, Sekar P, Haverbusch M, et al. Selective serotonin reuptake inhibitors and risk of hemorrhagic stroke. Stroke. 2007;38(11):3049–51.
206. Smoller JW, Allison M, Cochrane BB, et al. Antidepressant use and risk of incident cardiovascular morbidity and mortality among postmenopausal women in the Women's Health Initiative study. Arch Intern Med. 2009;169(22):2128–39.
207. Trifiro G, Dieleman J, Sen EF, Gambassi G, Sturkenboom MC. Risk of ischemic stroke associated with antidepressant drug use in elderly persons. J Clin Psychopharmacol. 2010;30(3):252–8.
208. Li N, Wallen NH, Ladjevardi M, Hjemdahl P. Effects of serotonin on platelet activation in whole blood. Blood Coagul Fibrinolysis. 1997;8(8):517–23.
209. Wgner A, Montero D, Martensson B, Siwers B, Asberg M. Effects of fluoxetine treatment of platelet 3H-imipramine binding, 5-HT uptake and 5-HT content in major depressive disorder. J Affect Disord. 1990;20(2):101–13.

210. Pacher P, Kecskemeti V. Cardiovascular side effects of new antidepressants and antipsychotics: new drugs, old concerns? Curr Pharm Des. 2004;10(20):2463–75.
211. Dawood T, Lambert EA, Barton DA, et al. Specific serotonin reuptake inhibition in major depressive disorder adversely affects novel markers of cardiac risk. Hypertens Res. 2007;30(4):285–93.
212. Kim EJ, Yu BH. Increased cholesterol levels after paroxetine treatment in patients with panic disorder. J Clin Psychopharmacol. 2005;25(6):597–9.
213. Ramasubbu R. Cerebrovascular effects of selective serotonin reuptake inhibitors: a systematic review. J Clin Psychiatry. 2004;65(12):1642–53.
214. Hamer M, David Batty G, Seldenrijk A, Kivimaki M. Antidepressant medication use and future risk of cardiovascular disease: the Scottish Health Survey. Eur Heart J. 2011;32(4):437–42.
215. Roose SP, Laghrissi-Thode F, Kennedy JS, et al. Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. JAMA. 1998;279(4):287–91.
216. Culic V, Eterovic D, Miric D. Meta-analysis of possible external triggers of acute myocardial infarction. Int J Cardiol. 2005;99(1):1–8.
217. Tofler GH, Muller JE. Triggering of acute cardiovascular disease and potential preventive strategies. Circulation. 2006;114(17):1863–72.
218. Stone PH. Triggering myocardial infarction. N Engl J Med. 2004;351(17):1716–8.
219. Maclure M, Mittleman MA. Should we use a case-crossover design? Annu Rev Public Health. 2000;21:193–221.
220. Austin H, Hill HA, Flanders WD, Greenberg RS. Limitations in the application of case-control methodology. Epidemiol Rev. 1994;16(1):65–76.
221. Redelmeier DA, Tibshirani RJ. Interpretation and bias in case-crossover studies. J Clin Epidemiol. 1997;50(11):1281–7.
222. Paykel ES. The interview for recent life events. Psychol Med. 1997;27(2):301–10.
223. Yoo SH, Yun SC, Kang DW, Kwon SU, Koh JY, Kim JS. Trigger factors among different stroke subtypes: a case-crossover study. Cerebrovasc Dis. 2008;25 Suppl 2:70.
224. Kop WJ, Krantz DS, Howell RH, et al. Effects of mental stress on coronary epicardial vasomotion and flow velocity in coronary artery disease: relationship with hemodynamic stress responses. J Am Coll Cardiol. 2001;37(5):1359–66.
225. Jern C, Eriksson E, Tengborn L, Risberg B, Wadenvik H, Jern S. Changes of plasma coagulation and fibrinolysis in response to mental stress. Thromb Haemost. 1989;62(2):767–71.
226. Muldoon MF, Herbert TB, Patterson SM, Kameneva M, Raible R, Manuck SB. Effects of acute psychological stress on serum lipid levels, hemoconcentration, and blood viscosity. Arch Intern Med. 1995;155(6):615–20.
227. Levine SP, Towell BL, Suarez AM, Knieriem LK, Harris MM, George JN. Platelet activation and secretion associated with emotional stress. Circulation. 1985;71(6):1129–34.
228. Spieker LE, Hurlimann D, Ruschitzka F, et al. Mental stress induces prolonged endothelial dysfunction via endothelin-A receptors. Circulation. 2002;105(24):2817–20.
229. Brodsky MA, Sato DA, Iseri LT, Wolff LJ, Allen BJ. Ventricular tachyarrhythmia associated with psychological stress. The role of the sympathetic nervous system. JAMA. 1987; 257(15):2064–7.
230. Rozanski A, Bairey CN, Krantz DS, et al. Mental stress and the induction of silent myocardial ischemia in patients with coronary artery disease. N Engl J Med. 1988;318(16):1005–12.
231. Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med. 2005;352(6):539–48.
232. Kleijer BC, van Marum RJ, Egberts AC, Jansen PA, Knol W, Heerdink ER. Risk of cerebrovascular events in elderly users of antipsychotics. J Psychopharmacol. 2009;23(8):909–14.
233. Pratt NL, Roughead EE, Ramsay E, Salter A, Ryan P. Risk of hospitalization for stroke associated with antipsychotic use in the elderly: a self-controlled case series. Drugs Aging. 2010;27(11):885–93.
234. Wang S, Linkletter C, Dore D, Mor V, Buka S, Maclure M. Age, antipsychotics, and the risk of ischemic stroke in the Veterans Health Administration. Stroke. 2012;43(1):28–31.
235. Wu CS, Wang SC, Cheng YC, Gau SS. Association of cerebrovascular events with antidepressant use: a case-crossover study. Am J Psychiatry. 2011;168(5):511–21.

Chapter 13
Vascular Depression

Alan J. Thomas

Abstract The "vascular depression" hypothesis postulates that cerebral ischaemic damage to frontal-subcortical circuits predisposes to and/or perpetuates depression in older people, but this concept has been criticized because community studies have failed to demonstrate a robust relationship between depression and vascular disease and because of the apparent inability to define the clinical entity of "vascular depression." However, evidence clearly demonstrates that depression has a bidirectional relationship with vascular disease (Thomas et al., J Affect Disord 79(1–3):81–95, 2004) and that there is an increase in late-life depression in MRI WMH, which are ischaemic lesions. The explanation for the differences in these findings probably reflects the insensitivity of (peripherally measured) conventional VRFs for actual ischaemic disease in the brain and the differences in samples, with the MRI and pathology studies assessing major depression in secondary care patients while the community studies sample milder cases of depression and one's which may have a different aetiology. More recent evidence supports a definition of "vascular depression" focusing on a subgroup defined by the burden of WMH and indicates such a subgroup is both robust and clinically important in that it appears to predict poor response to treatment, persistence of depressive symptoms and of neurocognitive impairments, and worse longer-term outcomes.

Keywords Depression • Late life • Vascular • Cerebrovascular disease • MRI • White matter hyperintensities

The current development of ICD-11 and DSM-V has encouraged clinicians to think again about our diagnostic systems and to realize their limitations. Although the reliability of some of the major diagnoses appears good validity remains a major

A.J. Thomas
Institute for Ageing and Health, Newcastle University,
Campus for Ageing and Vitality, Newcastle upon Tyne NE4 5PL, UK
e-mail: a.j.thomas@ncl.ac.uk

J.M. Ferro (ed.), *Neuropsychiatric Symptoms of Cerebrovascular Diseases*,
Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-1-4471-2428-3_13, © Springer-Verlag London 2013

concern and is likely to remain so while, necessarily, the vast majority of psychiatric diagnoses are symptom based. Research developments, especially in neuroimaging, raise the possibility that we may in some areas be able to move towards diagnoses based on a combination of clinically assessed symptoms and specific investigations, as has long been the case in the rest of medicine. One such potential diagnosis is vascular depression.

What Do We Mean by "Vascular Depression"?

The concept of vascular depression, proposed in the late 1990s, is now entering its difficult teenage years, causing difficulty to proponents and opponents alike. The concept has provoked a large flow of research data, and as is usually the case with new ideas, findings have appeared conflicting. However, the extent of disagreement is not as great as it may first appear to be since differences reflect different concepts of "vascular depression," e.g., all depression in people over a certain age is "vascular" versus only a tightly defined subgroup of depression has a vascular basis, as well as the usual differences in sampling, case ascertainment, and methods of analysis. Some have argued against the validity of the construct itself (e.g., [1]). This skeptical position has largely been based on community studies of late-life depression which have not identified an increase in clinically determined vascular risk factors (VRFs) [2–5]. This apparent absence of significant vascular disease casts doubt on the importance of specific VRFs in the genesis of late-life depression. It is important to note, however, that the same cohorts followed prospectively have reported an association of depression with some VRFs [6, 7], suggesting a subtle contribution to depression in such community subjects may be due to vascular disease. A criticism of such studies is that the ratings of vascular disease are necessarily indirect (i.e., they not direct assessments of vascular disease in the brain) and crude, being based on one-off questionnaire assessments. Thus a real increase in vascular disease in depression may have been missed, and the identification of such prospectively also suggests this might have been the case. However, it is important to note that studies of more severely ill depressed subjects from secondary care settings have also reported no differences in clinically assessed vascular risk factors or of increased vascular disease in older people with depression, and these subjects have had more detailed clinician assessments face to face of vascular disease [8, 9]. Therefore considering all older people with depression together as a group, the evidence only suggests that vascular disease may be a contributing factor to depression and not one which can be used to assist in diagnosis or to delineate a "vascular depression" subgroup.

While community- and hospital-based studies of vascular risk factors have not produced robust evidence to support a broadly defined "vascular depression," in which vascular risk factors make a discernible contribution across everyone with depression, there is nonetheless very strong evidence that cerebrovascular disease is increased in people with depression. It has long been recognized that depression has a bidirectional relationship with vascular disease [10]. Prospective studies of

vascular diseases have reported that previous major depression or depressive symptoms predict a two- to threefold increase in coronary heart disease (e.g., [11, 12]) and stroke disease (e.g., [13, 14]). And in older people with depression, there is a clear, large, and clinically important increase in brain white matter hyperintensities (WMH) on magnetic resonance imaging (MRI) [15]. This meta-analysis reported that this increase in WMH is present in WMH adjacent to the ventricular system (so-called periventricular lesions, PVH) and in WMH embedded within the white matter away from the ventricles (so-called deep white matter lesions, DWMH) and was more prominent in people whose first episode of depression was in later-life, late-onset depression (LOD). Interestingly, the increase in WMH seems to occur independently of any association with VRFs [15]. This has been directly demonstrated in a large study matching depressed and control groups for VRFs [16], thereby indicating that clinically determined VRFs are not a sensitive measure of the presence of cerebrovascular disease. A post-mortem study examining the pathology of WMH in people with depression reported that all DWMH in depression were due to cerebrovascular disease as the lesions all exhibited evidence of ischaemic tissue damage [17, 18]. While DWMH were frequently ischaemic in age-matched control subjects, not all were and there was a significant increase in ischaemic lesions in depression. In contrast PVH were largely not ischaemic and appeared to be due to leakage of cerebrospinal fluid throughout disrupted ependyma in both depressed and control subjects [19]. Importantly PVH which penetrated deeper into the white matter were due to cerebrovascular disease, and a distinction between such lesions and narrower lesions abutting the ventricles is not always made; the latter are unlikely to be ischaemic while the former are likely to be. Thus not only are WMH increased in older people with depression, but such lesions, at least DWMH and large PVH, are clearly ischaemic, and the likelihood of such lesions being clearly due to cerebrovascular disease is greater in people with depression. This increased burden of WMH in late-life depression provides direct evidence for "vascular depression," and the presence of these ischaemic WMH did not correlate with the presence of VRFs, again indicating VRFs are not a good way of assessing the impact of vascular disease on the brain. One reason for this discrepancy between WMH/cerebrovascular disease burden and clinical measures of VRFs is that drops in blood pressure and orthostatic hypotension (OH) are factors contributing to the development of WMH, but these are not assessed in these depression studies as VRFs since the VRF assessments are based on the standard assessments for stroke disease [20] which do not include OH. And drops in blood pressure and OH have been shown to be increased in older people with depression [8, 9] and to be associated with WMH [21].

Furthermore the effect sizes for the increase in WMH in the meta-analysis [15] were moderate to large, ranging from 0.39 to 0.9. Such effect sizes suggest these WMH are likely to be clinically important and other evidence supports this. Prospective studies now demonstrate that the baseline burden of WMH predicts the development of depressive symptoms at 1 and 3 years [22–24], worsening of depressive symptoms at 4 years [25], and new depressive episodes at 3 years [23] and 4 years [26]. Neurocognitive impairments in depression are now known to have a specific pattern consisting of deficits in information processing, memory, and executive function,

and such deficits persist even beyond clinical symptom recovery for at least 4 years [27]. The burden of WMH in depression has long been known to be associated with such neurocognitive impairments (e.g., [28]), and using MRI the specific location of WMH has been related to these neurocognitive impairments [16]. A prospective study reported that baseline WMH alone (not dysfunction in the hypothalamic pituitary adrenal axis or cerebral atrophy or clinical measures of depression) predicted persistent global cognitive impairment and executive and memory impairments at 18 months [29]. WMH are also associated with increased treatment resistance [30], lower remission rates at 2 years [31], higher relapse rates [32], and poorer global outcomes [33]. The increase in ischaemic WMH in late-life depression provides direct evidence for a role of cerebral ischaemia, and this is further strengthened by reports from diffusion tensor imaging studies of increased diffusivity in late-life depression [34], which is a further indicator of the presence of white matter tract disruption due to cerebral ischaemia. This increased diffusivity occurs in areas without WMH, suggesting a more widespread impact of cerebrovascular disease than that identified by MRI WMH, and this is further supported by neuropathology reports of increased cell adhesion molecule expression in the dorsolateral prefrontal cortex (DLPFC), showing vascular changes in frontal grey as well as white matter [35]. Consistent with the negative impact of WMH on treatment outcomes, increased diffusivity in the white matter has also been reported to be associated with reduced remission rates to antidepressants [36, 37]. It was the evidence from prospective studies of an increase in stroke and coronary heart disease in people initially free of these diseases many years after depression, the possible increase in vascular risk factors in people with depression, and the increase in WMH in depression that provided the initial evidence that led to and provided subsequent support for the "vascular depression" hypothesis [38]. This postulated that cerebral ischaemic damage to frontal-subcortical circuits predisposes to and/or perpetuates depression in older people. While in the years since this proposal the evidence of an increase in clinical vascular risk factors has been contentious (as reviewed above) and is likely if present to be weak in its effect, the evidence from direct studies of the brain (MRI WMH and neuropathology studies) has become much stronger, and it is clear that cerebrovascular disease is increased in older people with depression. Thus it appears there is a relationship between depression in older people and vascular disease, especially cerebrovascular disease, but one which is best identified in secondary care samples with late-life major depression, a much more homogeneous group with severe depression, and using direct measures of cerebral ischaemia (i.e., post-mortem evidence of cerebral ischaemia and in vivo evidence of an increase in cerebral WMH).

The explanation for these discrepant findings between community studies and imaging and pathology studies in largely secondary care settings probably reflects the insensitivity of (peripherally measured) conventional VRFs for actual ischaemic disease in the brain and the differences in samples, with the MRI and pathology studies assessing major depression in secondary care patients while the community studies sample milder cases of depression and one's which may have a different aetiology. It is therefore best to conceive the "vascular depression" model as one which postulates that cerebrovascular disease is an important aetiological factor in

late-life depression but likely to be an important one in only a proportion of such people, or to put it negatively, evidence does not support viewing vascular disease as a unifying mechanism for all people with late-life depression or even for late-life major depression. Estimates of the proportion of people with late-life major depression where vascular disease is important indicate this is likely to be the case in about 50 % [39], and this delineation was based on utilizing evidence of significant WMH on MRI rather than VRFs. Two intervention studies using the calcium channel blocker nimodipine have also provided encouraging results [40, 41], suggesting the "vascular depression" model may provide a way of developing new treatment approaches in late-life depression and such approaches are likely to target people with WMH who are those who generally have poorer responses and outcomes with current treatments.

Is it possible to delineate a subgroup of "vascular depression"? As historically in medicine diagnoses are best developed by clinicians assessing people within health services. Recent research has built on this growing evidence that a "vascular depression" subgroup might be delineated within those with late-life major depression by examining using MRI for evidence of significant WMH. Sneed and colleagues [39] reported that using a Fazekas rating cutoff score of 2 on DWMH distinguished a vascular depression from a nonvascular group with 100 % sensitivity across two large clinician-assessed studies. Diagnosing "vascular depression" as major depression in those over 60 who have significant DWMH has further support from the earlier work summarized above on WMH which demonstrates such a construct also has good predictive validity: late-life major depression with significant DWMH predicts persistence of clinical symptoms, poorer treatment response, poorer longer-term outcomes, and persistence of neurocognitive impairment. Thus utilizing WMH burden in defining a vascular depression subgroup could potentially define a subgroup prone to chronic depression, increased treatment resistance, and higher relapse rates and having more severe neurocognitive impairments. For clinicians, whether and how "vascular depression" can be defined may currently seem to remain an academic issue, but it is important to recognize robust evidence for the negative impact of WMH on depression, and this should encourage a more vigorous treatment approach when such lesions are identified. For researchers, it is important in future studies to utilize MRI in the diagnostic process to establish if using a Fazekas rating of the burden of WMH can indeed distinguish a "vascular depression" subgroup and to assess differences prospectively and in outcomes of such a subgroup compared with other nonvascular late-life depression.

References

1. Almeida OP. Vascular depression: myth or reality? Int Psychogeriatr. 2008;20(4):645–52.
2. Kim JM, Stewart R, Shin IS, Yoon JS. Vascular disease/risk and late-life depression in a Korean community population. Br J Psychiatry. 2004;185:102–7.
3. Lyness JM, Caine ED, Cox C, King DA, Conwell Y, Olivares T. Cerebrovascular risk factors and later-life major depression. Testing a small-vessel brain disease model. Am J Geriatr Psychiatry. 1998;6(1):5–13.

4. Lyness JM, Caine ED, King DA, Conwell Y, Cox C, Duberstein PR. Cerebrovascular risk factors and depression in older primary care patients: testing a vascular brain disease model of depression. Am J Geriatr Psychiatry. 1999;7(3):252–8.
5. Naarding P, Tiemeier H, Breteler MMB, Schoevers RA, Jonker C, Koudstaal PJ, et al. Clinically defined vascular depression in the general population. Psychol Med. 2007;37(3): 383–92.
6. Kim J-M, Stewart R, Kim S-W, Yang S-J, Shin I-S, Yoon J-S. Vascular risk factors and incident late-life depression in a Korean population. Br J Psychiatry. 2006;189:26–30.
7. Lyness JM, King DA, Conwell Y, Cox C, Caine ED. Cerebrovascular risk factors and 1-year depression outcome in older primary care patients. Am J Psychiatry. 2000;157(9):1499–501.
8. Richardson J, Kerr SRJ, Shaw F, Kenny RA, O'Brien JT, Thomas AJ. A study of orthostatic hypotension in late-life depression. Am J Geriatr Psychiatry. 2009;17(11):996–9. doi:10.1097/JGP.0b013e3181b4bf35.
9. Vasudev A, O'Brien JT, Tan MP, Parry SW, Thomas AJ. A study of orthostatic hypotension, heart rate variability and baroreflex sensitivity in late-life depression. J Affect Disord. 2011;131:374–8 (Epub 2010/12/03).
10. Thomas AJ, Kalaria RN, O'Brien JT. Depression and vascular disease: what is the relationship? J Affect Disord. 2004;79(1–3):81–95.
11. Ford DE, Mead LA, Chang PP, Cooper-Patrick L, Wang NY, Klag MJ. Depression is a risk factor for coronary artery disease in men: the precursors study. Arch Intern Med. 1998;158(13):1422–6.
12. Pratt LA, Ford DE, Crum RM, Armenian HK, Gallo JJ, Eaton WW. Depression, psychotropic medication, and risk of myocardial infarction. Prospective data from the Baltimore ECA follow-up. Circulation. 1996;94(12):3123–9.
13. Jonas BS, Mussolino ME. Symptoms of depression as a prospective risk factor for stroke. Psychosom Med. 2000;62(4):463–71.
14. Salaycik KJ, Kelly-Hayes M, Beiser A, Nguyen A-H, Brady SM, Kase CS, et al. Depressive symptoms and risk of stroke: the Framingham Study. Stroke. 2007;38(1):16–21.
15. Herrmann LL, Le Masurier M, Ebmeier KP. White matter hyperintensities in late life depression: a systematic review. J Neurol Neurosurg Psychiatry. 2008;79(6):619–24.
16. Sheline YI, Price JL, Vaishnavi SN, Mintun MA, Barch DM, Epstein AA, et al. Regional white matter hyperintensity burden in automated segmentation distinguishes late-life depressed subjects from comparison subjects matched for vascular risk factors. Am J Psychiatry. 2008;165(4): 524–32.
17. Thomas AJ, O'Brien JT, Davis S, Ballard C, Barber R, Kalaria RN, et al. Ischemic basis for deep white matter hyperintensities in major depression: a neuropathological study. Arch Gen Psychiatry. 2002;59(9):785–92.
18. Thomas AJ, Perry R, Kalaria RN, Oakley A, McMeekin W, O'Brien JT. Neuropathological evidence for ischemia in the white matter of the dorsolateral prefrontal cortex in late-life depression. Int J Geriatr Psychiatry. 2003;18(1):7–13.
19. Thomas AJ, O'Brien JT, Barber R, McMeekin W, Perry R. A neuropathological study of periventricular white matter hyperintensities in major depression. J Affect Disord. 2003;76: 49–54.
20. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke. 1991;22(3):312–8.
21. Colloby SJ, Vasudev A, et al. Relationship of orthostatic blood pressure to white matter hyperintensities and subcortical volumes in late-life depression. Br J Psychiatry. 2011;199:404–10.
22. Krishnan MS, O'Brien JT, Firbank MJ, Pantoni L, Carlucci G, Erkinjuntti T, et al. Relationship between periventricular and deep white matter lesions and depressive symptoms in older people: the LADIS Study. Int J Geriatr Psychiatry. 2006;21:983–9.
23. Teodorczuk A, Firbank MJ, Pantoni L, Poggesi A, Erkinjuntti T, Wallin A, et al. Relationship between baseline white-matter changes and development of late-life depressive symptoms: 3-year results from the LADIS study. Psychol Med. 2010;40(4):603–10.

24. Teodorczuk A, O'Brien JT, Firbank MJ, Pantoni L, Poggesi A, Erkinjuntti T, et al. White matter changes and late-life depressive symptoms: longitudinal study. Br J Psychiatry. 2007;191: 212–7.
25. Steffens DC, Krishnan KRR, Crump C, Burke GL. Cerebrovascular disease and evolution of depressive symptoms in the cardiovascular health study. Stroke. 2002;33(6):1636–44.
26. Godin O, Dufouil C, Maillard P, Delcroix N, Mazoyer B, Crivello F, et al. White matter lesions as a predictor of depression in the elderly: the 3C-Dijon study. Biol Psychiatry. 2008;63(7):663–9.
27. Kohler S, Thomas AJ, Barnett NA, O'Brien JT. The pattern and course of cognitive impairment in late-life depression. Psychol Med. 2010;40(4):591–602.
28. Kramer-Ginsberg E, Greenwald BS, Krishnan KR, Christiansen B, Hu J, Ashtari M, et al. Neuropsychological functioning and MRI signal hyperintensities in geriatric depression. Am J Psychiatry. 1999;156(3):438–44.
29. Kohler S, Thomas AJ, Lloyd A, Barber R, Almeida OP, O'Brien JT. White matter hyperintensities, cortisol levels, brain atrophy and continuing cognitive deficits in late-life depression. Br J Psychiatry. 2010;196(2):143–9.
30. Simpson S, Baldwin RC, Jackson A, Burns AS. Is subcortical disease associated with a poor response to antidepressants? Neurological, neuropsychological and neuroradiological findings in late life depression. Psychol Med. 1998;28:1015–26.
31. Taylor WD, Steffens DC, MacFall JR, McQuoid DR, Payne ME, Provenzale JM, et al. White matter hyperintensity progression and late-life depression outcomes. Arch Gen Psychiatry. 2003;60(11):1090–6.
32. O'Brien J, Ames D, Chiu E, Schweitzer I, Desmond P, Tress B. Severe deep white matter lesions and outcome in elderly patients with major depressive disorder: follow up study. BMJ. 1998;317(7164):982–4.
33. Hickie I, Scott E, Mitchell P, Wilhelm K, Austin M-P, Bennett B. Subcortical hyperintensities on magnetic resonance imaging: clinical correlates and prognostic significance in patients with severe depression. Biol Psychiatry. 1995;37:151–60.
34. Taylor WD, MacFall JR, Payne ME, McQuoid DR, Provenzale JM, Steffens DC, et al. Late-life depression and microstructural abnormalities in dorsolateral prefrontal cortex white matter. Am J Psychiatry. 2004;161(7):1293–6.
35. Thomas AJ, Ferrier IN, Kalaria RN, Davis S, O'Brien JT. Cell adhesion molecule expression in the dorsolateral prefrontal cortex and anterior cingulate cortex in major depression in the elderly. Br J Psychiatry. 2002;181:129–34.
36. Alexopoulos GS, Kiosses DN, Choi SJ, Murphy CF, Lim KO. Frontal white matter microstructure and treatment response of late-life depression: a preliminary study. Am J Psychiatry. 2002;159(11):1929–32.
37. Alexopoulos GS, Murphy CF, Gunning-Dixon FM, Latoussakis V, Kanellopoulos D, Klimstra S, et al. Microstructural white matter abnormalities and remission of geriatric depression. Am J Psychiatry. 2008;165(2):238–44.
38. Alexopoulos GS, Meyers BS, et al. Vascular depression hypothesis. Arch Gen Psychiatry. 1997;54(10):915–92.
39. Sneed JR, Rindskopf D, Steffens DC, Krishnan KRR, Roose SP. The vascular depression subtype: evidence of internal validity. Biol Psychiatry. 2008;64(6):491–7.
40. Taragano FE, Allegri R, Vicario A, Bagnatti P, Lyketsos CG. A double blind, randomized clinical trial assessing the efficacy and safety of augmenting standard antidepressant therapy with nimodipine in the treatment of "vascular depression". Int J Geriatr Psychiatry. 2001;16(3):254–60.
41. Taragano FE, Bagnatti P, Allegri RF. A double-blind, randomized clinical trial to assess the augmentation with nimodipine of antidepressant therapy in the treatment of "vascular depression". Int Psychogeriatr. 2005;17(3):487–98.

Chapter 14
Cerebrovascular Disease and Bipolar Disorder

Joanne A. Byars and Jess G. Fiedorowicz

Abstract Bipolar disorder has been strongly associated with cardiovascular disease although the relationship between the two conditions is complex with regard to directionality and mechanisms. The defining syndromes of bipolar disorder, mania and hypomania, can occur following stroke, including in individuals who are seemingly otherwise not at risk based on age, family history, and past psychiatric history. This has led many experts to conclude that bipolar disorder may occur secondary to stroke. Individuals with idiopathic forms of bipolar disorder further face a considerably increased risk for cerebrovascular mortality and stroke. This elevation in risk is large and estimated to be approximately twice that expected from general population estimates for both cerebrovascular mortality and events. There exist a variety of mechanisms that may link bipolar disorder with cerebrovascular disease, and some risk factors may predispose vulnerable individuals to both conditions. These mechanisms include–though are not limited to–inflammation, oxidative stress/mitochondrial dysfunction, abnormalities in the hypothalamic-pituitary-adrenal axis, and sleep disorders. Clinicians should be mindful of the potential for stroke to induce mania and recognize that individuals with bipolar disorder are at special risk for vascular disease, a risk that early and assertive clinical intervention may potentially mitigate.

J.A. Byars, MD (✉)
Department of Neurology, University of Florida College of Medicine,
HSC Box 100236, Gainesville, FL 32610-0236, USA
e-mail: joanne.byars@neurology.ufl.edu

J.G. Fiedorowicz, MD, PhD
Department of Psychiatry, Roy J. and Lucille A. Carver College of Medicine,
University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242, USA

Department of Internal Medicine, Roy J. and Lucille A. Carver College of Medicine,
University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242, USA

Department of Epidemiology, College of Public Health, The University of Iowa,
Iowa City, IA 52242, USA

J.M. Ferro (ed.), *Neuropsychiatric Symptoms of Cerebrovascular Diseases*,
Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-1-4471-2428-3_14, © Springer-Verlag London 2013

Keywords Bipolar disorder • Cerebrovascular disorders • Inflammation • Major depression • Obesity • Oxidative stress • Pituitary-adrenal function tests • Stroke • White matter hyperintensities • Vascular diseases

Introduction

Mania, the defining syndrome of bipolar disorder, is a well-described phenomenon after stroke [1], but the relationship between cerebrovascular disease and bipolar disorder extends beyond new-onset mania secondary to cerebrovascular infarction. There is also an established link between cerebrovascular disease and "idiopathic" bipolar disorder (BD), the nature of which remains to be elucidated. Diverse lines of evidence have affirmed this link, and a variety of mechanisms have been proposed. Much of the literature focuses on vascular disease in general, rather than cerebrovascular disease specifically, but cerebrovascular disease is a manifestation of vascular disease, and disease in other vascular beds strongly predicts cerebrovascular disease.

Samples of persons with BD have consistently demonstrated considerable excess mortality, in part due to excess vascular and cerebrovascular disease [2]. In recent large-scale, population-based epidemiologic studies, the standardized mortality ratio for cardiovascular deaths in BD has ranged from 1.6 to 3.0 and approximately 2 overall [3]. Thus, individuals with BD die from cardiovascular disease approximately twice as often as expected based on age and gender. Fewer studies have reported specifically on cerebrovascular disease, for which overlapping risk factors exist. Osby et al. assessed mortality in all patients with a hospital diagnosis of bipolar disorder between 1973 and 1995 in Sweden ($N = 15{,}386$) and found similar elevations in cerebrovascular mortality [4]. In their analysis, a hospital diagnosis of bipolar disorder nearly doubled the risk of cerebrovascular mortality, with standardized mortality ratios of 1.9 for men and 2.0 for women. The standardized mortality ratios for cerebrovascular disease were further notably higher for those with bipolar disorder relative to those with unipolar major depressive disorder (MDD). Figure 14.1 displays the standardized mortality ratios for cerebrovascular disease and their 95 % confidence intervals by gender and diagnosis. A similar increased risk for stroke was seen with national data from Taiwan in which 69 of 2,289 individuals hospitalized for BD experienced a stroke by 6-year follow-up. Those with bipolar disorder were twice as likely as controls who had been hospitalized for appendectomy to experience a stroke, even after controlling for hypertension, diabetes mellitus, hyperlipidemia, and alcohol and drug dependence, though smoking data was not available [5]. A sample of 2,007 individuals with bipolar disorder in Denmark, however, failed to confirm this finding, though had less power with only 26 strokes observed during follow-up [6].

Consistent with this increased risk of vascular events and mortality, individuals with BD have a higher prevalence of traditional risk factors for vascular disease than the general population. More persons with BD smoke than individuals in the

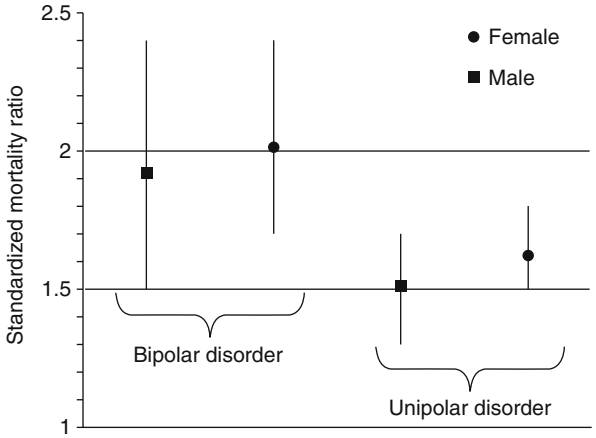


Fig. 14.1 Standardized mortality ratios for mortality due to cerebrovascular disease in bipolar disorder and unipolar depression. Individuals with bipolar disorder are twice as likely to die of cerebrovascular disease as expected from general population estimates and even more likely to die than individuals with unipolar major depression. This data comes from a large cohort of 15,386 individuals with bipolar disorder and 39,182 individuals with major depression from a Swedish inpatient registry. A total of 873 deaths secondary to cerebrovascular disease were observed (Figure is adapted from tabular data presented in Osby et al. [4])

general population or with other psychiatric illnesses [7]. BD patients also eat less healthy diets and exercise less [8]. Medications used for the treatment of BD, especially second-generation antipsychotics, can cause metabolic syndrome, a major risk factor for vascular disease; patients treated for BD with second-generation antipsychotics show higher rates of metabolic syndrome than those treated with lithium or antiepileptic mood stabilizers [9]. On top of these risk factors, people with BD receive less care for medical problems than people without major psychiatric illnesses, so diseases like hypertension and diabetes mellitus may have more opportunity to progress to vascular disease due to lack of appropriate treatment [10].

Although lifestyle factors and medications may contribute to higher rates of vascular disease in BD, they do not fully account for the relationship, corroborating the idea of an underlying pathophysiologic connection beyond these biobehavioral mediators. Individuals with schizophrenia show similar patterns of unhealthy lifestyle factors and psychotropic medication use, yet their vascular disease burden, while higher than the general population, fell below that of people with BD in one study [11], but not another in which those with bipolar disorder were less symptomatic and higher functioning [12]. The link between excessive vascular disease burden and BD existed long before the development of psychotropic medications; studies dating back to the 1920s document increased rates of cardiovascular disease in patients with BD, both compared to the general population and to patients with schizophrenia [3]. Despite the risk of metabolic syndrome associated with some psychotropic medications, patients with treated BD actually experience *lower* rates of vascular disease than individuals whose BD

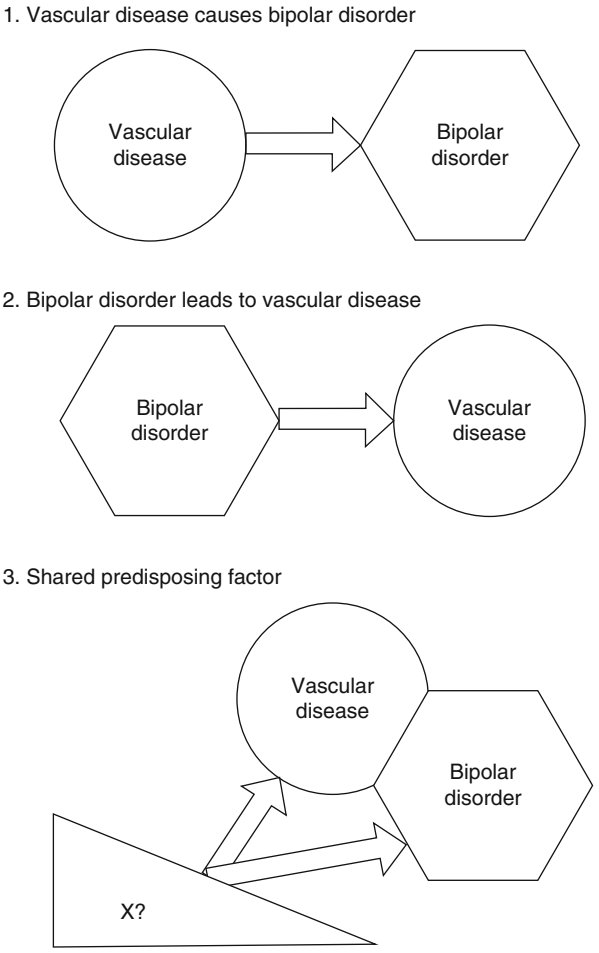


Fig. 14.2 Possible relationships between vascular disease and bipolar disorder. The following diagram illustrates the potential relationship between bipolar disorder and vascular disease. These potential relationships are not mutually exclusive, and the evidence supporting these relationships is highlighted in the chapter

goes untreated [13]; in particular, individuals treated with lithium for BD do not show higher mortality from vascular causes than the general population though this may reflect a healthy users bias [14, 15]. Among older adults with BD, the severity of cerebrovascular risk factors is not associated with duration of BD; in this population, individuals with later-onset BD actually have more cerebrovascular risk factors than those whose first manic episode occurred earlier in life [16], possibly due to greater representation of cases with BD secondary to cerebrovascular disease.

While BD and vascular disease share a clear association, its direction remains unknown. Three possible and potentially overlapping relationships include: vascular disease causes BD, BD causes vascular disease, or a third factor causes both. Figure 14.2 depicts these three potential relationships. The following sections review the evidence to support each of these potential causal pathways.

Case 1
A 71-year-old retired male was admitted to psychiatry after being brought in by his wife for difficult to manage behaviors. She complains he has been talking too much, being excessively friendly with strangers in shopping centers, and has been sleeping only a few hours per night. He reported hearing the voice of Jesus telling him that he would be the only person to never die. He has become increasingly preoccupied with the belief that several biblical passages refer specifically to him. His wife noted that his increased energy, decreased need for sleep, and increased talking first developed approximately 6 months earlier. Over the last several weeks, he has encountered social difficulties related to his inability to refrain from talking about his religious beliefs or other ideas and has even been escorted out of a shopping center by security. His past psychiatric history was significant for the development of a late-onset (in his mid- to late 60's) anxiety disorder for which he briefly received treatment with a serotonin reuptake inhibitor approximately 3 years ago, which resulted in only mild functional impairment. He has a remote history of heavy drinking but no recent alcohol or drug use. His family psychiatric history was significant only for alcoholism in second-degree relatives. He had a history of coronary artery disease with myocardial infarction. He takes medications for hypertension and hyperlipidemia, although blood pressure and low-density lipoprotein cholesterol are above the target range for someone with a history of heart disease. His body mass index is 31 kg/m^2. Magnetic resonance imaging (MRI) for evaluation of new-onset mania revealed two old cerebellar infarcts in the left inferior and right central cerebellum.

Does Cerebrovascular Disease Cause BD?

It is well-known that stroke can cause mania. The occurrence is uncommon enough, however, that precise prevalence estimates are lacking, though poststroke mania has been associated with right orbital frontal, basitemporal, basal ganglia, and thalamic lesions [17]. The clinical features do not appear to distinguish mania secondary to stroke from idiopathic mania [18]. New-onset mania and hypomania have been observed in the broader setting of cerebrovascular and systemic vascular disease. Steffens and Krishnan even postulated the existence of a distinct subtype of bipolar disorder which they termed vascular mania [19]. Table 14.1 outlines their proposed criteria to distinguish such vascular mania [19, 20]. While the clinical nosology has yet to establish a vascular subtype of BD, the evidence is substantial enough to warrant investigation into the role of cerebrovascular disease as a cause of bipolar disorder. In fact, significant data favors the hypothesis that vascular disease plays a broader role in bipolar disorder in general, not just the vascular mania subtype posited by Steffens and Krishnan.

Table 14.1 Stephens and Krishnan criteria for vascular mania

Specify vascular subtype (can be applied to the current or most recent manic episode in bipolar disorder) if A and either B1 or B2 or B3:
A. Mania occurring in the context of clinical and/or neuroimaging evidence of cerebrovascular disease or neuropsychological impairment
B1. Clinical manifestations may include history of stroke or transient ischemic attacks or focal neurologic signs or symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait disturbance, weakness of an extremity)
B2. Neuroimaging findings may include white or gray matter hyperintensities (Fazekas et al. criteria >2 or lesion >5 mm in diameter and irregular in shape) [20], confluent white matter lesions, or cortical or subcortical infarcts
B3. Cognitive impairment manifested by disturbance of executive function (e.g., planning, organizing, sequencing, abstracting), memory, or speed of processing of information
The diagnosis is supported by the following features:
1. Mania onset after 50 years of age or change in the course of mood disorder after the onset of vascular disease in patients with onset before 50 years of age
2. Lack of family history or mood disorders
3. Marked disability in instrumental or self-maintenance activities of daily living

Adapted from Steffens and Krishnan [19]
The above criteria have been proposed to delineate vascular mania from other or idiopathic forms of mania

Brain MRI studies in BD have robustly demonstrated an increased prevalence of white matter hyperintensities (WMH), which consist of periventricular or deep white matter areas of hyperintense T2 signal [21]. An example of these WMH and semiquantitative ratings thereof in mood disorders is illustrated in Fig. 14.3 from Takahashi et al. [22]. WMH occur significantly more frequently in BD than in the general population, with a prevalence of 2.5 times that of healthy controls; a recent meta-analysis found numerically more WMH in BD than in MDD or schizophrenia, but this finding did not reach statistical significance [21]. The significant majority of studies exploring WMH have found a strong association with BD; the few negative studies tended to have methodologic differences (such as thicker MRI slices, smaller sample size, and more simplified rating systems) that could impact their ability to detect the association [23, 24].

Some authors have proposed that the WMH in BD may not be ischemic, but rather due to some other pathology, such as impaired myelination/loss of glial cells, developmental abnormalities, inflammation, demyelination, or edema [23, 25]. The bulk of the evidence points to an ischemic etiology for the WMH in BD. Certainly, in the general elderly population, the vast majority of WMH represent ischemic cerebrovascular disease [26]; however, WMH in BD occur even in young individuals without significant risk factors for vascular disease, to whom evidence from elderly patients with vasculopathy does not necessarily generalize. Similar T2 WMH have been described in MDD; in a postmortem study of elderly patients with MDD, the WMH were found to be 100 % ischemic in nature [27]. WMH in BD are associated with abnormal brain glucose metabolism, which may indicate a pathophysiology similar to that of the ischemic WMH seen in diabetes mellitus [28].

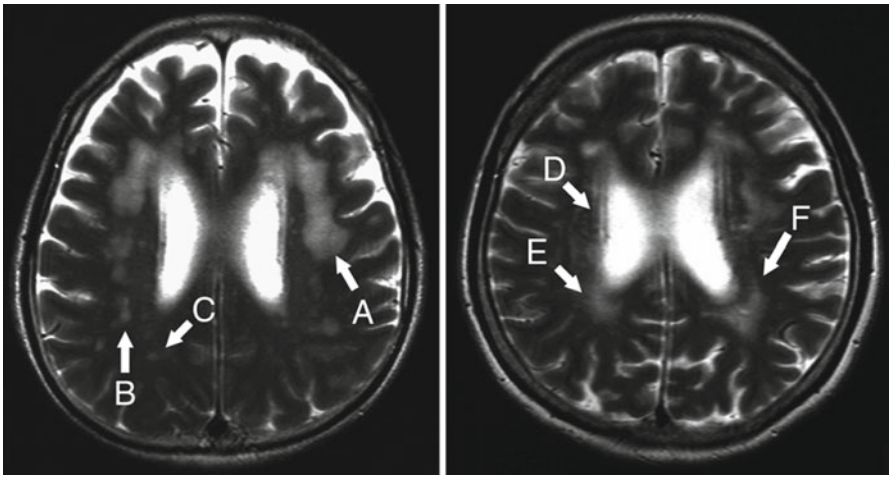


Fig. 14.3 Possible relationships between vascular disease and bipolar disorder. The following image illustrates Fazekas ratings for the WMH commonly reported in bipolar disorder. Grade 1 deep white matter hyperintensity ratings can be seen in *C* and *D*. Grade 2 ratings are represented in *B* and *E*. Grade 3 is illustrated in *A* and *F* (Reprinted from Takahashi et al. [22, p. 445], Copyright (2007), with permission from Elsevier)

Some data suggests the possibility of an overlap between the pathophysiology of the stroke syndrome of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and the WMH in BD: on MRI, the WMH in BD resemble the WMH seen in CADASIL, and in vitro and animal studies indicate that valproic acid may ameliorate abnormalities in the NOTCH signaling pathway implicated as causative in CADASIL [23, 29]; however, the NOTCH3 gene itself has not been associated with BD [30]. The neuropsychiatric manifestations of CADASIL are detailed in Chap. 11.

WMH may potentially play a causative role in the development of BD, rather than representing an incidental finding or a downstream event caused by BD. The development of WMH may precede the onset of mood symptoms, as WMH have been found in childhood-onset BD [31, 32], though one small sample with new-onset psychosis and bipolar disorder did not find greater WMH [33]. WMH occur primarily in brain regions believed to be etiologically involved in the pathophysiology of BD; a coincidental finding or one induced by some disease-related factor might be expected to randomly distribute throughout the brain, rather than clustering in these locations. WMH in BD may occur more frequently in the frontal lobes and/or the frontoparietal junction than in other brain regions, and individuals with BD may also have higher rates of similar T2 hyperintensities in the basal ganglia gray matter; these lesions could disrupt frontal-striatal pathways involved in BD [21, 31, 34]. Brain regions implicated in BD include the prefrontal cortex, anterior cingulate cortex, medial temporal lobes, basal ganglia, thalamus, and the connections between these regions [35– 37]. In addition to the WMH, other changes associated with increased risk for vascular disease (discussed below) may preferentially occur in these regions.

The presence of WMH may indicate a more severe course of illness in BD. Patients with higher amounts of WMH in deep white matter have more frequent hospitalizations for BD and more intractable illness in spite of adequate treatment; individuals with BD who have attempted suicide display more periventricular WMH than those without a history of suicide attempts [28, 38, 39]. Among individuals with BD, those who have vascular risk factors such as diabetes mellitus, obesity, and/or metabolic syndrome may experience a more severe course of illness, as manifested by more suicide attempts, faster relapses, more hospitalizations, and more mood episodes [40–43].

In addition to the WMH, other findings also bolster the possibility that vascular disease could lead to the development of BD. Lithium, long established as the gold standard for BD treatment of BD, may protect against brain damage during cerebral ischemia. In animal models of stroke, lithium treatment—whether prior to ischemia or after ischemia—may decrease infarct size, cell death, and neurologic deficits [44–47]. Valproate may similarly attenuate ischemia-related brain injury, as demonstrated in some animal studies [48–50]. Ameliorating cerebral ischemia could represent one of many potential mechanisms by which these medications improve outcomes in BD, in accordance with the vascular etiology hypothesis.

The potential causative role of vascular disease in BD may vary with age of onset, with some studies finding the strongest association between vascular disease and BD in late-onset BD—typically defined as onset after age 50, which represents about 10 % of patients with BD [51]. Among older adults with BD, those with late-onset illness have significantly more cerebrovascular disease risk factors and WMH than those with early-onset illness, and more often lack other typical risk factors such as family history of BD [52, 53].

Case 2

A 59-year-old male presents for ongoing management of bipolar disorder. His first depressive episode occurred at age 35 and his first manic episode at age 38. He has a master's degree in business administration and worked in a high-level administrative job prior to the onset of his severe mood disorder. He subsequently has had a chronic course of illness characterized predominantly by depressive syndromes, which are characterized by significant decreases in activity, anhedonia, low mood, impaired concentration, social withdrawal, hypersomnia, and frequent suicidal thoughts with no history of suicide attempts. Manias have been infrequent and characterized by significant increases in goal-directed activities, decreased need for sleep, increased energy, increased spending, elevated mood, perceiving colors as more vibrant, and frequent calls to family and friends through all hours of the night. He has a family history of bipolar disorder in his mother and maternal aunt. He drinks

alcohol only occasionally and has no history of using any illicit drugs. He obtains close follow-up from his family physician for the management of hypertension and hyperlipidemia. He has a body mass index of 33 kg/m^2. Head imaging obtained as part of a pre-electroconvulsive therapy workup reveals diffuse white matter disease suggestive of small-vessel ischemic disease and including several white matter hyperintensities as illustrated in Fig. 14.4.

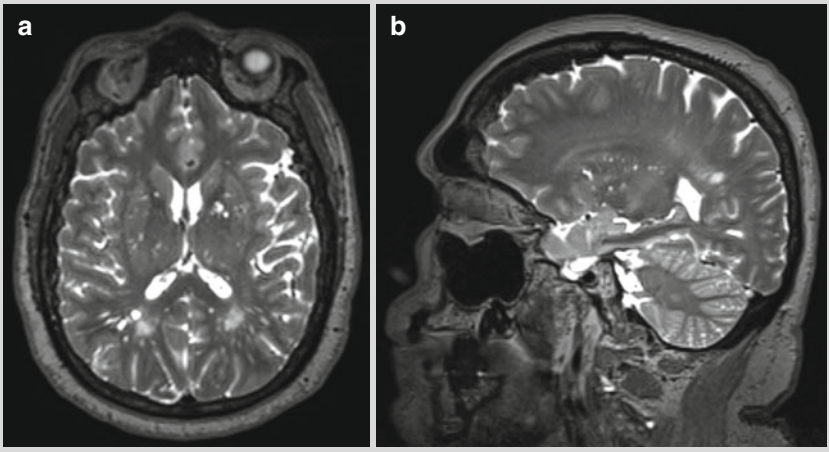


Fig. 14.4 White matter hyperintensities in bipolar disorder (case 2). The above MRI slices in the (**a**) horizontal and (**b**) sagittal planes illustrate white matter hyperintensities and changes suggestive of small-vessel ischemic disease in a patient following several decades with a chronic course of bipolar disorder

Does BD Cause Vascular Disease?

As highlighted the previously cited large population-based studies, BD has been strongly associated with impressive elevations in risk for vascular, including cerebrovascular, disease. This may be potentially explained by the high prevalence of traditional risk factors for vascular disease observed in BD.

Vascular risk factors such as diabetes mellitus, obesity, metabolic syndrome, hypertriglyceridemia, and hypertension are more prevalent in BD than in the general population [9, 12, 42, 54–59]. However, individuals with bipolar disorder still have elevated rates of vascular disease even after controlling for these risk factors, suggesting the risk is not mediated entirely by conventional risk factors [57]. Interestingly, serum from patients with BD can directly induce apoptosis of human endothelial cells in vitro, representing one pathway by which BD or some factor associated with it could directly engender vascular damage [60]. Cardiovascular disease may present over a decade earlier in individuals with BD than in those

without major mood disorders, even after controlling for obesity, smoking, and substance use, again indicating that the factors associated with vascular disease in BD may differ from those implicated in the general population [61].

A specific relationship may exist between vascular disease and BD, rather than mood disorders in general, as cerebrovascular and cardiovascular mortality are higher in BD than in MDD [4, 62]. Mania and hypomania, the defining features of bipolar disorder, have been associated with vascular disease in dose-dependent fashion. In a large, prospective cohort of individuals with BD, manic/hypomanic, but not depressive, symptom burden was associated with a higher risk of death from cardiovascular disease [62]. Another community-based study found that a history of manic or hypomanic episodes showed a stronger association with higher risk for subsequent development of cardiovascular disease than did unipolar major depressive episodes compared to healthy controls, although the difference between the mood episode groups did not reach statistical significance [63]. Another study has demonstrated that endothelial function is inversely related to manic/hypomanic, but not depressive, symptom burden [64].

The time course by which vascular risk factors develop in bipolar disorder has not been well elucidated and could provide some insight into the most relevant bipolar disorder-related mediators. In a case-control study, greater obesity was seen in individuals with BD relative to controls, though no differences in premorbid weight were estimated [65]. One study showed that patients with BD had higher rates of new-onset hypertension developing subsequent to BD diagnosis, while individuals with schizophrenia did not show increased risk for developing new-onset hypertension [58]. Recent data has demonstrated that younger adults with BD do not differ from general population reference values on measures of arterial stiffness, a marker for susceptibility for vascular disease; however, older adults with BD showed markedly increased arterial stiffness relative to age-based norms, indicating that vascular risk may develop over the long-term course of illness [66].

BD and obesity, which is associated with increased risk for incident ischemic stroke, may share overlapping risk factors [67]. Patients with atypical major depression—characterized by hyperphagia and/or weight gain, hypersomnia, and leaden paralysis—have higher body mass index (BMI) than those with typical major depression [68, 69]; atypical depressive episodes are more common in BD than in unipolar MDD, so this aspect of bipolar pathology could potentially directly influence the risk of cerebrovascular disease [67, 70]. Individuals with BD manifest an obesity rate up to 4.5 times the general population [55]. Obesity may be associated with a more severe course of BD, as obese BD patients have more frequent mood episodes, more severe mood symptoms, and are more likely to have attempted suicide than nonobese BD patients [40, 43, 70]. Morbidly obese individuals seeking bariatric surgery may be more likely to have a family history of BD and other psychiatric illnesses than healthy controls [71]; while currently it is not known whether obesity and psychopathology share a true genetic basis with these conditions, this may constitute another route by which shared factors contribute to both BD and vascular risk. Obesity may also be mediated by poor health behaviors that occur in the setting of illness [72].

Does a Third Risk Factor Cause both Vascular Disease and BD?

Vascular disease and BD may be at least partly caused by excessive activation of inflammatory factors, overactivity of HPA axis, and oxidative stress. Other shared mechanisms may also include sleep disturbances, hypercoagulability, endothelial damage, and adverse early-life experiences. Trait-dependent—as opposed to state-dependent—risk factors may be more likely to play an etiologic role in BD rather than emerging as a consequence of it.

Inflammation

BD, cerebrovascular disease, and cardiovascular disease all demonstrate excessive proinflammatory activity [73, 74], and it is possible that a propensity for inflammation may predispose to both BD and cerebrovascular disease. Some aspects of pro-inflammatory activity may be specific to BD, but other aspects may evince a more general vulnerability to psychiatric illness, occurring in MDD and schizophrenia as well [73].

Immunologic and cytokine activity is excessively weighted towards inflammation in BD, a finding which may encompass both trait and state aspects [73]. During mania, the proinflammatory cytokine IL-6 and the acute-phase protein high-sensitivity C-reactive protein (hsCRP) increase, while the anti-inflammatory cytokine IL-4 decreases; the proinflammatory cytokines tumor necrosis factor-alpha (TNF-α) and IL-8 increase in both mania and bipolar depression [75–77]. Some of these state abnormalities, such as increased IL-6 and TNF-α, may improve with treatment of the mood disturbance, raising the possibility of whether these proinflammatory disturbances cause mood episodes—although the mood disturbance could potentially cause the proinflammatory state as well [77]. Patients with BD have elevated circulating activated T cells and soluble IL-2 receptors across depression, mania, and euthymia, suggesting possible trait markers [78]. A shift towards increased Th1 versus Th2 activity, consistent with a pro-inflammatory state, is also seen in euthymia, again indicating these abnormalities may be persistent and stable findings in BD [79]. However, other studies have found somewhat different—though still pro-inflammatory—patterns of cytokines and inflammatory markers across euthymia, mania, and bipolar depression, which may reflect a complex relationship between inflammation and mood state [80]. Patterns of pro-inflammatory activity may vary with duration of illness: one study found that although TNF-α is elevated above levels in healthy controls in the early stage of BD, it increases even further with longer duration of illness; whereas IL-6 and IL-10 are elevated in early stage BD, this elevation decreases in late-stage BD, to the point where IL-10 no longer differs from healthy controls [81]. Elevated high-sensitivity C-reactive protein (hsCRP) may occur during mania and is also

associated with increased risk for ischemic stroke and cardiovascular disease even after controlling for other vascular risk factors, although its causative role for any condition is not yet established [75, 82].

There are plausible—albeit unproven—mechanisms by which abnormally increased inflammatory activity could damage the brain in ways which lead to mood disturbance. Postmortem studies of patients with bipolar disorder show increased protein and mRNA for the proinflammatory cytokine IL-1β and its receptor in the frontal cortex, and increases in the cerebral inflammatory marker intracellular adhesion molecule-1 (ICAM-1) in the ACC, both brain regions believed to be etiologically involved in BD [83, 84]. The finding of increased ICAM-1 may be particularly significant, as ICAM-1 increases with ischemia as well as inflammation, and this increase may be relatively specific to BD, as it occurs to a lesser degree in MDD and not at all in schizophrenia [83]. Mood-stabilizing treatments may lessen inflammatory activity, possibly representing one mechanism by which they improve mood symptoms. In euthymic patients with BD, lithium reduces populations of cells which secrete inflammatory cytokines [85]. In cell culture, valproate decreases production of the inflammatory cytokines TNF-α and IL-6 in response to an immune stimulus; however, carbamazepine, another antiepileptic mood stabilizer, does not [86].

Excessive levels of proinflammatory omega-6 fatty acids relative to anti-inflammatory omega-3 fatty acids may contribute to excessive inflammation, and correlate with both vascular disease and mood disorders. Epidemiologic studies link higher consumption of omega-3 fatty acids with lower risk of cardiovascular disease and possibly stroke, and omega-3 fatty acid supplements appear to lower the risk of cardiovascular events; mechanisms besides anti-inflammatory effects, such as improvement of triglyceride levels, blood pressure, and endothelial function, may also contribute to these benefits [87, 88]. Serum studies of individuals with BD show decreased omega-3 fatty acids and an increased omega-6 to omega-3 ratio, as compared to healthy controls; this abnormality appears in MDD as well but to a lesser degree than in BD [89]. First-degree relatives of patients with BD show decreased high-density lipoprotein cholesterol and increased omega-6 fatty acids, suggesting these derangements could represent an underlying causative risk factor rather than just a downstream consequence of BD [90]. Countries with higher rates of seafood consumption—a marker of omega-3 fatty acid dietary intake—have lower rates of bipolar disorder, as well as MDD but not schizophrenia, consistent with the hypothesis that omega-3 fatty acid deficiency may predispose to mood disorders [91]. One study found an increased ratio of arachidonic acid (a proinflammatory omega-6 fatty acid) to docosahexaenoic acid (an anti-inflammatory omega-3 fatty acid) in postmortem orbitofrontal cortex in patients with BD as compared to controls [92]. As damage to orbitofrontal cortex is known to cause impulsivity and other manifestations which resemble BD symptoms, the fatty acid abnormalities seen here could potentially lead to BD [92].

Several preliminary human studies indicate that omega-3 fatty acids may represent a helpful adjunctive treatment for bipolar depression, although not all studies have confirmed this. Omega-3 fatty acid supplementation does not appear to

improve mania, raising the question of whether the effects of fatty acid derangement vary with phase of illness [93]. If omega-3 fatty acids truly ameliorate the course of bipolar depression, improvement of vascular function and subsequent mitigation of cerebrovascular disease may represent one possible mechanism. Animal studies indicate that lithium treatment may increase anti-inflammatory brain omega-3 fatty acids and mitigate the increase in proinflammatory brain arachidonic acid in response to an inflammatory stressor, which also accords with the hypothesis that reducing inflammation represents one mechanism by which lithium treats BD [94].

Oxidative Stress and Mitochondrial Dysfunction

Mitochondrial dysfunction and excessive oxidative stress are linked to cerebrovascular and systemic vascular disease and to BD, as well as other psychiatric illnesses [95–97]. While still unproven, plausible pathophysiologic mechanisms exist by which oxidative stress and mitochondrial dysfunction could cause BD. Oxidative stress and mitochondrial dysfunction may adversely affect brain regions believed to be involved in BD, such as prefrontal and anterior cingulate cortex as well as the hippocampus [98–101]. Glutathione, which protects against oxidative stress, is decreased in postmortem prefrontal cortex of individuals with BD, as well as MDD and schizophrenia [102]. Postmortem hippocampus, prefrontal cortex, and anterior cingulate from patients with BD show decreased expression of antioxidant genes and enzymes, mitochondrial genes and proteins, and increased markers of oxidative damage, in agreement with a role for impaired antioxidant function in BD; lithium treatment may partially ameliorate these changes [98–101, 103]. These postmortem prefrontal cortex findings may be relatively specific to BD, as they are less strongly associated with MDD and schizophrenia [98, 101].

Magnetic resonance spectroscopy (MRS) in BD shows increased gray matter lactate and diffusely decreased pH throughout the whole brain, findings consistent with mitochondrial dysfunction [104, 105]. MRS studies have also shown decreased N-acetyl aspartate and decreased creatine + phosphocreatine, markers associated with mitochondrial energy production, in brain regions associated with BD, such as prefrontal cortex and hippocampus [106–115]. These findings cannot be accounted for by brain volume differences in these areas and may be present even in children, patients not currently taking psychotropic medications, and in first-episode mania and during euthymia, suggesting they may represent a stable trait marker; on the other hand, longer duration of illness may be associated with greater decreases in N-acetyl aspartate, suggesting a possible cumulative effect on the brain [107– 110, 112, 113, 115]. Cerebrospinal fluid from patients with BD shows elevated lactate, consistent with increased central nervous system anaerobic metabolism due to decreased mitochondrial activity; patients with schizophrenia also show similar cerebrospinal fluid abnormalities [116].

The role of oxidative stress in BD may vary with the phase of illness. In serum from patients with BD, thiobarbituric acid-reactive substances, markers of lipid

peroxidation from oxidative stress, are elevated across mania, depression, and euthymia, consistent with chronic ongoing oxidative stress; however, other markers of oxidative stress such as superoxide dismutase (SOD) increase in mood episodes—particularly mania—but not during euthymia, suggesting additional oxidative stress in mood episodes superimposed on a background of chronic oxidative stress [117, 118]; however, not all studies have confirmed these results [119, 120]. One potential interpretation of this variability is that increased oxidative stress causes mood episodes, and mood episodes remit when oxidative stress is lessened; however, so far no studies have been able to discern the question of temporality, much less causality. Individuals with schizophrenia may exhibit elevations in oxidative stress markers as well, signifying this mechanism may not be specific to BD [118].

Clinical evidence also supports the idea that oxidative stress and mitochondrial dysfunction could cause bipolar-like symptoms. Classic mitochondrial diseases such as Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia, and drug-induced ptosis can present with bipolar-like syndromes [96, 97, 121, 122]; however, patients with mitochondrial diseases can also have presentations which resemble MDD or psychosis, suggesting that mitochondrial dysfunction, like other risk factors for psychiatric disease, may cause more generalized vulnerability to psychiatric symptoms [121].

Mood stabilizers may reduce oxidative stress and mitochondrial dysfunction. Cell culture studies have shown that lithium and valproate may reduce neuronal damage from oxidative stress [123, 124]. Among patients with acute mania, unmedicated individuals show elevation in serum markers of oxidative stress, while those treated with lithium do not differ from healthy controls, even prior to the onset of clinical improvement in mood symptoms [125]. These findings raise the question of whether reducing the effects of oxidative stress is one mechanism by which medications help BD. Preliminary studies of the antioxidant N-acetylcysteine demonstrate improvement of depressive symptoms in BD as well as symptoms in schizophrenia [126, 127], a result consistent with the idea that oxidative stress plays a role in the mood disturbance of BD, although glutaminergic mechanisms for potential therapeutic effects are more often purported.

Hypothalamic-Pituitary-Adrenal Axis Abnormalities

In the general population, hypercortisolemia may worsen multiple risk factors for vascular disease, including hypertension, hyperglycemia, insulin resistance, dyslipidemia, and visceral obesity [128]. BD is associated with hypercortisolemia and excessive activity of the hypothalamic-pituitary-adrenal (HPA) axis; this hyperactivity may be a feature of mood disorders in general rather than just BD, as it is found in MDD as well [129]. Individuals with BD show an abnormal hypercortisolemic response to the dexamethasone suppression test and the dexamethasone/corticotropin-releasing hormone (DEX/CRH) test; these abnormal responses may tilt even more towards hypercortisolemia in bipolar depression than in unipolar

major depressive episodes and may increase further with greater severity of depressive episodes [129]. Fewer studies have examined HPA axis activity in mania and mixed states, but overactivity has been documented during these mood states as well [130].

Excessive HPA axis activity could potentially lead to the development of mood disturbance. The hippocampus and prefrontal cortex express high levels of glucocorticoid receptors, rendering them vulnerable to the effects of HPA dysfunction [131]. In healthy individuals, a single dose of hydrocortisone reduced activity in the prefrontal cortex and hippocampus on a memory task as assessed by fMRI [132]. In another study of healthy individuals, higher baseline salivary cortisol correlated with thinner prefrontal cortex [131]. These findings strengthen the idea that hypercortisolemia could damage brain regions which function abnormally in BD. HPA abnormalities may represent a trait, not just state, marker for BD, as the excessive cortisol response to the DEX/CRH challenge not only occurs during bipolar depression but also can persist in euthymia [133]. The healthy children of parents with BD exhibit elevated salivary cortisol compared to children with a negative family history in one study [134]. However, a different study found no elevation in salivary cortisol in patients with remitted BD on lithium nor in offspring of parents with BD who had a personal history of MDD, so the role of HPA abnormalities as a trait marker for BD is likely quite complex [135]. Animal models which experimentally modulate glucocorticoid receptor expression yield behaviors considered analogous to mania or depression [136]. Some preliminary data indicates that the glucocorticoid receptor antagonist mifepristone may improve depressive and cognitive symptoms in BD, in line with the hypothesis of hypercortisolemia as an etiologic factor for BD [137].

Other Risk Factors Common to BD and Vascular Disease

Disturbances of the sleep cycle, in addition to featuring prominently in BD, are also associated with conventional vascular risk factors, such as weight gain, hypertension, diabetes mellitus, and metabolic syndrome [138, 139]. Sleep disturbance may precede the first-ever mood episode in BD and also often precedes the development of subsequent mood episodes as well [138, 140, 141]. Sleep disturbance could potentially contribute to the subsequent development of both BD and vascular disease and could help explain the overlap between the two conditions.

Both BD and vascular disease display decreases in brain-derived neurotrophic growth factor (BDNF), a neuotrophin involved in long-term potentiation, neuronal survival and recovery from injury, and angiogenesis [142, 143]. Among individuals with coronary artery disease, lower plasma BDNF levels independently predict a 25 % increase in risk for subsequent major cardiac events, such as myocardial infarction and sudden cardiac death, as well as a higher prevalence of dyslipidemia and diabetes mellitus [142]. In animal models of stroke, interventions to increase BDNF decrease ischemia-induced cell death and improve neurologic function, while interventions which block BDNF impair functional recovery [144–146].

In human studies of patients with BD, serum BDNF decreases in mania and depression but normalizes during euthymia, potentially representing a state marker for BD [143]. However, additional data indicates that even during euthymia, BDNF may be normal in early BD but decreases with increasing length of illness, which could reflect ongoing brain injury from BD [81, 143]. Low BDNF could perhaps lead to both BD and cerebrovascular disease by increasing vascular risk factors while at the same time impairing the brain's ability to recover from insults.

Conclusions and Future Directions

Individuals with BD show a marked excess of cerebrovascular and systemic vascular disease. While the link between BD and vascular disease is clear, more research is needed to establish the direction or directions of the relationship. In the meantime, clinicians treating patients with BD need to appreciate the heightened risk for vascular disease in this population and intervene appropriately. As many patients with BD lack reliable access to primary care, psychiatrists and other mental health providers may need to take the lead to ensure patients with BD receive appropriate screening for vascular risk factors, such as hypertension, hyperlipidemia, and diabetes mellitus, and provide or refer for treatment as necessary. The high rates of smoking in patients with bipolar disorder, in combination with their increased baseline risk for vascular disorder, make smoking cessation an especially important treatment target in BD. When possible, it may be worthwhile to consider prescribing medications with a lower risk for metabolic syndrome, such as lithium or lamotrigine, over medications with higher risk, such as divalproex and the second-generation antipsychotics. In samples with dementia or related conditions, antipsychotics have been linked with greater risk of cerebrovascular events and greater overall mortality [147]. Omega-3 fatty acid supplementation in patients with BD may constitute a helpful treatment augmentation strategy; while the evidence of benefit for bipolar depression is preliminary, its effects on vascular risk factors are better established, and it tends to be a well-tolerated and safe intervention [87, 93].

Healthcare providers discuss nutrition and exercise less frequently with patients with BD than with other patient groups, signaling another important target for reducing this health disparity [8]. Clinicians should not hesitate to recommend or refer patients for assistance with nutrition and exercise, as randomized controlled trials have shown that lifestyle interventions to improve vascular risk factors may produce positive health benefits even in patients with serious psychiatric illnesses such as BD [148, 149]. Conversely, primary care providers and others treating patients with premature vascular disease in the absence of conventional risk factors should perhaps consider screening for mood disorders as a possible contributing factor. Neurologists who treat patients with BD who experience acute ischemic stroke should recognize that ongoing mood disturbance may increase risk and make sure to address the unique needs of this population—e.g., ensuring adequate follow-up care for BD and general health maintenance—in addition to standard secondary

stroke prevention measures. In both case illustrations, there exist opportunities to mitigate risk through assertive management of risk factors for vascular disease such as hypertension, hyperlipidemia, and obesity.

The relationship between vascular disease and BD offers intriguing possibilities for deeper understanding of both conditions and the development of novel interventions. As outlined in this chapter, a variety of potentially promising directions for future study exist.

References

1. Starkstein SE, Fedoroff P, Berthier ML, Robinson RG. Manic-depressive and pure manic states after brain lesions. Biol Psychiatry. 1991;29(2):149–58.
2. Murray DP, Weiner M, Prabhakar M, Fiedorowicz JG. Mania and mortality: why the excess cardiovascular risk in bipolar disorder? Curr Psychiatry Rep. 2009;11(6):475–80.
3. Weiner M, Warren L, Fiedorowicz JG. Cardiovascular morbidity and mortality in bipolar disorder. Ann Clin Psychiatry. 2011;23(1):40–7.
4. Osby U, Brandt L, Correia N, Ekbom A, Sparen P. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry. 2001;58(9):844–50.
5. Lin HC, Tsai SY, Lee HC. Increased risk of developing stroke among patients with bipolar disorder after an acute mood episode: a six-year follow-up study. J Affect Disord. 2007;100(1–3):49–54.
6. Nilsson FM, Kessing LV. Increased risk of developing stroke for patients with major affective disorder—a registry study. Eur Arch Psychiatry Clin Neurosci. 2004;254(6):387–91.
7. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. JAMA. 2000;284(20):2606–10.
8. Kilbourne AM, Rofey DL, McCarthy JF, Post EP, Welsh D, Blow FC. Nutrition and exercise behavior among patients with bipolar disorder. Bipolar Disord. 2007;9(5):443–52.
9. Yumru M, Savas HA, Kurt E, et al. Atypical antipsychotics related metabolic syndrome in bipolar patients. J Affect Disord. 2007;98(3):247–52.
10. Bradford DW, Kim MM, Braxton LE, Marx CE, Butterfield M, Elbogen EB. Access to medical care among persons with psychotic and major affective disorders. Psychiatr Serv. 2008;59(8):847–52.
11. Kilbourne AM, Brar JS, Drayer RA, Xu X, Post EP. Cardiovascular disease and metabolic risk factors in male patients with schizophrenia, schizoaffective disorder, and bipolar disorder. Psychosomatics. 2007;48(5):412–7.
12. Birkenaes AB, Opjordsmoen S, Brunborg C, et al. The level of cardiovascular risk factors in bipolar disorder equals that of schizophrenia: a comparative study. J Clin Psychiatry. 2007;68(6):917–23.
13. Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34–38 years. J Affect Disord. 2002;68(2–3):167–81.
14. Ahrens B, Muller-Oerlinghausen B, Schou M, et al. Excess cardiovascular and suicide mortality of affective disorders may be reduced by lithium prophylaxis. J Affect Disord. 1995;33(2):67–75.
15. Brodersen A, Licht RW, Vestergaard P, Olesen AV, Mortensen PB. Sixteen-year mortality in patients with affective disorder commenced on lithium. Br J Psychiatry. 2000;176:429–33.
16. Gildengers AG, Mulsant BH, Al Jurdi RK, et al. The relationship of bipolar disorder lifetime duration and vascular burden to cognition in older adults. Bipolar Disord. 2010; 12(8):851–8.
17. Robinson RG. Mood disorders secondary to stroke. Semin Clin Neuropsychiatry. 1997;2(4):244–51.

18. Starkstein SE, Robinson RG. Affective disorders and cerebral vascular disease. Br J Psychiatry. 1989;154:170–82.
19. Steffens DC, Krishnan KR. Structural neuroimaging and mood disorders: recent findings, implications for classification, and future directions. Biol Psychiatry. 1998;43(10): 705–12.
20. Fazekas F, Niederkorn K, Schmidt R, et al. White matter signal abnormalities in normal individuals: correlation with carotid ultrasonography, cerebral blood flow measurements, and cerebrovascular risk factors. Stroke. 1988;19(10):1285–8.
21. Beyer JL, Young R, Kuchibhatla M, Krishnan KR. Hyperintense MRI lesions in bipolar disorder: a meta-analysis and review. Int Rev Psychiatry. 2009;21(4):394–409.
22. Takahashi K, Oshima A, Ida I, et al. Relationship between age at onset and magnetic resonance image-defined hyperintensities in mood disorders. J Psychiatr Res. 2008;42(6):443–50.
23. Mahon K, Burdick KE, Szeszko PR. A role for white matter abnormalities in the pathophysiology of bipolar disorder. Neurosci Biobehav Rev. 2010;34(4):533–54.
24. Ahn KH, Lyoo IK, Lee HK, et al. White matter hyperintensities in subjects with bipolar disorder. Psychiatry Clin Neurosci. 2004;58(5):516–21.
25. Hajek T, Carrey N, Alda M. Neuroanatomical abnormalities as risk factors for bipolar disorder. Bipolar Disord. 2005;7(5):393–403.
26. Ovbiagele B, Saver JL. Cerebral white matter hyperintensities on MRI: current concepts and therapeutic implications. Cerebrovasc Dis. 2006;22(2–3):83–90.
27. Thomas AJ, O'Brien JT, Davis S, et al. Ischemic basis for deep white matter hyperintensities in major depression: a neuropathological study. Arch Gen Psychiatry. 2002;59(9): 785–92.
28. Regenold WT, Hisley KC, Phatak P, et al. Relationship of cerebrospinal fluid glucose metabolites to MRI deep white matter hyperintensities and treatment resistance in bipolar disorder patients. Bipolar Disord. 2008;10(7):753–64.
29. Yuan P, Salvadore G, Li X, et al. Valproate activates the Notch3/c-FLIP signaling cascade: a strategy to attenuate white matter hyperintensities in bipolar disorder in late life? Bipolar Disord. 2009;11(3):256–69.
30. Ahearn EP, Speer MC, Chen YT, et al. Investigation of Notch3 as a candidate gene for bipolar disorder using brain hyperintensities as an endophenotype. Am J Med Genet. 2002; 114(6):652–8.
31. Pillai JJ, Friedman L, Stuve TA, et al. Increased presence of white matter hyperintensities in adolescent patients with bipolar disorder. Psychiatry Res. 2002;114(1):51–6.
32. Lyoo IK, Lee HK, Jung JH, Noam GG, Renshaw PF. White matter hyperintensities on magnetic resonance imaging of the brain in children with psychiatric disorders. Compr Psychiatry. 2002;43(5):361–8.
33. Zanetti MV, Schaufelberger MS, de Castro CC, et al. White-matter hyperintensities in first-episode psychosis. Br J Psychiatry. 2008;193(1):25–30.
34. Lloyd AJ, Moore PB, Cousins DA, et al. White matter lesions in euthymic patients with bipolar disorder. Acta Psychiatr Scand. 2009;120(6):481–91.
35. Cerullo MA, Adler CM, Delbello MP, Strakowski SM. The functional neuroanatomy of bipolar disorder. Int Rev Psychiatry. 2009;21(4):314–22.
36. Sheline YI. Neuroimaging studies of mood disorder effects on the brain. Biol Psychiatry. 2003;54(3):338–52.
37. Chen CH, Suckling J, Lennox BR, Ooi C, Bullmore ET. A quantitative meta-analysis of fMRI studies in bipolar disorder. Bipolar Disord. 2011;13(1):1–15.
38. Pompili M, Innamorati M, Mann JJ, et al. Periventricular white matter hyperintensities as predictors of suicide attempts in bipolar disorders and unipolar depression. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(6):1501–7.
39. Moore PB, Shepherd DJ, Eccleston D, et al. Cerebral white matter lesions in bipolar affective disorder: relationship to outcome. Br J Psychiatry. 2001;178:172–6.
40. Fagiolini A, Kupfer DJ, Rucci P, Scott JA, Novick DM, Frank E. Suicide attempts and ideation in patients with bipolar I disorder. J Clin Psychiatry. 2004;65(4):509–14.

41. Fagiolini A, Frank E, Scott JA, Turkin S, Kupfer DJ. Metabolic syndrome in bipolar disorder: findings from the Bipolar Disorder Center for Pennsylvanians. Bipolar Disord. 2005; 7(5):424–30.
42. Cassidy F, Ahearn E, Carroll BJ. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. Am J Psychiatry. 1999;156(9):1417–20.
43. Fagiolini A, Kupfer DJ, Houck PR, Novick DM, Frank E. Obesity as a correlate of outcome in patients with bipolar I disorder. Am J Psychiatry. 2003;160(1):112–7.
44. Xu J, Culman J, Blume A, Brecht S, Gohlke P. Chronic treatment with a low dose of lithium protects the brain against ischemic injury by reducing apoptotic death. Stroke. 2003;34(5):1287–92.
45. Ren M, Senatorov VV, Chen RW, Chuang DM. Postinsult treatment with lithium reduces brain damage and facilitates neurological recovery in a rat ischemia/reperfusion model. Proc Natl Acad Sci USA. 2003;100(10):6210–5.
46. Yan XB, Wang SS, Hou HL, Ji R, Zhou JN. Lithium improves the behavioral disorder in rats subjected to transient global cerebral ischemia. Behav Brain Res. 2007;177(2):282–9.
47. Bian Q, Shi T, Chuang DM, Qian Y. Lithium reduces ischemia-induced hippocampal CA1 damage and behavioral deficits in gerbils. Brain Res. 2007;1184:270–6.
48. Xuan A, Long D, Li J, et al. Neuroprotective effects of valproic acid following transient global ischemia in rats. Life Sci. 2012;90(11–12):463–8.
49. Qian YR, Lee MJ, Hwang S, Kook JH, Kim JK, Bae CS. Neuroprotection by valproic Acid in mouse models of permanent and transient focal cerebral ischemia. Korean J Physiol Pharmacol. 2010;14(6):435–40.
50. Ren M, Leng Y, Jeong M, Leeds PR, Chuang DM. Valproic acid reduces brain damage induced by transient focal cerebral ischemia in rats: potential roles of histone deacetylase inhibition and heat shock protein induction. J Neurochem. 2004;89(6):1358–67.
51. Vasudev A, Thomas A. 'Bipolar disorder' in the elderly: what's in a name? Maturitas. 2010;66(3):231–5.
52. Tamashiro JH, Zung S, Zanetti MV, et al. Increased rates of white matter hyperintensities in late-onset bipolar disorder. Bipolar Disord. 2008;10(7):765–75.
53. Subramaniam H, Dennis MS, Byrne EJ. The role of vascular risk factors in late onset bipolar disorder. Int J Geriatr Psychiatry. 2007;22(8):733–7.
54. Kilbourne AM, Cornelius JR, Han X, et al. Burden of general medical conditions among individuals with bipolar disorder. Bipolar Disord. 2004;6(5):368–73.
55. Gurpegui M, Martinez-Ortega JM, Gutierrez-Rojas L, Rivero J, Rojas C, Jurado D. Overweight and obesity in patients with bipolar disorder or schizophrenia compared with a non-psychiatric sample. Prog Neuropsychopharmacol Biol Psychiatry. 2012;37(1):169–75.
56. Fiedorowicz JG, Palagummi NM, Forman-Hoffman VL, Miller DD, Haynes WG. Elevated prevalence of obesity, metabolic syndrome, and cardiovascular risk factors in bipolar disorder. Ann Clin Psychiatry. 2008;20(3):131–7.
57. Fiedorowicz JG, He J, Merikangas KR. The association between mood and anxiety disorders with vascular diseases and risk factors in a nationally representative sample. J Psychosom Res. 2011;70(2):145–54.
58. Johannessen L, Strudsholm U, Foldager L, Munk-Jorgensen P. Increased risk of hypertension in patients with bipolar disorder and patients with anxiety compared to background population and patients with schizophrenia. J Affect Disord. 2006;95(1–3):13–7.
59. Garcia-Portilla MP, Saiz PA, Benabarre A, et al. The prevalence of metabolic syndrome in patients with bipolar disorder. J Affect Disord. 2008;106(1–2):197–201.
60. Politi P, Brondino N, Emanuele E. Increased proapoptotic serum activity in patients with chronic mood disorders. Arch Med Res. 2008;39(2):242–5.
61. Goldstein BI, Fagiolini A, Houck P, Kupfer DJ. Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. Bipolar Disord. 2009; 11(6):657–62.
62. Fiedorowicz JG, Solomon DA, Endicott J, et al. Manic/hypomanic symptom burden and cardiovascular mortality in bipolar disorder. Psychosom Med. 2009;71(6):598–606.

63. Ramsey CM, Leoutsakos JM, Mayer LS, Eaton WW, Lee HB. History of manic and hypomanic episodes and risk of incident cardiovascular disease: 11.5 year follow-up from the Baltimore Epidemiologic Catchment Area Study. J Affect Disord. 2010;125(1–3):35–41.
64. Fiedorowicz JG, Coryell WH, Rice JP, Warren LL, Haynes W. Vasculopathy related to manic/hypomanic symptom burden and first generation antipsychotics in a sub-sample from the Collaborative Depression Study (CDS). Psychother Psychosom. 2012;81(4):235–43.
65. Shah A, Shen N, El-Mallakh RS. Weight gain occurs after onset of bipolar illness in overweight bipolar patients. Ann Clin Psychiatry. 2006;18(4):239–41.
66. Fiedorowicz JG. Course of illness and the development of vascular disease in individuals with bipolar disorder. Dissertation, The University of Iowa; 2001.
67. Yatsuya H, Folsom AR, Yamagishi K, North KE, Brancati FL, Stevens J. Race- and sex-specific associations of obesity measures with ischemic stroke incidence in the Atherosclerosis Risk in Communities (ARIC) study. Stroke. 2010;41(3):417–25.
68. Kendler KS, Eaves LJ, Walters EE, Neale MC, Heath AC, Kessler RC. The identification and validation of distinct depressive syndromes in a population-based sample of female twins. Arch Gen Psychiatry. 1996;53(5):391–9.
69. Sullivan PF, Prescott CA, Kendler KS. The subtypes of major depression in a twin registry. J Affect Disord. 2002;68(2–3):273–84.
70. Wildes JE, Marcus MD, Fagiolini A. Obesity in patients with bipolar disorder: a biopsychosocial-behavioral model. J Clin Psychiatry. 2006;67(6):904–15.
71. Black DW, Goldstein RB, Mason EE, Bell SE, Blum N. Depression and other mental disorders in the relatives of morbidly obese patients. J Affect Disord. 1992;25(2):91–5.
72. Chwastiak LA, Rosenheck RA, Kazis LE. Association of psychiatric illness and obesity, physical inactivity, and smoking among a national sample of veterans. Psychosomatics. 2011;52(3):230–6.
73. Langan C, McDonald C. Neurobiological trait abnormalities in bipolar disorder. Mol Psychiatry. 2009;14(9):833–46.
74. Muir KW, Tyrrell P, Sattar N, Warburton E. Inflammation and ischaemic stroke. Curr Opin Neurol. 2007;20(3):334–42.
75. Cunha AB, Andreazza AC, Gomes FA, et al. Investigation of serum high-sensitive C-reactive protein levels across all mood states in bipolar disorder. Eur Arch Psychiatry Clin Neurosci. 2008;258(5):300–4.
76. O'Brien SM, Scully P, Scott LV, Dinan TG. Cytokine profiles in bipolar affective disorder: focus on acutely ill patients. J Affect Disord. 2006;90(2–3):263–7.
77. Kim YK, Jung HG, Myint AM, Kim H, Park SH. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. J Affect Disord. 2007;104(1–3):91–5.
78. Breunis MN, Kupka RW, Nolen WA, et al. High numbers of circulating activated T cells and raised levels of serum IL-2 receptor in bipolar disorder. Biol Psychiatry. 2003;53(2):157–65.
79. Brietzke E, Kauer-Sant'Anna M, Teixeira AL, Kapczinski F. Abnormalities in serum chemokine levels in euthymic patients with bipolar disorder. Brain Behav Immun. 2009;23(8):1079–82.
80. Hope S, Dieset I, Agartz I, et al. Affective symptoms are associated with markers of inflammation and immune activation in bipolar disorders but not in schizophrenia. J Psychiatr Res. 2011;45(12):1608–16.
81. Kauer-Sant'Anna M, Kapczinski F, Andreazza AC, et al. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. Int J Neuropsychopharmacol. 2009;12(4):447–58.
82. Kaptoge S, Di Angelantonio E, Lowe G, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010;375(9709):132–40.
83. Thomas AJ, Davis S, Ferrier IN, Kalaria RN, O'Brien JT. Elevation of cell adhesion molecule immunoreactivity in the anterior cingulate cortex in bipolar disorder. Biol Psychiatry. 2004;55(6):652–5.

84. Rao JS, Harry GJ, Rapoport SI, Kim HW. Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients. Mol Psychiatry. 2010;15(4):384–92.
85. Boufidou F, Nikolaou C, Alevizos B, Liappas IA, Christodoulou GN. Cytokine production in bipolar affective disorder patients under lithium treatment. J Affect Disord. 2004;82(2):309–13.
86. Ichiyama T, Okada K, Lipton JM, Matsubara T, Hayashi T, Furukawa S. Sodium valproate inhibits production of TNF-alpha and IL-6 and activation of NF-kappaB. Brain Res. 2000;857(1–2):246–51.
87. Marik PE, Varon J. Omega-3 dietary supplements and the risk of cardiovascular events: a systematic review. Clin Cardiol. 2009;32(7):365–72.
88. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol. 2011;58(20):2047–67.
89. McNamara RK, Jandacek R, Rider T, Tso P, Dwivedi Y, Pandey GN. Selective deficits in erythrocyte docosahexaenoic acid composition in adult patients with bipolar disorder and major depressive disorder. J Affect Disord. 2010;126(1–2):303–11.
90. Sobczak S, Honig A, Christophe A, et al. Lower high-density lipoprotein cholesterol and increased omega-6 polyunsaturated fatty acids in first-degree relatives of bipolar patients. Psychol Med. 2004;34(1):103–12.
91. Noaghiul S, Hibbeln JR. Cross-national comparisons of seafood consumption and rates of bipolar disorders. Am J Psychiatry. 2003;160(12):2222–7.
92. McNamara RK, Jandacek R, Rider T, et al. Deficits in docosahexaenoic acid and associated elevations in the metabolism of arachidonic acid and saturated fatty acids in the postmortem orbitofrontal cortex of patients with bipolar disorder. Psychiatry Res. 2008;160(3):285–99.
93. Sarris J, Mischoulon D, Schweitzer I. Adjunctive nutraceuticals with standard pharmacotherapies in bipolar disorder: a systematic review of clinical trials. Bipolar Disord. 2011;13(5–6):454–65.
94. Basselin M, Kim HW, Chen M, et al. Lithium modifies brain arachidonic and docosahexaenoic metabolism in rat lipopolysaccharide model of neuroinflammation. J Lipid Res. 2010;51(5):1049–56.
95. Faraci FM. Protecting against vascular disease in brain. Am J Physiol Heart Circ Physiol. 2011;300(5):H1566–82.
96. Kato T, Kato N. Mitochondrial dysfunction in bipolar disorder. Bipolar Disord. 2000; 2(3 Pt 1):180–90.
97. Kato T. Role of mitochondrial DNA in calcium signaling abnormality in bipolar disorder. Cell Calcium. 2008;44(1):92–102.
98. Wang JF, Shao L, Sun X, Young LT. Increased oxidative stress in the anterior cingulate cortex of subjects with bipolar disorder and schizophrenia. Bipolar Disord. 2009;11(5):523–9.
99. Benes FM, Matzilevich D, Burke RE, Walsh J. The expression of proapoptosis genes is increased in bipolar disorder, but not in schizophrenia. Mol Psychiatry. 2006;11(3):241–51.
100. Sun X, Wang JF, Tseng M, Young LT. Downregulation in components of the mitochondrial electron transport chain in the postmortem frontal cortex of subjects with bipolar disorder. J Psychiatry Neurosci. 2006;31(3):189–96.
101. Andreazza AC, Shao L, Wang JF, Young LT. Mitochondrial complex I activity and oxidative damage to mitochondrial proteins in the prefrontal cortex of patients with bipolar disorder. Arch Gen Psychiatry. 2010;67(4):360–8.
102. Gawryluk JW, Wang JF, Andreazza AC, Shao L, Young LT. Decreased levels of glutathione, the major brain antioxidant, in post-mortem prefrontal cortex from patients with psychiatric disorders. Int J Neuropsychopharmacol. 2011;14(1):123–30.
103. Konradi C, Eaton M, MacDonald ML, Walsh J, Benes FM, Heckers S. Molecular evidence for mitochondrial dysfunction in bipolar disorder. Arch Gen Psychiatry. 2004;61(3):300–8.
104. Hamakawa H, Murashita J, Yamada N, Inubushi T, Kato N, Kato T. Reduced intracellular pH in the basal ganglia and whole brain measured by 31P-MRS in bipolar disorder. Psychiatry Clin Neurosci. 2004;58(1):82–8.

105. Dager SR, Friedman SD, Parow A, et al. Brain metabolic alterations in medication-free patients with bipolar disorder. Arch Gen Psychiatry. 2004;61(5):450–8.
106. Molina V, Sanchez J, Sanz J, et al. Dorsolateral prefrontal N-acetyl-aspartate concentration in male patients with chronic schizophrenia and with chronic bipolar disorder. Eur Psychiatry. 2007;22(8):505–12.
107. Caetano SC, Olvera RL, Hatch JP, et al. Lower N-acetyl-aspartate levels in prefrontal cortices in pediatric bipolar disorder: a (1)H magnetic resonance spectroscopy study. J Am Acad Child Adolesc Psychiatry. 2011;50(1):85–94.
108. Sassi RB, Stanley JA, Axelson D, et al. Reduced NAA levels in the dorsolateral prefrontal cortex of young bipolar patients. Am J Psychiatry. 2005;162(11):2109–15.
109. Winsberg ME, Sachs N, Tate DL, Adalsteinsson E, Spielman D, Ketter TA. Decreased dorsolateral prefrontal N-acetyl aspartate in bipolar disorder. Biol Psychiatry. 2000;47(6):475–81.
110. Atmaca M, Yildirim H, Ozdemir H, Poyraz AK, Tezcan E, Ogur E. Hippocampal 1H MRS in first-episode bipolar I patients. Prog Neuropsychopharmacol Biol Psychiatry. 2006;30(7):1235–9.
111. Bertolino A, Frye M, Callicott JH, et al. Neuronal pathology in the hippocampal area of patients with bipolar disorder: a study with proton magnetic resonance spectroscopic imaging. Biol Psychiatry. 2003;53(10):906–13.
112. Deicken RF, Pegues MP, Anzalone S, Feiwell R, Soher B. Lower concentration of hippocampal N-acetylaspartate in familial bipolar I disorder. Am J Psychiatry. 2003;160(5):873–82.
113. Scherk H, Backens M, Schneider-Axmann T, et al. Neurochemical pathology in hippocampus in euthymic patients with bipolar I disorder. Acta Psychiatr Scand. 2008;117(4):283–8.
114. Stork C, Renshaw PF. Mitochondrial dysfunction in bipolar disorder: evidence from magnetic resonance spectroscopy research. Mol Psychiatry. 2005;10(10):900–19.
115. Frey BN, Stanley JA, Nery FG, et al. Abnormal cellular energy and phospholipid metabolism in the left dorsolateral prefrontal cortex of medication-free individuals with bipolar disorder: an in vivo 1H MRS study. Bipolar Disord. 2007;9 Suppl 1:119–27.
116. Regenold WT, Phatak P, Marano CM, Sassan A, Conley RR, Kling MA. Elevated cerebrospinal fluid lactate concentrations in patients with bipolar disorder and schizophrenia: implications for the mitochondrial dysfunction hypothesis. Biol Psychiatry. 2009; 65(6):489–94.
117. Andreazza AC, Cassini C, Rosa AR, et al. Serum S100B and antioxidant enzymes in bipolar patients. J Psychiatr Res. 2007;41(6):523–9.
118. Kunz M, Gama CS, Andreazza AC, et al. Elevated serum superoxide dismutase and thiobarbituric acid reactive substances in different phases of bipolar disorder and in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(7):1677–81.
119. Gergerlioglu HS, Savas HA, Bulbul F, Selek S, Uz E, Yumru M. Changes in nitric oxide level and superoxide dismutase activity during antimanic treatment. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31(3):697–702.
120. Selek S, Savas HA, Gergerlioglu HS, Bulbul F, Uz E, Yumru M. The course of nitric oxide and superoxide dismutase during treatment of bipolar depressive episode. J Affect Disord. 2008;107(1–3):89–94.
121. Fattal O, Budur K, Vaughan AJ, Franco K. Review of the literature on major mental disorders in adult patients with mitochondrial diseases. Psychosomatics. 2006;47(1):1–7.
122. Shao L, Martin MV, Watson SJ, et al. Mitochondrial involvement in psychiatric disorders. Ann Med. 2008;40(4):281–95.
123. Nciri R, Desmoulin F, Allagui MS, et al. Neuroprotective effects of chronic exposure of SH-SY5Y to low lithium concentration involve glycolysis stimulation, extracellular pyruvate accumulation and resistance to oxidative stress. Int J Neuropsychopharmacol. 2013;16(2): 365–76.
124. Wang JF, Azzam JE, Young LT. Valproate inhibits oxidative damage to lipid and protein in primary cultured rat cerebrocortical cells. Neuroscience. 2003;116(2):485–9.

125. Machado-Vieira R, Andreazza AC, Viale CI, et al. Oxidative stress parameters in unmedicated and treated bipolar subjects during initial manic episode: a possible role for lithium antioxidant effects. Neurosci Lett. 2007;421(1):33–6.
126. Berk M, Copolov DL, Dean O, et al. N-acetyl cysteine for depressive symptoms in bipolar disorder—a double-blind randomized placebo-controlled trial. Biol Psychiatry. 2008;64(6):468–75.
127. Berk M, Copolov D, Dean O, et al. N-acetyl cysteine as a glutathione precursor for schizophrenia—a double-blind, randomized, placebo-controlled trial. Biol Psychiatry. 2008; 64(5):361–8.
128. Whitworth JA, Williamson PM, Mangos G, Kelly JJ. Cardiovascular consequences of cortisol excess. Vasc Health Risk Manag. 2005;1(4):291–9.
129. Rybakowski JK, Twardowska K. The dexamethasone/corticotropin-releasing hormone test in depression in bipolar and unipolar affective illness. J Psychiatr Res. 1999;33(5): 363–70.
130. Cassidy F, Ritchie JC, Carroll BJ. Plasma dexamethasone concentration and cortisol response during manic episodes. Biol Psychiatry. 1998;43(10):747–54.
131. Kremen WS, O'Brien RC, Panizzon MS, et al. Salivary cortisol and prefrontal cortical thickness in middle-aged men: a twin study. Neuroimage. 2010;53(3):1093–102.
132. Henckens MJ, Pu Z, Hermans EJ, van Wingen GA, Joels M, Fernandez G. Dynamically changing effects of corticosteroids on human hippocampal and prefrontal processing. Hum Brain Mapp. 2012;33(12):2885–97.
133. Watson S, Gallagher P, Ritchie JC, Ferrier IN, Young AH. Hypothalamic-pituitary-adrenal axis function in patients with bipolar disorder. Br J Psychiatry. 2004;184:496–502.
134. Ellenbogen MA, Santo JB, Linnen AM, Walker CD, Hodgins S. High cortisol levels in the offspring of parents with bipolar disorder during two weeks of daily sampling. Bipolar Disord. 2010;12(1):77–86.
135. Deshauer D, Duffy A, Meaney M, Sharma S, Grof P. Salivary cortisol secretion in remitted bipolar patients and offspring of bipolar parents. Bipolar Disord. 2006;8(4):345–9.
136. Einat H, Manji HK. Cellular plasticity cascades: genes-to-behavior pathways in animal models of bipolar disorder. Biol Psychiatry. 2006;59(12):1160–71.
137. Young AH, Gallagher P, Watson S, Del-Estal D, Owen BM, Ferrier IN. Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. Neuropsychopharmacology. 2004;29(8):1538–45.
138. Harvey AG. Sleep and circadian functioning: critical mechanisms in the mood disorders? Annu Rev Clin Psychol. 2011;7:297–319.
139. Lam JC, Ip MS. Sleep & the metabolic syndrome. Indian J Med Res. 2010;131:206–16.
140. Duffy A, Alda M, Crawford L, Milin R, Grof P. The early manifestations of bipolar disorder: a longitudinal prospective study of the offspring of bipolar parents. Bipolar Disord. 2007;9(8):828–38.
141. Jackson A, Cavanagh J, Scott J. A systematic review of manic and depressive prodromes. J Affect Disord. 2003;74(3):209–17.
142. Jiang H, Liu Y, Zhang Y, Chen ZY. Association of plasma brain-derived neurotrophic factor and cardiovascular risk factors and prognosis in angina pectoris. Biochem Biophys Res Commun. 2011;415(1):99–103.
143. Fernandes BS, Gama CS, Cereser KM, et al. Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis. J Psychiatr Res. 2011;45(8):995–1004.
144. Ferrer I, Krupinski J, Goutan E, Marti E, Ambrosio S, Arenas E. Brain-derived neurotrophic factor reduces cortical cell death by ischemia after middle cerebral artery occlusion in the rat. Acta Neuropathol. 2001;101(3):229–38.
145. Muller HD, Hanumanthiah KM, Diederich K, Schwab S, Schabitz WR, Sommer C. Brain-derived neurotrophic factor but not forced arm use improves long-term outcome after

photothrombotic stroke and transiently upregulates binding densities of excitatory glutamate receptors in the rat brain. Stroke. 2008;39(3):1012–21.
146. Ploughman M, Windle V, MacLellan CL, White N, Dore JJ, Corbett D. Brain-derived neurotrophic factor contributes to recovery of skilled reaching after focal ischemia in rats. Stroke. 2009;40(4):1490–5.
147. Jeste DV, Blazer D, Casey D, et al. ACNP White Paper: update on use of antipsychotic drugs in elderly persons with dementia. Neuropsychopharmacology. 2008;33(5):957–70.
148. Morriss R, Mohammed FA. Metabolism, lifestyle and bipolar affective disorder. J Psychopharmacol. 2005;19(6 Suppl):94–101.
149. Poulin MJ, Chaput JP, Simard V, et al. Management of antipsychotic-induced weight gain: prospective naturalistic study of the effectiveness of a supervised exercise programme. Aust N Z J Psychiatry. 2007;41(12):980–9.

Index

J.M. Ferro (ed.), *Neuropsychiatric Symptoms of Cerebrovascular Diseases,*
Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-1-4471-2428-3, © Springer-Verlag London 2013