Ronald M. Lazar
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Neurovascular Neuropsychology

Second Edition

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ISBN 978-3-030-49585-5 ISBN 978-3-030-49586-2 (eBook)
https://doi.org/10.1007/978-3-030-49586-2

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To Soody, my partner in all things.

—RML

To Doug, Ava, Riley, and Helen for always reminding me of what is most important.

—MAP

To Karen, Lauren, and Aria, who brighten my life, and to my parents for bestowing me with a bottomless sense of curiosity.

—JNP

Preface to the Second Edition

In the decade since the first edition of *Neurovascular Neuropsychology*, there has been an extraordinary growth in knowledge that has improved diagnosis, spurred development of novel treatment modalities, and improved outcomes for those with cerebrovascular disease. We are gratified to see that the role of neuropsychology and cognition in this enterprise has expanded commensurately. The increased recognition of the importance of cognition as an outcome in vascular neuroscience seems to have arisen because of not only the direct effects of disease on brain function but also the widening appreciation of the cognitive implications of other systemic conditions. Moreover, the cognitive sequela of vascular risk factors and the effectiveness of treatment have now led to a movement in targeting overall brain health and the rise of cognitive medicine in primary prevention of cognitive decline. Finally, there is increased appreciation for the interaction between cerebrovascular and neurodegenerative diseases. The advances in neurovascular neuropsychology reflect this evolution and give rise to the need for an updated edition of this book.

Focusing on updates for this field, we begin with our historical perspective, leading up to the contemporary view that cognitive impairment arising from cerebrovascular disease is probably more common than frank neurological events. Our chapter on the elements of neurovascular geography and the tools to assess its integrity informs the reader about a resurgence in the use of CT-based technology in the assessment of large-vessel occlusion. The chapter on functional imaging in stroke provides a cautionary tale about interpreting the cognitive effects of neurovascular disease when the disease itself disrupts the same biological system on which measurement depends. Subarachnoid hemorrhage discussed in the chapter on cerebral aneurysms remains a devastating condition, but the increase in survival from surgical repair has led to greater interest in quality of life among survivors, which includes cognitive function. Indeed, new interest in functional outcomes is permeating nearly all aspects of neurovascular disease.

There is perhaps no better example of the growth in understanding the impact of brain disease and disorders of higher-intellectual function than the explosion of research in vascular cognitive impairment. Here is the fundamental recognition that with the increase in life expectancy, there is an increased prevalence of those with

cognitive impairment, but with the encouraging news that cardiovascular risks are potentially treatable. A further implication is that with the new appreciation that cerebrovascular disease may have an important contribution to Alzheimer's disease, control of vascular risk factors may delay the onset of what is currently an otherwise untreatable neurodegenerative condition. The chapter on carotid artery disease has been completely revised to reflect our better understanding of the pathophysiology of this occlusive syndrome and its relationship to cognitive dysfunction. In the past, cerebral hypoperfusion had been hypothesized as the basis of cognitive decline; now there is evidence that perfusion failure in the absence of frank stroke is an independent cause of cognitive decline. Cardiac arrest undoubtedly represents the most extreme form of a sudden ischemic brain event, yet even in this setting, survival statistics are improving, but raising the need to prognosticate outcomes, including cognition.

This volume has increased emphasis on cardiothoracic disease and neuropsychological function, with particular attention to cardiovascular and pulmonary disorders. There are new chapters on surgically treated disease, including early and late postoperative cognitive decline following on- and off-pump coronary artery grafting, delirium, and cognitive dysfunction among individuals with pulmonary disease, and postoperative decline after transplant. Severe aortic valve disease is predominantly an elderly affliction, with transcatheter aorta valve replacement (TAVR) which is a new catheter-based alternative to conventional surgery now approved for treatment. This technology has raised new consideration of the cognitive effects of silent brain infarction, which is addressed in this new edition.

There were some major gaps in our first edition that are now addressed. First, there is a major expansion of systemic disease that particularly affects women that has important CNS consequences, with reviews of systemic lupus and hypoparathyroidism. Second, we now have a chapter on pediatric stroke, a growing field in a population in which the complex interaction between the effects of disease and CNS development needs to be addressed.

Among the major determinants of stroke outcomes are mood disorders and the nature and intensity of rehabilitation. The chapter on post-stroke depression tells us that it occurs in 33% of individuals, leading to reduced quality of life and increased mortality. The evidence presented here shows convincingly that depression is directly related to structural changes in both gray and white matter, with altered functional connectivity. There are now three contributions that address dimensions of rehabilitation, with a focus on restitution of brain function, in addition to compensation with adaptive behavior. There is an updated chapter on methods of post-stroke rehabilitation and a completely revised chapter on pharmacological intervention. Finally, there is an entirely new contribution on noninvasive brain stimulation, both as a diagnostic method and a therapeutic modality.

As in the first edition, we view neurovascular neuropsychology as an approach to discerning the relationships between vascular pathology and cognition that will lead

us to potential treatment targets. The advances over the last 10 years convince us more than ever that quality of life is intimately tied to cognitive function and that our field is in the forefront of this enterprise.

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Acknowledgment

We are grateful for the hard work and painstaking effort of our editorial assistant, Terina Myers. Without her, the second edition would never have come to pass.

Contents

Chapter 1
Historical Perspective

Mahmoud Reza Azarpazhooh, Jose Merino, and Vladimir Hachinski

The conceptual history of dementia probably originates in the history of human being. Throughout human history, dementia and cognitive decline were defined in different terms, and it is difficult to follow them in the literature. Dementia ("Démence") was first reported in the first edition of *Encyclopédie Française* and later in the *"Code Napoléon"* (1794–1799) (Berrios, 1987). The definition, classification, and etiology have been revised frequently. This chapter provides a summary of dementia from prehistoric medicine to the current literature, highlighting the trajectory of dementia evolution throughout world history.

1.1 Early Civilizations and the Pre-Hippocratic Period

Evidence about neuropsychiatric diseases can be found in prehistoric medicine and early civilization's documents. Based on medical papyri, Egyptians were aware of localization of lesions in the brain. For example, in the *Edwin Smith Papyrus*, a hemiplegia after a head injury can be clearly seen (Kamp, Tahsim-Oglou, Steiger, & Hänggi, 2012). In ancient Persia, physicians were divided into three major groups: surgeons, physicians with knowledge about herbal medicines, and experts in mental disorders with holy words (Zargaran, Mehdizadeh, Yarmohammadi, & Mohagheghzadeh, 2012). In fact, treatment for mental diseases might have been started by Zoroastrians, one of the oldest religious communities in the world (1200–600 BC), in ancient Persia, introducing a stimulant as an antidepressant (Zargaran et al., 2012).

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_1

1.2 Greco-Roman Period

The effect of advanced aging on mental abilities was first commented on by Pythagoras, a Greek physician; in the seventh century BC, Pythagoras classified age periods into ages 7, 21, 49, 63, and 81, the last two of which were defined as "senium" (old age). He then described the old age as a period of time when "the scene of mortal existence close" and the human body and mental capacities often decline ("imbecility") (Berchtold & Cotman, 1998).

Hippocrates (460–377 BC), the Father of Medicine, emphasized the brain instead of the heart as a center for thoughts and feelings and introduced the term "paranoia" instead of imbecility (Fukui, 2015). Although in Hippocrates' school of thought, a mental decline was not an inevitable consequence of aging, whereas the next generation of Greek philosophers, such as Plato (428–347 BC) and his student Aristotle (384–322 BC), believed that mental failure was an inseparable part of being elderly. Following this philosophy, Aristotle stated that old people did not deserve high administrative positions. He also identified the heart as the main center of thought. Interestingly, his amazing description of the heart (the seat of intelligence) and the brain system (a cooling mechanism) can be considered as one of the first scientific approaches, emphasizing on a close connection between vascular and neurologic systems.

For a long time, Aristotelian thought remained as dominant belief. *Cicero* (106–43 BC), a Roman philosopher, noticed that mental decline (senilis stultitia or "dotage") was not an inevitable consequence of aging and may appear in those with "weak will." In "De Senectute," he even provided preventive methods against dementia, which in fact can largely be applicable in the modern world: "Old men can retain their mental abilities if they preserve their interests." This is the base of "the use it or lose it" hypothesis (Hertzog, 2009). Later, Galen (130–216 AD), the leading physician of the Roman Empire, made a great contribution in the development of several scientific disciplines, including anatomy and neurology (Freemon, 1994). Galen's doctrine was based on the importance of the brain, as opposed to Aristotelian views. In the chapter on "morosis" (dementia) in his encyclopedia, Galen considered age as one of the risk factors for cognitive decline (Berchtold & Cotman, 1998).

1.3 From the Medieval Period to the Realm of Neuroanatomists and Neuropathologists

The medieval period started with a dark period for science in the western countries. A disease was considered a punishment for sins and not surprisingly, human research was forbidden due to religious beliefs. The pendulum of the heart and the brain swung by the Biblical writers who considered the heart as the seat of the soul (Rose, 2009). The medical doctrine at that time was based on the adaptive stress responses

theory: “Something bad often dispels a bad thing” (Demontis, 2015). A majority of the diseases were treated with poisonous medications at low doses. Physicians even tried to control aging process. With a mixture of several animal- and vegetable-based ingredients, one of the first anti-aging medications, theriaca, was introduced (Demontis, 2015). Despite all obstacles, some physicians were still influential, Franciscan friar Roger Bacon (1214–1294) being one of them. Although he was imprisoned for his brilliant ideas, he was lucky enough to not be executed and was even able to write an important book, providing one of the first anatomical localizations for cognition: “the posterior brain with memory, the middle with reasoning and anterior with imagination.”

On the other hand, major contributions from the Middle-East and Far-East were made to the scientific world. In Japan, dementia and its relation with aging was described in “The Tale of Genji” in the early eleventh century written by Lady Murasaki Shikibu (Fukui, 2015). Using one of the largest worldwide libraries of medicine, Avicenna, an Iranian philosopher and physician (980–1037 AD), wrote his famous book *Cannon* (Tan, 2002). This book remained as one of the most important references in the western medical schools until the sixteenth century. Following the Greco-Roman school of thought, including a wide range of knowledge including that of eastern countries, Avicenna, “the father of modern medicine,” described several neurologic and mental illnesses, including dementia and apoplexy (Namazi, 2001).

In contrast to the medical literature, several examples of madness and senile mental decline can be found in the western arts, among them, the best examples are Shakespeare’s masterpieces *Hamlet* (1599–1602) and *King Lear* (1605 or 1606) (Ottilingam, 2007). The mental symptoms of Hamlet and King Lear are by far beyond the imagination of even a genius writer, such as Shakespeare. In fact, Shakespeare would have had a great knowledge of human cognitive abilities to create such characters, apparently able to distinguish between cognitive decline and madness. After the death of a quite healthy centenarian, Leonardo da Vinci (1452–1519) performed an autopsy. Interestingly, Leonardo believed that the aging process was attributed to degeneration of the vessels: “This coat of the vessels acts in man as in oranges, in which the peel becomes thicker and the pulp diminishes the more they become old” (Boon, 2009).

The seventeenth century was a golden period of time for anatomists in the world. The importance of brain lesions as a common reason for cognitive decline had previously come to attention in the sixteenth century in the first English book of medicine, *The Castle of Health* (1539), written by Philip Barrough (Shklar, 2004). It was in the seventeenth century when anatomists, such as Thomas Willis (1621–1675), had this ability to examine different reasons of dementia. Not surprisingly, although he mentioned gross lesions related to dementia such as trauma, he did not report microscopic findings, such as infarcts. Other anatomists commented later on the shape and softening versus hardness of the brain in patients with cognitive changes.

1.4 The Eighteenth to Mid-Twentieth Century

Anatomists opened a door for the next generation in the eighteenth century, pathologists. The pendulum of the heart and the brain stopped when William Cullen, who criticized both the Hippocratic and Aristotle school of thoughts and chose neither of them. In his new classification of medicine, he introduced amentia senilis (senile dementia) in the elderly under the major category of neuroses (Berchtold & Cotman, 1998).

In 1761, Giovanni Battista Morgagni (1682–1771), the father of modern anatomical pathology, suggested that the "cerebral congestion" can cause apoplexy (Román, 1987). Apoplexy (an ancient Greek word, meaning a striking away) had been previously used in medicine to define a wide range of diseases with sudden onset. Johann Jakob Wepfer (1620–1695) also showed the role of the brain hemorrhage in patients with apoplexy (Pearce, 1997). Therefore, physicians such as Esquirol were probably aware of vascular reasons for dementia. In 1881, Ball and Chambard also introduced apoplectic dementia due to vascular lesions (Gold, Fontana, & Zekry, 2002). In 1842, Durand-Fardel described the brain atrophy (leukoaraiosis) and état criblé (cribriform state) as a result of a chronic cerebral congestion (Román, 2002). A year later, he wrote that changes of the intellect were among the most interesting features of apoplexy and could progress to "une véritable démence."

The nineteenth century started with a hard time to clear a stigma of mental disorders. Philippe Pinel (1745–1826), the father of modern psychiatry, stated that madness is not a crime and in fact is a consequence of mental illness. His student Jean Etienne Esquirol (1772–1840) classified mental diseases, including senile dementia (Román, 1999). In his book, Des Maladies Mentales, he explained some of the most important reasons of dementia, including head trauma, alcohol abuse, syphilis, and apoplexy (Boller & Forbes, 1998). The best description of vascular lesions and dementia was then proposed by Otto Ludwig Binswanger, a Swiss psychiatrist and neurologist (1852–1929). In 1894, in an attempt to distinguish between purely cerebrovascular pathology from general paresis, Binswanger described the clinical and pathological features of two subtypes of dementia due to atherosclerosis of the cerebral vessels: encephalitis subcorticalis chronica progressiva and arteriosclerotic cerebral degeneration (Blass, Hoyer, & Nitsch, 1991). He described patients with slowly developing cognitive impairment, called encephalitis subcorticalis chronica progressiva. He stated that vascular insufficiency may lead to subcortical white matter lesions and consequently cognitive decline. However, this brilliant idea was not supported by any microscopic investigations. In fact, his talented pupil Alois Alzheimer (1864–1915) and Franz Nissl (1860–1919) commented on the pathologic findings of their mentor (Caplan & Gomes, 2010). The following year in 1985, Alzheimer wrote about arteriosclerotic atrophy of the brain (Alzheimer, 1984), which was changed into arteriosclerotic dementia by Emil Kraepelin in 1896 (Román, 1999).

Later in 1898 and 1902, Alzheimer (Alzheimer, 1899, 1902) characterized two additional pathologic forms of focal cerebral disease leading to arteriosclerotic dementia: perivascular gliosis in the territory of the great vessels and senile sclerosis of the cerebral cortex due to degeneration of small cortical vessels. For Binswanger and Alzheimer, however, chronic ischemia and not discrete ischemic or hemorrhagic strokes was the cause of dementia (Alzheimer, 1902; Mast, Tatemichi, & Mohr, 1995). After 5 years of clinical follow-up of a 56-year-old female, Auguste Deter (1850–1906) with a history of cognitive decline, Alzheimer performed a historical brain autopsy on November 4, 1906, and described his findings at the 37th Annual Conference of German Psychiatrists (Maurer, Volk, & Gerbaldo, 1997).

Medical science should be grateful to Camillo Golgi (1843–1926) who had previously discovered the silver stain, a technique improved by Don Santiago Ramon Cajal (1852–1934) and Max Bielschowsky (1869–1940) to assess the central nervous system. Using the silver stain technique, Alzheimer described two kinds of abnormal deposits outside (amyloid plaques) and inside (neurofibrillary tangles) of the nerve cells. Following Alzheimer's legendary case report, several similar cases of relatively young people with cognitive decline were reported (Maurer et al., 1997). It was, in fact, Kraepelin, Alzheimer's boss (Weber, 1997) who described Auguste Deter in his book *Psychiatrie* (1910) and named this condition "Alzheimer's disease." Kraepelin swung the pendulum again: this time not from the heart to the brain, but from senile dementia to presenile dementia. Interestingly, Kraepelin himself was not quite sure of this category and therefore introduced presenile dementia under the category of senile dementia. However, the introduction of the term of presenile led to the assumption that Alzheimer's disease was presenile and rare.

In the first half of the twentieth century, it gradually became a common belief that aging can change vascular resistance and consequently may lead to neuronal death and dementia. The unitary view that considered post-apoplectic and arteriosclerotic dementias as the same entity prevailed for decades. The pendulum swung again, classifying dementia as "mental disorders of cerebral arteriosclerosis" (Barrett, 1913; Osler & McCrae, 1921). Then, scientists described reasons and clinical presentations of arteriosclerotic dementia. Ferraro (1959), for example, attributed the arteriosclerotic dementia to "the gradual strangulation of the cerebral circulation" (Ferraro, 1959). He also categorized clinical presentations: "The mental symptoms in cerebral arteriosclerosis may develop in an insidious and gradual manner or may be acute after an apoplectic attack…." The semiology of arteriosclerostic dementia focused on vague mental symptoms—mental lassitude, loss of memory for recent events, anxiety, emotional instability, and confusion—and "strokes were (considered) but the culmination of a process started years before"(Barrett, 1913; Denning & Berrios, 1991; Berrios, 1987). Not surprisingly, different types of vasodilators were introduced to treat "hardening of the arteries," and these medications remained as one of the most profitable drugs in the world market for several decades (Lloyd-Evans, Brocklehurst, & Palmer, 1978; Maclay, 1979).

Don Santiago Ramon Cajal (1941), in his book "*The World Seen at Eighty, Memoirs of an Arteriosclerotic*," describes how the process of arteriosclerotic dementia was conceived in the first half of the century (Ramón, 1948):

> *"I must abstain even of thoughtful and prolonged conversation. Woe to me if giving in to temptation, I get caught up in pedantic philosophical or scientific conversation! The face and brain blush, memory fails, as if blocked by an insurmountable obstacle, words become hesitant, the imagination becomes labored and unruly; saintly equanimity, the treasure of the prudent and discrete, is lost. And, with all this, verbal flow continues unstoppable. Alienated, the spirit ignores that internal voice, anguished protest of the over-excited brain, which reminds us, with clemency, of the danger of the hemorrhage and sudden paralysis. And, threatened by Damocles' sword, we, the old arteriosclerotic, are reduced, finally warned, to inertia and indolence … Allow me here to recall briefly how this process began in me or, at least, the clear conscience of it, since it is a slowly incubated lesion … It was about thirteen years ago. From day to day I noticed, on leaving the gatherings at the cafe … that my head was ablaze, and walking or absolute silence could not suppress it. One day, after a photographic session (in the heat), the cerebral congestion was such that I was forced to consult the wise and pleasant Doctor Achu Caro, my laboratory companion. He examined me, and after some oratorical precautions, hurled the terrible verdict: My friend, the cerebral arteriosclerosis of senility has set in."*[1]

By the early 1950s, the clinical and pathologic criteria for the diagnosis of the senile dementias "remained nebulous and confusing" (Fisher, 1951). Mental deterioration after ischemic or hemorrhagic stroke was termed arteriosclerotic. Clinically, cases of slowly progressive cognitive deterioration that began around age 50 years were classified as Alzheimer's or Pick's disease "although neither has specific clinical or pathological features." When the deterioration occurred at a later age, the patient was diagnosed with arteriosclerotic or senile dementia. In 1951, C. Miller Fisher (1913–2012) described several cases of dementia associated with occlusion of one or both carotid arteries, even in the absence of atherosclerosis of the cerebral vasculature. Based on observations by Kety (1950), who had found a 25% decrease in the cerebral blood flow in patients with senile dementia, he postulated that carotid occlusion may be a cause for the diminution in blood flow and that unilateral occlusion of the internal carotid, particularly the left, may be causally related to dementia (Kety, 1950). He proposed that some cases of senile dementia may be due to chronic ischemia caused by occlusion of the carotid tree. In a subsequent report, Fisher (1954) acknowledged that "the association of dementia and carotid occlusion … may be entirely fortuitous, and care must be exercised in drawing conclusions." Other investigators, such as Kapp et al. and Sours (Sours, 1964; Kapp, Cook, & Paulson, 1966), described cognitive and behavioral symptoms and syndromes associated with carotid occlusion, including "chronic brain syndrome associated with cerebral arteriosclerosis." There was, however, a gradual acknowledgment that discrete infarcts could be the main cause of the mental deterioration. In 1954, Mayer-Gross and Slater considered that half the patients with arteriosclerotic psychosis had hypertension and that gradual "personality change" and "anxious self-scrutiny" could precede the cognitive changes (Mayer-Gross & Slater,

[1] Our translation.

1954). In a subsequent edition of their textbook, Slater and Roth (1969) expanded the prodromal symptoms to include memory decline, anxiety, blackouts, giddiness, headache, sexual disinhibition, and "a caricature of one or more conspicuous personality traits." They considered that lasting intellectual deficits rarely developed until clinical evidence of focal infarction appeared, often having more than one stroke. In addition to cognitive impairment, the syndrome was characterized by a fluctuating course, somatic symptoms, and neurological abnormalities such as hemiparesis, aphasia, or field defects. They gradually shifted the focus from general ischemia to focal strokes (Slater & Roth, 1969).

1.5 The Twentieth Century: From Neuropathology to the Realm of Neuroradiology

In the second half of the twentieth century, the idea that dementia was due to stroke and not to global ischemia gained popularity. In 1968, Fisher affirmed that "cerebrovascular disease is therefore a very common cause of dementia … for all major middle cerebral strokes … brings some measurable loss of cortical function and the same is only slightly less true for anterior cerebral and posterior cerebral strokes" and that "cerebrovascular dementia is a matter of strokes large and small." Fisher had changed his point of view since 1959, and in 1968, he wrote that it was a mistake to think that hardening of the arteries was a cause of dementia. He thought atherosclerosis led to dementia in so far as it led to infarcts (Fisher, 1968). The gradual loss of memory and capabilities was not due to atherosclerosis of the cerebral arteries but due to a neurodegenerative process—Alzheimer's disease—which was not related to cerebral ischemia.

Tomlinson, Blessed, and Roth (1968, 1970) studied the differences between neurodegenerative and vascular processes (Tomlinson et al., 1968, 1970). They compared the pathological findings in 28 non-demented and 50 demented elderly patients and found that the degree of pathological changes (cerebral atrophy, ventricular dilatation, senile plaques, neurofibrillary tangles, granulovacuolar degeneration, and cerebral softening) was much greater in patients with dementia. In most cases, they found purely neurodegenerative pathology: they diagnosed arteriosclerotic dementia in only nine brains and mixed dementia in another nine. They concluded that from a clinical perspective, vascular dementia was overdiagnosed. Their results lent support to the idea that both the pathologies were distinct and that arteriosclerotic dementia was less common than previously believed. By 1973, Fields wrote that cerebral arteriosclerosis was a "non-cause" of dementia (Fields, 1972).

With the advent of neuroimaging studies in the second half of the twentieth century, the pendulum started swinging several times. It became gradually possible to assess brain functions using functional imaging studies. Hachinski, Lassen, and Marshall (1974) coined the term "multi-infarct dementia" to refer to dementia due

to the accumulation of cerebral infarcts (Hachinski et al., 1974). They considered that arteriosclerosis did not play an important role in the development of the progressive dementia of the elderly that was associated with Alzheimer-type changes in the brain. A year later, they described differences in blood flow between patients with "multi-infarct" and "primary degenerative" dementia and described an ischemic scale that could be used to classify patients in each group based on historical and clinical criteria (Hachinski et al., 1975); the scale incorporates the criteria delineated by Mayer-Gross, Slater, and Roth in 1954 (Mayer-Gross & Slater, 1954; Hachinski, Potter, & Merskey, 1986).

The pendulum swung again. In 1981, Frackowiak et al. (1981) strongly disapproved the idea of brain failure due to chronic ischemia. In patients with a diagnosis of dementia due to neurodegenerative and vascular lesions, they did not find any global increase in oxygen extraction ratio, as expected in ischemia (Frackowiak et al., 1981). The concept of multiple-infarct dementia rapidly became popular, but the use of brain imaging showed that infarcts due to cardiac embolism arising from carotid plaques were only one of several possible etiologies of dementia due to cerebrovascular disease (Rivera & Meyer, 1975; Loeb & Meyer, 1996). Regretfully, the strict method of diagnosis of "multi," "infarct," and "dementia" contributed to the impression that vascular lesion was a rare reason for cognitive decline. Alzheimer's disease suddenly became almost synonymous with dementia, in a similar way that "atherosclerosis of the brain arteries" had previously been. Elderly patients with dementia were increasingly diagnosed with Alzheimer's disease, even though clinical criteria to differentiate both the types of dementia were not well defined and relied mostly on the exclusion of a history of stroke.

The widespread usage of neuroimaging studies in the 1980s and 1990s led to the resurgence of vascular diseases as a factor in cognitive dysfunction. Those with cognitive impairments were frequently assessed by imaging studies, and in several cases, white matter changes were seen. Such lesions were immediately attributed with profligate ease to "Binswanger disease," "vascular encephalopathy," "microvascular disease," and "chronic ischemia." The same facile thinking used to explain how long-standing ischemia can affect gray matter was applied to white matter with no more evidence for either of them. The term "leukoaraiosis" (white matter rarefication) was introduced to explain nonspecific white matter changes in different conditions (Hachinski et al., 1986).

1.6 The Pendulum at Rest

Hippocrates believed that "the nature of the body can only be understood as a whole," which became a base of the "healthy mind in a healthy body" theory (Kleisiaris, Sfakianakis, & Papathanasiou, 2014). Despite a holistic healthcare model in Hippocratic philosophy, a dramatic rise in medical sciences since the twentieth century had led to several branches in modern medicine, with a dichotomized approach in definitions. Not surprisingly, a similar scenario can be seen in the

history of dementia, swinging several times from the vascular to the neurodegenerative types, with a dichotomized classification.

Using neuroimaging findings, several clinicians noticed that leukoaraiosis was commonly associated with what was being diagnosed as Alzheimer's disease, the prototypic neurodegenerative condition. It was then suggested that most cognitive impairment of the elderly is due to mixed pathologies, requiring a new and a holistic approach. The term "vascular dementia" was coined to capture the complexity of this heterogeneous syndrome (Loeb, 1984). In contrast to the dominant unitary view that was popular a few decades earlier, several etiologic subtypes were described between 1970s and 1990s: *multi-infarct dementia* (Hachinski et al., 1974), *strategic infarct dementia* (Tatemichi, Desmond, & Prohovnik, 1995), s*mall vessel dementia* (Mohr, 1982), *hypoperfusion dementia* (Brun, 1994), and *hemorrhagic dementia* (Cummings, 1994). Accordingly, several diagnostic criteria for vascular dementia were also proposed: these were commonly used despite being based on expert opinion and not on data (American Psychiatric Association, 1987, 1994; Chui et al., 1992; Román et al., 1993; World Health Organization, 1993). All of these criteria relied on memory impairment as the cardinal feature for the diagnosis of vascular dementia, despite the fact that the cognitive impairment seen in patients with cerebrovascular disease preferentially affects other cognitive domains (del Ser et al., 1990). This divergence of opinion was reviewed in a workshop convened by the Neuroepidemiology Section of the National Institute of Nervous Disease and Stroke (NINDS) in 1993 to define vascular dementia. A group of experts in this workshop defined the vascular dementia as a decline in memory function associated with one or more additional domain impairments in the presence of cerebrovascular disease. This was recognized as the NINDS/AIREN criteria (National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignementen Neurosciences) (Román et al., 1993).

Quite a different clinical course between dementia due to Alzheimer's disease and vascular lesions was also noticed, often a progressive and fatal condition in the former and not necessarily progressive in the later. It was also shown that cognitive impairment due to vascular lesions can present with a wide range of symptoms, from a mild cognitive impairment to a frank dementia. Hence, an alternative and a holistic approach was introduced: "*the vascular cognitive impairment approach*" (VCI), i.e., any impairment caused by or associated by vascular factors (Hachinski, 1992, 1994; Hachinski & Bowler, 1993). Furthermore, in recent years there has been a shift of focus toward early identification of people who are at risk of developing dementia. The concept of VCI broadens the idea of vascular dementia and "brain at risk" and includes the whole spectrum of cognitive impairment, from mild to frank dementia that is associated with vascular risk factors and cerebrovascular disease (Hachinski, 1992). This theory was later supported by several studies. It was shown that the most common outcome of cerebrovascular disease is not stroke but cognitive impairment (Vermeer et al., 2003), and almost all major dementias have a vascular component (Toledo et al., 2013).

The alterations in cognitive function may be milder than those produced by a focal syndrome. While VCI may include the classical syndromes, VCI may be diag-

nosed in the absence of these deficits. To avoid many of the pitfalls of earlier diagnostic schemes, prospective population-based data collection of the specific clinical, psychological, radiological, and pathological features of cognitive impairment, and dementia in patients with cerebrovascular disease is required before any diagnostic criteria can be established. As an initial step, a panel was convened by the National Institute of Neurological Disorders and Stroke and the Canadian Stroke Network to identify a minimal set of clinical, neuropsychological, radiological, and pathological data that should be prospectively collected in all studies of VCI to enable data sharing and comparison between studies, with the hope that further advances in the field will be driven by solid research data (Hachinski et al., 2006).

A holistic view of the VCI approach brought the pendulum to rest between the heart and the brain. It seems that the VCI approach is still providing the best definition of cognitive decline due to vascular lesions, with emphasis on the preventive measures in dementia.

1.7 Summary

The review of the literature regarding the history of dementia can provide important insights on the mechanism of dementia and its relation to vascular lesions. Nevertheless, many issues about the relationship between cerebrovascular disease and cognitive decline have been, and still are, hotly debated. A key question that has been the mechanism through which cerebrovascular disease leads to cognitive decline: some writers postulated that dementia due to cerebrovascular disease is a question of stroke, while others supported the idea that chronic ischemia is the main pathogenic mechanism. Current views hold that strokes, ischemia, and other mechanisms play a role. The emphasis has shifted from mutually exclusive diagnostic categories to the recognition that most dementias in the elderly have multiple and probably interactive pathologies.

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Chapter 2
Neurovascular Geography and Mapping the Consequences of Its Injury

Ronald M. Lazar, Amani Norling, and MaryKay A. Pavol

As with any organ in the body, the brain depends upon the integrity of its blood supply to maintain normal function. Despite the fact that it constitutes only about 2% of body weight, its metabolic demands consume about 20% of the cardiac output and a comparable proportion of the total amount of oxygen used by the body. To understand the cognitive and behavioral consequences of an interruption of normal blood flow, it is important to first provide a general description of the geography of the cerebral circulatory system. The purpose of this chapter is to provide this overview and then to describe the diagnostic tools that reveal the effects of diseases and conditions that disrupt supply. For a more detailed anatomical description of this system and investigative modalities, the reader is referred to *Stroke: Pathophysiology, Diagnosis and Management* (Grotta et al., 2016).

2.1 Neurovascular Anatomy

The brain is fed by two main arterial sources: the internal carotid arteries and the vertebral arteries. In its most common variant, the ascending aorta arises out of the left ventricle of the heart and from the aortic arch comes the brachiocephalic trunk, from which the right common carotid artery and right vertebral emanate. After the

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_2

brachiocephalic comes the left common carotid artery, followed by the left subclavian artery from which the left vertebral arises. Each common carotid artery splits, with the left and right internal carotid supplying the anterior cerebral circulation, about 80% of the brain's blood supply. The vertebral arteries unite at the border of the pons to form the basilar artery that supplies 20% of the brain's blood volume via the posterior cerebral circulation.

At the medial base of the cerebral hemispheres is a unique arterial ring, the circle of Willis, formed by early segments of the anterior, middle, and posterior cerebral arteries (PCAs) and the anterior and posterior communicating arteries. Figure 2.1 illustrates the distribution territories of the three major cerebral arteries.

The left and right anterior cerebral arteries (ACAs) arise from the anterior portion of the circle of Willis and are connected by the anterior communicating artery (ACoA). The ACoA, as well as small branches from the ACA, penetrates the brain to supply blood to the fornix, septal regions, anterior perforated substance, optic chiasm, optic tract, optic nerve, and suprachiasmatic area (Dunker & Harris, 1976). The ACA starts at the bifurcation of the internal carotid, entering the interhemispheric fissure, and then proceeds anteriorly and upward, and then posteriorly as it continues over the superior surface of the corpus callosum. Branches off the early segments of the ACA (e.g., Heubner's artery) supply the head of the caudate, the anterior part of the internal capsule, anterior globus pallidus, olfactory regions, and hypothalamus. The ACA gives rise to the medial striate artery, orbital branches, frontopolar branches, pericallosal artery, and callosomarginal artery. Important brain regions supplied by these branches include the superior frontal gyrus, cingulate gyrus, and the premotor, motor, and sensory areas of the paracentral lobule.

The left and right middle cerebral arteries (MCAs) represent the largest of the major branches of the internal carotid arteries and supply most of the convex surface of the brain. Off the stem of the MCA are the lenticulostriate branches, named for the structures comprising the lentiform nucleus and striatum (caudate and putamen), and the internal capsule. As the MCA begins its course over the cortical surface, it then subdivides into several different branch configurations, but the most common pattern is a bifurcation into an upper and lower division. The initial segments in these two divisions supply the insula region, before proceeding over a large expanse of the lateral surfaces of frontal, parietal, and temporal lobes, much in the fashion of a candelabra. In the upper, or superior, division there is supply to the frontal lobe, including the orbital region, the inferior and middle frontal gyri, the pre- and post-central gyri, as well as the superior and inferior parietal lobules. The lower or inferior division of the MCA provides circulation to the parietal and temporal opercula, the posterior temporal, posterior parietal, and temporo-occipital regions. The MCA can also exist in a trifurcation pattern so that the orbitofrontal, prefrontal, and precentral branches comprise an upper division, the rolandic, anterior parietal, and angular branches make up a middle division, and the inferior division mainly consists of supply to the temporal lobe and to the temporo-occipital region (Mohr, Lazar, Marshall, & Hier, 2004).

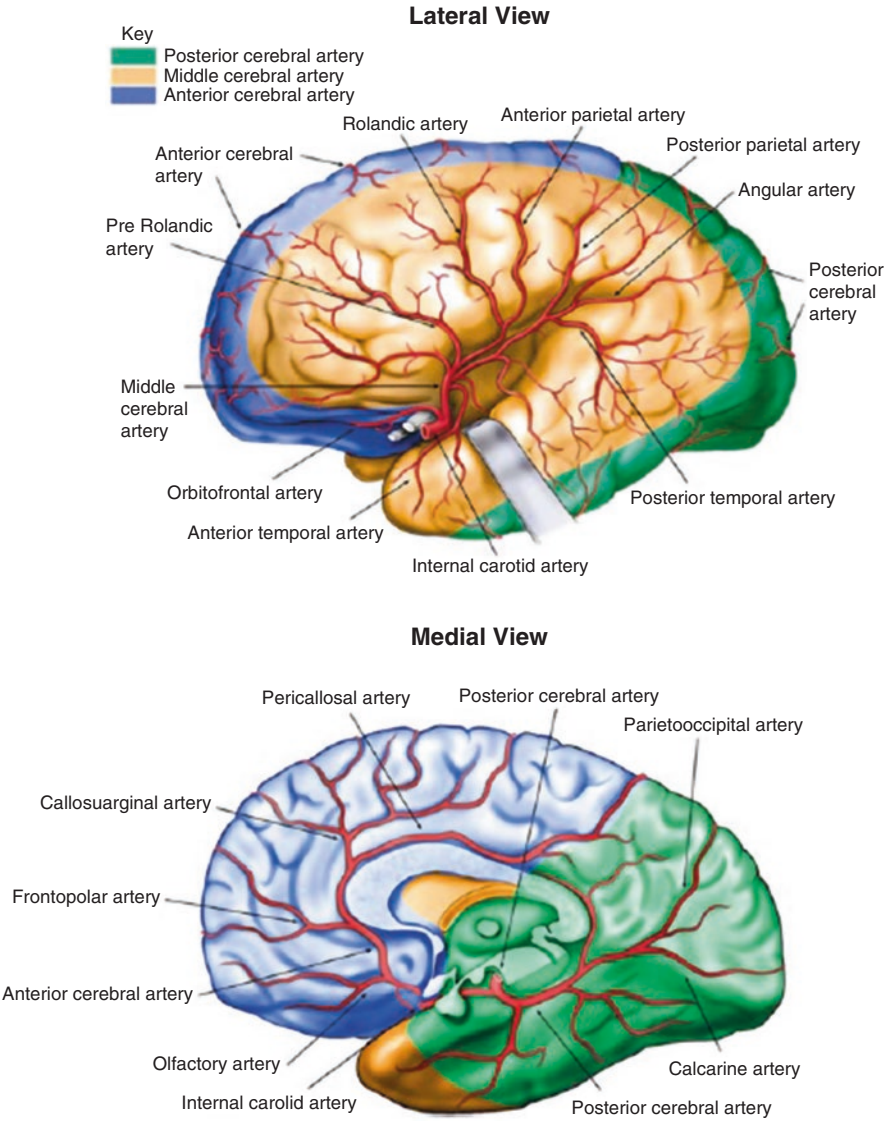

Fig. 2.1 Lateral (above) and medial (below) views of the major arterial territories in the cerebral hemispheres. (From Festa, J. F., Lazar, R. M., & Marshall, R. S. Ischemic stroke and aphasic disorders. In J. E. Morgan, & J. H. Rickers (Eds.), *Textbook of clinical neuropsychology*. London: Taylor & Francis, 2008, with permission)

The vertebral arteries, as they course up the spine into the skull, provide arterial supply to the brain stem and cerebellum, before merging into the basilar artery at the level of the pons. The posterior cerebral arteries (PCAs) are typically formed by the bifurcation of the basilar artery at the circle of Willis, where they are connected by the posterior communicating artery (PCoA). The PCAs continue to course superiorly

along the lateral part of the brainstem, with penetrators supplying segments of the thalamus, before turning posteriorly as they pass over the tentorium and onto the medial and inferior surfaces of the temporal and occipital lobes. The nomenclature for the cortical branches of the PCA seems to vary, but in general there are vessels that subdivide into those that feed the ventral temporal surface, the occipito-temporal region, and those that supply the calcarine cortex. There is a variant of the PCA, called a "fetal" PCA, in which the PCA arises directly from the internal carotid artery and occurs in 5–10% of cases.

In addition to the three major cerebral arterial territory distributions, there are so-called central arteries that provide penetrating branches into deep brain. Among these are the anterior and posterior choroidal arteries. The anterior choroidal artery, usually arising from the internal carotid artery, courses from the lateral and then to the medial optic tract until the lateral geniculate body where it splits into many small branches before entering the temporal horn and the choroid plexus of the lateral ventricle. It supplies the optic tract, lateral geniculate body, medial temporal lobe, and the anterior one-third of the hippocampus, the uncus, and part of the amygdala. Some of the perforating branches also feed the posterior limb of the internal capsule, optic radiations, the basal ganglia, and the ventrolateral region of the thalamus. Arising from the PCA, the posterior choroidal artery has one medial and two lateral branches, which collectively feed superior and medial parts of the thalamus, the choroid plexus of the lateral ventricle, and the posterior two-thirds of the hippocampus.

2.2 Autoregulation

In order to survive, the neurons and supportive tissue in the brain rely on a steady supply of oxygen and glucose via the circulatory system. Autoregulation occurs so that neither too little (hypoperfusion) nor too much (hyperperfusion) supply occurs. Depending on the degree and duration of disruption of the cerebral blood supply, the neuron undergoes a well-described series of pathophysiological steps in metabolic function before permanent cell death, or infarction, takes place. To maintain adequate function as long as possible, there are compensatory mechanisms that take place in response to disrupted blood flow.

Under normal circumstances, about one-third of the oxygen and one-tenth of the glucose circulating through the brain's circulation are metabolized (Zazulia, Markham, & Power, 2004), so that there is a uniform fraction of the available oxygen and glucose utilized, based on the amount needed for the resting metabolic rate of tissue. Autoregulation is the brain's ability to maintain cerebral perfusion pressure (CPP) when oxygen and glucose are not sufficient to meet its metabolic needs. Protection against abnormal blood flow (ischemia) begins to occur when the partial pressure of oxygen in the blood falls to about 50–60 mmHg (Buck et al., 1998). When the CPP falls, CBF can be maintained by dilation of the cerebral arterioles and recruitment of collateral vascular channels (Marshall et al., 2001).

Adequate blood flow across the circle of Willis, for example, can serve this purpose, from either the ACoA or the PCoA bringing flow from the vertebrobasilar system. The state of maximal vasodilation has been referred to as Stage I hemodynamic failure. If the CPP continues to fall and there is maximal dilatation of the arteries, autoregulation induces an increase in the oxygen extraction fraction (OEF). When the arterioles are maximally dilated and OEF is increasing, then Stage II hemodynamic failure, or "misery perfusion," is said to occur. If there is a restoration of normal CBF before OEF reaches its maximum level, then there can be good recovery of neuronal function. But once maximal OEF occurs, hypoxia begins and has a direct impact on neuronal function. Even after 30 s of hypoxia, glucose metabolism is reduced to 15% of normal levels (Pulsinelli, Levy, & Duffy, 1982). If ischemic-induced hypoxia occurs for a critical period of time, a breakdown of cell function will occur and neurons will sustain permanent injury or death. In human stroke, the CBF is very low in the ischemic core, but can be high enough in the surrounding region, known as the ischemic penumbra, so that hemodynamic rescue via thrombolysis (e.g., rTPA) or mechanical removal of clot may be achieved. In general, the brain can function for only 6–8 min if oxygen or glucose is reduced below critical levels.

2.3 Diagnostic Studies

2.3.1 Brain Imaging

Since there are multiple causes for similar clinical manifestations of neurological dysfunction, differentiating vascular from nonvascular causes (e.g., tumor, infection, demyelination), hemorrhage from ischemia, and ischemic subtypes is critical for diagnosis and treatment. Among diagnostic modalities, modern brain imaging represents a key investigative modality that can identify the presence of neurovascular diseases and conditions.

2.3.1.1 Computerized Tomography

Computerized tomography (CT) of the brain is the most common imaging modality in cerebrovascular disease. Separating anatomy at different depths, a CT of the head uses moving sources of X-rays and detectors that measure the ability of tissue to block X-ray beams, with data that are reconstructed by computer into 5–7 mm slices oriented to the orbitomeatal plane, or about 15° from the horizontal plane. An example of a CT showing an ischemic stroke is shown in Fig. 2.2.

A CT scan of the head still represents the best way of distinguishing ischemic from hemorrhagic stroke: low-density signal attenuation suggests ischemia while high-density indicates blood. Smaller hemorrhages may gradually lose signal inten-

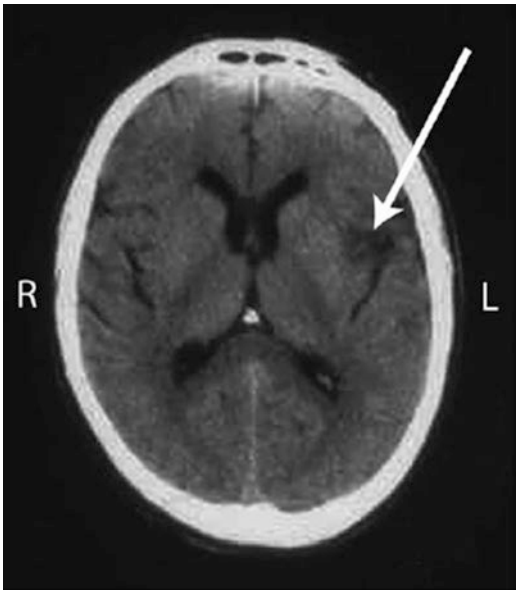

Fig. 2.2 A computerized tomographic (CT) image of the head without injection of contrast material. The top of the figure represents anterior and the bottom posterior locations in the brain. The arrow points to an ischemic infarct in the left hemisphere. *L* left, *R* right

sity over 1 week, but larger hemorrhages will produce high-density signal changes that can persist for much longer durations. But within the acute period, the ability of CT to detect blood associated with parenchymal hemorrhage or subarachnoid hemorrhage makes it the radiographic modality of choice over MRI (Williams & Snow, 1995). The disadvantage of CT is that bone within the posterior fossa makes detection of signal changes in the brainstem more difficult.

With regard to ischemic brain injury, acute infarction can be detected as early as 3 h, with half of the cases positive at 12 h, and in some instances, taking up to 3 days. But within 1 h after the onset of stroke symptoms, there is often loss of delineation between gray and white matter (Tomura et al., 1988). Ischemia resulting from embolic infarction seems more apparent on CT than ischemia associated with perfusion failure (Schuknecht, Ratzka, & Hofmann, 1990). With regard to the identification of ischemic changes in brain tissue supplied by small vessels, CT is capable of localizing injury as small as 1–2 mm.

2.3.1.2 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has become an important technique in the visualization of cerebrovascular disease because of its ability to depict the brain in any plane, including top to bottom (axial), side to side (sagittal), and front to back (coronal), and its superiority of resolution when compared to CT. Another advantage of MRI is that it does not use ionizing radiation or radioactive tracers.

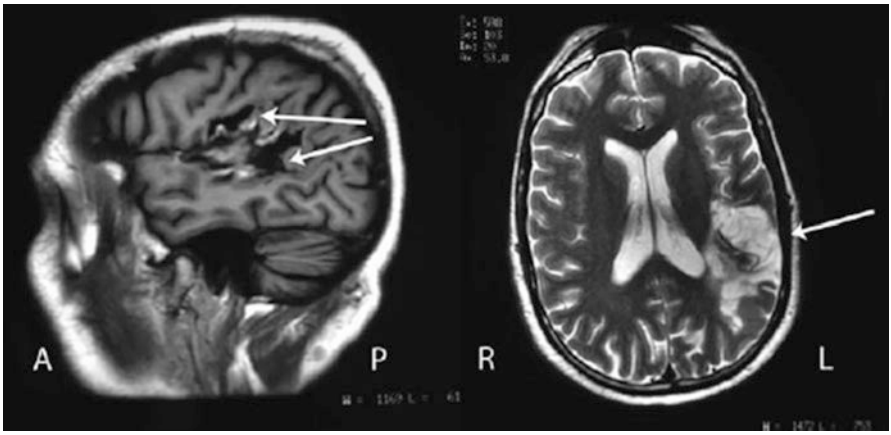

Fig. 2.3 Magnetic resonance images (MRI) of the brain. The left panel is a sagittal (lateral view) T_1-weighted image of an ischemic infarct in the left hemisphere. *A* anterior, *P* posterior. The right panel is an axial T_2-weighted image of the same infarct

The physics underlying MRI reveals that certain nuclei in tissue, mainly water and fat protons, when placed in a magnetic field align themselves with it. When radiofrequency (RF) pulses are then delivered, these nuclei absorb energy and then transfer energy back to a nearby detector coil at the same frequency. Over time, MR signal slowly fades away (relaxes) and the time constant for this decay varies in different tissues. The greater contrast resolution of MRI is based on its ability to detect the tissue-specific behavior of protons in different planes relative to the magnetic field. There are a number of different pulse sequences that have been used in MR imaging to assess cerebrovascular diseases and conditions; the most commonly used ones are described here. As of the moment, the magnetic strength of most clinical scanners ranges between 1.5 and 3.0 T, although more powerful magnets, now used only for research, will likely be used in the future.

A *T_1-weighted* image (see Fig. 2.3, Left) is based on the relaxation time when protons are aligned with the main (longitudinal) magnetic field. The T_1 image depicts white matter as brighter than gray matter. The cerebrospinal fluid (CSF) has low-signal intensity so that it appears dark. Because of the water content in ischemic infarcts, it is therefore not surprising that they appear as hypointense on the T_1 image. In general, anatomy is more clearly defined with this pulse sequence.

A *T_2-weighted* image (see Fig. 2.3, right) is derived when the RF pulses are delivered to hydrogen protons whose rotational spins are then flipped into the transverse plane relative to the main magnetic field. T_2 relaxation refers to the energy emitted back from the protons as they become realigned with the main magnetic field. The T_2 image shows cerebrospinal fluid (CSF) as a hyperintense (bright) signal. Ischemic brain lesions also appear hyperintense.

Fluid-attenuated inversion recovery (FLAIR) images (see Fig. 2.4, left) involve the delivery of another RF pulse sequence that has the ability to suppress the CSF hyperintense signal so that it appears dark like in a T_1 sequence but at the same time

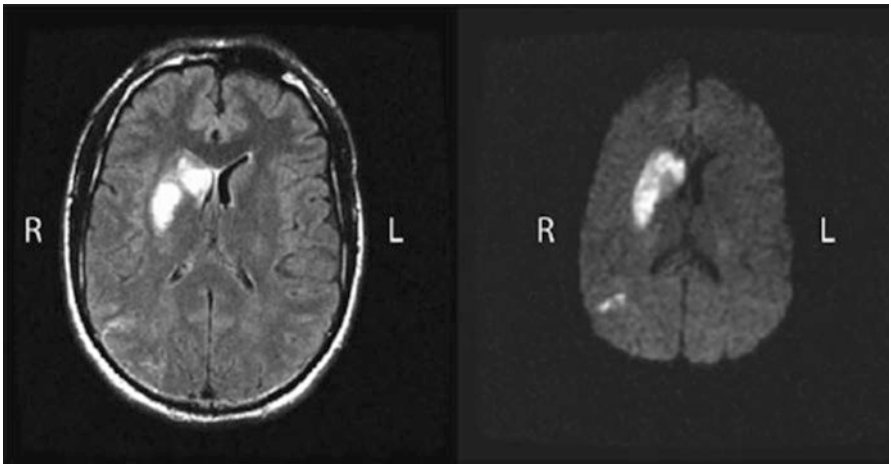

Fig. 2.4 MRI of the brain. The left panel is an axial fluid-attenuated inversion recovery (FLAIR) image of a subcortical stroke in the right hemisphere. The right panel is an axial, diffusion-weighted image (DWI) of the same clinical event

lesions appear bright like those in T_2 images. The result is an image that shows with greater contrast the presence of lesions. Another advantage of FLAIR imaging is excellent visualization of extra-axial blood, such as might be seen in subarachnoid hemorrhage or subdural hematoma (Noguchi et al., 1994).

The development of *diffusion-weighted imaging* (*DWI*) and more recently *perfusion-weighted imaging (PWI)* have improved identification of stroke in the acute phase, leading to a better understanding of acute pathophysiology and improving decision-making in acute stroke management (see Fig. 2.4, right). The detection of the DWI signal is based on the presence of cytotoxic edema in the extracellular space arising from ischemic tissue. Areas of hyperintensity most often represent areas of infarction. Comparing sensitivity in detecting acute clinical stroke within 3 h after symptoms onset, Chalela et al. showed that DWI was superior to CT (Chalela et al., 2007). The sensitivity of DWI is such that nearly one-half of transient ischemic attack cases, defined by negative CT and a syndrome lasting less than 24 h, are DWI positive and therefore are reclassified as ischemic stroke (Kidwell et al., 1999; Sacco et al., 2013).

Requiring the intravenous injection of the contrast agent gadolinium, PWI has the property of detecting the total brain volume of hemodynamically compromised tissue, regardless of whether it is infarcted or compromised by ischemia but capable of recovery (Quast, Huang, Hillman, & Kent, 1993; Schlaug et al., 1999). The signs and symptoms of acute stroke have been shown to correspond with the total region of hemodynamically compromised tissue, without distinguishing between the infarcted and the ischemic, still viable brain tissue. By assessing the volume of infarcted tissue as defined by the DWI image, and subtracting that from the PWI image, the DWI/PWI mismatch provides a visual representation of the tissue that is compromised but still capable of returning to normal function if blood flow could be

restored. This border zone between infarcted tissue and normally appearing tissue is commonly referred to as the "ischemic penumbra" and is the target for acute reperfusion therapy. When reperfusion of the ischemic territory has taken place, either naturally or from intervention, the lingering clinical deficits correspond only to the residual region of infarction (Lee, Kannan, & Hillis, 2006). CT perfusion (CTP) imaging is also playing an increasingly important role in the detection of acute infarction, with advantages of imaging speed, cost, and ease of patient monitoring (Lui, Tang, Allmendinger, & Spektor, 2010).

A relatively recent development in MRI sequencing is *diffusion tensor imaging (DTI)*. Although a thorough discussion of DTI is beyond the scope of this chapter, DTI takes advantage of edema detected in DWI by assessing the movement of water molecules in a region in which there are constraints in the direction of movement, such as in an intact white matter tract in which the cell membrane constrains movement in the direction of that tract. The process of reconstructing the vector of the diffusion of these molecules is the basis of DTI tractography and holds promise for delineating the integrity of white matter in ischemic disease (Sotak, 2002).

Finally, another technique that holds promise in neurovascular disease but as yet largely remains investigative is *magnetic resonance spectroscopy* (MRS), which measures the regional concentration of metabolites associated with, in this case, brain function. For example, proton MRS has demonstrated that following middle cerebral artery stroke, there was a relative decrease in *N*-acetyl aspartate (associated with axonal myelin sheaths) and an increase in lactate in the regions of T_2 hyperintensity, compared to the contralesional side (Gillard, Barker, van Zijl, Bryan, & Oppenheimer, 1996). More recently, MRS, used to assess the efficacy of hyperbaric oxygen treatment for neuroprotection in acute stroke, demonstrated improved aerobic metabolism and preserved neuronal integrity (Singhal et al., 2007).

Functional magnetic resonance imaging (fMRI), either correlating some form of behavior during MRI with changes in oxygenated hemoglobin or measuring connectivity during resting states, is increasingly used in cerebrovascular disease and will be discussed in the chapter on functional imaging (Chap. 18).

2.3.1.3 Other Imaging Studies of Blood Flow and Metabolism

Single-photon emission computed tomography (SPECT) involves the measurement of cerebral blood flow (CBF) in tomographic reconstruction of brain images following the injection of a radionuclide, most frequently 99mTc-HMPAO. Alteration in CBF is thought to arise as a result of its coupling to local brain metabolism and energy use, the pattern of which has been used to distinguish between dementia arising from Alzheimer's disease and that of vascular origin. More commonly, however, SPECT has been used to document CBF changes distal to stenosis or occlusion or to visualize the effects of vascular anomalies, such as the brain arteriovenous malformation shown in Fig. 2.5b. In this fashion, it becomes possible to dissociate the effects of focal ischemia arising from embolism from syndromes associated with perfusion failure from a more proximal location.

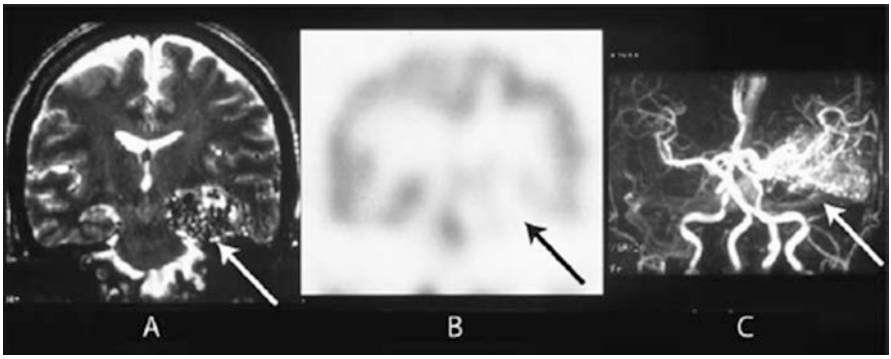

Fig. 2.5 Three images depicting a left medial temporal arteriovenous malformation (AVM). (**a**) A coronal (front view) T_2-weighted image. (**b**) A single-photon emission computed tomographic (SPECT) image showing diminished cerebral blood flow in the left temporal region. (**c**) A magnetic resonance angiogram (MRA) of the brain AVM

Positron emission tomography (PET), like SPECT, requires the injection of a radioactive tracer isotope. Whereas CBF is an indirect measurement of brain metabolism in SPECT, PET directly assesses neuronal integrity. Unfortunately, the agent most commonly used for this purpose is fluorodeoxyglucose (FDG), a glucose compound containing a radionuclide whose half-life is only a few hours and therefore requires a nearby cyclotron. PET can detect alterations in regional neuronal metabolism as well as determine the cerebral metabolic rate of oxygen. At this point, largely because of its limited availability, its application has largely been as a research tool with limited use in actual clinical practice in neurovascular disease.

2.3.1.4 Cerebral Angiography

In contrast to imaging brain tissue, the role of angiography is to visualize the inside of major vessels supplying to or returning blood from the brain, as well as the cerebral vessels within the brain itself. Angiography is used to ascertain whether there are any physical restrictions that could impede normal flow and to determine the presence of anomalies such as aneurysms and vascular malformations. The three principal methods are catheter-based digital subtraction angiography (DSA), magnetic resonance angiography (MRA), and CT angiography (CTA).

In DSA (see Fig. 2.6), a short catheter, or sheath, is placed into the common femoral artery, allowing the introduction of smaller catheters and guidewires that allow catheterization of the aortic arch and ultimately the carotid arteries and the anterior cerebral circulation, or the vertebrobasilar system, and the posterior cerebral circulation. Contrast material which absorbs X-rays is injected at the target site, and the X-ray image maps the distribution of the contrast agent as it courses through the vascular territory. Superselective angiography entails the use of microcatheters, which can be placed further into the circulation and permits a more detailed visual-

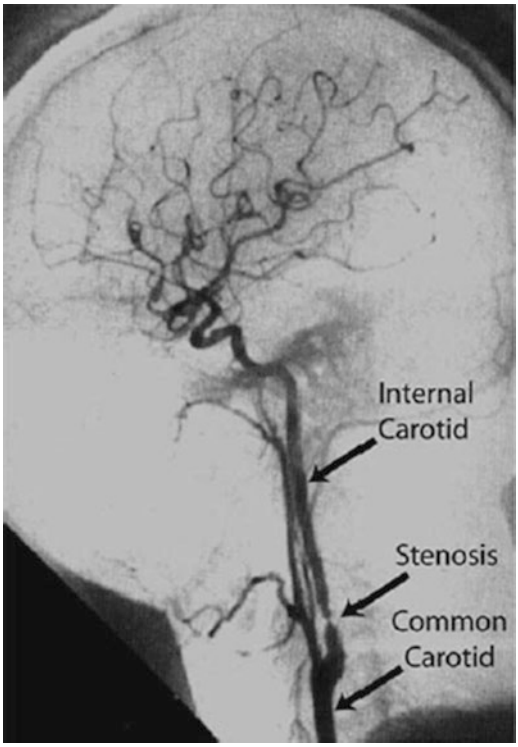

Fig. 2.6 A cerebral angiogram of the left anterior circulation demonstrating a severe stenosis in the left internal carotid artery

ization of smaller defects. This technique represents the gold standard of depicting vessels because of its high degree of resolution and its ability to show detail in vessels smaller than that can be seen with any other angiographic method. There are, however, more risks associated with DSA. Among these are punctures of the blood vessel wall, dislodgement of material adhered to the inner walls of vessels that can be carried downstream by the blood supply as emboli and cause ischemic stroke, and allergic reaction to the contrast agent. These risks have been declining, mainly due to the development of new kinds of contrast materials and innovative catheter designs.

By changing the way RF pulses are delivered and how the data are processed, it has become possible to use movement of blood to visualize large cerebral vessels during MRI, with the advantage that neither catheterization nor radiation is needed. MRA can render images in two dimensions, or as is more common, in three dimensions, which give better spatial resolution (see Fig. 2.5c). In some settings, the comparability of conventional angiography and MRA is quite high.

Finally, new CT-based technology has enabled scanners to acquire blood flow data after the injection of a contrast agent. In addition to not requiring the use of a catheter, CTA has the significant advantage of being able to acquire images faster than other methods on scanners that are widely available.

2.3.2 *Duplex and Transcranial Doppler Ultrasonography*

First introduced in the 1970s, Doppler ultrasonography techniques are now commonly used to assess hemodynamics in the intracranial and extracranial arteries. A diagnostic imaging technology based on the analysis of high-frequency sound waves, Doppler ultrasonography is a rapid, noninvasive, portable, and low-cost means of assessing cerebral blood flow and is often employed as the initial screen for carotid disease and other suspected cerebrovascular disorders. Ultrasound can determine the patency of blood vessels, from stenosis to occlusion, the direction and velocities of blood flow through the vasculature, and the presence of vascular anomalies.

The duplex test is a combination of ultrasound B-mode imaging, the black and white anatomic imaging, and color Doppler technology that can detect the movement of blood through the vessels by bouncing sound waves off blood cells. Using specified frequencies, the speed of blood flow in relation to the probe causes phase shifts with increases or decreases in sound frequency. The change in frequency directly correlates with the speed of blood flow. Typically used to assess the carotid and extracranial vertebral arteries, the duplex test results in an image of the artery, any plaque causing stenosis, as well as a wave form that indicates blood flow velocity and other flow characteristics. Velocities determine the degree of artery stenosis, and when no velocity is detected, the artery is considered occluded (see Fig. 2.7).

Transcranial Doppler (TCD) sonology uses the same technology to assess the intracranial vasculature through the transtemporal, transorbital, and transnuchal bone windows (see Fig. 2.8). The skull bones hamper ultrasound transmission, so insonation of windows (areas with thinner walls) must be utilized, such as the temporal region in front of the ear. Certain patient demographics, such as age, gender,

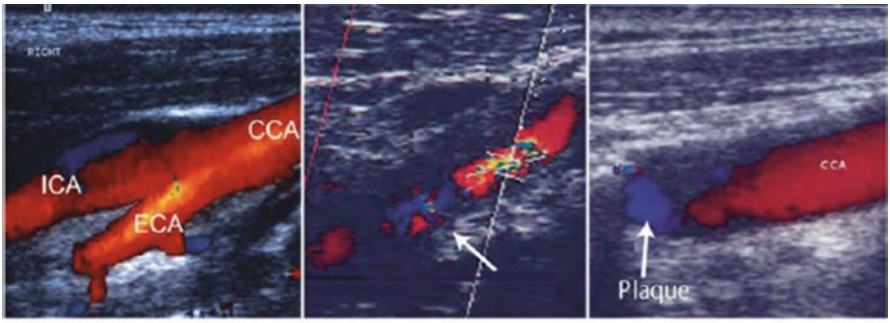

Fig. 2.7 Duplex Doppler ultrasonography of the carotid bifurcation in three different patients. (**a**) Normal blood flow through the common carotid artery (CCA), internal carotid artery (ICA), and external carotid artery (ECA) arteries; (**b**) blood flow through a stenotic segment of artery with arrow pointing to the area of stenosis; and (**c**) total artery occlusion with arrow pointing to the occluding plaque

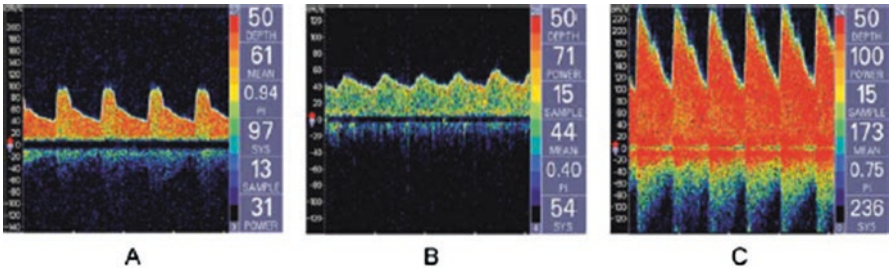

Fig. 2.8 Transcranial Doppler (TCD) ultrasonography of the middle cerebral artery. (**a**) Normal wave form; (**b**) blunted wave form representing flow distal to a stenosis; and (**c**) accelerated wave form of flow through the stenotic segment of the vessel

and race, affect bone thickness and composition and thus the ability to obtain data. The ability to accurately locate target vessels through these windows is highly dependent on individual training and experience. TCDs can be useful in identifying intracranial stenosis or occlusion, evaluation of collateral circulation, detection of intracranial aneurysms and AVMs, detection of vasospasm in subarachnoid hemorrhage (SAH), and assessment of cerebral autoregulation (Mohr et al., 2004). TCD monitoring may also be used in detecting microemboli entering the cerebral circulation from a proximal source such as the heart, or during vascular procedures.

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Chapter 3
Ischemic and Intracerebral Hemorrhagic Stroke

Victor W. Mark and Howard Kirshner

3.1 Introduction

Historically, stroke has been the source of much of our knowledge about the localization of higher cognitive functions in the brain. C. Miller Fisher, one of the founders of the field of vascular neurology, taught, "We learn Neurology stroke by stroke." Stroke can be considered an "experiment of nature," in which one part of the nervous system is damaged, while the rest remains structurally intact. Nineteenth century neurologists studied their patients in detail at the bedside, waited for them to die, and then correlated the syndrome described in life with the anatomy of the damage seen in the brain at autopsy.

Recent advances in brain imaging technologies have provided more immediate correlation of structure with function, in the living patient. Computed tomographic (CT) and magnetic resonance imaging (MRI) scans reveal the anatomic areas damaged by stroke. Functional brain imaging with positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) can delineate the areas of the brain that activate during a cognitive task, revealing not only discrete brain regions active in specific functions, but also networks of functionally connected neurons. These techniques can be used in normal subjects to study where specific functions occur in the brain, and as well they are being adapted increasingly to study patients with stroke and other brain disorders. Such techniques can identify which components of a network are rendered dysfunctional by a stroke, including areas that are directly structurally damaged, as well as those that are metabolically changed in function-

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_3

ally connected areas. We can inquire how the brain recovers: Do the same areas of the brain that are active in normal subjects recover function after stroke, or do new areas of the brain become recruited to regain the function? Are the newly recruited areas on the same side of the brain as the area of stroke damage, or are they located in the unaffected hemisphere? These questions underlie the study of brain imaging in patients with cerebrovascular disease and are discussed in this chapter.

3.2 Pathophysiology of Stroke Syndromes

A stroke, in general, is characterized by the abrupt onset of a focal neurological deficit in an awake patient, with signs and symptoms consistent with a vascular territory. A stroke syndrome refers to the neurobehavioral and neurological symptoms and signs produced by the stroke. Patients with cognitive deficits following stroke typically have larger lesions than do patients without cognitive deficits (Nys, van Zandvoort, de Kort, van der Worp, et al., 2005). Syndromes tend to be stereotypical, both because of consistencies among subjects in the anatomical organization of neurobehavioral functions in the brain, as well as the consistent distribution of parenchymal damage in specific vascular territories. It is important to recognize, however, that there are individual variations in both brain organization and vascular territories. In addition, stroke syndromes are moving targets, evolving in the early minutes and hours of the stroke, with areas of ischemia becoming either infarcted or recover, and the development and later resolution of cerebral edema. During recovery, individuals vary in the plasticity of brain areas that might potentially take over degraded functions. Nonetheless, larger stroke lesions are generally associated with reduced cognitive recovery (Nys, Van Zandvoort, de Kort, Jansen, et al., 2005).

This chapter is organized along the neurobehavioral features of the major stroke syndromes in relation to the major vascular territories. We describe the major neurobehavioral deficits of each syndrome and associate them with specific distributions and pathological mechanisms of ischemic and hemorrhagic strokes. This chapter will consider intracerebral hemorrhages, but syndromes related to subarachnoid hemorrhage, aneurysms, and arteriovenous malformations will be discussed in Chaps. 4 and 5. It will be apparent that often specific cognitive disturbances are not restricted to injury to one particular vascular territory. For convenience, we will discuss various cognitive disturbances in relation to the vascular territories most commonly associated with these deficits.

Where evidence is available, we will indicate the relationship between vascular lesion size and the extent of cognitive deficit, or its recovery. In most instances, larger lesions are associated with more severe deficits of specific cognitive functions, but there are exceptions. There may be several reasons for this limited association. In some behavioral disorders, a small lesion occupying a "strategic" location can cause extensive impairment (e.g., executive dysfunction) (Puy et al., 2018). Consequently, the ability of minor lesions to provoke major behavioral disturbances prevents the lesion's extent from predicting the severity of impairment. In other

instances where cognitive impairment is extreme (e.g., global aphasia), it may not be possible for lesion size effects to prevail simply because of a basement effect (i.e., only minimal clinical variation can occur in a disorder of extreme severity, despite greater variation in lesion size). Finally, it must be recognized that contemporary cognitive studies in neurovascular cognitive disorders are beset by various procedural limitations: cognitive assessments in general have had only meager psychometric validation (i.e., establishing their sensitivity, specificity, and test-retest reliability for a specific cognitive process); studies of specific cognitive disorders have not consistently applied the same tests or evaluated patients at the same phase of recovery; and many studies have evaluated only small numbers of patients (i.e., fewer than 30). It should also be recognized that asymptomatic cerebrovascular disease likely contributes to the overall cognitive profile of patients after stroke. Thus, for example, asymptomatic carotid stenosis of at least 50% is associated with impaired memory and cognitive processing speed (Lal et al., 2017). For these reasons, the indications of interactions between lesion size and cognitive impairment must be regarded cautiously.

3.2.1 Anterior Cerebral Artery Syndromes

Vascular disturbances of the anterior cerebral artery (ACA) are not as frequently noted clinically as are those in the territories of the middle or posterior cerebral arteries. There may be a few reasons. (1) The resulting dysfunctions often have the character of personality changes, without marked effects on motor, sensory, or language functions (Kumral, Bayulkem, Evyapan, & Yunten, 2002). In other instances, the acute lower extremity paresis that commonly results (Maeder-Ingvar et al., 2005) may steal clinical attention from the concurrent cognitive changes. Either way, despite the acute onset of a vascular lesion in the ACA territory, family members or clinicians, or even the patients themselves, may either fail to notice a behavioral change or may ascribe the change to various non-stroke causes, e.g., routine irritability, normal aging, being "under the weather" (i.e., nonspecific systemic illness), and depression. Mesulam (1986) has noted that prototypical frontal lobe cognitive disturbances, which would include behavioral deficits following ACA lesion, may also be found in clinical populations without structural brain injury, in contrast to the cognitive disorders that follow structural lesions to other brain areas. Thus, the public as well as perhaps most clinicians may not regard that typical frontal behavioral disturbances are consequent to focal brain injury. Therefore, affected patients may not be referred to clinicians with expertise in vascular cognitive neurology for evaluation. (2) Vascular territories that are posterior to the ACA may be more susceptible to vascular compromise, perhaps due to differences in hemodynamic properties or other vascular pathophysiological mechanisms. In one large series, ACA infarctions accounted for only 1% of all cerebral infarctions (Kumral et al., 2002). In contrast, infarctions of the posterior cerebral artery (PCA) and especially the middle cerebral artery (MCA) are far more frequent (Menezes et al., 2007;

Nys, van Zandvoort, de Kort, van der Worp, et al., 2005). However, it is possible that in such clinical surveys, ACA lesions were underrepresented because of the absence of clinically noticeable signs or symptoms, which may be less reliably detected than are clinical deficits that originate from lesions in other vascular territories. Ischemia in the ACA territory may also be less common than in the MCA or PCA territories because the MCA is a "straight shot" for emboli in the internal carotid artery, and the PCA is a "straight shot" for emboli coming up the basilar artery.

Fortunately, by now a small but growing body of literature has been able to register behavioral changes that occur with anterior circulatory disturbances.

3.2.1.1 Executive Dysfunctions

The term *executive disorder* (Lezak 1983) applies to a variety of disturbances related to impaired regulation of diverse subsidiary processes that are directly involved with movement, sensation, language, and memory. The model was that of a so-called central executive, such as an orchestra leader, who would guide the onset, offset, sequencing, intensity, and other modulatory aspects of diverse other neurologic processes (akin to the performances of the woodwinds, percussion instruments, and so on) without directly playing any instrument. If the executive or orchestra leader were to become impaired, the orchestra might still play on, but in a haphazard, displeasing, or offensive manner. The analogy with the orchestra departs, however, in that the actual orchestra members themselves would have their own executive abilities that could emerge if the orchestra leader were incapacitated and thus continue self-directing, while in the case of the executive brain functions, the subservient neurologic functions by definition are without executive abilities.

Disturbances of this sort had been recognized long before the term "executive functions" was coined but were generally referred to as "frontal lobe" or "prefrontal" dysfunctions, named because these functions are more characteristically disrupted following frontal injury than injury to other brain areas. However, with the increased preference for the term executive functions has come the recognition that these disorders do not strictly follow frontal lobe injury (Annoni et al., 2003; Mendez, Adams, & Lewandowski, 1989; Tullberg et al., 2004). Thus, while the executive disorders do not strictly follow ACA vascular injury, they will be reviewed in this section because of the relative paucity of distinct cognitive disorders that have been associated with ACA dysfunction, in contrast to dysfunction associated with the other vascular territories of the cerebral hemispheres.

Given the broad definition of executive disorders, standardization of executive assessment, and the vulnerability to executive dysfunction following stroke to widely distributed anatomical regions, the executive disorders have become recently recognized as the most prevalent of all cognitive disorders that follow stroke (Roussel et al., 2016).

Vascular dementia, including those cases with multiple subcortical infarctions, generally involves a disproportionate degree of executive dysfunction, compared to cortical neurodegenerative dementias such as Alzheimer's disease (McPherson &

Cummings, 1996). Although the neuropsychological patterns in vascular dementia vary considerably between patients, in general vascular dementia rarely presents with isolated memory loss and more often present with executive function deficits, whereas the reverse is true of Alzheimer's disease (Reed et al., 2007). Although the topic of vascular cognitive impairment and dementia is beyond the scope of this review (see Chap. 6), an important recent contribution toward distinguishing vascular cognitive impairment from degenerative dementing illness is the study by Levine et al. (2015). They showed that any stroke in patients without prior cognitive impairment caused substantial decline in both executive function and global cognition, but not verbal memory, along with more rapid cognitive decline over several years, compared to individuals without stroke over comparable follow-up periods.

Forms of executive dysfunction. Owing to the broad definition of executive function, there is lack of consensus for terming the various kinds of forms of executive dysfunction. One proposed classification that can be useful identifies the following main domains of executive function: (1) generation, fluency, and initiation; (2) planning, scheduling, strategy use, and rule adherence; (3) shifting and suppression; and (4) concept formation and abstract reasoning (Keil & Kaszniak, 2002).

(a) **Generation, fluency, and initiation** pertain to the engine of executive functions: the start, continuation, and stop of voluntary actions.

Impaired initiation of voluntary activities is a characteristic of ACA vascular injury. Abulia and akinetic mutism may accompany ACA infarction, particularly (but not exclusively) following bilateral infarction (Kumral et al., 2002; Lechevalier et al., 1996). Akinetic mutism, abulia, and apathy reflect disorders of voluntary initiation that are essentially on a continuum (Marin & Wilkosz, 2005). Akinetic mutism refers to absent voluntary behavior, with only the preservation of visual tracking and the appearance of wakefulness separating this syndrome from a vegetative state. Abulia indicates a milder, similar condition, in which responses are delayed or prolonged. Abulia may be associated with vascular lesions in either in the frontal cortex or the basal ganglia (Alarcón, Zijlmans, Dueñas, & Cevallos, 2004; Bhatia & Marsden, 1994). Apathy is regarded as disrupted goal-oriented, motivated activity, although there is not yet consensus for its diagnosis (Sasaki et al., 2017). In a large meta-analysis (n = 2221 stroke patients), apathy appeared in about 36% (Caeiro, Ferro, & Costa, 2013). In a different review, apathy was associated with diverse lesions, but especially with those involving the distribution of the anterior choroidal artery, affecting the basal ganglia, and the medial frontal lobe (Le Heron, Apps, & Husain, 2018). Consistent with the findings of Kumral et al. (2002) and Alexander, Stuss, Shallice, Picton, and Gillingham (2005) found that chronic vascular or other injury to the right superomedial frontal region (in the territory of the ACA) to disrupt manual reaction time in patients whose limb movements were otherwise not slowed.

A closely related disorder, primarily associated with left ACA infarction (Kumral et al., 2002), is transcortical motor aphasia (TMA). In some instances, lesions may be situated more laterally in the borderzone between the ACA and

the MCA (Freedman, Alexander, & Naeser, 1984). This disorder does not appear to involve essentially linguistic impairments as are found with other aphasias, but rather impoverished initiation of speech with generally retained good repetition (Alexander, 2006). TMA following stroke involving the ACA may be preceded by transient mutism (Chang, Lee, Lui, & Lai, 2007).

Fluency in this respect pertains to the steady continuation, or consistent flow, of repeated actions. Fluency is tested with either verbal or hand-performed design tasks (e.g., simple drawing under precise instruction). Verbal fluency is assessed by either the phonemic test of retrieving words that start with a specified letter or the semantic test, involving retrieving words from a specific category, such as animals. Either form of verbal fluency testing is limited to 60 s per category; often three categories are presented in succession at a single test session (e.g., the initial letters F, A, and S). Whereas verbal fluency tests require patients to reproduce words that they have already learned (as opposed to generating new words), design tasks require generating novel drawn patterns, typically using just four connected lines, and again within a time limit (2 min). Impaired phonemic and design fluency are most often associated with stroke occurring in the ACA distribution. Moreover, as one would expect, impaired phonemic fluency is more associated with the left frontal lobe and impaired design fluency with the right frontal lobe. In contrast, impaired semantic fluency is not associated with any particular cerebral region (Robinson et al., 2012). Fluency is referred to further under Broca aphasia.

Perseveration is the unwarranted repetition of a response and may reflect erroneous self-monitoring or self-inhibition. It has been observed to occur on the Wisconsin Card Sorting Test (WCST) following injuries of various etiologies that overlapped the ACA territory (Stuss et al., 2000), but the disorder was not consistently localized to a particular part of the brain. In the same study, however, patients with inferomedial frontal cortical injury (including stroke) were especially unable to respond consistently according to a previously provided rule, despite having correctly responded immediately before the erroneous response. The mechanism for the inconsistent deficit was unclear but was thought most likely to reflect an intermittent failure to engage automatic responding, rather than a memory deficit, since memory had to be intact to provide correct responses at all. Nys, van Zandvoort, van der Worp, Kappelle, and de Haan (2006) observed that perseveration during manual cancellation tests (which involve crossing out specific images scattered across a page, with nontarget images also present) could occur following lesions anywhere in the cerebral hemispheres but was especially associated with stroke involving the caudate or lentiform nuclei. Similarly, Kreisler et al. (2000) noted predominantly caudate involvement in speech perseveration among acute stroke patients with aphasia.

(b) **Planning, scheduling, strategy use, and rule adherence** pertain to imagining an efficient and effective solution to a problem, and then carrying out the action, obeying the rules that are provided. Several formal assessments have been developed to evaluate planning (Keil & Kaszniak, 2002). Most familiar are the

Tower of London and Tower of Hanoi tests, which require transferring discs across three pegs, to end up with the specified final pattern of the discs following strict rules to move them from the initial configuration. Among the outcomes are the number of disc moves to attain the specified final pattern and any rule violations (e.g., moving more than one disc). Although deficient responses in stroke patients were not studied in relation to a particular cerebral arterial distribution, the poorest responses have been associated with frontal strokes (Glosser and Goodglass, 1990; Andrews et al., 2014).

(c) **Shifting and suppression** pertain to regulating tasks to flexibly adapt to procedural rules for either frequently alternating the kind of response [as with the Trail Making Test (TMT) part B, which involves drawing lines alternating between letters and numbers in ascending value order] or inhibiting prepotent spoken responses (as with the Stroop test, which requires *speaking the colors* of the font of printed color words rather than *reading aloud the words* themselves). Errors on the TMT part B are most commonly associated with right frontal stroke, particularly the dorsal-lateral prefrontal cortex area associated with the ACA distribution (Kopp et al., 2015). In contrast, the TMT part A, which requires drawing only between numbers in ascending value (thus, no alternating behavior), is only rarely associated with errors. TMT part A is one of the most common assessments of cognitive processing speed in neurological populations. However, pathologically slow completion on either part A or B, as opposed to errors, has not been reported in relation to specific stroke lesions. Unlike the TMT, little attention has been directed at performance on the Stoop assessment following stroke. In a sample of 51 stroke patients, deficient Stroop performance was primarily associated with frontal lesion (Stuss, Gallup, & Alexander, 2001).

A subclass of impaired suppression is the *environmental dependency syndrome* (Lhermitte, 1986), which can follow frontal lobe infarction. In this disorder, the patient's behavior is driven directly by specific objects, settings, or social situations of the environment with which the patient interacts, rather than being determined by the patient's initiation, thus reflecting impaired response inhibition. A case report of the environmental dependency syndrome was described following bilateral frontal infarctions, in which the patient (a teacher) spontaneously began lecturing when he was led to a classroom (Hoffmann & Bill, 1991). Compulsive tool use is one form of environmental dependency, in which the patient unhesitatingly begins to use an object placed before him or her without invitation, such as the instruments on a physician's table. This disturbance, also termed utilization behavior, has been observed to follow ACA infarction (Chamorro, Marshall, Valls-Solé, Tolosa, & Mohr, 1997; Mori & Yamadori, 1982).

Another form of environmental dependency is imitation behavior, in which the patient uncritically mimes or parrots the examiner. In a series of patients with focal brain injury (mostly of vascular etiology), De Renzi, Cavalleri, and Facchini (1996) observed imitation behavior to be much more prevalent than

utilization behavior and to have a slight predilection for lesions of the ACA territory.

(d) **Concept formation and abstraction** refer to inferring rules from observing consistent patterns of external phenomena, in the absence of direct verbal explanation, in effect, inductive reasoning. Moreover, the healthy mind must rapidly adapt when the rules unexpectedly change, which forces the individual to generate a revised concept of the rules. The most common assessment of concept formation after brain disease is the WCST (see above), in which patients must derive rules from limited feedback from the examiner concerning how cards must be piled according to specific printed characteristics (e.g., color, shape, or number of symbols on each card). After numerous cards are dealt one at a time for which the patient's concept of the unstated rule of grouping has been developed and reinforced, the examiner abruptly changes without warning the kind of feedback for grouping the successively dealt cards. One of the test outcomes is the number of the patient responses that occur until the patient's revised grouping of dealt cards is correct, signifying learning the new rule. Such a complex assessment can model real-life problem-solving, for example, diagnosing car engine malfunction through trial and error. While the diverse errors on the WCST do not strictly follow frontal vs. non-frontal lesion location, deficits of flexibility of learning new grouping rules on the WCST most often follow stroke lesion to the lateral prefrontal cortex, particularly on the right side (Jodzio & Biechowska, 2010).

Lesion size effects. Hoffmann and Schmitt (2006) developed a bedside comprehensive evaluation of cognitive functions associated with frontal lobe stroke, the frontal network syndrome score (FNSS). The battery was found to have sensitivity and specificity for frontal stroke diagnosis of 93% and 79%, respectively. Although the FNSS was correlated with stroke severity, among the 132 patients who had abnormal scores, there was no correlation of performance with lesion volume ($r = 0.07$, $P = 0.5$). The absence of a lesion volume correlation may have reflected the ability of minor lesions to exert considerable "frontal" cognitive disturbance due to their occupying critical, "strategic" locations. Dementia following a single infarction has been noted to occur at a limited number of specific brain regions, most often the thalamus (Auchus, Chen, Sodagar, Thong, & Sng, 2002). However, such "single strategic infarct dementia" has also been strikingly associated with lesions involving the ACA territory, according to this same study, thus suggesting the basis for the failure of lesion volume to predict extent of "frontal" cognitive deficit.

However, in contrast to the foregoing, Nys, Van Zandvoort, de Kort, Jansen, et al. (2005) in a sample of 111 patients found that post-stroke lesion volume mildly predicted poor recovery on their own battery of executive functions ($r = 0.18$, $P = 0.02$). The reasons for the discrepancy from the study by Hoffmann and Schmitt are unclear but could be related to differences in the extent of recovery, lesion volume ranges or location, or the elements of the test batteries themselves. In the same sample Nys et al. (2006) also found that lesion volume

after stroke was significantly correlated with the degree of perseveration on manual cancellation tests ($r = 0.24$, $P = 0.001$). Similarly, Kertesz and Dobrowolski (1981) in a study of 37 right hemisphere stroke patients found infarction cross-sectional area to correlate with perseveration on drawing tasks (Spearman's $\rho = -0.358$, $P = 0.04$).

3.2.1.2 Alien Hand Syndromes

Alien hand syndromes characteristically follow ACA territory injury. Alien hand refers to involuntary movement of (usually) one hand that appears to be stimulus- or goal-directed, but without the patient's awareness of initiating the behavior. The hand thus behaves in a manner that is alien to the patient's intent, and the patient commonly indicates that the hand behaves as if guided by another individual or it possesses a mind of its own.

Although some variations in conventional classification have been noted, essentially two alien hand syndromes are widely recognized (Feinberg, Schindler, Flanagan, & Haber, 1992). The first is the frontal alien hand, involving repetitive grasping by the involved hand of objects that occur within reaching distance. It is, essentially, an exaggerated grasp reflex, except that visual contact with an object is sufficient to launch the behavior, although disinhibited grasp to tactile contact is generally found as well. Frontal alien hand generally appears after combined contralateral medial frontal and anterior callosal infarction (Chan & Liu, 1999). Some reports have indicated complex, involuntary movements of both hands following unilateral ACA infarction (Mark, Mc Alaster, & Laser, 1991; McNabb, Carroll, & Mastaglia, 1988).

In contrast is the callosal alien hand, which is generally not associated with medial frontal lobe lesions, but rather primarily damage to the corpus callosum, usually more posteriorly located than the callosal damage in frontal alien hand (Chan & Liu, 1999). Callosal infarctions are uncommon, with a frequency of only 3% of all infarctions reported in one series (Giroud & Dumas, 1995), owing to the callosum's extensive vascular supply (Spengos et al., 2006). The behavior is strikingly more complex than the frontal variant, in which the afflicted hand (usually the nondominant hand) reacts at cross-purposes to the activity of the uninvolved hand, which behaves according to the patient's self-recognized intention. Thus, a patient may find that the alien hand closes a drawer that had been opened moments before by the normal hand, pulls down a sock, takes away a cigarette, and so on. Intermanual conflict is commonly observed, such that the alien hand may attempt to snatch away the object from the normal hand or try to impede the normal hand's actions. Classic interhemispheric disconnection signs are often found: left hand apraxia and agraphia, left hand tactile anomia (failure to name objects felt by the left hand, despite awareness that the hand palpated the object), and failure to imitate with one hand the position into which the examiner has molded the other hand based solely on kinesthetic input (i.e., without visual guidance).

The physiologic basis for these disorders is not well understood. The frontal alien hand variant may reflect the consequences of an imbalance between the hypothesized normally mutually inhibitory functions of frontal and parietal areas (Mesulam, 1986). Consequently, frontal injury, by disinhibiting the parietal cortex, may induce excessive exploration of extra-personal space, as found also in environmental dependency. In contrast, callosal alien hand is more puzzling, possibly reflecting a failure of interhemispheric integration and hence the simultaneous expression of dual forms of consciousness or personality, residing in each hemisphere (Mark, 1996). Nonetheless, this does not explain why the reactions by the callosal alien hand more often involve *undoing* the actions of the normal hand, rather than initiating completely independent activities.

3.2.1.3 Theory of Mind Disturbances

In recent years a cognitive process termed *theory of mind* has become increasingly investigated; this involves the ability to imagine or model the viewpoint or plans of another individual whose actions are witnessed. Little is known concerning the vascular neurology of disorders of theory of mind. Functional imaging studies have implicated medial frontal cortex (which is supplied by the ACA) in inferring the thoughts of other individuals (Frith & Frith, 1999). Stuss et al. (2001) found that right medial frontal injury rendered patients unable to improve their responses when examiners repeatedly pointed incorrectly to the location of a hidden object that patients were required to locate, in contrast to injury to other brain areas. Stuss et al. also tested the ability of individuals with focal brain injury to correctly deduce which of two observers could be relied upon to correctly indicate the location of a hidden object, based on the spatial locations of the observers relative to the examiner. Patients with right frontal injury were especially vulnerable to impairment on this task, without an effect of medial vs lateral lesion localization. In contrast, Apperly, Samson, Chiavarino, and Humphreys (2004) indicated that lesions of the temporoparietal junction appeared to impair selectively the evaluation of mental processes in other individuals. Bird, Castelli, Malik, Frith, and Husain (2004) failed to uncover a theory of mind deficit in a patient with bilateral ACA infarction. Consequently, at present investigations have not identified a brain region that appears to be consistently involved with deficits of this process.

3.2.1.4 Motor Neglect

Motor neglect is a form of unilateral spatial neglect (see below) that indicates a spatially selective deficiency of limb movement initiation. The term, unfortunately, has confusingly been applied to a wide variety of clinical phenomena (Mark, Heilman, & Watson, 1996). Chamorro et al. (1997) found that patients with medial frontal lobe infarction were vulnerable to a form of motor neglect characterized by failure of spontaneous contralateral limb movement despite the demonstration of

intact, albeit slowed, movement to command. However, it was unclear whether such a putative unlearned, attentional deficit could be distinguished from a *learned* deficit of spontaneous unilateral limb movement that has been observed to commonly follow hemiparetic stroke, termed learned nonuse (Taub, Uswatte, Mark, & Morris, 2006). The motor aspects of neglect are discussed later in this chapter, under neglect.

3.2.2 Left Middle Cerebral Artery Syndromes

3.2.2.1 The Aphasias

The left MCA is particularly likely to cause aphasia as a part of the symptom complex. Aphasia is the loss or degradation of language secondary to acquired brain disease. Aphasia has been described in historical writings as early as ancient Egypt, but in the nineteenth century, through the work of Paul Broca, the impairment of language was specifically related to dysfunction of the left cerebral hemisphere. Virtually 99% of right-handed people have at least relative language dominance in the left cerebral hemisphere, and studies of left-handers have suggested that a majority also have relative left hemisphere dominance for language. While the subject of aphasia has always seemed complex, language disorders do have practical usefulness in localizing lesions and in defining stroke syndromes. A French study of 107 stroke patients, all documented with MR imaging, confirmed the general rule of localizations of clinical studies over the past 140 years: frontal lesions were associated with nonfluent aphasia, whereas posterior temporal lesions affected comprehension (Kreisler et al., 2000).

Lesion size effects. In general, larger lesion volumes or cross-sectional areas have been associated with more severe aphasia and impaired recovery of aphasia (Demeurisse, Capon, & Verhas, 1985; Kertesz, Harlock, & Coates, 1979; Yarnell, Monroe, & Sobel, 1976). However, the last study found the relationship to apply only for lesions that involved cortical and not for deep-seated lesions. Nys, Van Zandvoort, de Kort, Jansen, et al. (2005) in a series of 24 acutely aphasic stroke patients found lesion volume not to be correlated with a combined language score derived from the Token Test (generally regarded to test speech comprehension) and the Boston Naming Test. Discrepancy from previous studies may have been related to differences in tests used.

(a) **Broca aphasia**

Broca aphasia is characterized by reduced speech fluency, or difficulty getting words out. Many patients have associated dysarthria, or misarticulation of phonemes, and some have apraxia of speech, defined as an inconsistent pattern of articulatory errors not attributable to weakness or sensory loss, in addition to the aphasia or language disorder. The patient with Broca aphasia has nonfluent speech, in both spontaneous and attempts to repeat. Naming is also impaired, with long pauses for word finding, but patients do respond to cues such as the

initial sound or phoneme of the target word. Auditory comprehension is usually functional for simple communication such as following simple commands or engaging in conversations with friends and family members, but on more detailed testing, deficits are apparent in the comprehension of complex syntax. Reading aloud is hesitant and reading for meaning is often more impaired than auditory comprehension. Writing is affected at least as severely as spontaneous speech.

The lesion localization of Broca aphasia is usually in the left inferior frontal cortex, anterior to the motor strip. Patients with lesions restricted to this area usually recover well, whereas patients with lasting Broca aphasia usually have larger frontoparietal lesions (Lazar & Mohr, 2011). Alexander, Naeser, and Palumbo (1990) reported from their analysis of patients with left frontal infarctions that the full syndrome of Broca aphasia required a lesion of the frontal operculum (Brodmann areas 44 and 45), together with the lower motor cortex, or motor face area. Patients with only the area 44 and 45 lesions had a deficit in speech initiation, but not a full-blown Broca aphasia. Patients whose lesions involved only the inferior motor cortex had only hesitant speech and dysarthria. In terms of vascular anatomy, Broca aphasia of the more severe, chronic type often results from occlusion of the internal carotid artery, or proximal MCA, with a large area of MCA territory infarction. The more isolated syndrome of Broca aphasia, soon after onset, may reflect an embolus of cardiac origin to a frontal lobe branch of the MCA or an embolus arising from a plaque in the internal carotid artery. Naeser, Palumbo, Helm-Estabrooks, Stiassny-Eder, and Albert (1989) reported that lesions associated with chronic nonfluent aphasia and poor recovery always include, in addition to the cortical frontal damage, subcortical damage in the subcallosal fasciculus deep to Broca's area and the periventricular white matter along the body of the left lateral ventricle.

Case 1

This 82-year-old lady presented with nonfluent speech, and both dysarthria and inconsistent phoneme errors (speech apraxia), only mild comprehension disturbance, and a mild right hemiparesis, affecting the arm more than the leg. During a rehabilitation hospital admission, she regained independent ambulation with a cane and recovered partial use of the right arm and hand. Her speech fluency remained impaired at discharge. Figure 3.1 shows an MR image, indicating infarction of a small area of the left inferior frontal cortex, with involvement of the subjacent insula.

The apraxia of speech seen with Broca aphasia has been the subject of conflicting anatomical analysis. In the series of Dronkers (1996), an overlapping lesion analysis pointed to the left insula as the structure correlating most consistently with apraxia of speech. In the series of Hillis et al. (2004), involving patients studied very acutely after stroke onset, the traditional Broca's area in the left frontal lobe correlated more closely with apraxia of speech.

Case 2

This 38-year-old male truck driver, with a history of elevated blood pressure and smoking, presented with difficulty speaking, followed by the onset of right arm and

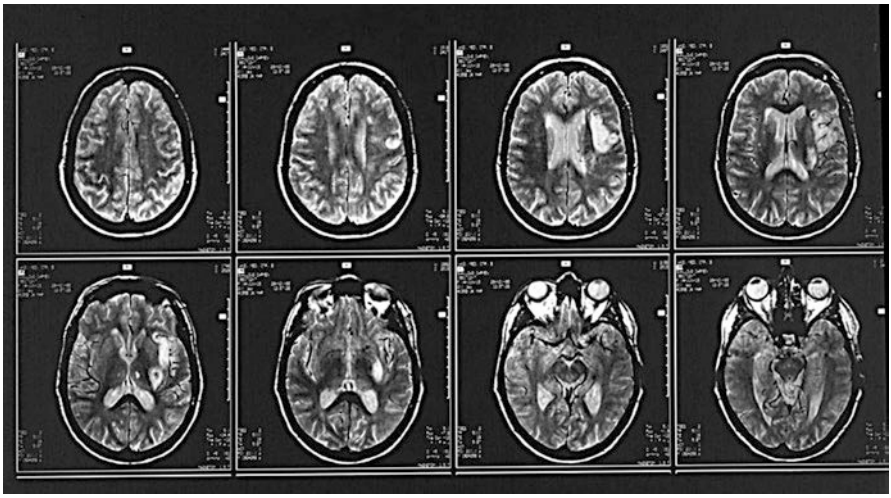

Fig. 3.1 Broca's aphasia with apraxia of speech

leg weakness. He recalled two or three episodes of dim vision in his left eye over the preceding weeks for which he did not seek medical attention because of these. In the Emergency Department, he developed worsening ability to speak, combined with comprehension disturbance and increasing right hemiparesis. MRI (Fig. 3.2) showed an evolving infarction in the left frontoparietal region. Magnetic resonance angiography (Fig. 3.3) suggested severe stenosis of the left internal carotid artery. This was confirmed by arteriography (Fig. 3.4). The patient underwent carotid endarterectomy but was left with residual aphasia and right hemiparesis.

A variant of Broca aphasia is the more restricted syndrome now referred to as "aphemia" (Schiff, Alexander, Naeser, & Galaburda, 1983). Although Broca originally intended to use the term "aphemie" to describe the articulatory disorder later renamed as "Broca aphasia," "aphemia" is now used to designate a syndrome of nonfluent speech, with normal comprehension and writing. Patients with aphemia are often mute initially, with hesitant speech emerging over the next few days, often with prominent phonemic errors.

Patients with aphemia often have right facial weakness but no major motor deficits, and their comprehension, reading, and writing are largely normal. The lesions may involve the face area of the motor cortex (Alexander et al., 1990). Alexander, Benson, and Stuss (1989) equated aphemia with isolated apraxia of speech. In stroke terms, aphemia usually results from a cortical infarct, likely the result of an embolus to a frontal branch of the left MCA.

Lesion size effects. The combined deficits in Broca aphasia have not been analyzed in relation to lesion size. However, component disturbances associated with Broca aphasia have been evaluated separately in this regard. Kertesz et al. (1979) found fluency impairment to be correlated with lesion cross-sectional area in a mixed sample of chronic aphasic stroke patients ($n = 33$, $r = -0.67$, $P \leq 0.01$), but

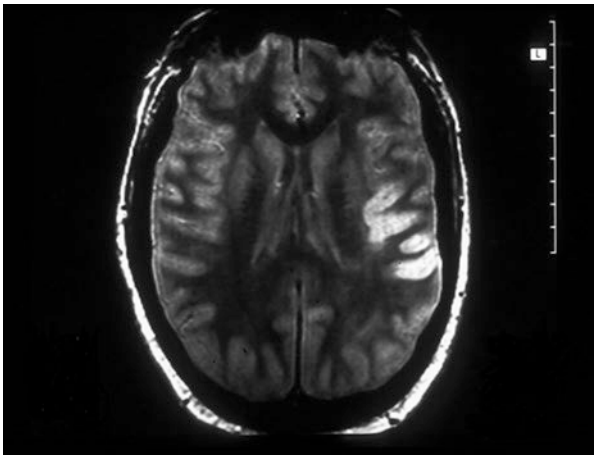

Fig. 3.2 Diffusion-weighted MR image showing L posterior frontal acute infarction

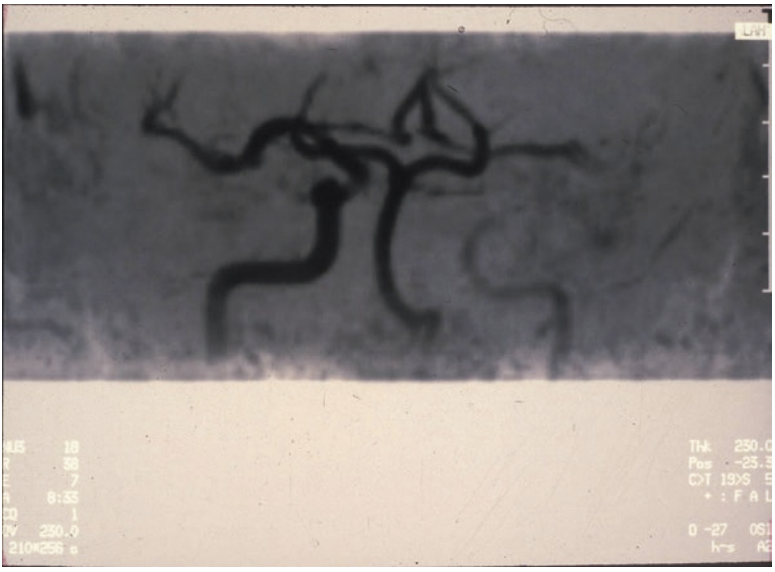

Fig. 3.3 MR angiogram showing very little flow in the distal left internal carotid artery, reduced flow in the left

no significant relationship was observed among acute aphasic patients. In contrast, lesion size did not predict the extent of recovery of speech fluency in this sample, possibly because dysfluency has been found to recover more poorly (if at all) than do other aspects of language that are affected by aphasia (Lomas & Kertesz, 1978). Among 18 patients with speech apraxia with or without aphasia (but primarily with Broca aphasia), Ogar et al. (2006) found lesion volume to be correlated with apraxia severity ($r = 0.61$, $P < 0.01$).

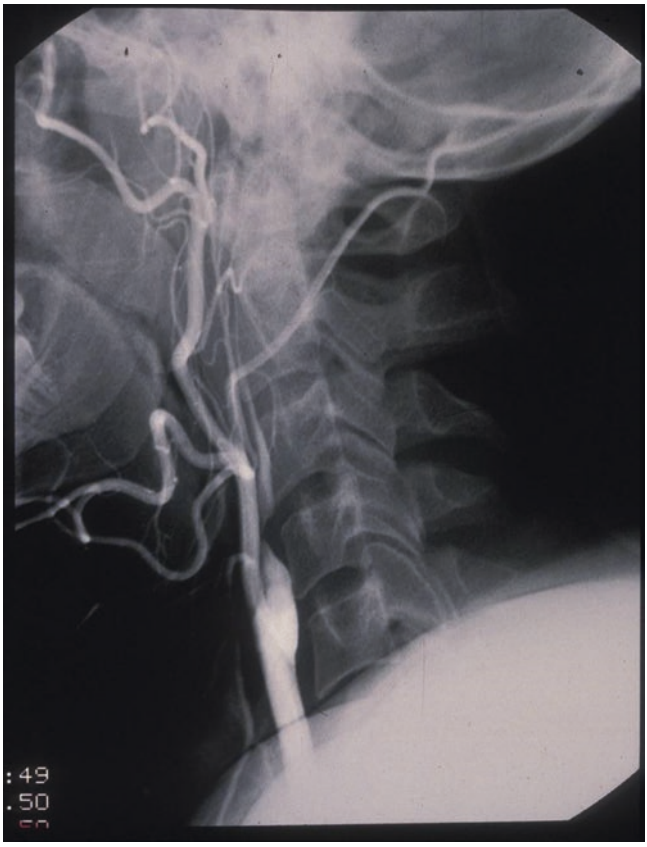

Fig. 3.4 Carotid arteriogram demonstrating sever stenosis of the left internal carotid artery just above the carotid

(b) **Wernicke aphasia**

Wernicke aphasia is a fluent aphasia syndrome, in which paraphasic errors make the utterances difficult for the listener to understand. Auditory comprehension is also affected, sometimes to a severe degree. Naming is usually impaired; whereas the Broca aphasic struggles to get out phonemes, the patient with Wernicke aphasia might effortlessly utter a completely incorrect name. Repetition is typically affected, as well. Reading is typically affected much like auditory comprehension, but exceptional cases have been described in which either auditory comprehension or reading comprehension is relatively spared. It is important to look for such discrepancies to find a successful channel of communication with the patient. Writing is often produced with good penmanship, but the writing has spelling errors, nonwords, and nonsensical constructions, much like the speech. Errors in spelling may be a clue to a mild Wernicke aphasia.

Wernicke aphasia typically involves an infarction in the left superior temporal region, sometimes extending into the inferior parietal lobule. This is the

territory of the posterior inferior branches of the MCA, and Wernicke aphasia classically results from an embolic stroke of cardiac origin. Rarely, a hemorrhage into the temporal lobe might produce Wernicke aphasia. One personal case had a temporal lobe arteriovenous malformation that presented with hemorrhage and Wernicke aphasia.

Studies have shown that destruction of Wernicke's area is most likely to result in lasting loss of auditory comprehension (Naeser, Helm-Estabrooks, Haas, Auerbach, & Srinivasan, 1987), though other authors have stressed the coexistence of lesions in the adjacent cortex of the temporal and inferior parietal lobes (Kertesz, Lau, & Polk, 1993; Selnes, Niccum, Knopman, & Rubens, 1984). Cases with disproportionately impaired auditory comprehension have lesions restricted to the temporal lobe, while those with more severe reading comprehension deficits may have lesions involving the parietal lobe (Kirshner, Casey, Henson, & Heinrich, 1989). Hillis et al. (2001) have shown in a series of acute stroke patients that the degree of impairment of auditory word–picture matching correlated with the degree of hyperperfusion of Wernicke's area on perfusion-weighted MR imaging. This study suggested that imaging in the acute phase of stroke may show less variability between subjects than imaging performed weeks or months into recovery.

A recent paper by Binder (2017) reviews evidence that Wernicke's area (the superior temporal gyrus and adjacent angular gyrus) actually subserves phoneme sequences rather than word comprehension. Focal lesions of this area produce phonemic paraphasia, or conduction aphasia (described further below), without marked impairment of comprehension. The brain areas involved in auditory comprehension, according to Binder, involve a network in the frontal, temporal, and parietal lobes (Pillay, Binder, Humphries, Gross, & Book, 2017).

Lazar, Marshall, Prell, and Pile-Spellman (2000) explored the subjective experience of a patient who had transient Wernicke aphasia during a superselective Wada test (amobarbital infusion into the inferior division of the left MCA) for planned resection of a left temporal arteriovenous malformation. The patient recalled the episodes afterwards, and he appeared to understand questions: "In general, my mind seemed to work except that words could not be found or had turned into other words. I also perceived throughout this procedure what a terrible disorder that would be if it were not reversible."

Case 3

This 51-year-old lady was admitted to the hospital for elective total knee replacement. She had no history of vascular risk factors except for obesity, smoking, and hormone replacement therapy. On the evening after the procedure, she was reported by the nurse to be "confused," not expressing herself clearly. The next morning, she had fluent, paraphasic speech and severely impaired auditory language comprehension, without any facial or extremity weakness. MRI (Fig. 3.5) showed a left superior temporal lesion by diffusion-weighted imaging.

Lesion size effects. Kertesz et al. (1979) noted that severe Wernicke aphasia could follow a small but strategically located infarction. It therefore seems unlikely that lesion size would correlate with severity of Wernicke aphasia, although research to

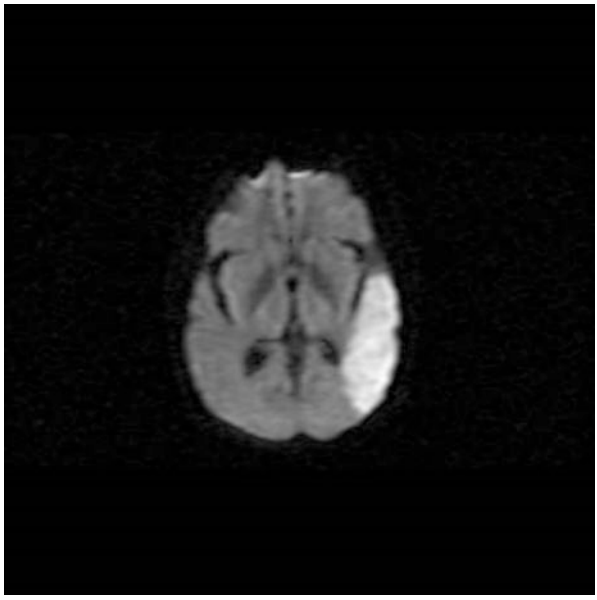

Fig. 3.5 Diffusion-weighted MRI showing acute left superior temporal lobe infarction

date has not directly evaluated this possibility. However, post-stroke lesion volume effects have been evaluated with respect to severity of impaired speech comprehension alone, regardless of specific aphasia subtype. Among 39 consecutive stroke admissions to an aphasia unit, Selnes, Knopman, Niccum, Rubens, and Larson (1983) observed that lesion volume grossly predicted comprehension disturbance as assessed by the Token Test. The relationship was particularly true for lesions at the extremes of volume, while intermediate lesion volumes did not vary consistently with the Token Test score. Similar observations were made by Kertesz et al. (1979) across all aphasic subtypes, based on the comprehension subtests of the Western Aphasia Battery ($n = 33$, $r = -0.74$, $P \leq 0.01$; low scores signified more severe aphasia). In addition, Kertesz et al. observed that lesion size significantly predicted recovery from comprehension impairment, such that larger lesions were associated with greater recovery ($n = 32$, $r = 0.35$, $P \leq 0.05$). This was viewed as due to the fact that patients with marked comprehension impairment had considerably more room for linguistic improvement than did patients with smaller lesions and less impairment.

(c) **Global aphasia**

Global aphasia is the complete disruption of language, including nonfluent speech, as in Broca aphasia, or nearly complete loss of speech, and poor comprehension, as in Wernicke aphasia, with severe impairment also of naming, repetition, reading, and writing. Global aphasia is the most commonly identified aphasia subtype in acute stroke (Kreisler et al., 2000; Pedersen, Vinter, & Olsen, 2004). The lesion is typically large, involving most of the left MCA territory in the frontal, parietal, and temporal lobes (Kertesz et al., 1979; Kreisler

et al., 2000). Most patients have associated deficits such as right hemiparesis and right hemisensory deficits, though occasionally patients may have lesions sparing the motor area, without hemiparesis (Legatt, Rubin, Kaplan, Healton, & Brust, 1987; Tranel, Biller, Damasio, Adams, & Cornell, 1987). Tranel et al. (1987) furthermore suggested that global aphasia without hemiparesis has an improved prognosis for recovery relative to such patients with hemiparesis. Patients with mixed expressive and receptive deficits but without the severe impairment of global aphasia are sometimes referred to as "mixed aphasia."

With regard to stroke mechanism, global aphasia can be caused by a complete occlusion of the left internal carotid artery, or an embolus of cardiac origin that lodges in the left MCA stem. Finally, large subcortical lesions such as those occurring in large left basal ganglia intracerebral hemorrhages can also produce global aphasia. This syndrome is thus less helpful in identifying the stroke mechanism than some other syndromes.

Lesion size effects. In a small acute stroke sample presenting with global aphasia (n = 13), Mark, Thomas, and Berndt (1992) failed to find a significant correlation between lesion volume and general aphasia severity as assessed by the Western Aphasia Battery. The ability to detect a relationship between lesion volume and aphasia severity may have been limited by the narrow range of test scores in this severely affected sample, in comparison to the range of lesion volumes. However, this study only used clinically available CT scans that had been obtained in the acute stroke phase, which may have limited the ability to measure final lesion volumes precisely, due to changes in lesion appearance that can occur during the first several days following stroke onset. As mentioned earlier, strategically located cerebral infarctions may provoke global aphasia without hemiparesis; such lesions may be smaller than lesions associated with global aphasia with hemiparesis (Deleval, Leonard, Mavroudakis, & Rodesch, 1989; Legatt et al., 1987; Tranel et al., 1987).

(d) **Conduction aphasia**

Conduction aphasia is a syndrome of fluent speech that may involve frequent literal paraphasic substitutions (i.e., incorrect phoneme selection) and generally preserved comprehension, but always impaired repetition. Repetition is often the most severely impaired language skill in these patients, though naming, reading, and writing may also be impaired. By classical aphasia localization, this syndrome reflects a lesion that does not damage either Wernicke's or Broca's areas, but rather it is alleged to disconnect the two. Patient studies, however, have not always supported this simple localization. Cases of conduction aphasia have been reported with either temporal or parietal lesions, and many of the parietal lesions involve the cortex of the inferior parietal lobule, especially the supramarginal gyrus (Benson et al., 1973; Damasio, Damasio, & Chui, 1980). The inferior parietal lobule, particularly the supramarginal gyrus, appears to play a role in perceiving sounds and generating phonemes (Hickok & Poeppel, 2000), which perhaps explains the frequent occurrence of phonemic paraphasic errors in the speech of patients with conduction aphasia. In terms of stroke syndromes, conduction aphasia can reflect a stage of recovery from a

Wernicke aphasia of embolic origin, or it may reflect an embolus to a left MCA branch supplying the parietal lobe.

Lesion size effect. The relationship between general aphasia severity in conduction aphasia and lesion size has not been evaluated. In contrast, repetition disturbance was found by Kertesz et al. (1979) to correlate with infarction cross-sectional area across a variety of chronic aphasia subtypes ($n = 33$, $r = -0.68$, $P \leq 0.01$), but not in acute aphasia. Furthermore, recovery from repetition disturbance was not found to be related to lesion size.

(e) **Anomic aphasia**

Anomic aphasia is a syndrome in which naming is the language function most severely affected, with fluent expression, intact repetition and comprehension, and intact ability to read and write, except for the naming difficulty. Anomic aphasia is not commonly seen as an acute stroke syndrome. It can be a stage in recovery of almost any of the aphasias, since naming is affected by lesions in the frontal, temporal, and parietal lobes. The patient mentioned above, under Wernicke aphasia, with a temporal lobe arteriovenous malformation, had a nearly pure anomic aphasia after several months of recovery from Wernicke aphasia. When last seen she had recovered to a very mild naming deficit. In some studies, naming of verbs is more affected by frontal lesions, naming of nouns more in temporal lesions. Anomic aphasia is also seen as a part of acute confusion and dementing illnesses, again indicating that anomic aphasia is less localizing in terms of vascular diseases than the other aphasia syndromes.

Lesion size effect. Kertesz et al. (1979) observed a significant correlation between greatest cross-sectional infarction area on CT scan and general aphasia severity among anomic aphasics, based on evaluation with the Western Aphasia Battery ($n = 13$, $r = -0.70$, $P \leq 0.01$). Of all the aphasia subtypes in their study, only the severity of anomic aphasia varied significantly with lesion size, suggesting that processes involved with naming or word retrieval are anatomically widely distributed, in contrast to processes that are characteristically affected in other aphasic subtypes. This observation is consistent with the wide range of lesion locations that can be found in anomic aphasia. The observation must be regarded cautiously, however, since the study by Kertesz et al. did not evaluate comparable numbers of individuals with various aphasia subtypes.

(f) **Transcortical aphasias**

Transcortical aphasias make up the remaining syndromes of the eight classical aphasia syndromes described in the nineteenth century. All have in common the sparing of repetition. In anatomic terms, this means that the "perisylvian language circuit" involving Wernicke's area and its connections to Broca's area is not affected. The lesion lies outside this perisylvian circuit in an area referred to by Lichtheim as the "area of concepts," and which we now think of as the various association cortices that project into the language system. In vascular terms, transcortical aphasias often reflect "watershed" infarctions, related to reduced flow from the internal carotid artery, borderzones between ACA and MCA, or MCA and PCA territories.

f.1. Transcortical motor aphasia (TMA) is described in the Sect. 3.2.1.

f.2. Transcortical sensory aphasia (TSA)

Transcortical sensory aphasia is a syndrome of fluent but paraphasic speech output and impaired comprehension, but unlike Wernicke aphasia, the patient can repeat. The lesion lies in the confluence of the temporal, parietal, and occipital lobes (Kertesz, Sheppard, & MacKenzie, 1982). TSA is not a common stroke syndrome, though it can occur in watershed infarctions between the left middle and posterior cerebral artery territories and is often associated with perfusion failure such as that seen in cardiac arrest.

f.3. Mixed transcortical aphasia

Mixed transcortical aphasia, or the "syndrome of the isolation of the speech area," is a rare syndrome in which the patient acts like a global aphasic yet can repeat. The patient has no propositional expressive speech, does not comprehend either spoken or written language, and yet he or she can repeat flawlessly and even complete familiar utterances (such as "Roses are red, violets are…"). In a classical case (Geschwind, Quadfasel, & Segarra, 1968), the etiology of the syndrome was a very large watershed infarction in both hemispheres secondary to carbon monoxide poisoning. The patient had an intact perisylvian language circuit, but it was not connected to the association cortex in order for spontaneous speech or comprehension to take place in a meaningful way. This syndrome has also been reported in advanced dementing illnesses such as Alzheimer's disease.

(g) **Subcortical aphasias**

Aphasias do not always reflect disease of the left hemisphere perisylvian cortex. Lesions in the left hemisphere subcortical areas can also cause aphasia. The history of such vascular injury is such that lesions mapped by brain imaging studies led to the delineation of the subcortical aphasia syndromes, rather than analysis of symptoms and signs alone, as was the case with the cortical aphasia syndromes. In vascular terms, the subcortical lesions generally involve the distribution of proximal, lenticulostriate branches of the left MCA. Aphasia was first described with hemorrhages of the left basal ganglia, usually beginning in the putamen or internal capsule and involving a severe right hemiparesis and a prominent dysarthria, along with language disturbance (Alexander & LoVerme, 1980). Patients with basal ganglia hemorrhages are often mute initially; later, varying degrees of aphasia remain, often with relatively preserved comprehension and repetition. The aphasia characteristics in lateral basal ganglia hemorrhage vary with the exact location and size of the bleed, varying from dysarthria and mild aphasia to severe global aphasia.

A distinctively different aphasia syndrome has been described with infarctions of the anterior limb of the internal capsule, caudate head, and anterior putamen. This syndrome has been referred to as the "anterior subcortical aphasia syndrome." Features of this syndrome include dysarthria and decreased fluency, resembling Broca aphasia, but typically with more dysarthria and greater

fluency. Comprehension and repetition are usually less affected as compared to Broca aphasia (Alexander, Naeser, & Palumbo, 1987). Most patients have an associated right hemiparesis. Recovery is typically good. Writing may also be affected more than expected in lesions of the internal capsule and putamen (Tanridag & Kirshner, 1985). The neuroanatomy of this syndrome likely involves disruption in the caudate nucleus or anterior limb of fibers projecting to the caudate from the auditory cortex, and from the caudate to the globus pallidus, ventrolateral thalamus, and premotor cortex.

Case 4

This 56-year-old lady walked into the outpatient clinic after noting difficulty with speech, without any hemiparesis, on the day prior to the visit. She had a history of hypertension and hyperlipidemia. On examination, she was alert, but she had hesitant, nonfluent speech, with some dysarthria. Naming was also slow, with some deficits. She had similar difficulty with repetition, but her comprehension was excellent. Figure 3.6 shows an MRI scan from this patient. This is an example of the anterior subcortical aphasia syndrome, but a relatively mild version. She made a gradual recovery with outpatient speech therapy. She has had a permanent, mild dysfluency and anomia, present especially when she was fatigued, but she was able to resume her normal life activities.

Subcortical aphasia syndromes are the subject of ongoing research. Published case studies differ, perhaps relating to the use of CT in earlier studies, which might have failed to detect cortical involvement. A good summary of correlations of strokes involving subcortical structures is that of Alexander et al. (1987). They reported that lesions restricted to the putamen or head of the caudate nucleus were not associated with language disturbance, or at worst mild anomia. Lesions of the

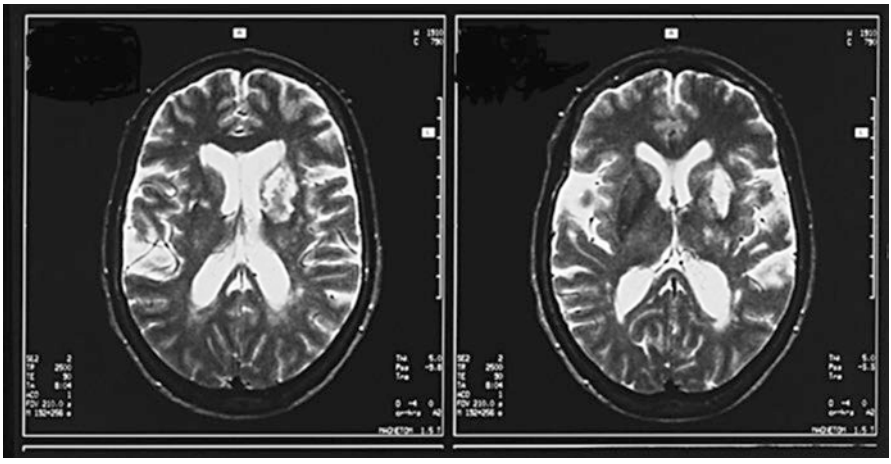

Fig. 3.6 T2-weighted MRI cuts demonstrating infarction of the left head of caudate, anterior limb of internal capsule, and anterior putamen

anterior limb of the internal capsule were associated with language disturbance only if the adjacent structures of the caudate and putamen were also involved (anterior subcortical aphasia syndrome). Lesions involving the more posterior putamen were associated with hypophonia. Dysarthria was prominent if the damage extended to the white matter of the periventricular region or the genu of the internal capsule. Lesions located more posteriorly, converging on the temporal isthmus, produced fluent aphasia, neologisms, and impaired comprehension, resembling Wernicke aphasia. Lesions involving both areas, including the anterior caudate and putamen, internal capsule, periventricular white matter, and temporal isthmus, produced global aphasia. Finally, lesions more laterally placed, involving the insular cortex, extreme capsule, claustrum, and internal capsule, produced a good mimic of conduction aphasia, with phonemic paraphasias and impaired repetition. A variety of syndromes can thus be associated with subcortical lesions, including imitators of most of the cortical aphasia syndromes. These relatively uncommon syndromes should not detract from the more typical conclusion that a stroke causing aphasia is likely to involve the language cortex. In addition, a recent meta-analysis of studies on behavioral and language manifestations of basal ganglia vascular lesions found only weak correlations between structural lesion localization and aphasia characteristics (Radanovic & Mansur, 2017).

Another neurobehavioral syndrome associated with a subcortical lesion localization is a frontal-like syndrome associated with caudate lesions. Patients may show impaired attention, sequencing, planning, and speech fluency (Mendez et al., 1989). The caudate has extensive connections to the frontal lobe.

The basis of subcortical aphasia likely involves connections between the basal ganglia and the cortex. Motor speech is likely similar in its organization to the general motor control system, involving a feedback loop from the cerebral cortex to the striatum (putamen and caudate), then to the globus pallidus, then via projections to the lateral thalamus, via the anterior limb of internal capsule, back to the cerebral cortex. This loop is familiar to neurologists from discussion of movement disorders and Parkinson disease. There are clear analogies between the motor and speech systems. The hesitancy and reduced fluency of speech parallel the abnormal limb control seen in basal ganglia disorders. Hesitancy, initiation difficulty, and disturbed motor control can be seen in the dysarthrias and aphasias, just as limb movements and gait are deranged in basal ganglia disorders.

A very separate type of subcortical aphasia is “thalamic aphasia.” Like the anterior subcortical aphasia syndrome, thalamic aphasia was first described in patients with thalamic hemorrhage (Fisher, 1959; Mohr, Watters, & Duncan, 1975; Reynolds, Turner, Harris, Ojemann, & Lavis, 1979). The aphasia pattern usually associated with thalamic damage is fluent, with paraphasic errors, but with less impairment of comprehension and repetition as compared to Wernicke aphasia. Mohr et al. (1975) described a “dichotomous” state in which patients fluctuate between relatively normal, intelligible speech when they are alert, but mumbling unintelligibly when they are somnolent. Luria (1977) called thalamic aphasia a “quasiaphasic disturbance of vigilance,” meaning a failure of the alerting mechanism of the thalamus in activat-

ing the temporal cortex; the posterior thalamus has extensive projections to Wernicke's area, and the anterior and paramedian thalamic nuclei connect to structures involved in memory and attention (Crosson, 1985). Thalamic aphasia also has implications for cerebral dominance. Hemorrhages in the right thalamus have produced aphasia in left-handed patients, indicating that language dominance in one hemisphere extends down to the level of the thalamus (Kirshner & Kistler, 1982).

More precise anatomic localization in thalamic aphasia has come from cases of ischemic infarction of the thalamus, since ischemic strokes are associated with less swelling and mass effect than hemorrhages. Bogousslavsky, Regli, and Uske (1988), in a study of 40 cases of thalamic infarction, distinguished four separate vascular territories, later updated by Schmahmann (2003) and Carrera, Michel, and Bogousslavsky (2004). Aphasia correlated best with infarctions in the territory of the tuberothalamic artery, which supplies the anterior thalamus, including the ventral anterior and part of the ventral lateral nuclei. Strokes in this vicinity were associated with hypophonia, verbal paraphasias, impaired comprehension, and intact repetition. Strokes in this location on either side are also associated with apathy, personality changes, and impaired memory. Similar aphasic deficits occurred in patients with paramedian thalamic infarcts, within the territory of the thalamoperforating artery (now referred to as the "paramedian artery"), sometimes associated with depressed level of consciousness. The other two thalamic syndromes, posterior choroidal artery infarcts with infarction of the lateral geniculate body, and ventroposterolateral infarcts in the territory of the inferolateral arteries, were associated with hemianopia and hemisensory loss, respectively, without language disturbance. Graff-Radford, Eslinger, Damasio, and Yamada (1984) also described fluent aphasia, anomia, perseveration, reduced comprehension, preserved reading, and intact repetition in cases of thalamic infarction. Deficits in short-term memory and attention have also been reported in cases of paramedian thalamic infarction (Fensore, Lazzarino, Nappo, & Nicolai, 1988; Schmahmann, 2004; Stuss, Guberman, Nelson, & Larochelle, 1988). Carrera et al. (2004) stated that anteromedian thalamic infarcts were often cardioembolic in origin, central thalamic infarcts were often lacunar, and posterolateral infarctions were either cardioembolic or artery-to-artery emboli.

3.2.2.2 Pure Alexia with Agraphia

Traditionally, the alexias are divided into three categories: pure alexia with agraphia, pure alexia without agraphia, and alexia associated with aphasia ("aphasic alexia"). The syndrome of pure alexia with agraphia, described by the French physician Dejerine (1891), is an acquired illiteracy. Reading and writing are disrupted more than other language modalities, though many patients with alexia with agraphia have some degree of paraphasic speech and dysnomia. Repetition and auditory comprehension are preserved. Occasional cases of alexia with agraphia evolve from an initial deficit of Wernicke aphasia, with some impairment of auditory comprehension as well as reading. Both reading words aloud and reading comprehension

are abnormal. The patient cannot understand words spelled orally, though exceptional cases with sparing of oral spelling have been reported. Writing is also severely impaired, such that the patient cannot write or spell even single words. This difficulty with words and letters is also reflected in difficulties with numbers and calculations (acalculia), as well as musical notation. Other, associated neurological deficits in alexia with agraphia include a right hemianopsia or inferior quadrantanopsia; sensory and motor signs are usually mild or completely absent. Other features of Gerstmann syndrome (see below) may be associated.

The lesions in alexia with agraphia involve the left inferior parietal lobule, especially the left angular gyrus. Dejerine conceived of the angular gyrus as a "visual word center," important to the understanding of visual language symbols. Current models consider the inferior parietal lobule a "heteromodal cortex" involved in cross-associations between different sensory modalities, such as auditory and visual language symbols. The syndrome of alexia with agraphia is not a common stroke syndrome, but it may be seen in infarctions involving the inferior division of the left middle cerebral artery or a "watershed" infarct between the left middle and posterior cerebral arteries. Hemorrhages in the left occipital lobe can also be associated with the syndrome of alexia with agraphia.

3.2.2.3 Gerstmann and Angular Gyrus Syndromes

Gerstmann (1930) associated four cognitive deficits with left parietal lesions: agraphia, right-left confusion, disorientation, acalculia, and finger agnosia. Finger agnosia refers to a topographical difficulty with body parts, tested by having the patient point to specific fingers on his or her or the examiner's hand on either side. Gerstmann syndrome has become controversial, but most recent studies have reconfirmed its validity, at least as a collection of symptoms that can occur in varying combination with lesions in the inferior parietal region. Other deficits, including deficits in reading and naming, often accompany the four cardinal elements of Gerstmann syndrome.

Benson, Cummings, and Tsai (1982) described the "angular gyrus syndrome" as a variant of Gerstmann syndrome and a mimicker of dementia. A patient with a single lesion in the left angular gyrus, documented by PET scan but not by CT, had combined deficits of anomia, fluent aphasia, alexia, agraphia, acalculia, right–left disorientation, finger agnosia, and constructional apraxia. These multiple cognitive impairments mimicked a generalized dementia, though the absence of a lesion on CT makes it questionable that this was truly a focal infarction. The multiplicity of deficits also underlines the importance of the inferior parietal region as a "heteromodal" association cortex. The inferior parietal association cortex, along with the prefrontal cortex, has expanded the most of any brain region in comparing ape to human brains.

3.2.2.4 Ideomotor Apraxia

The term "apraxia" is broadly used in clinical neuroscience to refer to a context-specific disorder of voluntary movement with the preservation of such movement under other situations. Applications of the term include "gait apraxia," which refers to impaired walking despite the preservation of leg power while the patient is supine during formal testing; the various eyelid apraxias, in which patients cannot open or close the eyes when instructed and yet show automatic eyelid movements at other times (blinking, sleep); and speech apraxia, which was described in the section "Broca Aphasia". The application of the term "apraxia" to these diverse disorders invites confusion and warrants alternate terms (Zadikoff & Lang, 2005). Apraxia of eyelid opening is sometimes seen in patients with right hemisphere strokes, who seem awake and converse with the examiner, while keeping their eyes closed, though they spontaneously open their eyes (Johnston, Rosenbaum, Picone, & Grotta, 1989).

Ideomotor apraxia is a widely studied impairment that involves the inability to reproduce skilled voluntary movements, i.e., movements that have been acquired through complex learning (e.g., formal instruction; social reinforcement), in contrast to voluntary behaviors that are acquired spontaneously during maturation (e.g., walking, scratching oneself, eyelid movements). Ideomotor apraxia may be further evaluated with respect to whether the actions are *transitive* (involving manipulation of a tool) or *intransitive* (no tool involved). Transitive actions include use of common objects such as a pencil, baseball bat, or soda straw. Intransitive skills (which are also called *emblems*) generally pertain to learned actions not involving tools, such as beckoning an individual to come forward, making the sign of the cross, or hushing another individual. As shown by the preceding examples, the actions pertinent to apraxia concern usually the upper extremity or the mouth, although other body parts are involved with skilled movements as well (e.g., rope skipping).

Ideomotor apraxia seldom comes to a clinician's attention through a patient's complaint or observations by family. As a context-specific disorder, ideomotor apraxia generally does not interfere with daily living activities following stroke to the extent that occurs with generally impaired limb movement (Sunderland, 2000), if at all. This observation does not contradict numerous reports indicating that ideomotor apraxia predicts post-stroke functional impairment (Donkervoort, Dekker, Stehmann-Saris, & Deelman, 2001; Hanna-Pladdy, Heilman, & Foundas, 2003; Smania et al., 2006; van Heugten et al., 2000). However, ideomotor apraxia is generally recognized on the basis of formal testing rather than through observations of impairment on real-world tasks (De Renzi, Motti, & Nichelli, 1980). Moreover, although it has been well established that ideomotor apraxia can predict post-stroke disability at the group level, research has not yet determined whether the finding of ideomotor apraxia is directly responsible for real-world disability in the individual stroke patient or alternatively whether ideomotor apraxia may instead be a biomarker for other cognitive disabilities that may disrupt everyday activities (e.g., impaired abstraction that is not restricted to tool use). Formal testing for apraxia typically involves relatively uncommon situations such as asking the patient to

simulate (pantomime) transitive actions, produce emblems to command or to imitate the examiner on skilled or novel movements, as opposed to observing degraded movement patterns during spontaneous skilled activities.

Ideomotor apraxia is more common after left hemisphere than right hemisphere stroke, with a reported frequency of 7% after left hemisphere stroke and 4% after right hemisphere stroke (Pedersen et al., 2001). Lesion sites that are most often involved with ideomotor apraxia are the left middle frontal gyrus and the left parietal lobe (Haaland, Harrington, & Knight, 2000). Civilek, Atalay, and Turhan (2015) found ideomotor apraxia with left more than right hemisphere lesions, but it could be present with lesion to either hemisphere, and associated with neglect, larger strokes, and lower functional status.

Lesion size effect. Among 177 patients with left hemisphere stroke (Kertesz & Ferro, 1984), lesion volume correlated with apraxia score acutely ($r = 0.39$, $P < 0.05$) and chronically ($r = 0.5$, $P < 0.005$).

3.2.3 Right Middle Cerebral Artery Syndromes

The right hemisphere is often dismissively referred to as the "minor" or "nondominant" hemisphere because it does not play a critical role in language in most people. The right hemisphere, however, carries out very important neurobehavioral functions. Right hemisphere strokes are very disabling, including cognitive, behavioral, and personality changes. Right hemisphere neurobehavioral impairments include constructional and dressing difficulties, spatial and topographical disorientation, in attention to the left side of the body and of space, neglect and denial of neurological deficits, emotional disturbances, and alterations in the emotional aspect of communication.

With regard to stroke syndromes, a lesion in the territory of the right MCA is the cause of most of the deficits to be discussed. Stroke syndromes involving the right ACA territory, PCA territory, and deep structures will be discussed in passing.

3.2.3.1 Neglect and Anosognosia

One of the most striking deficits following stroke is neglect of the left side of the body or surrounding space, as well as the deficit itself. A patient with an acute right hemisphere stroke may lie with the head and eyes turned to the right, turning toward stimuli or people on the right but completely ignoring stimuli on the left. The patient may neglect the left side of the body when dressing or shaving or may eat the food on the right side of the plate but leave the left side untouched. If the patient is ambulatory, he or she may bump into obstacles on the left side; when reading, he or she may omit words at the left side of a line; or when driving, he or she may fail to notice oncoming vehicles on the left. Unilateral neglect can be very disabling.

The patient may or may not have a left hemianopsia; some patients can see stimuli in the left visual field but pay no attention to them ("visual neglect"). Neglect can involve the left side of the body or the left side of space (Calvanio, Petrone, & Levine, 1987; Heilman, Valenstein, & Watson, 2000). Right hemispatial neglect can also occur, usually following left hemispheric stroke, but is generally less common, less severe, and recovers more completely than left hemispatial neglect (Beis et al., 2004; Stone, Patel, Greenwood, & Hallligan, 1992). One study found equal incidence of peripersonal neglect after left or right hemisphere stroke, with a predilection for lesions of the temporal and parietal lobes; occasionally the neglect was ipsilateral to the lesion (Kamtchum Tatuene et al., 2016). Although right-sided neglect is usually less severe, it can still appear to impede recovery from a stroke (Ten Brink, Verwer, Biesbroek, Visser-Meily, & Nijboer, 2017). Neglect can affect all sensory modalities. One aspect of spatial neglect is "extinction" of left-sided stimuli when bilateral stimuli are presented (Critchley, 1966). Some patients grimace when pinched on the left limbs but cannot localize the source of pain. Occasional patients with right hemisphere lesions experience peculiar sensations of the left limbs, e.g., the sense of unilateral limb absence or phantom-limb feeling or the presence of either "extra" limbs or even an extra person in the bed. Functional MRI studies have indicated that the right occipital cortex is activated in response to left-sided visual stimuli, even when they are "extinguished" and not reported by the subject; these stimuli are perceived in the visual cortex but not made available to conscious awareness (Rees et al., 2000). Recovery from left-sided neglect is associated with functional activation of the left prefrontal cortex and the right parietal cortex (Umarova et al., 2016).

Neglect of hemiplegia in a patient with a right hemisphere stroke was termed "anosognosia" by Babinski (1914). Patients with acute right hemisphere stroke may be completely unaware of their paralysis. When asked to lift up both arms, the patient may lift only the right arm, yet deny being weak. He or she often seems to be unconcerned about the paralysis ("anosodiaphoria"). In the most severe form of the neglect syndrome, the patient may even deny the presence of his own left arm or leg or claim that his left arm is the examiner's arm. As neglect improves, recovery occurs in stages. After a few days, the patient no longer denies the hemiparesis and may acknowledge both the stroke and the left-sided weakness. The patient may still not be fully aware of the deficit, however, with the result of attempting to get up, but only to fall; right hemisphere stroke patients are thus at great risk for falling. Patients may also speak of the deficit in neutral terms, such as "They say my left side is paralyzed." Finally, in the mildest stage of neglect, the patient is aware of the deficit but seems inappropriately unconcerned, joking or asking when he or she can go home, despite deficits that render a patient unable to walk or to work. Such unawareness of functional disability is an interfering factor with rehabilitation (Denes, Semenza, Stoppa, & Lis, 1982). Anosognosia for neglect itself—in effect, neglect of neglect—is also inherent in the neglect syndrome (Berti, Làdavas, & Della, 1996). Anosognosia for other cognitive deficits is not unusual as well for other stroke syndromes, including aphasia, apraxia, and amnesia (Boosman, van Heugten, Winkens, Heijnen, &

Visser-Meily, 2014; Canzano, Scandola, Pernigo, Aglioti, & Moro, 2014; Lebrun, 1987).

In terms of stroke anatomy, a number of separate lesion sites can produce neglect. An extensive classical literature links neglect to the right parietal lobe, and particularly the inferior parietal lobule (Critchley, 1966; Denny-Brown & Chambers, 1958). In the study of Hier, Mondlock, and Caplan (1983), those patients with strokes associated with neglect and denial of deficit had large infarcts, usually involving much of the parietal lobe, but the lesion diagrams in this study largely represented the distribution of large right MCA infarctions. Samuelsson, Jenson, Ekholm, Naver, and Blomstrand (1997) correlated visuospatial neglect with lesions on CT imaging of the middle temporal gyrus and temporoparietal paraventricular white matter; 12/18 right hemisphere stroke patients with neglect had lesions involving one or both of these areas, whereas 1/35 patients without neglect had a lesion of these areas. Isolated right frontal lesions have also been associated with neglect (Damasio et al., 1980; Heilman & Valenstein, 1972). The lesions in these cases involved either the medial or dorsolateral surfaces of the frontal lobe or the cingulate gyrus. Thus, stroke involving the right ACA territory is also a source of neglect. Deep, subcortical strokes in the right hemisphere, specifically in the striatum and deep white matter (Bogousslavsky, Regli, et al., 1988; Damasio et al., 1980), posterior limb of the internal capsule (Ferro & Kertesz, 1984), and thalamus (Watson, Valenstein, & Heilman, 1981) have been associated with left-sided neglect. As with syndromes of aphasia associated with left hemisphere subcortical lesions, these right hemisphere subcortical lesions may disrupt cortical function either from mass effect or damaging ascending or descending fiber pathways. SPECT studies in patients with subcortical neglect (Bogousslavsky, Miklossy, et al., 1988) have shown hypoperfusion of the right parietal lobe as well as of the subcortical structures directly involved in CT scans.

Mechanism of hemineglect. Many theories have been advanced to explain the cerebral mechanisms underlying neglect and hemi-inattention (Heilman & Valenstein, 1979). Early theories emphasized afferent sensory defects, including altered sensation or disordered body schema. Accounts of neglect based on sensory abnormalities, however, cannot explain impaired motor acts, such as denial of hemiparesis or omission of the left side of a drawing.

A second possible mechanism of neglect is a disorder of attention. In early studies, both Brain (1941) and Critchley (1966) cited the importance of right hemisphere activity in maintaining attention. Heilman and colleagues developed an "attention-arousal" hypothesis, involving right hemisphere dominance for attention. Anatomically, the attentional system in the brain involves the ascending reticular activating system and its connections to the frontal and inferior parietal cortices. Disruption of this ascending system may account for neglect seen with thalamic and other subcortical strokes (Watson et al., 1981). Evidence for the dominance of the right hemisphere for attention has come from measures of reaction time, galvanic skin response, and EEG desynchronization in right hemisphere stroke patients.

A third cerebral mechanism related to neglect is unilateral hypokinesia or decreased spontaneous use of either the left limbs themselves or of any limbs on the

left side of space. This mechanism can be thought of as the "motor" aspect of neglect, or "intentional" as opposed to "attentional" neglect. Some right hemisphere stroke patients spontaneously move the left limbs much less than the right, even in the absence of weakness or sensory extinction (Valenstein & Heilman, 1981); this is the phenomenon of motor neglect that is described in the Sect. 3.2.1. Hemiakinesia may also explain the omission of left-sided details in the spontaneous drawings of patients with right hemisphere lesions.

Coslett and Heilman (1989) suggested that the right hemisphere is dominant for motor intention of both sides, whereas the left hemisphere is dominant only for motor intention of the right side of the body. These authors matched nine patients with similar infarcts in the middle cerebral artery territory of the right and left hemispheres; the right hemisphere group had much less elevation of the contralateral shoulder when subjects were asked to lift both shoulders than did the left hemisphere group.

Mesulam (1981) synthesized the behavioral and neuroanatomical data on neglect into a "network" approach. In this model, the right inferior parietal region contains the sensory schema for the contralateral body, and hence right parietal lesions produce sensory inattention, extinction, and abnormalities of spatial and topographical function. The frontal lobe subserves movement and exploration in contralateral space, and hence right frontal lesions produce inattention and hypokinesia. The cingulate gyrus, a limbic structure also implicated in neglect (Heilman & Valenstein, 1972), relates to the motivation to explore or attend to contralateral space. The cingulate gyrus has extensive connections to other limbic structures though related to motivation and rewards. Finally, the reticular activating system in the brain stem and thalamus is necessary for arousal, vigilance, and attention, especially as directed to the contralateral body and space. Support for a right hemisphere network subserving attention has also come from PET studies (Fiorelli, Blin, Bakchine, Laplane, & Baron, 1991), which showed hypometabolism throughout the frontal, temporal, and parietal cortex and subcortical structures in the right hemisphere stroke patients with neglect, even if the anatomic lesion was much smaller. This "network" theory brings together the three mechanisms of sensory alteration, inattention, and hypokinesia and takes into account much of the clinical and experimental evidence relating to neglect.

Lesion size effects. Through using various methods of evaluation, studies have concurred that stroke lesion size or volume is significantly correlated with neglect severity (Cappa, Guariglia, Messa, Pizzamiglio, & Zoccolotti, 1991; Leibovitch et al., 1998; Levine, Warach, Benowitz, & Calvanio, 1986). Starkstein, Fedoroff, Price, Leiguarda, and Robinson (1992) observed lesion size not to predict the occurrence of anosognosia for either hemiparesis or hemianopia among 51 acute stroke patients (18 with various degrees of anosognosia), based on their anosognosia questionnaire. Preexisting cerebral atrophy appeared to be necessary for stroke to provoke anosognosia.

3.2.3.2 Post Stroke Delirium

A syndrome occasionally seen in acute right hemisphere stroke patients is delirium, with agitation, disorientation, and hallucinations. Acute confusional states can occur shortly after a right MCA territory stroke (Mesulam et al., 1976) or after recovery (Levine and Finklestein, 1982). Factors associated with the occurrence of delirium in right hemisphere stroke patients include preexisting cerebral atrophy, as seen on CT or MRI scans (Levine & Grek, 1984). Rabins et al. (1991) found the following associations between delusions and hallucinations in stroke patients: older age; family history of psychiatric disorder; right hemisphere lesions, particularly involving the temporo–parieto–occipital junction; cortical atrophy; and seizures. Caplan et al. (1986) described agitated delirium in association with acute infarction of the inferior division of the right middle cerebral artery, a stroke syndrome often not associated with hemiparesis. The authors called this the "mirror image of Wernicke aphasia" in the left hemisphere. Acute confusional states have also been described in patients with right PCA territory strokes.

Lesion size effect. Levine and Grek (1984) found that infarction size did not predict delusions in a sample of 25 patients with acute right hemispheric infarction (9 of whom were delusional). They noted also that delusions appeared to require the combination of acute cerebrovascular injury and preexisting cerebral atrophy.

3.2.3.3 Constructional Impairment

Patients with right parietal infarctions often have deficits on bedside tests of constructional function, such as drawing and copying figures such as a clock or a house, or even the intersecting pentagon figure from the Mini Mental State Examination. These functions are more elaborately tested by neuropsychologists in measures such as the block design subtest of the Wechsler Adult Intelligence Scale, the Bender Gestalt drawings, the Rey–Osterrieth figure, and the Benton Visual Retention Test (Lezak, 1983).

Patients with right MCA territory strokes frequently fail on copying drawings both because they cannot perceive spatial relationships and because they do not pay attention to the left side of space or of a figure. Figure 3.7 shows drawings of a flower and a clock by a patient with a right parietal stroke; the patient's CT scan is shown in Fig. 3.8. The upper left petals are missing, along with misplacement of the flower stem, while the numbers of the clock are crowded into the right side of the provided circle, and the numbers are perseverated. Drawings of patients with right hemisphere lesions frequently misplace lines or show distorted spatial relationships in two-dimensional forms.

The deficits seen in these visuoconstructional tasks probably reflect a variety of behavioral impairments: altered visuospatial perception, poor conceptualization of spatial relationships, left-sided inattention, motor difficulties in the execution of drawings, and impersistence, or inability to sustain attention to a task. The anatomic localization of constructional impairment is most typically in the right parietal lobe.

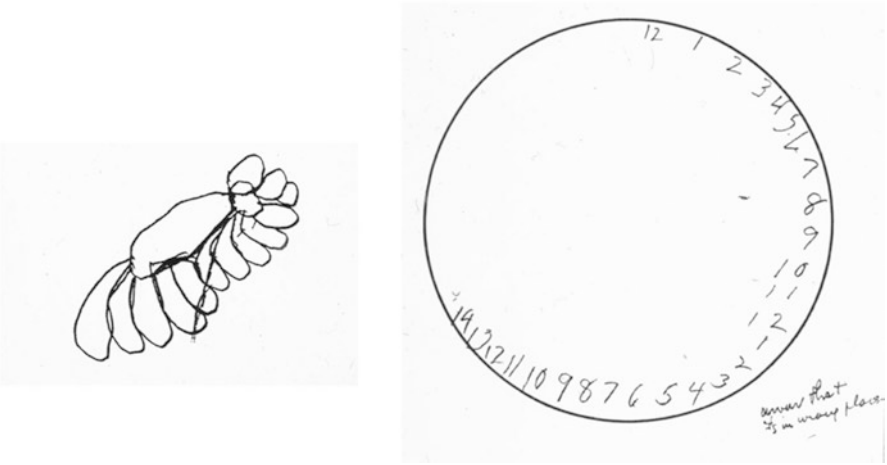

Fig. 3.7 Flower and clock drawing produced by patient after right parietal stroke

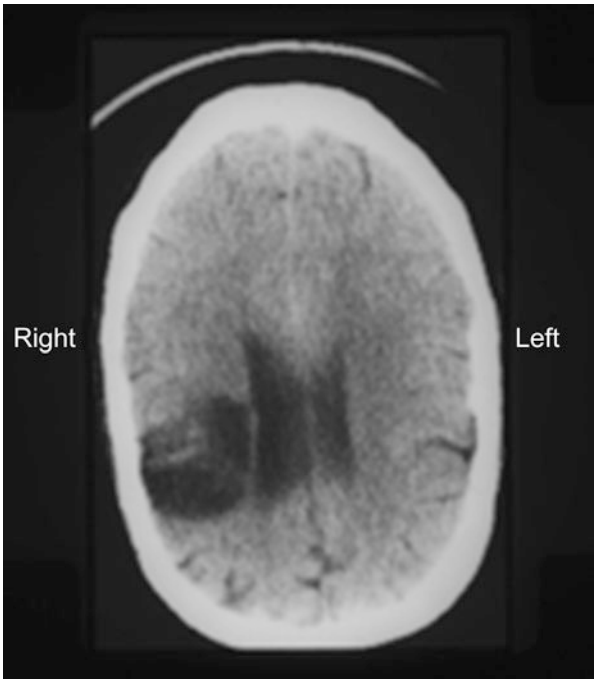

Fig. 3.8 CT scan of patient with right parietal stroke who produced the drawings in Fig. 3.7

Several studies have documented that constructional impairment occurs with lesions of either hemisphere, more with posterior than anterior lesions (Benton, 1967, 1973; Black & Strub, 1976). Constructional impairment from left hemisphere lesions correlates closely with receptive language deficits and is infrequent with purely expres-

sive or no language dysfunction (Benton, 1973). More complex visuoconstructional tasks, such as the copying of drawings or three-dimensional block designs, are impaired more frequently by right than left hemisphere lesions, though deficits in simple block design may occur with equal incidence in the presence of lesions in either hemisphere (Benton, 1967). In a CT scan study of neuropsychological deficits in 41 right hemisphere stroke patients, Hier et al. (1983) found a close correlation among impaired block design, poor performance on the Rey figure, and unilateral neglect in drawing; all three deficits were associated with right parietal lesions posterior to the Rolandic fissure.

Constructional impairment is a common accompaniment of right hemisphere lesions, occurring in 36–93% of patients (Benton, 1967; Hier et al., 1983). Constructional impairment can be taken to indicate a disorder of the right parietal lobe, until proved otherwise.

Lesion size effects. Kirk and Kertesz (1989) administered to a series of stroke patients the task of drawing familiar objects to command and observed a significant correlation between lesion volume and drawing impairment ($r = 0.60$, $P < 0.001$) among the 41 right hemisphere lesioned patients in the sample. However, there was no lesion volume interaction with severity of drawing impairment among the 28 left hemisphere lesioned patients in the same study.

3.2.3.4 Dressing Impairment

Patients with right hemisphere lesions frequently have difficulty with dressing or getting garments onto their bodies. This deficit has traditionally been referred to as "dressing apraxia," but the deficit seems to stem more from a perceptual difficulty than a true apraxia. Dressing impairment is largely related to an inability to conceive the spatial relationships of garments to parts of the body, though neglect of the left side may also play a role (Brain, 1941). Whereas constructional impairment must be detected by bedside testing, dressing impairment is apparent to the patient and family, and it is often mentioned in the history. Dressing apraxia correlates most closely with strokes involving the right parietal lobe. In the study of Hier et al. (1983), dressing impairment correlated with both left-sided neglect and visuospatial and visuoconstructional deficits, and the localization by CT scan was nearly always right parietal.

3.2.3.5 Spatial and Topographical Impairment

Patients with right hemisphere lesions frequently manifest spatial disorientation for both the body image and external space. Stroke rehabilitation patients often become lost in trying to wheel themselves to the cafeteria or back to their rooms. Patients also manifest topographical impairment when drawing maps and locating cities on a map, or on bedside tests such as the Judgment of Line Orientation Test (Benton, Hannay, & Varney, 1975). Spatial and topographical deficits have a strong associa-

tion with right parietal lesions, though they do occur occasionally in left hemisphere stroke patients (Benton, Levin, & Van Allen, 1974). As in constructional and dressing impairments, left neglect contributes to this deficit. In addition, the right parietal lobe appears to have direct involvement in the sense of topographical relationships between the body and space. Takahashi, Kawamura, Shiota, Kasahata, and Hirayama (1997) described three patients with focal intracerebral hemorrhages in the retrosplenial area of the right medial occipital lobe, extending into the medial parietal lobe. These patients lost the ability to recall the spatial relationships of streets and buildings, though they recalled the streets and buildings themselves. The retrosplenial region of the right occipital lobe, within the territory of the PCA, appears to be involved in topographical sense.

Another right parietal deficit is "reduplicative paramnesia," a syndrome in which patients are aware of their correct location but also say that they are at or near home. The patient may be oriented in other respects and not globally confused. This syndrome, named by Benson and colleagues in 1976, may reflect right parietal or bilateral posterior hemisphere lesions (Benson, Gardner, & Meadows, 1976). A patient in our hospital manifested prolonged and consistent reduplicative paramnesia, thinking he was both in our hospital in Nashville but also in his hometown of Knoxville, Tennessee. He repeatedly said that Vanderbilt Hospital was in Knox County. This patient had suffered a single, right MCA territory infarction.

Bisiach and Luzzatti (1978) studied the neglect of visual space in imaginary, as opposed to actual, visual situations. These investigators asked patients to describe, from memory, the Piazza del Duomo in Milan, Italy. Patients described more details on the imagined right side of the Piazza than on the left. When they were asked what they imagined from a vantage point at the other end of the Piazza, however, they then described the buildings on the side of the square that they had previously neglected. Marshall and Halligan (1993) have shown that neglect of actual and imaginary spaces do not strictly parallel each other; neglect can be selective for either actual or imagined space. Beschin, Cocchini, Della Sala, and Logie (1997) have also reported a patient with "representative" or imaginary neglect, without neglect for actually perceived scenes.

3.2.3.6 Motor Impersistence

Another neurobehavioral deficit described in association with right hemisphere strokes is "motor impersistence," a tendency for patients to stop performing a motor task even when asked to continue it. Such impersistence is seen even in simple tasks such as closing the eyes or protruding the tongue (Kertesz, Nicholson, Cancelliere, Kassa, & Black, 1985). Hier et al. (1983) tested motor impersistence in their study of right hemisphere stroke patients; like neglect, motor impersistence correlated with right parietal lesions. Motor impersistence is a functionally important deficit, because it can interfere with activities of daily living and job responsibilities.

3.2.3.7 Right Hemisphere Language and Communication Impairments

Although the left hemisphere is dominant for language in most people, the right hemisphere plays important roles in communication. Aside from left-handed patients, a minority of whom have partial or complete right hemisphere dominance for language, and the rare, right-handed patients with "crossed" aphasia after right hemisphere strokes, the right hemisphere plays important roles in communication even in right-handed people. The right hemisphere is especially involved in "extralinguistic," emotional aspects of communication. Patients with right hemisphere strokes may understand "what is said but not how it is said" (Tucker, Watson, & Heilman, 1977). Heilman and colleagues used the term "affective agnosia" to denote the inability of right hemisphere stroke patients to understand the emotional tone of dictated sentences, tested by having the patient match the intoned emotion to emotional drawings of faces. Left hemisphere stroke patients, even those with aphasia, performed the task well (Heilman, Scholes, & Watson, 1975). Subsequent studies demonstrated that right hemisphere stroke patients are impaired in both the expression and the comprehension of emotional tone (Ross & Mesulam, 1979; Tucker et al., 1977). Ross refers to deficits in the emotional aspect of communication as "aprosodias," and he has divided the aprosodias into expressive and receptive subtypes, similar to the classification of the aphasias (Ross, 1981). We found that all 20 of a sample of right hemisphere stroke patients had affective prosody disturbance, but there were only weak correlations between expressive and receptive aprosodia, and lesion localization (Wertz, Henschel, Auther, Ashford, & Kirshner, 1998). In a recent review, Wright et al. (2016) found that most patients with right hemisphere lesions and impaired prosody had both expressive and receptive prosody deficits; a minority had isolated expressive or receptive prosody impairment. Lesions of the right temporal pole impaired both expressive and receptive prosody. However, aprosodia may not be specific to right hemisphere injury. Van Lancker and Sidtis (1992) found no difference between stroke patients of either the left or the right hemisphere with regard to the interpretation of vocal emotional tone.

Prosody of speech involves not only emotional tone but also such elements of speech as the placement of stress or emphasis within a sentence (Weintraub, Mesulam, & Kramer, 1981). Right hemisphere stroke patients also have problems in understanding humor or irony (Wapner, Hamby, & Gardner, 1981). These extralinguistic and "pragmatic" aspects of communication such as intonation, emphasis, context, humor, turn-taking in conversation, and emotional tone place right hemisphere stroke patients at a disadvantage in interpersonal communication. Rehabilitative therapies should address these communication difficulties (Kirshner, Alexander, Lorch, & Wertz, 1999). At present, however, there has been only limited progress with developing and testing techniques to improve communication disorders following right hemisphere injury (Tompkins, 2012).

Lesion size effect. Starkstein, Federoff, Price, Leiguarda, and Robinson (1994) found no predictive value of cross-sectional lesion area on cranial CT for the ability of acute stroke patients ($n = 65$) to comprehend affective intonation of speech.

3.2.4 Unilateral Posterior Cerebral Artery Syndromes

3.2.4.1 Pure Alexia Without Agraphia

Dejerine (1892) also described the syndrome of pure alexia without agraphia, also called pure alexia, pure word blindness, and letter-by-letter alexia. Patients with pure alexia have little abnormality of spoken language modalities. They can speak fluently, name objects (though sometimes not colors), repeat, and understand spoken language, even words spelled orally to them. Strikingly, they can write. The hallmark of this syndrome is the paradoxical inability of the patients to read words they have just written. Pure alexia is a true "word blindness," in which printed words have lost their meaning, though the patient is not blind. Initially, patients may be unable to read at all. Over time, they may regain the ability to recognize letters and to spell words out, letter-by-letter (hence the name "letter-by-letter alexia;" Patterson & Kay, 1982). During recovery, patients with pure alexia learn to read silently, but still slowly. Reading remains effortful, and patients rarely read for pleasure again. Some patients make visual errors in reading; they perceive the beginning letters of the word and then guess the rest, incorrectly. For example, the patient may read the word "automatic" as "automobile." Patients with pure alexia are not illiterate, as in alexia with agraphia, but they act as if they have a linguistic blindfold.

Associated symptoms and signs in pure alexia include an almost invariable right visual field defect, either a hemianopsia or right upper quadrantanopsia. Occasional patients have intact visual fields; some of these lose color vision in the right visual field ("hemiachromatopsia"; Damasio & Damasio, 1983). Primary motor and sensory deficits are usually absent, though mild right hemiparesis or hemisensory loss may be present. Associated neurobehavioral deficits in pure alexia include color anomia and memory loss. The inability of these patients to name colors is not a perceptual problem; as described by Geschwind and Fusillo (1966), they can match and sort colors normally, indicating that the deficit is not a problem of visual perception. They can also name colors in the abstract, such as the color of a banana or a school bus, which excludes an anomia. The deficit is an inability to associate a perceived color with its name, a deficit called "color agnosia." Occasionally, the deficit in naming colors may extend to pictures or objects, in which case the patient has visual agnosia; usually, visual agnosias develop only in patients with bihemispheric lesions. Deficits in memory may manifest initially as an acute confusional state; as the sensorium clears, a pure short-term memory impairment remains (Benson, Marsden, & Meadows, 1974; Von Cramon, Hebel, & Schuri, 1988). Immediate memory and memory for remote events are preserved in patients with PCA infarctions. Patients with pure alexia typically have no parietal lobe signs, such as calculation difficulty or the other elements of the Gerstmann and angular gyrus syndromes.

Pure alexia without agraphia correlates with strokes in the distribution of the left PCA, involving the medial occipital and medial temporal lobes, and the splenium of the corpus callosum. The left occipital lobe lesion produces a right homonymous

hemianopia, while the lesion in the corpus callosum prevents visual information from the right occipital lobe from reaching left hemisphere language centers. Alexia without agraphia is one of the syndromes referred to by Geschwind (1965) as "disconnection syndromes." The features of pure alexia without agraphia correlate with specific branches of the PCA; alexia correlates with the medial occipital and splenial lesion; motor and sensory involvement, when present, correlates with involvement of proximal branches to the thalamus and cerebral peduncle. The short-term memory loss correlates with medial temporal involvement, especially the hippocampus. In the study of Von Cramon et al. (1988) of 30 patients with PCA territory infarction, verbal short-term memory impairment correlated with left-sided strokes, and in particular, infarction of the posterior parahippocampal gyrus and collateral isthmus, disrupting afferent and efferent connections to the hippocampus. Patients with more lateral occipital infarctions, sparing the splenium and medial occipital and temporal regions, have a partial or transient alexia, sparing letters, and often sparing memory, color-naming, and visual field deficits (Damasio & Damasio, 1983).

Case 5
This 81-year-old man with atrial fibrillation developed the abrupt onset of a mild confusional state, with memory difficulty and visual disturbance. On examination, he spoke fluently and named objects well, though he was totally unable to read, and he had difficulty naming colors. He could write sentences, but he could not read them later. His short-term memory was mildly impaired. He had a dense R homonymous hemianopsia. He had no motor or sensory disturbance. MRI scan (Fig. 3.9) showed a left occipital infarction, with infarction of the splenium of the corpus callosum.

3.2.4.2 Memory Impairments

Students of neuroscience are familiar with a bihemispheric system called "Papez's circuit" that is involved in memory. Classically, memory loss results when parts of this system are damaged on both sides, resulting in the "amnestic syndrome," classically described in patients with Wernicke–Korsakoff encephalopathy, herpes simplex encephalitis, and bilateral surgical ablation of the hippocampus. In stroke, bilateral infarctions within the PCA territory cause a permanent amnestic syndrome. Many such patients are also cortically blind from bilateral occipital damage. Unilateral PCA territory strokes can also be associated with less severe impairments of short-term memory. Left PCA strokes, as discussed earlier in this chapter, frequently result in a short-term memory loss as well as right hemianopsia, alexia without agraphia, and color-naming deficits. Unilateral right PCA territory strokes produce left hemianopsia and often a degree of nonverbal memory difficulty.

Lesion size effects. Lesion volume predicted recovery of visual memory in a sample of 18 patients with acute stroke ($r = -0.34$, $P = 0.001$) but not recovery of verbal memory among 24 acutely impaired patients (Nys, Van Zandvoort, de Kort, Jansen, et al., 2005). Exner, Weniger, and Irle (2001) observed that lesion volume

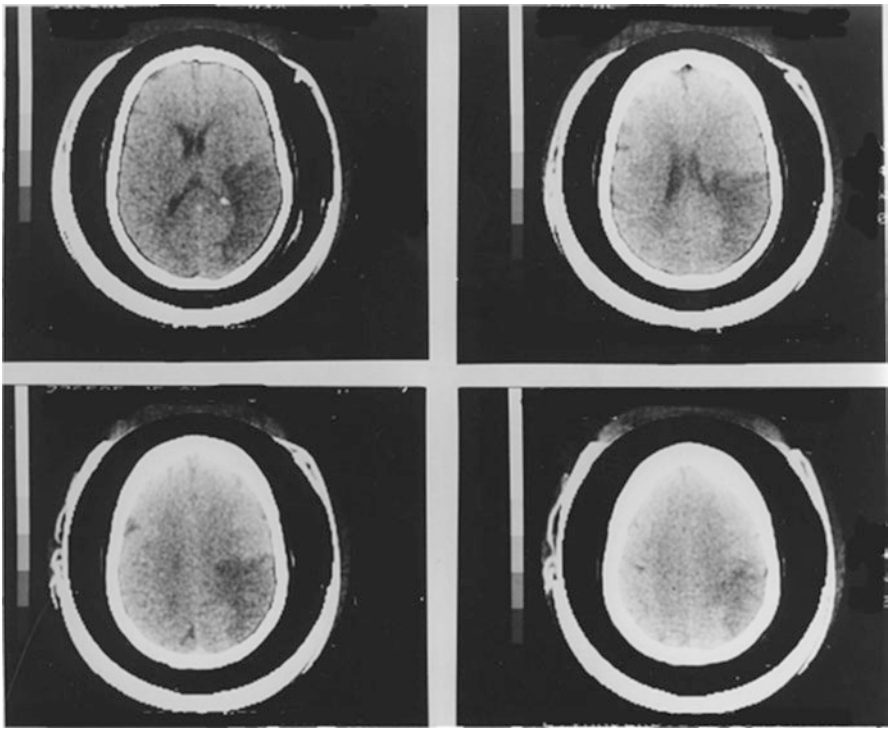

Fig. 3.9 Left occipital infarction, with infarction of the splenium of the corpus callosum

predicted immediate verbal recall ($r = -0.63$, $P = 0.015$) and delayed verbal recall ($r = -0.56$, $P = 0.039$) among 15 patients with chronic thalamic infarctions.

3.2.5 Bilateral Syndromes

3.2.5.1 Cortical Auditory Syndromes

Cortical deafness is classically caused by bilateral lesions of the temporal lobe, as caused, for example, by bilateral infarctions in the MCA territory. In fact, very few such patients are completely deaf to pure tones. In most cases, patients have more selective deficits for understanding spoken words (pure word deafness), understanding nonverbal noises such as animal cries (auditory nonverbal agnosia), and recognizing familiar voices (phonagnosia) (Polster & Rose, 1998). Pure word deafness typically arises from bilateral temporal lesions; one such patient was reported to be able to learn over 100 signs of American Sign Language and communicate via visual language modalities (Kirshner & Webb, 1981). Cases with unilateral temporal lesions have also been reported (Stefanatos, Gershkoff, & Madigan, 2005;

Takahashi et al., 1992). Geschwind interpreted pure word deafness as a disconnection syndrome, in which both primary auditory cortices ("Heschl's gyrus," part of the superior temporal gyrus) were cut off from Wernicke's area, such that sounds could be heard but not processed as language. A unilateral, left temporal stroke could conceivably create a similar disconnection from the auditory cortices. More likely, however, unilateral, left temporal strokes, without parietal damage, can affect the auditory comprehension modality disproportionately, as in Wernicke's aphasia (Kirshner et al., 1989).

Case 6

This 51-year-old man had a Tetralogy of Fallot repaired at age 17 years. He had reportedly suffered ischemic events involving transitory headache and memory disturbance, without any obvious neurological residua. CT and MRI scans showed an infarction in the right temporal lobe. A few months later, he developed an acute, left hemisphere stroke. His international normalized ratio (INR) of prothrombin was subtherapeutic, and he received intravenous tissue plasminogen activator (tPA). Initially, he had a severe, Wernicke-type aphasia, as well as right hemiparesis. Over time, his hemiparesis resolved, and his ability to read and write returned, but he was left with a nearly complete inability to speak or to understand spoken language. He describes his difficulty with hearing: "I hear all sounds at the same time with the same volume. I can't ignore subtle sounds, like computer fans, air conditioning."

On examination, the patient was alert and cooperative. He sent several emails of 2–3 paragraphs, with only minor spelling errors. By contrast, he could not speak intelligibly, producing sounds but no fully formed words. His auditory comprehension was severely impaired. He failed to match spoken words to pictures. He was not deaf; he could identify nonverbal sounds, such as snapping fingers or the bark of a dog, with his eyes closed. He followed printed commands, wrote answers to printed questions, and wrote the names of pictures. His cranial nerve, motor, and sensory examinations were essentially normal. CT and MRI scans showed bilateral temporal lobe infarctions. Pure tone hearing on audiography showed minimal impairment. This is a classic case of pure word deafness secondary to bilateral infarctions involving the temporal lobes.

Figure 3.10 is a CT scan from another case of bilateral temporal infarctions and pure word deafness.

3.2.5.2 Cortical Blindness and Related Disorders

As in the auditory system, several syndromes can result from bilateral lesions of the occipital lobe. Bilateral primary visual cortex lesions do produce complete cortical blindness. Some patients are unaware that they are blind, a syndrome called "Anton syndrome." In other cases, patients report not seeing anything, yet they can avoid obstacles and occasionally react as if they have seen objects. Such unconscious visual processing is called "blindsight."

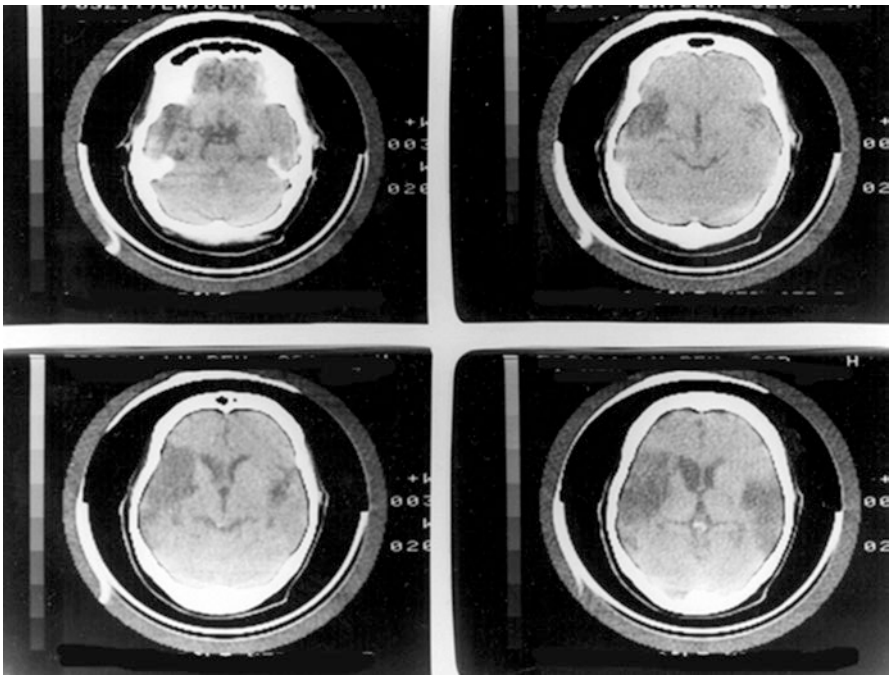

Fig. 3.10 CT scan, bilateral temporal infarctions

Another variation of cortical blindness is Balint syndrome, in which a patient can see small visual details but fail to perceive the overall object, or literally, the patient "cannot see the forest for the trees." This deficit is related to descriptions of inability to perceive two visual stimuli simultaneously ("simultanagnosia"). Balint syndrome is a triad of visual agnosia, optic ataxia, and ocular apraxia. In addition to the visual disorder, the patient cannot scan a scene or picture, gazing at only one part of the display, and the patient cannot visually guide the reaching for an object with either hand. The syndrome is usually seen with bilateral lesions, but usually not involving the visual cortex. The lesions are often bilateral parietal, but other combinations of lesions have also been reported [occipital, parietal, or even frontal (Rizzo & Vecera, 2002)]. This syndrome is not strictly seen in strokes; any bihemispheric disease process can be associated.

3.2.5.3 Prosopagnosia

Prosopagnosia refers to the inability to recognize faces. Descriptions of this syndrome have involved either bilateral or unilateral right hemisphere lesions, most often involving the fusiform ("fusiform face area") or inferior occipital gyri ("occipital face area"). Studies suggest a feed-forward processing of faces from the occipital cortex to the fusiform cortex, with involvement also of the anterior temporal lobe

for memory of specific faces (Barton & Cherkasova, 2003; Rossion et al., 2003; Steeves et al., 2006). The syndrome can occur in unilateral right hemisphere strokes, though congenital cases and progressive syndromes related to neurodegenerative disorders of the temporal or occipital lobes have been reported. A striking example, reported by Semenza, Sartori, and D'Andrea (2003), was of a patient who could look at a Venetian vase and name the artist, but could not name a picture of the Pope.

3.2.5.4 Bithalamic Syndromes

Strokes involving the left thalamus are involved in subcortical aphasia, and those involving the right thalamus are implicated in neglect, as discussed earlier in this chapter. Less commonly seen are ischemic strokes involving both thalami. These occur in patients who have a single artery, sometimes termed the artery of Percheron, arising off the basilar artery or one PCA. The resultant infarction involves paramedian areas of the thalamus on both sides, and sometimes the upper midbrain as well. The resultant syndrome can involve coma, somnolence, akinetic mutism, extraocular and pupillary abnormalities if the midbrain is involved, and often profound apathy and deficits in short-term memory (Meissner, Sapir, Kokmen, & Stein, 1987; Schmahmann, 2003). As patients with this bithalamic syndrome awaken, they sometimes become impulsive and aggressive, even physically violent. Rarely, bilateral thalamic infarctions can result from venous thrombosis in the deep cerebral venous system.

Case 7

This 42-year-old man was found slumped over the steering wheel in his car, which was pulled off the road onto a median. He had been expected to pick up his child after soccer practice, and he failed to appear. His family indicated that he had suffered a myocardial infarction in the past, and he was a smoker. He had been told of high blood pressure as well, but he was not on medications. On arrival in the emergency room, he was comatose, without meaningful response to stimuli. His pupils were midposition and only sluggishly reactive, but he moved all limbs to pinch, reflexes were symmetric, and his plantar responses were downgoing. A head CT was negative. The initial impression of the Emergency Department resident was that he might have a drug overdose or metabolic encephalopathy. Initial laboratory studies were unremarkable, as was a drug screen. Over several hours, he did not awaken, and a neurological consultant found that he had horizontal eye movements by oculocephalic maneuver, but no upward gaze could be induced. An MRI was then done (Fig. 3.11). This indicated a bilateral paramedian thalamic and upper midbrain infarction. His subsequent course was one of gradual improvement in alertness, and in the Rehabilitation Unit he became fully ambulatory, but he remained disoriented and completely amnestic for the events leading up to hospitalizations, as well as for ongoing events. He became agitated at times, angry with his family for not taking him home. He ultimately required placement in a psychiatric facility.

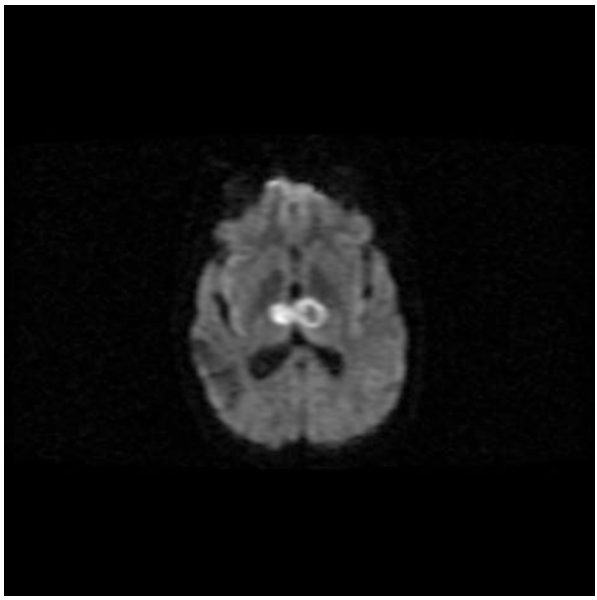

Fig. 3.11 Bithalamic infarctions

3.2.6 Cerebellar Syndromes

Most strokes involving the brainstem and cerebellum do not produce striking cognitive or behavioral changes. A growing literature, however, has documented cognitive changes with cerebellar infarctions. One study found cognitive deficits in both isolated brainstem and cerebellar infarctions, though no characteristic syndrome was reported (Hoffman & Schmitt, 2004). A recent study found greater cognitive and memory impairment with infarctions in the territory of the posterior inferior cerebellar artery than in the superior cerebellar artery (Exner, Weniger, & Irle, 2004). Hokkanen, Kauranen, Roine, Salonen, and Kotila (2006) reported verbal memory impairment related to right cerebellar infarctions, and visuospatial deficits related to left cerebellar lesions, reflecting the crossed input between the cortex and cerebellum. Most patients recovered well by 3 months after stroke. Schmahmann (2004) and Schmahmann and Caplan (2006) has described a "cerebellar cognitive affective syndrome" that includes impairments in executive function, visuospatial tasks, verbal memory, and language, and affective changes such as depression and emotional blunting. Schmahmann also refers to "dysmetria of thought." The lesions correlating with this syndrome are mainly in the posterior, lateral cerebellar hemisphere, and also the vermis. Disruption of cortical-cerebellar loops is presumably the basis of the syndrome. Lesions of the right cerebellum have also been linked to deficits in speech.

3.2.7 Brainstem Syndromes

The cognitive consequences of brainstem vascular damage have received less attention than those of other brain regions, possibly in part because brainstem strokes are less common than hemispheric lesions, and in addition because of the common, yet rarely investigated impression that the brainstem grey regions do not process cognitive functions (New & Thomas, 2005). D'aes and Mariën (2015) most comprehensively reviewed cognitive disorders of brainstem stroke ($n = 33$). The majority of the patients had such deficits, primarily disturbances of executive function, attention, or memory. Moreover, where metabolic scans were conducted, most patients had hypometabolism of the frontal lobes, and less often also in the parietal or temporal lobes. Their review suggested that diaschisis contributes to the cognitive disorder of brainstem stroke.

Apart from the relative paucity of detailed cognitive profiling of brainstem stroke, at present there are many other limitations to this area of research. First, brainstem stroke is more likely to impede manual or vocal responses than stroke involving more rostral brain regions, which thus may curtail detailed cognitive evaluation of such patients. Second, it is unclear whether diaschisis of cerebral hemispheric regions following brainstem stroke imparts a distinct effect on cognition. Third, most of the case studies involved patients with pontine stroke, leaving open the question for whether distinct cognitive profiles can be related to the other brainstem regions, as well as to laterality effects. Fourth, further work is needed to clarify whether the specific kind of cognitive deficits that follow brainstem stroke differ from the grossly similar deficits that follow from hemispheric lesion.

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Chapter 4
Cerebral Aneurysms and Subarachnoid Hemorrhage

John DeLuca and Charles J. Prestigiacomo

4.1 Introduction/Background

Though a recognized entity since the days preceding Morgagni in the seventeenth century, a clear understanding of why aneurysms form, grow, and rupture as well as the best strategies for treating unruptured and ruptured aneurysms still elude the neuroscience community (Prestigiacomo, 2006). Recent advances in neurosurgical techniques and neuro-intensive care have resulted in progressive improvement in mortality, morbidity, and functional status following subarachnoid hemorrhage (SAH) secondary to the rupture of a cerebral aneurysm (Heros & Morcos, 2000; Rhoton, 2002).

Unlike other causes of stroke, SAH occurs in people in the prime of their working years, with a mean age of onset between 40 and 60 years (Sethi, Moore, Dervin, Clifton, & MacSweeney, 2000). With an estimated incidence of 37,500 in the United States alone, and a 1-year post SAH cost for the elderly of over $113,000 per individual, spontaneous aneurysmal SAH cost the United States over $5.6 billion in 1990 dollars (Bekelis et al., 2017; Taylor et al., 1996). Thus, a critical part of the treatment of patients sustaining SAH is the successful rehabilitation of these individuals to improve quality of life and their reintegration as productive members of society. This chapter will review the pathophysiology, natural history, and treatment of patients sustaining spontaneous aneurysmal SAH, with a particular focus upon the recent advances in rehabilitative efforts for these patients. Though traumatic

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_4

SAH is indeed the most common form of SAH reported in the literature, it is a separate disease entity with a different epidemiology, etiology, and outcome, and as such, it is beyond the scope of this chapter.

4.2 Neuropathology/Pathophysiology

Cerebral aneurysms are the fourth leading cause of cerebrovascular accident (behind artherothrombosis, embolism, and intracerebral hemorrhage) and account for 5–10% of all strokes (Dombovy, Drew-Cates, & Serdans, 1998). Saccular or "berry" aneurysms are the most common type and occur primarily at bifurcations or branch-points of the vasculature. Recent estimates of the prevalence of intracranial aneurysms range between 1 and 2% of the general population, although most will never rupture (Winn, Jane Sr., Taylor, Kaiser, & Britz, 2002). Rupture of an aneurysm causes blood to flow into the subarachnoid space, resulting in an SAH. Rupture of an intracranial aneurysm is the most common cause of spontaneous SAH, accounting for approximately 80% of all SAH. SAH can result in a high mortality rate estimated at 10–15% before hospitalization, 40% in the first week, and 50% in the first 6 months (Schievink, 1997). The incidence of nontraumatic SAH in the United States is 6–25 per 100,000 (Clinchot, Bogner, & Kaplan, 1997; Schievink, 1997). Risk factors for the formation and rupture of cerebral aneurysms include aneurysm size, female gender, increasing age, cigarette smoking, alcohol consumption, and high life stress (See Weir, 2002 for an extensive review). While hypertension is more frequent among those with an aneurysm, aneurysms occur most frequently among those with normal blood pressure. The genetics of aneurysm formation are quite complex but have been summarized in Hussain, Duffis, Gandhi, & Prestigiacomo, 2013. First-degree relatives of patients with SAH are at increased risk of SAH, which can be up to seven times higher than the general population (Raaymakers & the MARS Study Group, 1999). About 90–95% of saccular aneurysms lie at the anterior portion of the circle of Willis, most commonly around the anterior communicating artery (ACoA), the origin of the posterior communicating artery (PCoA), the first major bifurcation of the middle cerebral artery (MCA), and the bifurcation of the internal carotid into the middle and anterior cerebral arteries (Victor & Ropper, 2001). In addition to the many biological factors that have been associated with subarachnoid hemorrhage, studies in the biomathematics and flow dynamics of aneurysm formation have helped shed light on the many physical aspects of aneurysm formation, growth, and rupture (Prestigiacomo et al., 2009).

Complications after SAH include vasospasm, hydrocephalus, seizure, rebleeding, electrolyte imbalance, and cardiopulmonary dysfunction. Vasospasm typically occurs within 2 weeks of the SAH, angiographically occurring in 50–70% of patients, and can result in cerebral ischemia in up to 46% of patients or death in about 10–30% of patients (Stern, Chang, Odell, & Sperber, 2006; Velat, Kimball, Mocco, & Hoh, 2011). Hydrocephalus after SAH ranges from 6 to 67%. Though most patients do well with temporary diversion of the cerebral spinal fluid via an

external ventricular drain, approximately 10% of patients will require placement of a ventriculoperitoneal shunt (Sheehan, Polin, Sheehan, Baskaya, & Kassell, 1999; Vale, Bradley, & Fisher III, 1997; Wilson et al., 2017).

4.3 Diagnostic Criteria

The diagnosis and management of ruptured and unruptured aneurysms are substantially different and should be treated independently since outcomes in these two groups differ. As will be demonstrated, because of its varied presentation, and its relative infrequency, the diagnosis of SAH can be missed in 5–51% of patients (Vermeulen & Schull, 2007), a truly broad range which reflects differences in outpatient versus inpatient screening.

4.3.1 Subarachnoid Hemorrhage

The *sine qua non* of SAH is the presence of blood in the subarachnoid space. Prior to the era of modern imaging, when SAH was suspected clinically, the patient required a lumbar puncture to visually inspect the cerebrospinal fluid (CSF) and determine if blood was present. Careful analysis of the CSF was necessary because in many instances blood could be introduced into the CSF from the puncture itself (a traumatic tap). The distinguishing characteristic of CSF in the setting of SAH is that when blood sits in CSF for an extended period of time (over 2 h), it undergoes partial metabolism resulting in the presence of bilirubin. This metabolite gives CSF a xanthochromic appearance, which is not seen in the setting of a traumatic tap. Another important criterion to determining whether blood in the CSF is secondary to SAH is a serial cell count at the time of the lumbar puncture. By analyzing the first and last tubes of CSF during a lumbar puncture, a diminishing red cell count suggests a traumatic tap, whereas a relative steady red cell count points to the presence of true subarachnoid blood.

The advent of noninvasive imaging has displaced, though not rendered obsolete, the lumbar puncture. With a sensitivity of over 98% within several hours of the ictus, a non-contrast CT scan of the head has become the initial study of choice for the detection of SAH. In the setting where the clinical suspicion is high and the CT scan is negative, a lumbar puncture must be performed to definitively rule out SAH.

Once diagnosed with SAH, detection of the aneurysm (accounting for approximately 95% of all spontaneous SAH) is paramount. Though diagnostic, catheter-based cerebral angiography has been the gold standard for detecting intracranial aneurysms, CT angiography has been shown to approach a high degree of sensitivity in detecting these lesions (Hoh et al., 2004). Among its many advantages, CT angiography allows for performing the study at the moment the SAH is detected on the initial non-contrast study.

Table 4.1 Hunt and Hess classification for subarachnoid hemorrhage

I.	Asymptomatic, mild headache, and/or slight nuchal rigidity
II.	Cranial nerve palsy, moderate-to-severe headache, nuchal rigidity
III.	Mild focal deficit, lethargy, or confusion
IV.	Stupor, moderate to severe hemiparesis, early extensor posturing
V.	Rigidity, deep coma, decerebrate rigidity, moribund appearance

Table 4.2 Fisher grade (on CT scan)

1.	No blood detected on CT
2.	Diffuse or vertical layers <1 mm thick
3.	Localized clot and/or vertical layers ≥1 mm
4.	Intracerebral or intraventricular clot with diffuse or no subarachnoid hemorrhage

Patients with SAH can present with a wide spectrum of symptoms. The "classic" presentation is that of a sudden-onset, thunderclap headache, usually described as "the worst headache of my life," and is oftentimes associated with nausea and vomiting. The hemorrhage can be so severe as to cause sudden death in 12% of individuals (Huang & van Gelder, 2002). Because the condition at presentation is associated with varied clinical outcomes, several classification schemes have been developed to help describe and categorize how patients present, ranging from a mild-to-moderate headache to a moribund state (Table 4.1, Hunt & Hess, 1968).

In patients with CT findings consistent with SAH, the amount of blood present at the time of hemorrhage has been correlated with outcome as it relates to the onset of cerebral vasospasm, a potentially debilitating and sometimes lethal complication of SAH (Table 4.2, Fisher, Kistler, & Davis, 1980).

4.3.2 Unruptured Aneurysms

Prevalence of intracranial aneurysms in the general population is estimated at about 0.65–5% of the population, with an estimated yearly rate of rupture of 1–2% (Juvela, Porras, & Poussa, 2000; Winn et al., 2002). Unruptured cerebral aneurysms are usually detected incidentally, though at times focal neurologic findings such as seizures or a third nerve palsy may be the presenting sign that warrants imaging studies. In this setting, an MRI with MRA provides excellent resolution and exquisite sensitivity for aneurysms greater than 2 mm in size. Equivocal studies would then undergo either CTA or catheter-based diagnostic angiography. Decisions for surgical or endovascular treatment depend on the relative risks of rupture versus the risks of

treatment; however, no definite standard of care is currently available (Weir, 2002). Current data suggest that aneurysms of greater than 7 mm in maximum size, posterior circulation, irregular shape, or configuration (the presence of a bleb or daughter sac) predicted a higher risk of rupture and thus suggested the need for treatment (Pierot, Gawlitza, & Soize, 2017; Tominari et al., 2015).

4.4 Characteristic Neurobehavioral Syndrome

With the recent increase in survival from surgical repair of cerebral aneurysms, investigators have become more interested in quality of life issues among survivors (Heros & Morcos, 2000; Crago et al., 2016). Despite these improvements, and the subsequent decrease in mortality following SAH, some reports suggest long-term cognitive impairment (be it mild to severe) in almost 95% of all survivors (Nieuwkamp et al., 2009, Hackett & Anderson, 2000; Passier et al., 2010;Ogden, Levin, & Mee, 1990). A number of outcome studies have demonstrated that cognitive and behavioral impairments are frequent sequelae of such aneurysms, even among patients who show "no neurologic impairments" or who show "good outcome" (DeLuca & Diamond, 1995; Kim, Haney, & Van Ginhoven, 2005; Powell, Kitchen, Heslin, & Greenwood, 2002).

There is somewhat conflicting data regarding outcome with some studies suggesting that most SAH patients have few long-term sequelae (Hellawell & Pentland, 2001; Hillis, Anderson, Sampath, & Rigamonti, 2000), while others show significant disability (e.g., Dombovy et al., 1998). For example, some studies report that approximately 50% of SAH patients return to full-time employment 5–7 years post insult (Hellawell & Pentland, 2001), while others report that no patients return to work after 1 year, even among those who receive rehabilitation (Dombovy et al., 1998). However, methodological differences often explain discrepant findings across studies. Thus, studies that examine consecutive admissions to an acute hospital (e.g., Hellawell & Pentland, 2001), which include all patients as subjects, lead to different results from studies that are selective in subject inclusion. As such, it is not surprising that none of the SAH subjects in Dombovy et al. (1998) returned to work, since only the more severe SAH patients were referred for rehabilitation services, thus having poorer long-term outcome. In aneurysmal SAH patients with "good neurological recovery" post surgery, 20 years later, 90% had returned to work in some capacity, 40% returned to "normal living," 55% and 38% reported mild-to-moderate readjustment, respectively, and 5% with severe difficulties (Sonesson et al., 2017). Other recent studies clearly show that neuropsychological deficits (Crago et al., 2016) as well as stress and depression (Krajewski et al., 2014) significantly affect work quality following aneurysmal SAH.

Overall, recent studies of long-term outcome generally show that about 50% of SAH patients report significant cognitive difficulties (i.e., at least moderately disabling) and everyday life problems up to 7 years post discharge from the acute hospital, even among patients with presumed "good recovery" (e.g., Hellawell &

Pentland, 2001), including a large international population-based study (Hackett & Anderson, 2000). Problems include cognition (mostly memory), mood, fatigue, passivity, speech, language, and self-care issues. Behavioral and cognitive dysfunction, especially executive functioning, are not uncommon and should be evaluated with appropriate cognitive and behavioral assessments (Roussel et al., 2016; Zweifel-Zehnder et al., 2015). For instance, Buunk et al. (2016) reported numerous cognitive impairments following ruptured cerebral aneurysms including problems in attention and processing speed as well as higher order functions such as memory, executive functions, and emotional recognition. In this study, angiographically negative SAH patients showed some degree of cognitive problems, but to a much lesser degree than the aneurysmal SAH group. Hillis et al. (2000) conducted neuropsychological assessment both pre- and post-surgery, including data up to 1 year post surgery in persons with ruptured and unruptured cerebral aneurysms. They concluded that moderate to severe cognitive impairment was observed in a minority of patients. Further, they showed that such impairments were attributed to a variety of reasons including the SAH itself in some subjects, while cognitive impairment in other cases results from the effects of the brain surgery (e.g., prolonged anesthesia, brain retraction, temporary regional blood flow restriction), and still some may simply reflect reduced premorbid levels. Recent studies suggest that genetic factors can significantly affect cognitive and other neurological sequelae after SAH. Lanterna et al. (2005) reported that aneurysmal SAH patients with the E4 allele of the APoE genotype displayed significantly worse cognitive performance as well as worse overall outcome and were at higher risk for developing clinical vasospasm and long-term neurologic deficits. The APoE E4 allele is known to be associated with dementia in Alzheimer's disease, stroke, and traumatic brain injury (Mayeux et al., 1993; Slooter, Tang, van Dujin, Hoffman, & van Dujin, 1997). Fatigue is a frequent, under-appreciated, and not-well-understood consequence of SAH (Ogden et al., 1990). However, such studies rely primarily on self or family report of functioning.

The relationship between various medical variables and outcome following SAH is unclear. There is no clear consensus on perioperative variables in predicting outcome such as vasospasm, postoperative imaging, clinical severity, or timing of surgery. For example, while some studies demonstrate an effect of variables such as vasospasm, or timing of surgery on outcome (e.g., Macdonald et al., 2012; Saveland et al., 1992), others show no relationship with medical variables such as clinical severity, type of SAH, timing of surgery (e.g., Hackett & Anderson, 2000; Ogden et al., 1990), or effects of subarachnoid blood (Germano et al., 1998) on outcome. Aneurysmal SAH with delayed cerebral ischemia during the hospital course has been found to have a fivefold increased risk of neuropsychological deficits than those who do not develop delayed ischemia (Stienen et al. 2014). Clearly, prediction of functional outcome is multifaceted and must take into account a variety of factors, most of which have some impact at the individual level, but overall are too diffuse in nature to have global predictive validity. Indeed, current studies are redefining the outcome measures for subarachnoid hemorrhage and include psychological and neurocognitive outcomes in addition to the more "traditional" neurological outcome measures.

Several studies have compared cognitive outcomes of patients with SAH from ruptured aneurysms following endovascular coiling versus surgical (i.e., clipping) procedures. Most studies found that surgical procedures were more likely to result in cognitive dysfunction than endovascular coiling (Brundle et al., 2016; Latimer, Wilson, McCusker, Caldwell, & Rennie, 2013; Scott et al., 2010; Viera et al., 2012), although not in all studies (Mukerji et al., 2010). Areas of reduced gray matter were more pronounced after surgical versus endovascular treatment in ruptured anterior cerebral artery aneurysms (Bendel et al., 2009).

Of the approximately 50% of SAH patients who display more disabling outcome, a wide range of cognitive impairment can be observed, largely due to both severity and location of the SAH. Increased severity of the initial SAH results in more severe and long-lasting cognitive difficulties and also leads to a wider range of impaired areas of cognition (see Table 4.3). Studies that have examined the influence of aneurysm location on severity of neurobehavioral symptoms following SAH have been mixed and largely influenced by design type (i.e., case studies versus group studies). In general, group studies such as population-based or those

Table 4.3 Cognitive, physical, and psychosocial consequences following SAH

Cognition
Episodic memory
Attention/concentration (working memory)
Processing speed (e.g., reaction time)
Psychomotor slowing
Executive dysfunction
Aphasia
Visual perceptual difficulties
Akinesia/Abulia
Lack of initiative
Motor
Hemiparesis
Quadriparesis
Other
Debilitating fatigue
Sleep disturbance (e.g., daytime sleepiness, problems sleeping at night)
Behavioral dyscontrol
Headache
Emotional distress (anxiety, depression, frustration, temperament)
Altered personality
Difficulties returning to premorbid leisure and social activities
Difficulties returning to work
Health-related quality of life

which include consecutive admissions to acute care tend to show little to no consistent findings across aneurysm sites, although there still seems to be a propensity for worse outcome following ACoA aneurysm (e.g., Bornstein, Weir, Petruk, & Disney, 1987; c.f., DeLuca & Diamond, 1995). For instance, ACoA subjects were more likely to show impairments on frontal/executive tests, problems in initiation, and visual memory compared to MCA aneurysm patients, but the two groups did not differ in health-related quality of life (Haug et al., 2009). In contrast, there are numerous "case report" studies (single or multiple cases) that tend to show that the ACoA is particularly susceptible to neurobehavioral impairments (cf., DeLuca & Diamond, 1995). Located at the circle of Willis at the ventral portion of the brain, the ACoA is the most common site of aneurysm rupture and cerebral infarct (Weir, Disney, & Karrison, 2002). ACoA aneurysm can result in a triad of impairments, which have been collectively referred to as the "ACoA syndrome" (See DeLuca & Diamond, 1995 for a review). This triad consists of a memory deficit often described as "Korsakoff-like" in nature, confabulation, and personality change. While reference to an "ACoA syndrome" is plentiful in the literature, most ACoA subjects do not show this discrete pattern. For instance, some subjects are amnesic but do not confabulate (e.g., Vilkki, 1985), while others may show changes in personality without amnesia (see DeLuca & Diamond, 1995). The most common and disabling neuropsychological deficits among persons with ACoA aneurysm are in episodic memory and executive functions (DeLuca & Diamond, 1995; Haug et al., 2009; Simard, Rouleau, Brosseau, Laframboise, & Bojanowsky, 2003). One recent study found impaired decision-making in ACoA patients who underwent clipping but not those who received endovascular treatment relative to controls, confirming a prior study on 237 ACoA patients (De Santis et al., 2007). Impaired memory in ACoA patients is thought to result from loss of cholinergic modulation of the basal forebrain on hippocampal activity (Myers, DeLuca, Hopkins, & Gluck, 2006; Yeo & Jang, 2013). Nonetheless, despite the fact that neurobehavioral syndromes are seen most often following ACoA aneurysm, it should be noted that up to 85% of cases have been reported to show "good outcome" (e.g., Chalif & Weinberg, 1998) or return to work (c.f., DeLuca & Diamond, 1995). However, as stated above, even patients with "good outcome" or showing "no neurological impairment" often still have significant cognitive, emotional, psychosocial, and everyday life difficulties.

The psychosocial outcomes following SAH can be devastating, even among those with "good neurological outcome." Numerous studies show that despite overwhelming positive recovery in most individuals, many continue to display psychosocial challenges up to 20 years post onset (Sonesson et al., 2017). Examining a consecutive series of 83 patients with SAH, Vilkki, Holst, Ohman, Servo, and Heiskanen (1990) found that the degree of cognitive and neurologic deficit was associated with social competence 1 year after surgery, but not with anxiety and depression. Powell et al. (2002) reported that SAH patients with "good recovery" showed significant psychosocial distress 3–6 months post onset, including post-traumatic stress symptoms (60% and 30% for 3 and 6 months, respectively), reduced independence in activities of daily living (about 50% and 33%, respectively), and decreased level of productive employment. Ogden, Utley, and Mee (1997) found

that while most survivors interviewed reported good psychosocial recovery, a subset continue to report emotional distress, sleep disturbances (up to 35%), decreased ability to work (about 20%), serious and long-term family disruption (although rare), and personality change (48%) 4–7 years post SAH. Clinchot et al. (1997) examined rehabilitation outcomes in SAH. Since this sample consists of SAH patients who required continued inpatient care at a rehabilitation facility, they likely represent a more severely impaired sample than the studies above. Right-sided lesions and more severe motor impairment were associated with increased length of hospital stay. In contrast to the studies mentioned earlier, which examined patients with "good outcome," 85% of SAH patients in the Clinchot study required supervision at discharge, most requiring constant supervision, despite most of these patients being discharged to home. There was a trend for those with better motor scores and functional level at admission to be less likely to require supervision at discharge.

4.5 Relatively Rare Neurobehavioral Syndromes Following Aneurysmal SAH

There are a number of cognitive and behavioral disorders that are relatively rare but do occur after SAH. Alien hand syndrome is a rare condition whereby the left hand interferes with the actions of the right hand, resulting in intermanual conflict. It is an involuntary and autonomous, but apparently purposeful, behavior of the affected limb, which is perceived by the patient to be controlled by an external force. When caused by stroke, it can be observed by either ischemic or hemorrhagic and is often associated with ACoA aneurysm (e.g., DeLuca and Diamond, 1995; Kikkert, Ribbers, & Koudstall, 2006; Kim, Lee, Lee, & Lee, 2014).

Reduplicative paramnesia is a delusion regarding location in which the patient insists that a particular location (e.g., hospital and home) exists in two or more places simultaneously. Although rare following SAH, Hinkebein, Callahan, and Gelber (2001) reported a case of reduplicative paramnesia in a patient with SAH from a right MCA aneurysm rupture and clipping.

Akinesia, or absence of movement, has been observed following rupture of the ACoA and was presumably mediated by damage to the dopamine system or its projections (Tanaka, Bachman, & Miyazaki, 1991). A few reports of paresis are also present in the literature (e.g., Ohno, Masaoka, Suzuki, Monma, & Matsushima, 1991). Hemiparesis or other motor impairments are more typically observed following SAH from sites other than the ACoA, such as the MCA or aneurysms of the posterior circulation. Loss of sense of taste or smell can occur, even following treatment for unruptured intracranial aneurysm patients (Towgood, Ogden, & Mee, 2005).

Hanlon, Clontz, and Thomas (1993) reported a patient with severe behavioral dyscontrol following SAH secondary to right MCA aneurysm. This patient developed an unusual neurobehavioral syndrome characterized by "persistent, repetitive, involuntary, forceful oral exhalations; repetitive involuntary vocalizations; and oral-

facial dyskinesia, involving facial grimacing, tongue protrusion, lip smacking, and eye closure." Three months of conventional rehabilitation as well as several medication trials proved ineffective in decreasing the uncontrollable vocal and motor behaviors. In contrast, a target behavioral intervention significantly decreased these involuntary behaviors, which was maintained at 3 months post inpatient discharge. Decreased behavioral dyscontrol was also associated with improved cognition and daily functioning. Although rare, unilateral spatial neglect has been seen after SAH (Wilson, Manly, Coyle, & Robertson, 2000).

4.6 Unruptured Aneurysms

Published reviews suggest that overall outcome is generally good following treatment for unruptured cerebral aneurysms. Estimated mortality rates are between 0 and 7% and morbidity between 5 and 25%, although morbidity is typically limited to gross neurological impairment (Towgood, Ogden, & Mee, 2004). While outcome is generally better for patients with unruptured versus ruptured aneurysms (Wiebers et al., 2003), few studies have examined cognitive status, psychosocial functioning, and quality of life as part of the outcomes examined for unruptured aneurysms (Towgood et al., 2004, 2005). In general, neuropsychological deficits, when present, are less severe than those with ruptured aneurysms and are often transient in that recovery is often observed (Bonares, Manoel, Macdonald, & Schweizer, 2014; Inoue, Ohwaki, Tamura, Saito, & Saito, 2014; Kang, Hwang, Bae, & Lee, 2013), although not all studies show impaired cognition (Bonares et al., 2016; Kubo et al., 2010). Like ruptured aneurysms, there is some evidence that transient cognitive impairment is worse in those who are treated with microsurgery versus endovascular occlusion (Brundle et al., 2016). Also, like ruptured aneurysms, there is evidence that neuropsychological outcome is worse in persons with unruptured ACoA aneurysm relative to other aneurysm sites (Fukunaga, Uchida, Hashimoto, & Kawase, 1999). ACoA subjects in this study also showed reduced cerebral blood flow using SPECT following surgery.

4.7 Supporting Laboratory Studies Following SAH

In addition to the initial CT scan that is critical in the diagnosis of SAH and the subsequent CT angiogram or catheter-based angiogram to determine the location, size, and configuration of the aneurysm, the patient undergoes numerous additional studies over the course of the patient's 10- to 12-day stay in the intensive care unit. Patients sustaining spontaneous SAH have a high incidence of hyponatremia secondary to excessive antidiuretic hormone secretion of cerebral salt-wasting syndrome (Harrigan, 1996). Because the sodium fluctuations can be quite signifi-

cant and may result in mental status changes, daily (or more frequent) assessment of sodium and all electrolytes is performed.

In addition to the potential electrolyte abnormalities that can ensue, daily transcranial Doppler (TCD) evaluation is often performed to monitor the potential onset of cerebral vasospasm (Lysakowski, Walder, Costanza, & Tramer, 2001). At present, though cerebral vasospasm remains primarily a clinical diagnosis of exclusion (ruling out hyponatremia, fever, and hydrocephalus as other potential causes for mental status changes in the days following subarachnoid hemorrhage), TCD and other methods of determining blood flow (such as CT perfusion studies or SPECT scans) are useful adjuncts to the diagnosis of cerebral vasospasm.

4.7.1 Treatment and Prognosis

The outcomes for patients suffering from a subarachnoid hemorrhage secondary to aneurysmal rupture, despite the many years of clinical and benchtop research, are still quite unsatisfactory with a combined morbidity and mortality of approximately 75% (Prestigiacomo, Connolly Jr., & Quest, 1996). Current research suggests that a substantial portion of the long-term poor outcomes is associated with neuropsychological and cognitive dysfunction, which had not been previously detected. Thus, recent research in subarachnoid hemorrhage now is beginning to address management algorithms in the acute phase that may in fact alter the long-term neurocognitive as well as overall neurological outcome in this population of patients.

Currently, invasive treatment for cerebral aneurysm includes a craniotomy with microsurgical clipping of the aneurysm at its neck or endovascular coiling. Endovascular coiling, also termed embolization, represents one of the more significant recent advances in the treatment of cerebral aneurysms. It was particularly useful for medically fragile patients or aneurysms with a narrow neck (Heros & Morcos, 2000). Since then, there have been numerous trials that have demonstrated efficacy with endovascular coiling in the setting of clinical equipoise (Johnston et al., 2008; Molyneux et al., 2005; Molyneux, Birks, Clarke, Sneade, & Kerr, 2015; Spetzler et al., 2013; Spetzler 2015). Thus, surgical therapy and endovascular therapy serve as complementary partners in the treatment of patients with aneurysms.

Because of the many technological advances in the endovascular management of cerebral aneurysms, complete or near-complete occlusion rates of 54% with early generation devices have now increased to nearly 90% complete or near-complete occlusion at 1 year follow-up as seen in a meta-analysis of aneurysm therapy in the elderly (Brilstra, Rinkel, van der Graff, van Rooij, & Algra, 1999; Struriale, Brinjikji, Murad, & Lanzino, 2013). Additional studies confirm that endovascular coiling is safer to perform in certain settings with good overall outcomes (Johnston, 2002; Spetzler et al., 2015).

Molyneux et al. (2005) completed a multicenter trial of 2143 intracranial aneurysm patients who were randomly assigned to neurosurgical clipping or endovascular coiling. They found that the survival at 1 year was significantly better in the

endovascular coiling group, a benefit that continued for at least 7 years. However, while the risk for rebleeding was low overall, it was more common after coiling versus clipping. Hadjivassiliou et al. (2001) presented preliminary evidence that endovascular coiling caused less structural brain damage than surgical clipping and more favorable cognitive outcome, although cognitive impairment was observed after both procedures. While similar findings have been observed by others (e.g., Bellebaum et al., 2004; Chan, Ho, & Poon, 2002), not all studies have found a clear benefit from endovascular coiling (e.g., Koivisto et al., 2000). Interestingly, patients with ACoA aneurysm may show particular benefit from the endovascular coiling procedure, where significant fewer and less severe cognitive impairment was observed relative to surgical clipping (Bellebaum et al., 2004) likely due to the less invasive nature of the procedure (De Santis et al., 2007; Escartin et al., 2012).

Although SAH is a subtype of stroke, its rehabilitation and treatment differs significantly from ischemic or embolic stroke (Stern et al., 2006). Overall, there are very few studies closely examining rehabilitation outcome after SAH. Regarding rehabilitation, SAH survivors make significant functional gains in rehabilitation, but the rate of gain is less than that observed in TBI or ischemic stroke (Dombovy et al., 1998). For example, SAH tends to have longer length of stays in rehabilitation compared to TBI or stroke, but no significant difference in overall outcome (Westerkam, Cifu, & Keyser, 1997). Longer rehabilitation stays have been associated with right-sided lesions and significant motor impairments (Clinchot et al., 1997). A recent study showed that the ability of cerebrovasculature to buffer against fluctuations and to increase blood flow in response to increasing pressure acutely after SAH onset, in conjunction with SAH severity on admission to rehabilitation, explains up to 80% of the variance in rehabilitation efficiency and long-term functional outcome (Brooks et al., 2018). Outcome for those patients with normal pressure hydrocephalus is better when a ventriculoperitoneal shunt is paired with rehabilitation versus rehabilitation alone (Chen et al., 2009). One significant problem with examining functional outcome is that graded scales such as the Glasgow Outcome Scale (GOS) and Functional Independence Measure (FIM) correlate poorly with actual everyday life outcome. Scales with improved ecological validity are clearly required in order to more closely examine rehabilitation effectiveness (Stern et al., 2006).

Rehabilitation costs can be significant after SAH. A recent study (Ridwan et al., 2017) found that rehabilitation costs were significantly higher for aneurysmal SAH patients who underwent neurosurgical clipping (20,290 euro) versus coiling (11,771 euro). This was driven in large part due to the significantly longer increased duration of rehabilitation in the clipping group (54.4 days) versus coiling (40.5 days). Other factors which contributed significantly to increased costs were longer ICU stay, age > 51 years, and poor-grade SAH. ICU stay and Hunt and Hess grade were independent predictors of rehabilitation costs.

4.8 Summary

While much has been learned about identification, treatment, and outcome in patients with cerebral aneurysms and SAH, much remains to be done. Neurobehavioral and everyday functional difficulties can be a significant outcome following treatment, with a higher likelihood of both with ruptured versus unruptured aneurysms. There is increasing data to suggest that endovascular coiling can result in better outcome and lower treatment cost, although there remain adequate indications for microsurgical approaches. Far fewer studies exist regarding rehabilitation effectiveness and outcome, and this should be a major focus of future research.

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Chapter 5
Neuropsychological Effects of Brain Arteriovenous Malformations

Ronald M. Lazar and Philip M. Meyers

5.1 Introduction

Brain arteriovenous malformations (AVMs) are congenital vascular malformations, which can be located in any part of the brain (cortical, subcortical, dural, or brain stem). They are vascular anomalies which are made up of a complex tangle of abnormal veins and arteries that are missing a capillary bed (AVM Study Group, 1999; Stapf et al., 2001), and instead, artery and vein are connected by fistulas and characterized by "shunting" of blood from artery to vein (Bambakidis et al., 2001; Klimo Jr., Rao, & Brockmeyer, 2007; O'Brien, Neyastani, Buckley, Chang, & Legiehn, 2006). This shunting mechanism causes hypertension within the AVM and in the draining vein (AVM Study Group, 1999; Iwama, Hayashida, Takahashi, Nagata, & Hashimoto, 2002; Loring, 1999) and hypotension in the surrounding and feeding vessels (AVM Study Group, 1999). The feeding arteries have high-volume flow with low pressure, creating hypoperfusion in surrounding normal brain tissue with little apparent clinical effect (Diehl, Henkes, Nahser, Kuhne, & Berlit, 1994; Fogarty-Mack et al., 1996; Mast et al., 1995; Murphy, 1954). AVMs are often found in the borderzone region and thus share anterior cerebral artery (ACA), middle cerebral artery (MCA), and/or posterior cerebral artery (PCA) circulation (Stapf et al., 2001) (Fig. 5.1).

Often, AVMs are asymptomatic and go undetected unless there is a clinical event (such as hemorrhage or seizure). Unlike other brain lesions, the AVM itself often does not cause cognitive dysfunction. This phenomenon has been explained by

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_5

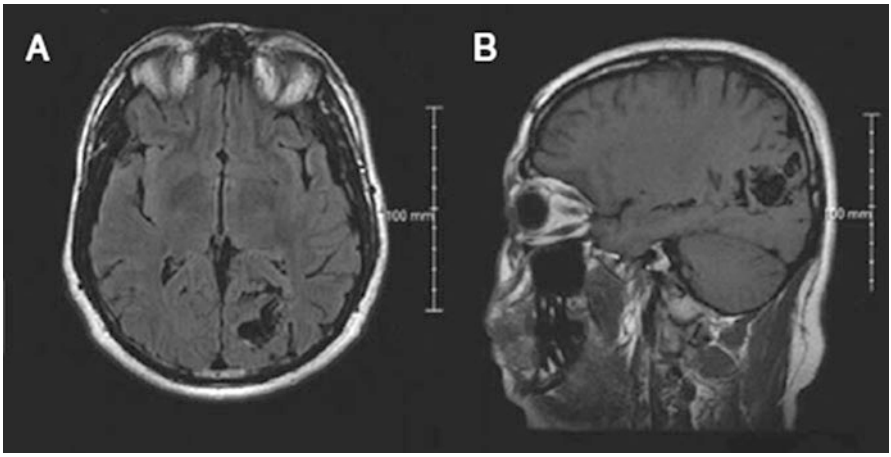

Fig. 5.1 MRI T_1-weighted images of a brain arteriovenous malformation (AVM) in the left occipitoparietal region. (**a**) Axial view; (**b**) Saggital view

Lazar et al. (1997, 2000), who suggested that brain reorganization could be due to the chronic nature of the AVM. Rather, it is usually a hemorrhage that is responsible for functional/cognitive changes seen in patients with AVM. Pathological data have shown that approximately 12% of AVMs are symptomatic and the others are captured either inadvertently or on autopsy (Hashimoto, Iida, Kawaguchi, & Sakaki, 2004; McCormick, 1978).

5.2 Neuropathology and Pathophysiology

The central point of abnormal development in the AVM is the nidus (Loring, 1999), which is a tangle of arteries and veins in which there are feeding arteries and draining veins. The feeding artery can include branches from the main cerebral arteries (e.g., MCA, PCA, ACA), carotid or vertebral arteries, or the choroidal arteries from the subcortical regions (AVM Study Group, 1999). The feeding arteries can have multiple destinations. They may terminate at the nidus or continue beyond the AVM to feed healthy brain tissue (Choi & Mohr, 2005).

Arteriovenous malformations can be in the parenchyma (located in essential neural tissue) or dural (located in dura). Both parenchymal and dural AVMs have the potential to cause a more focal deficit (similar to that seen in stroke), while dural AVM can also cause a more global dementia-like syndrome (Festa et al., 2004; Hurst et al., 1998; Ito, Sonokawa, Mishina, & Sato, 1995; Lantz et al., 2009; Matsuda et al., 1999; Tanaka, Morooka, Nakagawa, & Shimizu, 1999). Subcortical (deep) AVMs have been associated with deficits such as neglect and memory disturbance (Buklina, 2001, 2002). AVMs are equally common in all parts of the brain

and are proportionally represented (i.e., frontal lobe is 30% of the brain, and frontal AVMs represent 30% of all AVMs) (Mohr, Mast, Pile-Spellman, Schumacher, & Stapf, 2004).

Research has demonstrated significant structural changes in the vessels of an AVM as compared to normal vessels (McCormick, 1966; Mohr et al., 2004; Yamada, Liwnicz, Lonser, & Knierim, 1999). Pathology has demonstrated that the neurons within the AVM are nonfunctional and devoid of any normal brain tissue (Mohr et al., 2004). At the molecular level, brain AVMs have been shown to demonstrate genetic abnormalities when compared with normal tissue (Hashimoto et al., 2004; Pawlikowska et al., 2004; Takemori, 1992).

Hemodynamic changes are well documented in brains with AVM. Van Roost and Schramm (2001) found abnormal regional cerebral blood flow in AVM territory (distal from the nidus). In general, regional cerebral blood flow (rCBF) was reduced (20% less than the contralateral side) and impaired (<10.0 mL per 100 g per min) in vessels that supply the AVM (Van Roost & Schramm). In addition, increased regional cerebral blood volume (rCBV)has been found in both the ipsilateral and contralateral hemispheres (Tyler et al., 1989).

5.3 Demographics and Epidemiology

Arteriovenous malformations are an uncommon vascular phenomenon occurring in approximately 4.3% of the population based on 4530 consecutive autopsies (McCormick & Rosenfield, 1973). Pathology data have shown that approximately 12% of AVMs are symptomatic (Hashimoto, Iida, et al., 2004; McCormick, 1978), and researchers report that approximately 0.1–1% of the population will have a symptomatic AVM annually (AVM Study Group, 1999; Brown Jr., Wiebers, Torner, & O'Fallon, 1996; Hofmeister et al., 2000; Mohr et al., 2004; Redekop, TerBrugge, Montanera, & Willinsky, 1998). Females account for 45–51% of AVM cases (Hofmeister et al., 2000). The mean age of diagnosis is 31.2 years, with significant variability in reporting across clinical sites. Sixty-nine to seventy-four percent of patients had AVM location in eloquent (functional) brain regions and the majority (52–59%) showed deep venous drainage (Hofmeister et al., 2000). As for AVM size, 38% were small (<3 cm), 55% were medium AVMs (3–6 cm), and 7% were large AVMs (>6 cm) (Hofmeister et al., 2000).

5.3.1 Natural History

While AVMs are considered to be congenital or developmental, there are currently no in utero reports of AVM, suggesting that it may not be due to embryonic vessel development as once theorized (Stapf et al., 2001). Rather, they are likely formed during the late fetal or immediate postpartum periods (Stapf et al., 2001), although

the mechanism is still unknown. Most researchers classify AVM clinical presentation into two major categories, hemorrhagic and nonhemorrhagic, which can present with identical symptoms (e.g., headache, seizure, or neurological deficit) with one significant differentiation: a bleed (Stapf et al., 2006).

5.3.2 Hemorrhage

Hemorrhage related to AVMs accounts for approximately 1–2% of all strokes (Furlan, Whisnant, & Elveback, 1979; Gross, Kase, Mohr, Cunningham, & Baker, 1984; Hashimoto, Iida, et al., 2004; Perret & Nishioka, 1966). Intracranial hemorrhage (ICH) is the most frequent symptom of AVM, occurring annually in 2–4% of the AVM population (Brown Jr., Wiebers, & Forbes, 1990; Graf, Perret, & Torner, 1983; Ondra, Troupp, George, & Schwab, 1990). Other authors have proposed a higher probability by using a formula for calculating hemorrhage risk ($1–0.97^{\text{expected years of remaining life}}$), and they have estimated approximately a 60% lifetime risk (Kondziolka, McLaughlin, & Kestle, 1995). In general, patients with posterior fossa AVMs are more likely to present with hemorrhage than those with supratentorial AVMs (Abla et al., 2014). Overall lifetime risk for initial ICH is 35–50% (Choi & Mohr, 2005). Rehemorrhage was found in 18% of the population, suggesting that initial hemorrhage was a significant predictor of repeat hemorrhage (Mast et al., 1997; Mohr et al., 2004). Other researchers have found that previous hemorrhage does not predict future hemorrhage (Ondra et al., 1990). Arteriovenous malformation is implicated in subarachnoid hemorrhage only 9% of the time as compared to ICH in which AVM is more often the culprit, especially in younger adults (4–33% of first time ICH) (Furlan et al., 1979; Kloster, 1997; Ruiz-Sandoval, Cantu, & Barinagarrementeria, 1999).

Multiple factors have been associated with increased risk of hemorrhage, such as AVM size, venous drainage characteristics (i.e., deep drainage), and high intranidal pressure (Duong et al., 1998; Spetzler et al., 1992). Additionally, location, cerebellar hypertension, size, and deep venous drainage may be related to increased risk of hemorrhage (Langer et al., 1998). AVMs fed by dural arteries demonstrate a decreased risk of hemorrhage (Langer et al., 1998). More recently, Stapf, Mast, et al. (2006) analyzed a prospective database (Columbia AVM Databank) and found that hemorrhagic AVM presentation in combination with additional significant risk factors (increased age, deep AVM location, and exclusive deep venous drainage) were the only factors that were associated with increased hemorrhage risk. They created a risk model in which 0.9% of AVM patients with no risk factors bled, while bleeding occurs in up to 34.4% of patients with three risk factors. These data alter the previous estimated hemorrhage risk of 2–4% and help guide treatment decisions based on a modified risk factor model.

5.3.3 Seizure

Nonhemorrhagic seizures co-occur in 16–53% of the AVM population (AVM Study Group, 1999; Hofmeister et al., 2000) and are the second most common presentation. The AVM Data Bank of the Columbia–Presbyterian Medical Center demonstrated 49% of AVM-related seizure activity is generalized tonic-clonic, 22% are focal, 22% are focal with secondary generalization, 4% are complex partial, and 4% were not classified (Choi & Mohr, 2005).

Temporal lobe AVMs frequently cause seizures. Temporal lobe AVMs account for 12–16% of all AVMs (Brown Jr. et al., 1988; Drake, 1979; Malik, Seyfried, & Morgan, 1996), and 46% of patients with temporal lobe AVMs report seizures, as compared to the 24% in nontemporal lobe AVMs (Kumar, Malik, & Demeria, 2002; Nagata, Morioka, Matsukado, Natori, & Sasaki, 2006). Factors significantly associated with seizure occurrence were male sex, age below 62 years, AVM size (>3 cm), and temporal lobe location (Hoh, Chapman, Loeffler, Carter, & Ogilvy, 2002). In general, seizures are associated with cerebral location and not with subcortical/deep AVMs (Garrido & Stein, 1978; Graeb & Dolman, 1986; Hoh et al., 2002; Perret & Nishioka, 1966; Turjman et al., 1995). Hoh et al. found a minority (22%) of seizures occurred in deep AVM, although deep location and posterior fossa were statistically unrelated to seizure occurrence. Most epileptogenic AVMs are superficial and supratentorial and are fed by the MCA (Turjman et al., 1995).

Treatment outcomes of AVM-related seizures are mixed, but generally surgical obliteration of the AVM is associated with improved seizure outcome (Hoh et al., 2002; Piepgras, Sundt Jr., Ragoowansi, & Stevens, 1993). Other factors such as short seizure history, hemorrhage-related seizures, generalized tonic-clonic seizure type, and deep and posterior fossa location are associated with positive outcome (Hoh et al., 2002). Piepgras et al. (1993) found 83% of patients with AVM-related seizures were seizure free after surgery; however, the majority (52%) still required anti-convulsant medications following AVM resection. Another factor that has been associated with seizure control in AVM patients is age of onset. Yeh, Tew, and Gartner (1993) demonstrated that older age was associated with better treatment outcome (60% seizure control in age 30 years and under, 83.3% seizure control in age 31 years and older).

5.3.4 Headache

Arteriovenous malformations are occasionally associated with headache. Within the AVM population, approximately 14–16% of the population reported headaches (Ghossoub et al., 2001; Hofmeister et al., 2000). In a sample of 700 AVM patients, headaches that were unrelated to hemorrhage or seizure occurred in only 6% (Ghossoub et al.). Arteriovenous malformation–related headaches were mostly nonpulsating and ipsilateral to the AVM, and they were found to correspond with the

AVM location in the brain of 80–97.4% of patients (Ghossoub et al., 2001). Frishberg reported that only 0.3% of headache patients harbored cerebral AVMs (Frishberg, 1994). Even less frequent were migraines, only 0.07% were found to be related to AVM incidence (Frishberg, 1997).

5.3.5 Neurological/Neuropsychological Deficits

Neurological deficit associated with brain AVMs is reported with varying frequency (1.3%–48%), with reversible deficits significantly more common (8%) than persistent deficits (7%) (Hofmeister et al., 2000; Mast et al., 1995; Wenz et al., 1998). Some researchers have demonstrated significant deficits in neuropsychological functioning of patients, some of which unfortunately combined the outcomes of ruptured and unruptured AVMs (Baker, McCarter, & Porter, 2004; Mahalick, Ruff, Heary, & U, 1993; Marshall, Jonker, Morgan, & Taylor, 2003; Steinvorth et al., 2002; Wenz et al., 1998). Wenz et al. found that AVM patients (both with and without hemorrhage) demonstrated below normal performance on tests of general IQ (24% of patients), attention (34% of patients), and memory (48% of patients). However, this study did not differentiate between ruptured and unruptured AVMs so the actual occurrence of cognitive deficit in AVM, per se, cannot be determined. Mahalick et al. also demonstrated significantly lower performance on tests of neuropsychological functioning for AVM patients as compared to "normals," but they also did not control for prior hemorrhage. In another study combining ruptured and unruptured AVM, it was found that AVM patients were again significantly below normals on tests of intelligence, memory, and attention (Steinvorth et al., 2002).

In contrast, when only patients with unruptured AVMs were included, researchers found a much lower incidence of neurological deficit. Mast et al. (1995) studied patients from their prospective database (AVM Data Bank of the Columbia–Presbyterian Medical Center) with unruptured AVMs and found that only 1.3% of AVM patients met criteria for progressive functional neurological deficit, while 7.2% met criteria for nonprogressive functional neurological deficits. The difference in incidence of neurological deficits in these studies (1.3% up to 48%) can be explained by hemorrhage status, rather than the AVM itself. Hemorrhage is likely accounting for the vast difference in neurological deficit seen among these AVM patients.

Researchers have demonstrated improvement in neuropsychological functioning postsurgery (Malik et al., 1996; Wenz et al., 1998). Cognitive improvements after AVM treatment have been attributed to improved cerebral blood flow and reduction of the "steal effect" (Malik et al., 1996; Steinvorth et al., 2002; Wenz et al., 1998). The steal effect refers to the assumption that shunting and hypertension through the AVM decreases cerebral perfusion in the region surrounding the AVM, thus causing cerebral ischemia and ultimately neurological deficits (Mast et al., 1995). Iwama et al. (2002) demonstrated that intracranial steal and venous hypertension, and not

decreased neurological activity or mass effect, are responsible for the hemodynamic changes seen in high-flow AVMs.

Other researchers disagree with the "steal" hypotheses (Mast et al., 1995; Stabell & Nornes, 1994). Stabell and Nornes reported that AVM patients performed the same as normal controls on presurigcal cognitive assessment. While some significant improvement was observed, Stabell and Nornes dispute the "steal" hypothesis as an explanation for cognitive improvement after AVM surgery. Mast et al. (1995) were unable to replicate the "steal effect" using their prospective database. They demonstrated that an AVM patient with chronic cerebral hypotension did not have any functional cognitive impairment. In addition, they used positron emission tomography (PET) to study 14 AVM patients and demonstrated that while these patients did have hypoperfusion in surrounding tissue, they did not have any parenchymal volume loss and metabolism was normal (Mast et al., 1995). Kumar, Fox, Vinuela, and Rosenbaum (1984) found that the mass effect (space-taking effect of the AVM nidus itself or edema surrounding the AVM) was present in 55% of AVMs on computed tomography (Kumar et al.). Mast et al. (1995) commented on this study and proposed that it is mass effect rather than "steal" effect that may help to explain functional neurological deficits seen in unruptured AVM patients.

More recent studies have focused on postsurgical cognitive functioning associated with AVM (Lantz & Meyers, 2008). A case series that included three preadolescents (age 10 and 11 years) and two adolescents (age 15 years), considered to be cognitively intact before AVM discovery, showed that regardless of the AVM location, mild to moderate executive dysfunction was evident after surgical excision of the AVM (Whigham & O'Toole, 2007). Whigham and O'Toole suggested that perhaps the age of their adolescent patients (executive functions thought to develop at this point in development) helps explain the vulnerability toward executive dysfunction after AVM treatment. In contrast, a study on neurocognition and radiosurgery in adults ($N = 34$) demonstrated that AVM patients improved significantly ($p < 0.001$) on the Wisconsin Card Sorting Test (WCST) after radiosurgical treatment (Guo, Lee, Chang, & Pan, 2006).

In addition, developmental learning disorders have been found in 66% of adults with AVMs (Lazar et al., 1999). In this study, AVM patients reported four times the rate of learning disability than the normal population (17%). Lazar et al. reported that perhaps these disorders of higher intellectual functioning (e.g., learning) may serve as a marker for subtle developmental cerebral dysfunction in AVM patients.

5.3.6 Related Vascular Anomalies

Dural arteriovenous fistulas consist of shunts that are located within the dural layer. They make up approximately 10–15% of cerebrovascular malformations and account for 1% of all strokes (Festa et al., 2004; Hurst et al., 1998; Kurl, Saari, Vanninen, & Hernesniemi, 1996; Newton & Cronqvist, 1969). Dural AV fistulas

(while located in the dura and not directly associated with eloquent cortex) have been found to cause focal deficits, such as Wernicke's aphasia and transient right hemiparesis, identical to symptoms caused by a focal stoke (Festa et al., 2004). Unlike AVMs located within the parenchyma, which are not likely to cause global neuropsychological dysfunction, dural AV fistulas have been demonstrated to cause a dementia syndrome, which presents like encephalopathy (Hurst et al., 1998; Matsuda et al., 1999; Tanaka et al., 1999). These authors reported patients with angiographically confirmed dural AV fistulas who presented with global cognitive dysfunction including progressive memory decline, slowed mentation, and low initiation, and almost all patients reported focal headaches. This dementia-like syndrome may be reversible, since multiple case reports have presented data on patients with dural AVM dementia that was reversed after treatment of the fistula (Hurst et al., 1998; Tanaka et al., 1999; Zeidman et al., 1995).

Aneurysms have also been associated (approximately 10–20%) with AVMs (Redekop et al., 1998). One study reported 46% of AVM patients presented with aneurysms (Meisel et al., 2000). Another author reported a prevalence rate of 15.3% of AVM patients who presented with aneurysm (Redekop et al., 1998). Aneurysms associated with AVM are considered "weak points" and are associated with greater risk for hemorrhage (Meisel et al., 2000). Brown et al. reported the risk of hemorrhage was 7% for the first year in patients with AVM and aneurysms and 3% per year with AVM alone. While the risk decreased to 1.7% with AVM alone, AVM and aneurysm remained at 7% risk of hemorrhage at 5 years (Brown Jr. et al., 1990).

5.3.7 Imaging Studies

Multiple imaging techniques are currently used to diagnose brain AVM. With the availability of technology such as computerized tomography (CT), magnetic resonance imaging (MRI), and angiography, AVMs are often detected before they rupture, allowing treatment options to be explored. While CT and MRI are often the first and least invasive methods for detecting AVM in the brain, angiography is the "gold standard" for formal diagnosis, mapping the vascular anatomy of the AVM, and subsequent treatment planning (Ogilvy et al., 2001).

5.3.7.1 Angiography

An angiogram is a radiograph of the vascular system designed to show detailed anatomy of the arteries and veins by injecting a contrast agent through a microcatheter. In the past, catheters were placed into very large vessels such as the internal carotid artery in order to map AVMs supplied by the middle or anterior cerebral

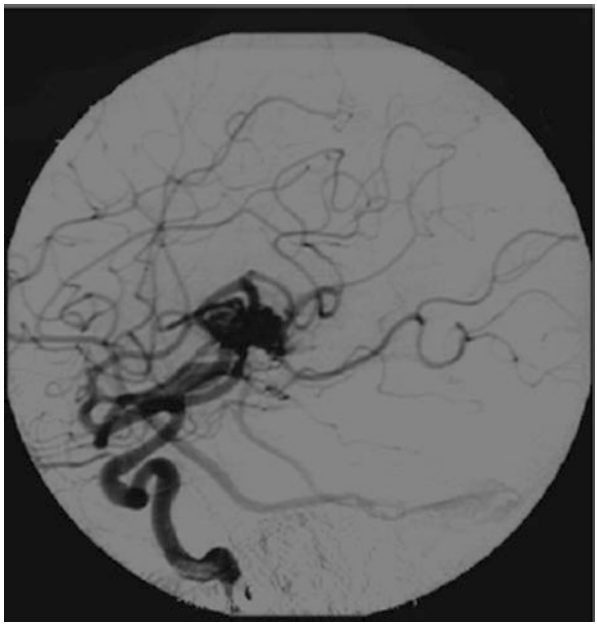

Fig. 5.2 Cerebral angiogram of a right hemisphere AVM following a right internal carotid artery injection

arteries. With the recent development of microcatheters, it became possible to selectively inject vessels distal to the circle of Willis for a more detailed view of the neurovascular geography of vascular malformations such as AVMs. Superselective catheterized angiography is now the most reliable and considered to be the standard procedure for diagnosis and assessment of brain AVM. Researchers have demonstrated a significantly lower risk for angiography-related morbidity with AVM (0.3–0.8%) than with stroke (3.0–3.7%) (Cloft, Joseph, & Dion, 1999) (Fig. 5.2).

5.3.7.2 CT and MR

Although catheter angiography is standard and has the highest spatial resolution (approximately 0.2 mm), researchers continue to look for less-invasive techniques (Warren et al., 2001). CT, CT-angiography, CT-perfusion, MRI, MR angiography (MR-A), and MR perfusion (MR-P) are important diagnostic tools used to evaluate patients with AVMs. In the future, these tests may supplant some of the diagnostic need for catheter cerebral angiography.

A CT scan is used to assess gross changes in the brain due to AVM. It can determine current and past hemorrhage, as well as the presence of draining veins (Riina & Gobin, 2001). While it has low sensitivity, calcification and hypointensity can still be seen demonstrating the mass effect of the AVM (Ogilvy et al., 2001).

An MRI is used to determine size, localization, and topography (Ogilvy et al., 2001; Riina & Gobin, 2001). Functional MRI (fMRI) is also used with AVM patients. fMRI measures regional cerebral blood flow and has been used with AVM patients to study brain reorganization and help with presurgical planning (Cannestra et al., 2004). Cannestra et al. found that fMRI testing was sensitive when identifying eloquent language regions in patients with left perisylvian AVMs. They were able to categorize the patients into three surgical risk groups from fMRI alone and predicted surgical outcomes from their classification system. They reported that 75% of patients avoided awake, invasive brain mapping by using fMRI. However, in 25% of patients, they were not able to successfully determine operative risk, and electrocortical stimulation mapping (ESM) was required. In addition, ESM suggested nidus eloquence in some patients, which was not initially detected on fMRI.

The utility of fMRI in studying AVMs remains controversial. Hemodynamic abnormalities in AVMs make measuring regional cerebral blood flow on fMRI problematic (Alkadhi et al., 2000; Cannestra et al., 2004; Lehericy et al., 2002). Therefore, it has been proposed that fMRI should be followed up with superselective Wada testing or ESM for AVMs with significant blood flow disruptions or when eloquent cortex is thought to be bordering the AVM (Cannestra et al., 2004; Lehericy et al., 2002).

Magnetic resonance angiography (MRA), a variant of MRI, shows the anatomical structure of feeding arteries, draining veins, and the nidus in three-dimensional detail. Contrast-enhanced MRA, for example, provides significantly better morphological information about the vessels and correlates with angiography at 95% sensitivity (Teminzoz et al., 2006; Warren et al., 2001). One advantage of contrast-enhanced MRA in AVM studies is that it is less vulnerable than fMRI to signal loss due to slow-flowing blood (Ogilvy et al., 2001), which is a general problem with imaging AVM due to abnormal blood flow. Most authors agree, however, that MRA should be used only as an adjunct to standard diagnostic angiography because it cannot provide the necessary vascular detail, information which can be obtained from angiography (St George, Butler, & Plowman, 2002; Teminzoz et al., 2006; Warren et al., 2001).

5.3.7.3 Disease Course

People with brain AVMs can live their entire life without symptoms. As previously stated, AVMs rarely cause cognitive or neurological deficits in the absence of hemorrhage or seizures. It is suspected that the brain reorganizes early in development, thus compensating for mass effect of the AVM nidus (Lazar, et al, 1999). Because AVM is often not associated with cognitive decline and the natural history for risk of hemorrhage is relatively low, some authors argue that treatment of unruptured AVMs (those that have not caused hemorrhage) may not be justified (Stapf, Mast, et al., 2006).

5.3.8 Treatment and Prognosis

Because only 0.1–1% of the population will have a symptomatic AVM, there is extensive research and discussion within the field regarding whether to perform preemptive surgery on unruptured AVMs (Stapf, Mohr, Choi, Hartmann, & Mast, 2006). Natural history risk must be weighed with surgical risks in order to determine the risk-to-benefit ratio of treating unruptured AVMs. Because the risk of rebleeding after initial ICH is significant, most researchers agree that treating a ruptured AVM is worth the risk. Whether treating an unruptured AVMs is worth the risk, however, is more controversial. A randomized multicenter clinical trial of unruptured AVMs (ARUBA) reported that procedural treatment yielded significantly more adverse events than medical management alone (Mohr et al., 2004), but others have suggested that follow-up was too short, among other criticisms (Bambakidis et al., 2014). Meanwhile, individual AVM patients are provided with current data of natural history risk versus risk of surgery and are left to decide whether to treat their AVM. To date, however, there are no specific neuropsychological outcomes.

Treatment decisions are determined by appearance (size, location, etc.) of the AVM (Mohr et al., 2004). The Spetzler–Martin grading system has been adopted as a standardized system to rate AVMs according to their size, location (functional importance, often referred to as eloquence, of surrounding brain tissue), and venous drainage (Riina & Gobin, 2001). AVM can be graded from I to V. Research has demonstrated that higher grades have increased risk of negative outcomes during and after surgery. Spetzler and Martin (1986) found that 98% of grade I and II AVMs were successfully removed in one-stage procedure, while grade III and IV AVM required additional treatment stages. Similarly, other researchers confirmed the reliability of the grading system and have demonstrated that grade I and II AVMs have a 100% to 94.3% chance of good outcome, while III and IV AVMs have a 88.6% to 28.6% chance of full removal with positive outcome (Heros, Korosue, & Diebold, 1990).

The current treatments for AVM are embolization, radiosurgery (gamma knife), and craniotomy. Each treatment can be given on its own, but are more often administered in combination. One goal of embolization and radiosurgery is to minimize the size of the AVM, thereby lowering the grade and improving treatment outcome after craniotomy. The ultimate goal of treatment is complete obliteration of the AVM nidus allowing for a return to normal hymodynamics and preservation of neurological functioning (Lunsford et al., 1991).

5.3.8.1 Embolization

Embolization is a procedure in which a microcatheter guided by superselective angiography is used to locate the feeding vessels, and a thrombotic substance is injected into the vessel with the goal of reducing blood flow to the AVM.

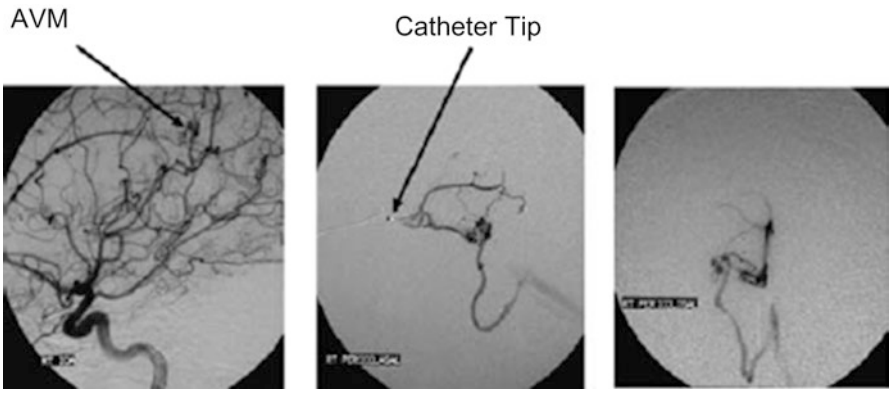

Fig. 5.3 Left panel: a lateral view of a cerebral angiogram following injection of the right internal carotid artery; middle panel: a lateral view of the same AVM following superselective injection in the right pericallosal artery, a segment of the anterior cerebral artery; right panel: an anterior–posterior view of the same right pericallosal segment after injection

The microcatheter is pulled by blood flow and can be guided by the interventional neuroradiologist with precision to almost any vessel in the brain (Richling et al., 2006). The embolizing substance consists of acrylic glue (e.g., NBCA, Glubran-2, Neuroacryl) and oily dye (Lipiodol), so the injection is visible under X-ray (Richling et al., 2006). While embolization sometimes can be used as a stand-alone treatment, it is often used as a presurgical staged treatment for larger and more difficult AVMs. Patients who undergo staged embolizations have better treatment outcome because their brain has time to slowly adjust to the change in hemodynamics, making surgical excision less risky (Spetzler et al., 1987). Embolization is also used for surgically inaccessible, deep, or dural feeding AVMs (Fig. 5.3).

5.3.8.2 Neurosurgery

Complete removal of the AVM through craniotomy has been suggested when the risk of neurosurgery is less than that of the natural history risk of hemorrhage (Lunsford et al., 1991; Spetzler & Martin, 1986). The biggest advantage of complete surgical excision is that the chance of rebleeding is eliminated (Heros et al., 1990). The chance of developing postoperative seizures is 7.4%, and approximately 58% of patients with preoperative seizures had no recurrence of seizures (Heros et al., 1990). One downfall of neurosurgery is that if the lesion is not fully removed then rebleeding remains a risk (Spetzler & Martin, 1986). One population-based study found that neurosurgery is the ideal form of treatment for low-grade AVMs with the goal of total obliteration (Hillman, 2001). Mahalick et al. (1993) reported that surgical excision of the AVM resulted in significant improvements in tasks involving short- and long-term verbal memory, long-term visual-spatial memory, verbal learning, and verbal and non-verbal intelligence. Overall, they found 60% of

AVM patients performed in the normal range on neuropsychological examination postsurgery (Mahalick et al., 1993).

5.3.8.3 Radiosurgery

When an AVM is inoperable due to size and/or location or a patient chooses not to undergo surgery given the natural history of risk of bleeding, stereotactic gamma knife radiosurgery is the treatment of choice. Gamma knife (radiation therapy) is most effective in smaller lesions, but unlike neurosurgery, complete removal is not always possible, leading to future risk of rebleeding. The complete obliteration of the AVM takes 2–3 years after the treatment and possible risk for hemorrhage during this time remains. Some researchers reported the incidence of hemorrhage after radiosurgery is 2–4%, which is almost equivalent to the rate from natural history (Lunsford et al., 1991; Ogilvy, 1990; Steiner & Lindquist, 1987). If the AVM is fully obliterated, radiosurgery provides the same level of protection against hemorrhage as neurosurgical excision. Approximately 80% of patients who received radiosurgery have full obliteration of the AVM.

Wenz et al. (1998) found that radiosurgery improved attention by 14% and memory functioning by 12%. Similarly, they found statistically significant improvements in cognitive functioning after radiosurgery, which is an unanticipated finding since the authors were initially investigating the neurotoxic side effects of radiosurgery. In addition, Steinvorth et al. (2002) compared patients with and without presurgical ICH. They found that presurgical ICH status was not related to cognitive improvement after radiosurgery.

Other researchers have looked at seizure morbidity after radiosurgery. Lundsford et al. found that 51% reported decline in seizure activity while Steiner et al. reported a 69.4% improvement rate. In addition, Lundsford et al. reported a 75% improvement in headaches, and Steiner et al. also demonstrated a significant decline in headaches (66.3% headaches disappeared, 9.2% some improvement).

5.3.8.4 Superselective Wada Testing and Electrocortical Stimulation Mapping

Superselective Wada testing and ESM are in vivo procedures used to help interventional neuroradiologists and neurosurgeons to identify eloquent cortex that may be surrounding the AVM and helps to predict neurological and cognitive changes that would occur as an adverse effect of treatment. Currently, the Spetzler–Martin grading system aids surgeons by establishing a risk model to assess the size and location of the AVM. The treating physician must assume eloquence from the location of the AVM (i.e., if the AVM is located in Broca's area, the surgeon will assume this area is crucial for expressive language). However, because brain

reorganization has been widely associated with AVM (Lazar et al., 1997, 2000), the grading system without empirical data from in vivo testing of eloquence cannot establish true treatment risk.

Superselective Wada testing is a clinical procedure that is used to help the interventional neuroradiologist determine prior to embolization whether a feeding artery to an AVM also supplies blood necessary for eloquent function in nearby brain areas. With the microcatheter in place for embolization (see Fig. 5.3), the neuroradiologist injects a short-acting anesthetic (usually amobarbital, or a combination of amobarbital and lidocaine) that lasts for approximately 3–5 min. During this brief testing period, a neuropsychologist (who has previously collected baseline neurocognitive data for this particular patient) performs tests of cognitive functioning typically associated with brain region supplied by the feeding vessel. For example, if the neuroradiologist is embolizing a vessel in the left MCA territory, tests of language will be performed. The neuroradiologist will use the results of Wada testing to help determine the course of treatment. If a deficit is apparent during Wada testing, the radiologist may choose to embolize closer to the AVM nidus to diminish neurocognitive damage or perhaps decide not to embolize at all. A negative Wada test result allows the neuroradiologist to embolize the feeding vessel with diminished risk for significant neurological damage. Most evaluations during superselective Wada testing are typically adapted from well-known neuropsychological tests (i.e., Boston Diagnostic Aphasia Tests, Wechsler Memory Scale) with well-established norms (Fitzsimmons, Marshall, Pile-Spellman, & Lazar, 2003; Goodglass & Kaplan, 1983; Wechsler, 1987).

While amobarbital and lidocaine can be used in combination, they can be administered separately for superselective Wada testing. Amobarbital is a GABA inhibitor that acts only on gray matter, while lidocaine is an anesthetic that acts on both gray and white matter (Fitzsimmons et al., 2003). Based on four case studies, Fitzsimmons et al. (2003) found that lidocaine alone can cause clinical deficits while amobarbital alone did not. They theorized that the use of lidocaine was more sensitive to white matter changes and therefore helped to determine eloquent brain structures that may be affected from embolization. The authors concluded that lidocaine should be included in combination with amobarbital as part of preembolization Wada testing.

Another in vivo procedure that can be used to determine eloquence of surrounding cortex is ESM. ESM is performed intraoperatively, during an awake craniotomy. While the patient performs different tasks, the brain is stimulated and essential versus nonessential cortical sites can be mapped out (Cannestra et al., 2004).

Cannestra et al. (2004) compared fMRI, superselective Wada testing, and ESM for efficacy as presurgical tools to identify eloquent cortex surrounding the AVM. They reported that superselective Wada testing was not sensitive in identifying eloquent cortex and that fMRI in combination with ESM was required to adequately predict surgical risk.

5.3.8.5 AVM and Cerebral Reorganization

Because AVMs are developmental, chronic lesions, they have been able to provide unique information about the brain. Researchers have demonstrated brain reorganization of language function using superselective Wada testing, MRI, and fMRI studies (Lazar et al., 1997, 2000; Maldjian et al., 1996). Lazar et al. reported on three cases (all with left frontal AVMs) in which expressive language function was at least partially controlled by the right hemisphere and had also been transferred to ipsilesional territory not typically associated with language (Lazar et al. 2000).

Some authors propose functional displacement simply due to the fact that brain tissue located within the AVM is nonfunctional (Alkadhi et al., 2000; Burchiel, Clarke, Ojemann, Dacey, & Winn, 1989; Choi & Mohr, 2005). Further, Lazar et al. (2000) demonstrated that the left frontal region, which is normally responsible for expressive language, was no longer responsible for that function. They did so by using superselective Wada testing in which the target region (left frontal AVM feeder) was anesthetized and language function was not disrupted. Receptive language, as expected, was controlled by the left temporoparietal region. Lazar et al. (2000) hypothesized that expressive language had been reorganized to the right hemisphere of these AVM patients. Using fMRI, they determined that in fact these AVM patients did show activation in the right hemisphere where normal controls do not show activation for such language functions. In another study, Lazar et al. (1997) found that patients with left posterior AVMs in the receptive language region had receptive language deficits when the frontal lobe (typically expressive language regions) was anesthetized. This finding again suggested the presence of language reorganization in brains of AVM patients. Lazar et al. (1997, 2000) concluded that brain reorganization was likely a function of the chronic AVM lesion and suggested that there is a preexisting language network that is malleable to change with structural reorganization due to chronic neuronal lesions.

Other researchers have demonstrated similar structural reorganization involving the motor cortex (Alkadhi et al., 2000). They examined six cases of AVMs located within the motor cortex with fMRI studies and found functional displacement of motor control in all six patients. For example, one patient with a right hemisphere AVM (located in the foot representation region of primary motor cortex, M1) showed activation in the ipsilateral M1 region, supplementary motor area (SMA), cingulate motor area (CMA), and bilateral dorsal premotor and parietal areas (Alkadhi et al., 2000). They concluded that AVMs located in primary motor cortex were related to reorganization of motor function to primary and nonprimary motor regions.

5.4 Conclusions

Arteriovenous malformations continue to provide researchers with information about reorganization and hemodynamics of the human brain. When an AVM has ruptured, the isolated, functional effect of AVM can no longer be studied. Therefore,

future studies that wish to explain neurological/cognitive deficits associated with AVM must exclude ruptured AVMs. Future studies comparing the incidence of cognitive deficits associated with unruptured versus ruptured AVMs would also help neurologists, neuroradiologists, and surgeons to better assess the natural history risk to their AVM patients.

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Chapter 6
Vascular Cognitive Impairment

Philip B. Gorelick

6.1 Introduction

Cognitive function is an important component of successful aging, quality of life, functional independence, and risk of institutionalization (Fiocco & Yaffe, 2010). A healthy brain is necessary for cognitive abilities such as learning, judgment, recall, and communication (Centers for Disease Control and Prevention, 2017). With increases of life expectancy in developed regions, it is expected that there will be gains in longevity among older persons, particularly women, leading to a higher prevalence of those with cognitive impairment and dementia (Kontis et al., 2017; Santosa, 2017). By 2030, it is estimated that there will be 75 million persons with dementia worldwide and by 2050, 131 million persons (Winblad et al., 2016). Based on these estimates, it is important that we establish preventatives for cognitive impairment and treatments to delay cognitive decline (Gorelick et al., 2017).

Stroke and cardiovascular risks have been major targets for the prevention of cognitive impairment and for the reduction of cognitive decline because these factors are modifiable, easy to measure, and can be monitored (Gorelick, 2017; Gorelick et al. 2017). Over time, there has been acceptance of stroke and cardiovascular risks as factors predisposing to certain types of dementia including Alzheimer's disease (AD) and other cognitively impairing disorders. And, as discussed in this chapter, major guidance statements relating to the prevention of cognitive impairment are now suggesting that stroke and cardiovascular risks be managed in an attempt to prevent cognitive impairment or possibly to slow the progression of cognitive decline (Gorelick et al., 2017).

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_6

In this chapter, we discuss a brief history of vascular cognitive impairment (VCI) and vascular dementia (VaD), the definition of the terms VCI, VaD, and other related classification terms, the epidemiology and vascular risks associated with cognitive impairment, clinical manifestations, diagnostic tests, and prospects for prevention and treatment.

6.2 Brief History of VCI and VaD

According to a review of the historical evolution of the concept of VaD by Roman, the term dementia was used in France in 1381, and by 1754, it was clearly defined based on legal and medical viewpoints (Roman, 2003). Furthermore, from the late 1800s and during most of the twentieth century, AD, senile dementia, and VaD were used as closely intertwined terms, and for more than 100 years were categorizations referring to the same entity (Roman, 2003). Roman credits Thomas Willis in 1672 for providing the first accurate clinical description of patients with VaD, and Kraepelin in the first two decades of the 1900s for recognizing the presenile form of dementia or AD and for acknowledging that the most common form of senile dementia was arteriosclerotic insanity or arteriosclerotic psychosis, conditions caused by underlying cerebral arteriosclerosis.

As early as the early 1900s, it was recognized that arteriosclerotic and senile processes underlying cognitive impairment were unrelated. This was as acknowledged by Alzheimer, and in relation to the classification of disease, such an acknowledgment likely led to the classification of cognitively impairing disorders as distinct or pure entities. This classification philosophy predominated our thinking for many years (Gorelick & Mangone, 1991). Drawing from the work of Slater and Roth, in the 1970s, Hachinski et al. published seminal work to help us better understand "multi-infarct dementia" (MID). The latter work spawned the Hachinski Ischemic Score designed to distinguish "primary" causes of dementia from cerebrovascular-based dementia (Gorelick & Mangone, 1991). Later, there were refinements in the definition of MID or cognitive impairment associated with cerebrovascular disease, and subsequently more modern classification terms such as VaD, VCI, and vascular cognitive disorders (VCD) appeared (discussed in Sect. 6.3) (Gorelick et al., 2011, 2017).

With the establishment of new classification terminology for cognitive disorders associated with stroke or vascular risks, we have evolved from attempting to neatly classify and separate "vascular" from "neurodegenerative" disorders based on clinical, neuroradiological, and neuropathological study, and thinking of these disorders as distinct entities, to focusing on upstream mechanisms and vascular risks that may be shared by both so-called traditional "vascular" and "neurodegenerative" cognitively impairing disorders (Gorelick, 2010). Thus, our focus has shifted from a classification-based system steeped in separation of cognitively impairing disorders

to an upstream and mechanistic one that highlights shared risks and the possibility of intervening at an appropriate time window to prevent or reverse processes leading to cognitive impairment.

6.3 Definition of Vascular Cognitive Impairment and Vascular Dementia

This chapter now focuses on defining or classifying contemporary terms used to refer to cognitively impairing disorders associated with stroke. As noted in the above section, such terms as "arteriosclerotic psychosis or insanity" and "MID" have been used to refer to these disorders (Gorelick & Mangone, 1991). In fact in the 1950s, Roth described "arteriosclerotic psychosis" in those with focal signs and symptoms of stroke, and fluctuating or remitting course (e.g., with emotional incontinence, preservation of insight, and seizures) (Roth, 1955). The criteria were later refined by Mayer-Gross, Slater, and Roth to refer to a condition that occurred in the 60- to 70-year age group among those with hypertension and symptoms following a stroke (e.g., memory disturbance, restlessness, wandering at night, and emotionality). In addition, there were somatic complaints, maintenance of creative abilities, cooling of emotions, diminished drive and initiative, and preservation of judgment and personality (Mayer-Gross, Slater, & Roth, 1969). The latter criterion evolved and was subsequently replaced by the term MID, which was coined by Hachinski and colleagues, and referred to persons with a condition characterized by progressive loss of cognitive function, impairment of social skills, abrupt onset of signs and symptoms, stepwise deterioration, fluctuating course, and focal neurological signs in conjunction with cerebral infarcts (Hachinski, Lassen, & Marshall, 1974). The aforementioned criteria as mentioned in an above section were a forerunner to the Hachinski Ischemic Score, a clinical tool to help differentiate dementia associated with ischemic stroke from neurodegenerative dementia such as AD.

Another contemporary term VaD referred to the occurrence of stroke, the presence of significant cognitive impairment, and a temporal linkage between stroke and cognitive symptoms (Gorelick et al., 2011). The term VaD was used to account for any dementia related to underlying disease of the cerebral blood vessels (Hachinski, 1990). Thus, VaD was a heterogeneous entity based on underlying stroke mechanism and took into account location of stroke and underlying stroke subtype (Gorelick & Mangone, 1991). The term VaD helped to expand our understanding of VCI beyond brain infarcts because it included ischemic stroke and brain hemorrhage, and in the latter case, the consequent vascular mechanism responsible for extravasation of blood in the brain tissue. Thus, use of the term VaD to define or categorize cognitive impairment associated with cerebrovascular disease emphasized the need for a search for the underlying cerebrovascular mechanism responsible for cognitive impairment.

The most common type of stroke associated with cognitive impairment is cerebral small vessel disease with subcortical brain changes (e.g., white matter disease, small deep infarcts, and cerebral microhemorrhages) (Pantoni & Gorelick, 2014). The underlying and dominant mechanistic theme for cognitive impairment associated with cerebral small vessel disease may be hypoxic hypoperfusion, lacunar infarction, oxidative stress, and inflammation with disruption of the blood–brain barrier and brain myelin (Pantoni & Gorelick, 2014). Once the neurovascular unit (NVU) succumbs to oxidative stress and inflammation, there is resultant neurovascular dysfunction, brain injury, and VCI. Prevention of the latter cascade of events by an upstream intervention such as reduction of vascular risks has been advocated as a prevention approach (Hachinski & Sposato, 2013).

Contemporarily, we now use terms such as VCI and VCD to refer to cognitive impairment associated with cerebrovascular disease. I now review definitions and diagnostic criteria for cognitive impairment associated with cerebrovascular disease that have been utilized since the 1990s.

6.4 National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) Research Diagnostic Criteria

These VaD criteria emphasize heterogeneity of vascular dementia syndromes and neuropathologic correlation, the importance of a temporal relationship between stroke and dementia occurrence, clinical features, and variability of clinical course (i.e., deviation from the classic stepwise cognitive deterioration expected with stroke and instead a static, remitting, or progressive time course of cognitive change) (Roman et al., 1993). Early in the course of VaD, there may be gait dysfunction, urinary incontinence, and mood or personality changes. Furthermore, the value of neuroimaging, formal neuropsychological testing including the study of multiple cognitive domains, and correlative neuropathological evaluation to establish a proper diagnosis are emphasized by this research diagnostic criteria. In addition, probabilistic categories are defined and include possible, probable, and definite cases.

NINDS-AIREN VaD research diagnostic criteria may be thought of as consisting of the following key but broad components: (1) presence of dementia; (2) stroke according to neurological history, clinical examination, or brain imaging; and (3) a temporal linkage between the occurrence of stroke and dementia (Roman et al., 1993). Dementia is diagnosed with evidence of impairment of memory, loss of cognitive abilities sufficient to cause impairment of activities of daily living (ADLs), and deficits in two or more other major cognitive domains. The inclusion of memory loss to establish a diagnosis of VaD has been a point of contention because it may draw in or select out for AD cases (Farooq, Min, Goshgarian, & Gorelick, 2017).

6.5 State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) Criteria for Ischemic Vascular Dementia (IVD)

ADDTC research diagnostic criteria are comprehensive, draw a distinction between IVD and VaD, emphasize a broader concept than VaD, support the value of neuroimaging to establish the diagnosis, and acknowledge the need for validation of the criteria and list research gaps (Chui et al., 1992). Dementia is defined as deterioration in cognition from a higher level of intellectual function sufficient to result in loss of one's ability to carry out usual affairs of life and requires corroboration by bedside mental status assessment or formal neuropsychological testing. Similar to the NINDS-AIREN criteria, there is a probabilistic scheme including probable, possible, and definite IVD classifications (Chui et al., 1992).

Probable IVD is described as the presence of dementia, evidence of one or more strokes based on neurological history, examination, and/or neuroimaging, or the occurrence of a single stroke clearly and temporally linked to the presence of dementia. The occurrence of at least one brain infarct is required to be outside the cerebellum. The following are suggestive features to establish a diagnosis of IVD: multiple brain infarcts in regions known to be associated with cognitive dysfunction, history of transient ischemic attack (TIA), and other features (Chui et al., 1992). The following are supportive features: abnormal gait early in the course of illness and "neutral" features (e.g., a slowly progressive time course rather than stepwise cognitive deterioration).

Possible IVD is diagnosed in the presence of dementia and a single stroke or in the case of Binswanger's disease. Definite IVD is operationally defined as the presence of dementia and multiple brain infarcts on neuropathologic examination with some infarcts being found outside the cerebellum (Chui et al., 1992). Mixed dementia is diagnosed when there is dementia associated with stroke, and AD is present on neuropathological examination.

6.6 Consensus Statement for Diagnosis of Subcortical Small Vessel Disease (SSVD)

This statement is designed to establish diagnostic criteria for SSVD and emphasizes elucidation of the underlying stroke mechanisms (Rosenberg et al., 2016). The basis for the definition is the presence of subcortical gray and white matter lacunar infarcts and white matter hyperintensities based on brain MRI study. The neuropathological or mechanistic underpinnings of SSVD are lipohyalinosis and fibrinoid change for lacunar infarcts, and blood–brain barrier leakage of substances toxic to myelin is thought to be responsible for white matter lesions (Rosenberg et al., 2016). A number of SSVD subtypes exist, including Binswanger's disease (gait and executive dysfunction, active deep tendon reflexes, apathy, and depression) and cerebral auto-

somal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) attributed to a notch-3 gene mutation with resultant vascular-based white matter changes and lacunar infarcts. In addition, mixed dementias are discussed. The work of this group serves as model to establish clinical trials for SSVD based on future biomarker-enabled trials.

6.7 American Heart Association/American Stroke Association (AHA/ASA) Diagnostic Criteria for VCI

VCI is a continuum of cognitive impairment associated with stroke spanning the at-risk brain stage to slight to moderate to severe cognitive impairment (Gorelick et al., 2011). VaD is considered to be the most severe form of cognitive impairment. Thus, VCI is a term that takes into consideration the continuum of severity of cognitive impairment and the mechanism and prevention of cognitive impairment.

The core of the definition of VCI is linked to the occurrence of cognitive impairment and vascular disease, establishment of cognitive impairment based on neuropsychological testing, and a history of stroke or evidence of vascular brain injury associated with some form of stroke (Gorelick et al., 2011). In contrast to the definition of VaD (Roman et al., 1993), VCI criteria do not require a diagnosis of memory loss and emphasize that the presence of white matter lesions in the elderly may be of less diagnostic value than the occurrence of those in younger patients. A diagnosis of dementia is defined as a decline in cognitive function from a higher level and requires involvement of two or more cognitive domains sufficient to impair one's ability to carry out ADLs (Gorelick et al., 2011). Furthermore, there are probabilistic categories—possible and probable VaD, and additional categories (e.g., vascular mild cognitive impairment [VaMCI] and unstable MCI). The reader is referred to the AHA/ASA publication for additional details (Gorelick et al., 2011).

6.8 International Society of Vascular Behavioral and Cognitive Disorders Criteria (ISVBCDC)

The work group that developed these criteria was comprised of members of the VasCog Society and was charged with reexamining VaD criteria in light of new criteria for AD (e.g., taking into account biomarkers and pre-dementia stages) and the opportunity to harmonize with the *Diagnostic and Statistical Manual of Mental Disorders 5* (*DSM-5*) corresponding definitions (Sachdev et al., 2014). The term VCD was selected to categorize stroke-associated cognitive impairment based on a heterogeneity of vascular disorders underlying cognitive dysfunction and varying neuropathologies and clinical manifestations associated with stroke and cognitive dysfunction. Similar to VCI and other diagnostic criteria, the presence of cognitive

impairment coupled with the occurrence of underlying brain vascular disease/injury serves as the anchor for the definition of VCD (Sachdev et al., 2014). Furthermore, mild cognitive dysfunction was distinguished from dementia based on the presence or absence of one's ability to maintain independent function. Other associated topics covered in detail in this paper were brain neuroimaging, vascular risks, a probabilistic classification, psychiatric and behavioral symptoms, subtypes of VCD, biomarkers and other information.

6.9 *DSM-5* Criteria

This set of diagnostic criteria links cognitive dysfunction of different severities temporally to stroke or the occurrence of decline in attention and fronto-executive function in the presence of a history of stroke according to neurologic history, physical examination, or brain imaging (American Psychiatric Association 2013). Clinical phenotypic and genetic manifestations are discussed for genetic disorders predisposing to cognitive impairment (e.g., CADASIL).

6.10 Vascular Impairment of Cognitive Classification Consensus Study Criteria (VICCCS)

These criteria were developed by a group of international experts to establish a consensus about cognitive dysfunction associated with vascular brain injury and standard nomenclature (Skrobot et al., 2017). Key vascular cognitive subtypes are post-stroke dementia, mixed dementia, subcortical ischemic vascular dementia, and MID. The criteria indicate that post-stroke dementia is linked to an acute stroke presentation followed by cognitive decline within 6 months after stroke. Mixed dementia includes persons with AD plus VCI (or VCI-AD), and VCI-dementia with Lewy bodies (note: the order of the disorder signifies the relative contribution according to the underlying mechanism of cognitive impairment). Subcortical ischemic vascular dementia is characterized by underlying small vessel ischemic processes, whereas MID is mechanistically characterized by multiple large cortical infarcts (Skrobot et al., 2017).

The many above-mentioned diagnostic criteria serve as important springboards to a better understanding of the broad categories of cerebrovascular disease and its subtypes in relation to cognitive impairment. The current direction that the overall field is taking based on advances in the classification of cognitive disorders associated with stroke is one to affect a better understanding of the mechanisms underlying cognitive impairment associated with stroke, especially upstream mechanisms and an understanding of how the brain reacts and responds to vascular sources of injury to maintain its resilience or succumb to the insult(s). Such responses and

reactions may be better understood as we unravel the role of neurodevelopmental factors as they relate to vascular injury and repair.

6.11 Epidemiology and Risk Factors

6.11.1 Descriptive Epidemiology

Stroke and AD frequently occur together. It is estimated that one in three persons will be afflicted by stroke, dementia, or both (Hachinski, 2011). Furthermore, silent (or covert) infarction is thought to outnumber clinically manifest stroke by a ratio of approximately 11 to 1, and the former serves as a harbinger of not only future stroke but also cognitive dysfunction (Hachinski, 2011). Traditionally, AD is considered the most common form of dementia followed by VaD (Gorelick & Nyenhuis, 2013). More recently with greater awareness of Lewy body dementia, this disorder is considered by some as challenging for the position as the second leading cause of dementia. Over time, it has been thought that AD is the leading cause of dementia in Europe and in predominantly white elderly populations, whereas because stroke is common in many Asian countries, VCI may be more common in Asia (Gorelick & Nyenhuis, 2013). However, when one takes into account autopsy study data, most people with dementia and about 50% with clinically probable AD have mixed pathology that is most commonly AD plus infarcts (Gorelick et al., 2011). Finally, when one examines survival in persons with AD or VaD, AD patients have been reported to survive longer than those with VaD. Survival may be influenced, however, by age, race, and ethnicity which need to be taken into consideration when survival curves are calculated (Freels, Nyenhuis, & Gorelick, 2002). Also, one must consider the possibility of mixed pathologies (e.g., AD plus VCI) in patients with dementia because this may help to explain the lack of difference in survival in some AD and VaD studies reported previously (Freels et al., 2002).

6.11.2 Risks for VCI

Risks for VCI have long been thought to be the same risks as those for stroke (Gorelick, 2005). In an AHA/ASA statement on vascular contributions to cognitive impairment, the following risk categories and possible risks were linked to VCI (Gorelick et al., 2011):

1. *Demographic factors*: older age
2. *Lifestyle or discretionary factors*: low education, dietary status (e.g., consumption of antioxidants, fish oil, B-complex vitamins, Mediterranean diet, moderate alcohol consumption), exercise, obesity, smoking, and lack of social support or social networking

3. *Psychological factors*: depression*
4. *Physiologic factors*: high blood pressure, elevated blood sugar, insulin resistance, metabolic syndrome, diabetes mellitus, and hyperlipidemia*
5. *Cardiovascular diseases*: coronary artery disease, stroke, chronic kidney disease, atrial fibrillation, peripheral arterial disease, and low cardiac output

*Uncertain linkage to VCI

In this section, I review recent evidence-based studies that are being used to guide clinical practice in relation to possibly preventing cognitive impairment based on cardiovascular risk modification. It should be kept in mind that a 2010 National Institutes of Health State-of-the-Science Conference statement indicated that firm conclusions could not be drawn about the relation of modifiable risk and cognitive decline or AD (Daviglus et al., 2010). There was acknowledgment by the writing team, however, that the recommendations were based on insufficient data and low-quality evidence leading one to conclude that there is a need for additional sufficient and high-level study. The information reviewed below has moved clinicians in the direction of prevention and treatment of cardiovascular risks for possible reduction of the occurrence of cognitive impairment or cognitive decline.

Institute of Medicine (IOM) Report (Blazer, Yaffe, & Liverman, 2015). The IOM report, a formal evidence-based review, discusses public health aspects of cognitive aging to better understand the brain's journey in relation to cognition and aging. A significant section of the report is an assessment of risks and protective factors, and interventions for maintenance of cognition with hypertension as the centerpiece. The authors recognize that hypertension is common in persons 60 years of age or older and represents a possible, preventable risk factor for cognitive decline and dementia. The strength of the recommendation to manage hypertension to prevent loss of cognitive vitality is primarily based on the results of observational studies as clinical trials have not shown a consistent benefit of blood pressure lowering for the preservation of cognitive function.

Pertinent limitations of the available blood pressure study databases included the need for additional study information regarding class of antihypertensive medication, timing and duration of treatment, and type of underlying cognitive impairment with the contention that AD may not respond to antihypertensive therapy. Also, the authors discussed the importance of blood pressure control for the prevention of heart disease and stroke as an umbrella rationale for a clinical and public health strategy for blood pressure lowering given uncertainties about the effect of blood pressure lowering on cognitive function. The authors concluded, however, that it would be useful to reduce and manage elevated blood pressure in an attempt to prevent loss of cognitive vitality.

As review of the entire IOM report in relation to cardiovascular risk modification and preservation of cognitive vitality is beyond the scope of this chapter, key IOM messages about cardiovascular risks and related factors and maintenance of cognition are listed in Tables 6.1 and 6.2. The IOM recommendations place major cardiovascular risks as a possible central focus for prevention of cognitive loss or decline.

Table 6.1 Steps to take to preserve cognitive health based on the Institute of Medicine Report (Blazer et al., 2015)

Maintain physical activity
Reduce and manage cardiovascular risks (e.g., hypertension, diabetes mellitus, smoking)
Discuss one's medical conditions and medications (e.g., anticholinergic medications) that might influence cognitive health

Table 6.2 Steps to take to preserve cognitive health where there is some scientific evidence to support the action based on the Institute of Medicine Report (Blazer et al., 2015)

Be socially and intellectual active and seek opportunities to learn
Obtain adequate sleep and receive treatment for sleep disorders as needed
Avoid delirium in hospitalized patients

Report of the National Academies of Sciences, Engineering, Medicine (NASEM) (Leshner, Landis, Stroud, & Downey, 2017). The NASEM report represents an evidence-based update of the IOM report from 2015 (Blazer et al., 2015) and addresses the state of knowledge about what interventions may be effective to prevent or slow cognitive loss. Recommendations in this report are based largely on randomized controlled trials. Like the IOM report, the NASEM report emphasizes a major possible role for blood pressure lowering in relation to reduction of major cardiovascular events. The NASEM findings emphasize encouraging but inconclusive evidence for the efficacy of blood pressure lowering on maintenance of cognitive vitality. In addition, the report indicates that there is insufficient evidence to favor one class of blood pressure lowering agent over another class for prevention of cognitive loss. Key NASEM recommendations primarily focused on cardiovascular risks are listed in Table 6.3.

Finally, a series of recent systematic reviews funded by the Agency for Healthcare Research and Quality conclude that there is insufficient evidence or lack of evidence to support pharmacologic treatments for cognitive protection in persons with normal cognition or mild cognitive impairment, over-the-counter supplements, short-term, single-component physical activity interventions in older adults, and cognitive training (Brasure et al., 2017; Butler, McCreedy et al., 2017; Butler, Nelson et al., 2017; Fink et al., 2017). The report leaves open the possibility that multi-domain interventions could be beneficial for preservation of cognitive vitality.

6.11.3 Clinical Manifestations

Because VCI represents a continuum of cognitive impairment from slight to moderate to severe categories, its clinical manifestations may be quite variable (Gorelick & Nyenhuis, 2013). In addition, the clinical picture may vary according to volume,

Table 6.3 Key Recommendations from the National Academies of Sciences, Engineering and Medicine in Relation to Prevention of Cognitive Decline and Dementia (Leshner et al., 2017)

Interventions supported by encouraging but inconclusive evidence
Cognitive training
Blood pressure management for persons with high blood pressure to prevent, delay, or slow clinical Alzheimer's disease
Increased physical activity to delay or slow age-related cognitive decline
Interventions with insufficient research to support their effectiveness
New anti-dementia treatments
Diabetes treatments
Depression treatments
Dietary interventions
Lipid-lowering treatments including statins
Sleep quality interventions
Social engagement interventions
Vitamin B12 plus folic acid supplementation

location, and number of brain infarcts or hemorrhages. In fact, strategic areas of single infarction may underlie cognitive impairment (Grysiewicz & Gorelick, 2012). For example, a strategic stroke of the dominant thalamus or angular gyrus, the left hemisphere, mesial frontal lobe, or hippocampus may be associated with cognitive impairment. In addition, cerebral microbleeds and cerebral microinfarcts may be associated with cognitive impairment (Grysiewicz & Gorelick, 2012).

In contrast to focal or strategic stroke lesions, a more diffuse pattern of cognitive impairment may exist when there is subcortical cerebral vascular brain injury (Gorelick & Nyenhuis, 2013). The clinical manifestations may include bradyphrenia (slowness of mentation), executive dysfunction, and memory deficits characterized by inconsistent acquisition of information rather than rapid forgetting. Thus, patients with VCI may show focal cognitive deficits associated with a strategic lesion location or a more diffuse pattern of cognitive deficits based on the presence and extent of subcortical vascular brain injury. One should note that executive dysfunction which may manifest as impaired planning, organizing, and synthesizing behaviors is a common feature of subcortical vascular brain injury, but is not specific to VCI (Gorelick & Nyenhuis, 2013). There are a number of neuropathologies that disrupt subfrontal white matter circuits that may result in impairment of executive function. Finally, the memory impairment associated with AD, a rapid forgetting of newly learned information, differs from that typical of VCI. In the latter case, there is inefficient encoding of new information with less information acquired.

Noncognitive manifestations may also be common in VCI. Such characteristics in patients with stroke may include a frontal gait disorder, lower-body parkinsonism, apathy, depression, urinary incontinence, spasticity, hyperreflexia, and frontal release signs (Smith, 2016). Other typical focal stroke manifestations such as hemi-

paresis, sensory loss, limb ataxia, visual loss, and other focal features may be observed.

6.11.4 Diagnostic Studies

The three key areas to explore in relation to diagnostic studies are discussed below. Because neuroimaging is an important aspect of the diagnostic paradigm in persons suspected of having VCI, the reader is referred to a publication about a harmonization approach to carrying out, interpreting, and reporting neuroimaging in patients with subcortical vascular brain injury (Wardlaw et al., 2013).

Assessment of Cognition (Smith, 2016). After performing a neurological history and physical examination, for those suspected of having VCI, screening cognitive testing is indicated. Because it is important to assess executive function in these patients, a screening test such as the Montreal Cognitive Assessment (MoCA) is useful to administer and is more sensitive than the Mini-Mental State Examination (MMSE) in VCI patients. If doubt exists after neurological history, neurologic physical examination, and a cognitive screening test, formal neuropsychological testing is indicated.

Assessment of Cerebrovascular Disease (Smith, 2016). Neurological history and examination help to establish the presence of a clinically manifest stroke. The cognitive signs of clinically manifest stroke have been discussed in the section above (clinical manifestations) and in the section on defining VCI and VCD. In some cases, the history is vague, and one may not be certain if stroke has occurred. Since silent stroke is common and clinically manifest stroke should be verified by diagnostic testing, neuroimaging is recommended (Gorelick et al., 2011). Stroke extent, type, location, volume, and number can be elucidated by cranial computed tomography (CT) or magnetic resonance imaging (MRI) of the brain. MRI sequences are more sensitive than CT as the former diagnostic test may reveal smaller infarcts, cerebral microbleeds, rarefaction of the white matter (leukoaraiosis), and macroinfarcts in greater detail, and thus is the test of choice, when available.

Assessing the Relationship between Stroke and Cognitive Impairment (Smith, 2016). A major challenge is to determine if the presence of stroke is sufficient to cause cognitive dysfunction. Clinical judgment is required to determine this because there is no simple prediction model or scale to assure such. Here are pointers to consider when pondering a diagnosis of VCI, though one must keep in mind that mixed neuropathologies are common in elderly with cognitive impairment:

1. A normal pre-stroke cognitive assessment or prediction of cognitive assessment (e.g., Informant Questionnaire on Cognitive Decline in the Elderly) plus post-stroke cognitive impairment sufficient to explain the cognitive abnormality support a diagnosis of VCI.
2. There is an acute strategic infarction associated with cognitive impairment.
3. A younger patient (less likely to have AD) with multiple strokes and cognitive impairment.

A review of neuropathological diagnostic criteria for VCI is beyond the scope of this chapter. The reader is referred to other sources for a review of this topic (Barnes et al., 2015; Kalra, 2016).

6.12 Prospects for Prevention and Treatment

6.12.1 Prevention

Cardiovascular risks have been linked to brain health based largely on observational epidemiological studies (Gorelick et al., 2017). Recently, an AHA/ASA work group published a Presidential Advisory defining optimal brain health in adults according to cardiovascular factors (i.e., AHA's Life's Simple 7) that may be modified, easily measured, and monitored. Table 6.4 lists the seven factors from AHA's Life's Simple 7 used to define optimal brain health in the advisory. Whereas persons who meet this profile have a substantially reduced risk of cognitive impairment, many persons have cardiovascular risks and have been the focus of recent multi-domain or other clinical trials designed to determine if lifestyle and risk factor interventions will help to maintain cognitive vitality. Before reviewing the recent multi-domain and related trials, one should be aware of select key findings from recent AHA/ASA guidance statements:

1. Whereas elevated blood pressure disrupts brain blood vessel structure and function and leads to ischemic brain damage especially to subcortical white matter, cognitive impairment, and possibly AD; the evidence is more convincing that midlife hypertension is associated with cognitive impairment, but it is less clear that this is the case for late-life hypertension (Iadecola et al., 2016).
2. For persons at risk of VCI, recommendations for management of lifestyle and physiological factors as a possible means to prevent cognitive impairment or decline are listed in Table 6.5 (Gorelick et al., 2011).

6.12.2 Multi-domain and Related Interventions

A number of recent multi-domain and related interventional studies have been designed and carried out to assess the possibility of maintenance of cognitive vitality in different patient populations. For more detailed critical reviews of these studies, the reader is referred elsewhere (Gorelick, 2017; Gorelick et al., 2017). Overall, many of the studies failed to show a beneficial result and have been criticized for limitations based on study design (Gorelick, 2017). Criticism of the studies has ranged from enrollment of persons who were not at high enough cardiovascular risk despite the application of lifestyle and cardiovascular risk factor management interventions (e.g., Prevention of Dementia by Intensive Vascular care [preDIVA]

Table 6.4 Metrics for defining optimal brain health in adults (Gorelick et al., 2017)

Health-related behaviors
Nonsmoking status
Physical activity at guidance recommendations
Body mass index <25 kg/m^2
Healthy diet based on guidance recommendations
Health-related factors
Untreated blood pressure <120/<80 mmHg
Untreated total cholesterol <200 mg/dL
Fasting blood glucose <100 mg/dL

Table 6.5 American Heart Association/American Stroke Association recommendations for management of lifestyle and physiological risks for persons at risk of VCI (Gorelick et al., 2011)

Strategies that are recommended
Treatment of hypertension
Strategies that may be reasonable
Smoking cessation
Moderation of alcohol consumption
Weight control
Physical activity
Treatment of hyperglycemia
Treatment of hypercholesterolemia
Strategies of uncertain value
Treatment of inflammation
Strategies that are not beneficial
Antioxidants and B-complex vitamins

(Moll van Charante et al., 2016) to inadequate study sample size and duration of follow-up (e.g., Austrian Poly-intervention Study to Prevent Cognitive Decline after Ischemic Stroke [ASPIS]) (Matz et al., 2015) to single-factor interventions rather than multi-domain interventions (e.g., Prevention of Alzheimer's Disease by Vitamin E and Selenium Trial [PREADVISE]) (Kryscio et al., 2017).

One study, however, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) was a multi-domain intervention to prevent cognitive impairment that enrolled subjects 60–77 years of age and used a screening tool to select study subjects at high enough cardiovascular risk (Ngandu et al., 2015). The interventions were diet, exercise, cognitive training, and cardiovascular risk monitoring. The control group received general health advice. Over 2500 study subjects were randomized, and the multi-domain intervention proved to be superior to the control experience. Specifically, there were benefits for the primary outcome (overall cognitive function) and the cognitive subcategories of executive function and processing speed. However, there was no significant benefit of the multi-domain

intervention for memory function with the exception of more complex memory tasks.

Thus far, the findings of FINGER, a well-designed trial, have been encouraging. Additional ongoing follow-up will determine if the effect is sustained and clinically meaningful. Longer-term follow-up will include determination of the occurrence of dementia, AD, and other pertinent outcomes.

6.12.3 Treatment

The World Stroke Day Proclamation 2015 called for an integration of post-stroke dementia care into routine stroke management and highlighted the need to increase public knowledge to heighten awareness that stroke and some dementias may be prevented (Hachinski, 2015). Such an approach is in step with the World Health Organization Global Action Against Dementia policy to reduce the burden of dementia by 2025 (Shah et al., 2016).

Like other patients with cognitive impairment, patient and caregiver support is focused on safety at home, driving safety, advanced financial and medical planning, management of neurobehavioral manifestations, and consideration of palliative care options (Smith, 2016). Thus, an interdisciplinary team (e.g., neurological provider, nurse, social worker, geriatric psychiatrist, neuropsychologist, and palliative care expert), when available, can be of substantial advantage in the management of patients with VCI.

The Lancet Commission on Dementia Prevention, Intervention, and Care has suggested recently the following key messages in relation to dementia management: be ambitious about prevention, treat cognitive and neurobehavioral symptoms, individualize dementia care, care for family caregivers, plan for the future and end of life, protect the patient from risks such as self-neglect and other vulnerabilities, and consider application of technology (Livingston et al., 2017). In relation to treatment of hypertension, The Lancet Commission recommends treatment of raised blood pressure in middle aged (45–65 years) and older persons (>65 years) without dementia to reduce dementia incidence.

A host of drugs including vasodilators, neurotransmitter modulators, neurotrophic drugs, antiplatelet agents, antioxidants, and cholinesterase inhibitors and nonpharmacological interventions have been tested and are reviewed in more detail elsewhere (Farooq et al., 2017; Smith et al., 2017). There are no proven treatments to reduce the risk of cognitive or functional decline in persons with VCI. Cholinesterase inhibitors provide a modest but inconsistent benefit for VaD patients which seems to be more pronounced in those with mixed AD-VaD.

I believe that it is reasonable to follow the AHA/ASA 2011 recommendations for the treatment of VCI (Gorelick et al., 2011):

1. See Table 6.5 for recommendations to treat lifestyle and cardiovascular risks. An ideal blood pressure target in relation to maintenance of cognitive vitality has not

been established, and it is reasonable to follow national guidance for blood pressure goals noting that persons with hypertension or arterial stiffness may be at risk of loss of autoregulation and the complications thereof (e.g., brain ischemia), and thus certain patients may not tolerate lowering of blood pressure (Gorelick, 2014).

2. Based on the evidence of modest but inconsistent results, the following pharmacological strategies may be useful for cognitive enhancement in VaD (Gorelick et al., 2011):

   (a) Donepezil.
   (b) Galantamine when there is mixed AD-VaD.

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Chapter 7
The Neurovascular Neuropsychology of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) and Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-Like Episodes (MELAS)

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7.1 CADASIL

7.1.1 Definition, Genetics, and Pathological Aspects

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is an inherited small artery disease of the brain caused by mutations of the *NOTCH3* gene on chromosome 19 (Joutel et al., 1996). 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 (Charlton, Morris, Nitkunan, & Markus, 2006). CADASIL is not limited to Caucasians families, although the disorder was initially recognized in European pedigrees. It has been now diagnosed in Asiatic, African, American, as well as Australian and European families. In France, Germany, and the United Kingdom, several hundreds of CADASIL families have been identified (Chabriat, Bousser, & Pappata, 1995; Dichgans et al., 1998; Opherk, Peters, Herzog, Luedtke, & Dichgans, 2004; Singhal, Bevan, Barrick, Rich, & Markus, 2004). Though the exact frequency of CADASIL remains unknown, it is now considered as one of the most frequent of

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_7

the hereditary neurological disorders. Its prevalence has been estimated between 2 and 5/100,000, but may vary between populations (Bianchi et al., 2015; Moreton, Razvi, Davidson, & Muir, 2014; Narayan, Gorman, Kalaria, Ford, & Chinnery, 2012; Razvi, Davidson, Bone, & Muir, 2005).

CADASIL is caused by stereotyped mutations of the *NOTCH3* gene (Joutel et al., 1996). Unlike other members of the *Notch* gene family whose expression is ubiquitous, the *NOTCH3* gene is expressed only in vascular smooth muscle cells of arterial vessels (Joutel et al., 2000; Villa et al., 2001). Domenga et al. (2004) showed that *NOTCH3* is required specifically to generate functional arteries in mice by regulating arterial differentiation and maturation of vascular smooth muscle cells (Domenga et al., 2004). The stereotyped missense mutations (Joutel et al., 1996) or deletions (Joutel, Chabriat, et al., 2000; Joutel, Francois, et al., 2000) responsible for CADASIL are within epidermal growth factor-like (EGF-like) repeats and only located in the extracellular domain of the NOTCH3 protein (Dotti et al., 2005; Joutel, Corpechot, et al., 1997; Peters, Opherk, Bergmann, et al., 2005). 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 (Blaumueller, Qi, Zagouras, & Artavanis-Tsakonas, 1997). After cleavage, 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 (Joutel, Andreux, et al., 2000). This accumulation is included in the granular osmiophilic material seen on electron microscopy. It is observed in all vascular smooth muscle cells and in pericytes within all organs (i.e., brain, heart, muscles, lungs, and skin). An abnormal clearance of the *NOTCH3* ectodomain from the smooth muscle cell surface is presumed to cause this accumulation (Joutel, Andreux, et al., 2000; Joutel, Francois, et al., 2000; Joutel & Tournier-Lasserve, 2002). Accumulation of *NOTCH3* leads to aggregates of other proteins from the vascular matrix, such as TIMP3 (tissue inhibitor of metalloproteinases-3) or vitronectin (Monet-Lepretre et al., 2013). The increase of TIMP3 was recently found related to a reduction of cerebral blood flow in CADASIL mice secondary to abnormal TIMP3-ADAM17 signaling, which, in turn, increases the number of voltage-dependent potassium channels in the membrane of vascular smooth muscle cells (Dabertrand et al, 2015; Capone et al., 2016).

Macroscopic examination of the brain in CADASIL shows a diffuse myelin pallor and rarefaction of hemispheric white matter with sparing of the U fibers (Baudrimont, Dubas, Joutel, Tournier-Lasserve, & Bousser, 1993). Lesions predominate in the periventricular areas and centrum semiovale. They are associated with lacunar infarcts located in the white matter and basal ganglia (lentiform nucleus, thalamus, caudate) (Ruchoux et al., 2002; Ruchoux & Maurage, 1997), and the most severe hemispheric lesions are profound (Baudrimont et al., 1993; Davous & Fallet-Bianco, 1991; Ruchoux et al., 1995). In the brainstem, the lesions are markedly present in the pons and are similar to the pontine ischemic rarefaction of myelin described by Pullicino, Ostrow, Miller, Snyder, & Munschauer (1995).

Small deep infarcts and dilated Virchow–Robin spaces are also associated with the white matter lesions. The vessels close to these lesions do not appear occluded (Santa et al., 2003). Microscopic investigations show that the wall of cerebral and leptomeningeal arterioles is thickened with a significant reduction of the lumen (Baudrimont et al., 1993); thus, penetrating arteries in the cortex and white matter appear stenosed (Miao et al., 2004; Okeda, Arima, & Kawai, 2002). At late stage, some inconstant features appear similar to those reported in patients with hypertensive encephalopathy, such as duplication and splitting of internal elastic lamina, adventitial hyalinosis and fibrosis, and media hypertrophy (Zhang et al., 1994). However, a distinctive feature is the presence of agranular material within the media extending into the adventitia (Baudrimont et al., 1993; Bergmann et al., 1996; Desmond et al., 1998, 1999; Mikol et al., 2001; Ruchoux et al., 1995). On electron microscopy, the smooth muscle cells appear swollen and often degenerated, some of them with multiple nuclei. There is an electron-dense, granular osmiophilic material (GOM) within the media (Gutierrez-Molina et al., 1994). This material consists of granules of about 10–15 nm of diameter. It is localized close to the cell membrane of the smooth muscle cells where it appears very dense. The smooth muscle cells are separated by large amounts of this unidentified material. Rafalowska et al. (2003) made the observation that this material can also be detected in capillaries deprived of smooth muscle cells, close to pericytes, and that it is sometimes associated with perivascular inflammatory infiltrates or with eosinophilic fibrinoid necrosis (Rafalowska et al., 2003).

The diagnosis of CADASIL is made by genetic testing or skin biopsy. Genetic tests are initially focused on exons where the mutations are most frequent (Joutel, Vahedi, et al., 1997; Joutel, Corpechot, et al., 1997). Peters et al. found 90% of mutations within exons 2–6 (Peters, Opherk, Bergmann, et al., 2005). Ruchoux et al. (1995, 1997) *made the observation that the vascular abnormalities observed in the brain were also detectable in other organs or territories* (Ruchoux et al., 1995; Ruchoux & Maurage, 1997). *These vascular lesions can be detected by nerve or muscle biopsy* (Goebel, Meyermann, Rosin, & Schlote, 1997; Schroder, Sellhaus, & Jorg, 1995). *The presence of the granular osmiophilic material in the skin vessels allows to confirm the intra vitam diagnosis of CADASIL using skin punch biopsies* (Ebke et al., 1997; Lucas, Pasquier, Leys, Ruchoux, & Pruvo, 1995; Ruchoux et al., 1995; Ruchoux, Chabriat, Bousser, Baudrimont, & Tournier-Lasserve, 1994)*, although the sensitivity and specificity of this method are not yet completely established. In some cases, the vessel changes may be focal requiring a thorough evaluation of a biopsy specimen* (Schultz, Santoianni, & Hewan-Lowe, 1999). *The use of anti-NOCTH3 antibodies to reveal the accumulation of NOCTH3 products within the vessel wall in CADASIL patients is an alternative diagnostic method* (Joutel et al., 2001)*, and this method appears highly sensitive (96%) and specific (100%).*

7.1.2 Primary Clinical Features and Cognitive Symptoms

The primary clinical manifestations of CADASIL are: (1) attacks of migraine with aura, mainly occurring between age 20 and 40 years (often the earliest symptom); (2) ischemic episodes, such as transient ischemic attacks or completed subcortical ischemic strokes, occurring after age 40 years (reported in 60–80% of patients); (3) mood disturbances; and (4) cognitive impairment (Chabriat et al., 1997).

Cognitive impairment represents the second most common clinical manifestation in CADASIL and may be observed in the absence of any other clinical symptoms. The degree of impairment may vary with the course of the disease, the age of the patient, and the co-occurrence of stroke (Amberla et al., 2004; Buffon et al., 2006). In most cases, the impairment is mild in severity for several decades, but by the age of 65 years, two-thirds of patients show signs of dementia (Dichgans et al., 1998) and more than 80% of deceased patients were reported to be demented before death (Chabriat et al., 1995). In a cross-sectional study including 115 CADASIL patients, mean age 53.7 ± 11.7 years, 20% fulfilled the *DSM-IV* criteria for dementia (Benisty et al., 2007). In this sample, dementia often co-occurred with pyramidal signs, gait disorders, and urinary disturbances, whereas focal deficits such as sensory or visual field defects were more scarce.

The onset of cognitive deficit in CADASIL is insidious, and its exact time of onset is difficult to ascertain. Cross-sectional studies have shown that early in the disease cognitive functions, most frequently attention and executive functions may be impaired (Amberla et al., 2004; Buffon et al., 2006; Peters, Opherk, Danek, et al., 2005; Taillia et al., 1998). In a sample of 42 patients, attention and executive functions were affected in nearly 90% of patients between the ages of 35 and 50 years. In contrast, other functions such as verbal episodic memory and visuospatial abilities may remain spared till late stages of the disease (Buffon et al., 2006).

Some tests are particularly sensitive to the detection of early cognitive changes. They include the Digit Span backwards and forwards trials, the Trail Making Test, Part B, the Stroop Color–Word Test, and the Wisconsin Card Sorting Test (Taillia et al., 1998). The errors of CADASIL patients may predominantly affect the time component in timed tasks (e.g., Stroop, Trail Making Test, Symbol Digit, Digit Cancellation), though errors in monitoring are also observed to a lesser extent (Peters, Opherk, Danek, et al., 2005)**.** Thus, as shown by Jouvent et al., a simple reaction time used in daily clinical practice may serve as a proxy of early cognitive impairment (Jouvent et al., 2014). Patients may also show poor strategy and planning when completing tasks, such as the Wisconsin Card Sorting Test (WCST) and the Rey–Osterrieth Complex Figure Test (RCFT). When dementia occurs, the cognitive decline becomes more homogenous with significant alterations in most cognitive domains. Still, executive functions and attention remain predominantly affected, while the memory encoding appears preserved even at late stages of the disease. A similar pattern of cognitive impairment, with prominent early executive dysfunction has been observed in patients with sporadic small vessel disease (Charlton et al., 2006).

Verbal memory deficit may be associated with executive dysfunction. Its profile can be characterized by procedures such as the Free and Cued Selective Reminding Test (FCSRT). This test assesses different phases of episodic verbal memory processes (encoding, storage, and retrieval) and is likely to show the preservation of the storage process even though the retrieval is impaired. It is composed of: (1) an encoding phase where 16 words belonging to 16 different semantic categories must be retrieved; (2) four phases of free recall and cued recall, the last being delayed; and (3) a recognition test component. Using this procedure, the pattern and frequency of episodic verbal memory impairment were assessed in a cohort of 140 CADASIL patients (Epelbaum et al., 2011), and about 30% of the patients presented with memory deficit on this test. The pattern of memory deficit was heterogeneous. The most frequent, however, was a reduction of spontaneous recall with preserved reactivity to cueing, a typical pattern of subcortical memory impairment. This error pattern was observed in almost half of the patients with memory deficit. Less than 20% patients with verbal memory deficit presented with adequate encoding but poor free or delayed recall and improving less than 71% with cueing; a pattern suggestive of anterograde amnestic difficulties and mesial temporal lobe dysfunction. These patients were more cognitively impaired and disabled, suggesting that this pattern, considered as an early feature of Alzheimer's disease, develops at advanced stages of the disease. The frequency of memory deficit depends on the population and the tests used for assessment. Thus, in a smaller sample of patients, memory deficit was observed in about two-thirds of the patients using the FCSRT and also in the recall of the RCFT figure and the Wechsler Adult Intelligence Scale-Revised (Buffon et al., 2006).

Global cognitive scales may also be used in the assessment of cognition in CADASIL patients. The Mini-Mental Status Examination (MMSE) and the Mattis Dementia Rating Scale (M-DRS) have been used in a predictive model of the clinical course of CADASIL (Jouvent et al., 2016). Still, the MMSE, which is poorly sensitive to executive dysfunction, is a poor screening test for cognitive impairment in CADASIL. The Brief Memory and Executive Test (BMET) and the Montreal Cognitive Assessment (MoCA) may be more useful and sensitive screening measures for early cognitive impairment (Brookes, Hollocks, Tan, Morris, & Markus, 2016).

The temporal progression of cognitive symptoms varies among CADASIL patients from rapid and marked deterioration to stable or even slightly improving performances (Peters, Herzog, Opherk, & Dichgans, 2004). The development of cognitive impairment is associated with the occurrence of clinically apparent stroke. Nevertheless, a cognitive deficit and even dementia state may also occur in 40% of patients without any clinical history of obvious stroke (Benisty et al., 2007). Two patterns of deterioration can be distinguished, although they often coexist in a given patient. The course may be stepwise and the worsening mostly associated with repeated acute ischemic events related to an accumulation of lesions within strategic regions critically involved in cognition, such as the thalamus. The cognitive performances can also deteriorate progressively with dementia occurring parallel to the

accumulation of new cognitive deficits. This progressive pattern is detected in about 10% of CADASIL patients (Chabriat, Danchot, Hugues, & Joire, 1997).

As with other neurodegenerative diseases, such as Alzheimer's disease, cognitive reserve, assessed by years of formal education, appears to have a significant clinical impact on cognitive performances in patients with mild and moderate degrees of CADASIL brain pathology, but not in patients with severe MRI changes. This interaction with the cognitive reserve was found for processing speed, the cognitive domain most impaired in CADASIL patients (Zieren et al., 2013).

The behavioral symptoms of CADASIL are associated with cognitive impairment. Apathy and irritability are frequent and may occur independently of a depressive episode. In a group of 132 patients, apathy, diagnosed by the Neuropsychiatric Inventory, was observed in 41% of CADASIL patients. Apathetic patients had more global physical disability, severe cognitive impairment, and additional neuropsychiatric symptoms, such as depression (Reyes et al., 2009). Other emotional disturbances, such as recognition of facial emotion, have been explored in a group of 23 CADASIL patients by Valenti et al. (2013), particularly for fear expression in comparison to controls. This emotion recognition effect was not mediated by patients' depression or cognitive impairment levels and could represent an early manifestation of the disease (Valenti et al., 2013). In two of their CADASIL patients, this behavioral phenotype was found to be similar to the behavioral variant of frontotemporal dementia with marked personality changes (Alexander, Brown, Graham, & Nestor, 2014).

The occurrence of psychiatric symptoms has an estimated incidence of 20%–41% of cases (Valenti, Poggesi, Pescini, Inzitari, & Pantoni, 2008), and psychiatric symptoms may be inaugural or dominate the clinical course of the disease, often leading to misdiagnosis. CADASIL patients with a long period of psychiatric symptoms before the onset of dementia have been reported (Filley et al., 1999). Among psychiatric symptoms, mood disturbances are reported with the highest frequency (i.e., 9%–41%) (Valenti et al., 2008). Depression, sometimes severe, is the most common manifestation and may be resistant to antidepressant pharmacotherapy (Chabriat, Vahedi, et al., 1995). In addition to typical symptoms, some CADASIL patients demonstrate somatization and anxiety (Valenti et al., 2011). In few patients, major depression may alternate with manic episodes suggesting bipolar mood disorders (Kumar & Mahr, 1997; Valenti et al., 2011), and panic disorder, delusional episodes, and psychotic symptoms have also been reported in CADASIL patients (Kumar & Mahr, 1997).

7.1.3 Cerebral Tissue Lesions and Cognitive Dysfunction in CADASIL

Magnetic resonance imaging (MRI) is crucial for the diagnosis of CADASIL and is much more sensitive than computed tomography (CT) scans. MRI results are always abnormal in CADASIL patients with neurological symptoms other than migraine

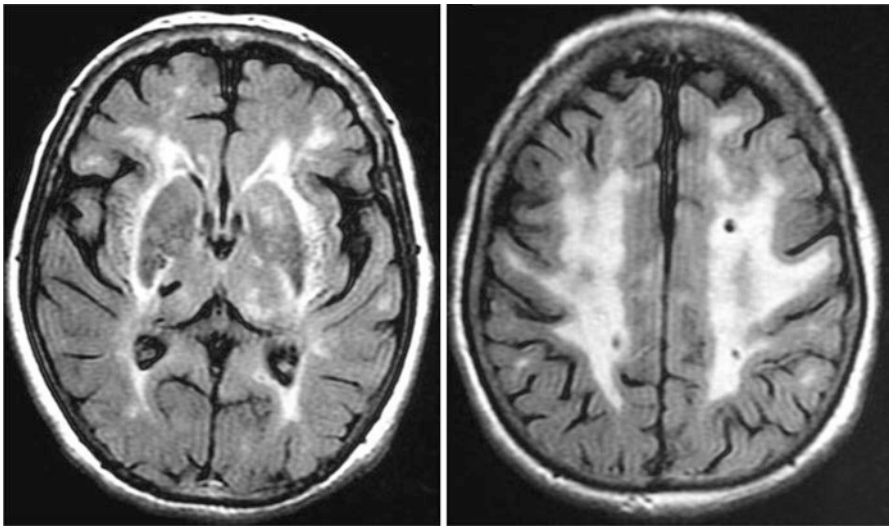

Fig. 7.1 T2-weighted MRI (FLAIR images) showing widespread and symmetrical hyperintensities in the white matter and small deep infarcts (hypointensities) located in the thalamus and within the centrum semiovale. Note the involvement of the external capsules observed in two-thirds of CADASIL patients

headache. MRI signal abnormalities can also be detected during a presymptomatic period of variable duration, and they can be observed as early as 20 years of age. After 35 years of age, all CADASIL patients having the mutated *NOTCH3* gene have an abnormal MRI (Tournier-Lasserve et al., 1993). The frequency of asymptomatic subjects with abnormal MRI decreases progressively with aging and becomes less than 5% after 60 years (Chabriat et al., 1998).

T2-weighted MRI images typically show widespread areas of increased signal in the white matter associated with focal hyperintensities in basal ganglia, thalamus, and brainstem (Chabriat et al., 1998, Chabriat, Mrissa, et al. 1999; Dichgans et al., 1999) (Fig. 7.1). The extent of white matter signal abnormalities is highly variable and increases dramatically with age. In subjects of age under 40 years, T2-weighted imaging-detected lesions are usually punctuate or nodular with a symmetrical distribution, and predominate in periventricular areas and within the centrum semiovale. Later in life, the white matter lesions are diffuse and can involve the whole of white matter, including cortical U-fibers (Coulthard, Blank, Bushby, Kalaria, & Burn, 2000; Dichgans et al., 1999). Lesion severity scores based on semiquantitative rating scales significantly increase with age not only in the white matter but also in the basal ganglia and brainstem. 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 temporal lobes (60%) is noteworthy and particularly useful for differential diagnosis with other small vessel diseases (Fig. 7.2). Interestingly, unlike in elderly people, extensive white matter hyperintensities (WMH) may be associated with increase of brain volume

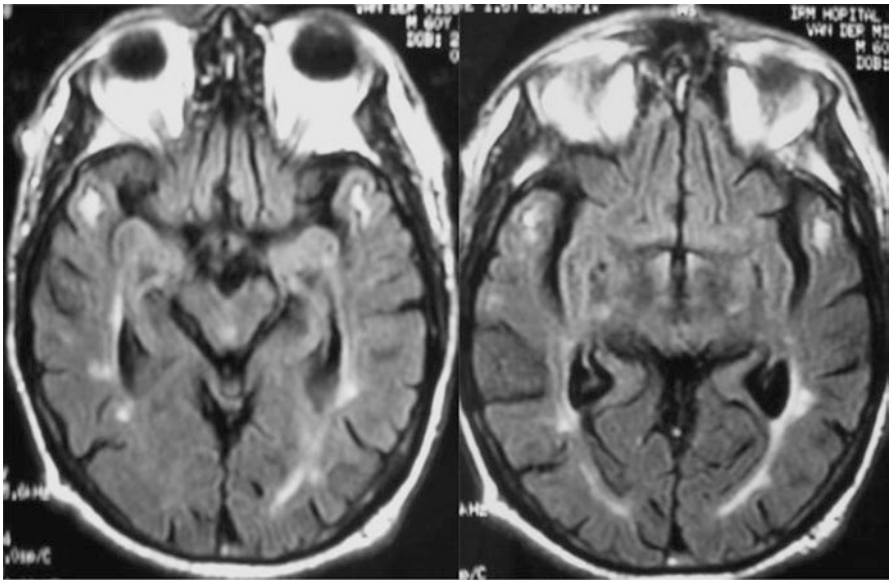

Fig. 7.2 MRI (FLAIR images) showing the characteristic bilateral signal changes in the subcortical white matter of CADASIL patients within the anterior part of temporal lobes; note the linear signal hypointensity between the cortical rim and the hyperintense white matter corresponding to the accumulation of multiple dilated perivascular spaces

suggesting that these lesions may be related not only to loss of white matter components but also to a global increase of water content in the cerebral tissue (Yao et al., 2012). T2-weighted MRI WMH can be detected in the corpus callosum (Iwatsuki et al., 2001), while brainstem lesions predominate in the pons, in areas supplied by perforating arteries, and can involve the mesencephalon (Chabriat, Mrissa, et al., 1999). In contrast, the medulla is usually spared.

On T1-weighted MRI, punctiform or larger focal hypointensities are frequent in the same areas and detected in about two-thirds of individuals with T2 hyperintensities (Chabriat et al., 1998); n.b., identical to hypointense lesions as seen on T2-weighted images (see Fig. 7.2). Lesions are observed not only in both the white matter and basal ganglia but also in the brainstem and correspond mostly to lacunar infarctions. Numerous hypointensities on T1-weighted MRI may also correspond to dilated perivascular spaces (dPVS) which are more frequent and extensive in CADASIL than in healthy subjects (Cumurciuc et al., 2006). Their radiological features and clinical relevance have been evaluated in a large cohort of CADASIL patients. The severity of dPVS was found to increase with age regardless of location. In contrast with dPVS in other locations, the severity of dPVS in temporal lobes or subinsular areas was also found strongly and specifically related to the extent of WMH. A high degree of dPVS in the white matter was associated with lower cognitive performances independently of age and other MRI markers of the disease, including brain parenchymal fraction (Yao et al., 2014).

Cognitive dysfunction in CADASIL is presumably related to these white matter lesions, mainly represented by lacunar infarcts and microstructural tissues changes detected within the white and gray matter. However, the contribution of these lesions to the cognitive status is variable. In a large multicenter study, Viswanathan et al. demonstrated that lacunar infarcts but not white matter lesions were independently correlated with cognitive dysfunction and disability (Viswanathan et al., 2007a, 2007b). An observational study performed in the same population showed that CADASIL patients with isolated white matter lesions may present with executive and attention deficit but not with dementia or severe disability, unlike patients with lacunar infarcts (Benisty et al., 2012). This impact of lacunar lesions, as an important correlate of cognitive impairment, was confirmed in other studies (Holtmannspotter et al., 2005; Liem et al., 2007). Besides the degree of tissue destruction reflected by the load of T1-weighted MRI lesions, the location of tissue lesions—mainly lacunar infarcts—may also play a key role in the occurrence of cognitive deficit and dementia. "Strategic" lacunar infarcts are frequent in the basal ganglia, especially in the thalamus. This is supported by the findings of a positron emission tomography (PET) study performed in two CADASIL-affected brothers, one demented and the other asymptomatic. A severe cortical metabolic depression was found in the only demented subject who had infarcts within the basal ganglia and thalamus (Chabriat, Bousser, & Pappata, 1995). This finding is also in line with MRI data obtained in sporadic small vessel diseases in the general population (Benisty et al., 2009; Chabriat et al., 1995; Vermeer et al., 2003).

Diffusion tensor imaging (DTI) allows in vivo imaging of white matter tracts and provides measures of diffusivity reflecting the severity of microstructural tissue alterations. This technique provides a more powerful marker of the severity of subcortical damage than the classical T2-weighted images (e.g., FLAIR scans). In CADASIL patients, an increase in diffusion is detected in the white matter and gray matter (thalamus, putamen, globus pallidum) appearing unaffected on conventional T1- or T2-weighted MRI (Chabriat, Vahedi, et al., 1995; O'Sullivan, Singhal, Charlton, & Markus, 2004) sequences, and these diffusion increases are better correlated with cognitive function than the load of T2-weighted lesions. Thus, Chabriat, Pappata, et al. (1999) demonstrated that global DTI measures over the whole brain were strongly correlated with MMSE performance in CADASIL patients. Sullivan et al. also reported that diffusion changes at the subcortical level were correlated with executive function in these patients (O'Sullivan et al., 2004).

While DTI shows promise as a neuroimaging biomarker closely associated with cognitive performance in CADASIL patients, brain atrophy remains the strongest neuroimaging correlate of cognitive impairment. In a multivariate analysis accounting for lesion burden and location, volume of lacunar lesions, white matter lesions, number of microbleeds, whole-brain mean apparent diffusion coefficient (mean-ADC), and brain parenchymal fraction performed on 147 patients; brain atrophy explained the largest portion of the variance in cognitive and disability scores (35–38%) and has the strongest independent influence on clinical impairment in CADASIL (Viswanathan et al., 2010). Cortical atrophy may also be linked to intracortical small-sized infarcts observed in neuropathological studies and by

high-resolution MRI (Jouvent, Poupon, et al., 2011; Viswanathan, Gray, Bousser, Baudrimont, & Chabriat, 2006).

Other studies confirmed the relation between cortical dysfunction and cognitive impairment. Jouvent et al. described morphological changes of cortical sulci in 54 CADASIL patients, strongly related to cognitive scores and disability scales (Jouvent et al., 2008). A longitudinal study performed by the same group showed that processing speed but not global cognitive function was related to alterations of sulcal morphology, suggesting that early cognitive changes may be more specifically related to sulcal morphology than to other MRI markers. These cortical alterations evolve parallel to clinical worsening (Jouvent et al., 2012) and are also related to apathy (Jouvent, Reyes, et al., 2011). These alterations in sulcal morphology may appear at early stages of the disease as suggested by diffuse cortical alterations observed on 7-T T2*-weighted imaging in CADASIL patients with no or only mild symptomatology (De Guio et al., 2014).

The mechanisms of cortical lesions are not completely understood. Experimental data support that brain atrophy is related to the volume of lacunes and tissue microstructural changes. Duering et al. examined the effects of incident subcortical infarcts on cortical morphology by MRI follow-up over 54 months in 276 CADASIL patients. In subjects with incident infarcts, they observed a focal cortical thinning in cortical regions with high probability of connectivity with the incident infarct, providing evidence of secondary cortical neurodegeneration (Duering et al., 2012). In a neuropathological study, Viswanathan et al. reported the presence of neuronal apoptosis and microinfarcts in the cerebral cortex of four CADASIL patients. Semiquantitative analysis suggested that the degree of cortical neuronal apoptosis was related to the extent of white matter lesions, the intensity of axonal damage in subcortical areas, and associated with the severity of cognitive impairment (Viswanathan et al., 2006). Therefore, subcortical axonal damage may induce cortical apoptosis through deafferentation and/or retrograde neuronal degeneration in CADASIL. 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 from Sullivan et al. who observed: (1) a strong correlation between mean diffusivity measured in the thalamus (which could reflect either direct pathological damage or secondary degeneration due to disruption of white matter tracts relaying in this structure) and executive dysfunction (O'Sullivan et al., 2004) and (2) executive performances were also correlated with 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 (O'Sullivan, Barrick, Morris, Clark, & Markus, 2005).

MRI markers may also allow to predict clinical course. Data obtained in a prospective study of 236 CADASIL patients showed that the prediction of 3-year changes in global cognitive scales (MMSE and M-DRS), Trail Making Test—Part B, and disability scale for a given patient can be obtained using simple models relying on the initial test performance scores and on the brain parenchymal fraction and volume of lacunar infarcts (Jouvent et al., 2016).

Noteworthily, if cognitive dysfunction is associated with cortical lesions and cholinergic denervation, their distribution with the relative sparing of hippocampal areas appears distinct from the pattern of lesions observed in Alzheimer's disease (Mesulam, Siddique, & Cohen, 2003). There are only a few cases showing the association of lesions typical of Alzheimer's disease with ischemic cerebral lesions caused by CADASIL (Filley et al., 1999; Gray et al., 1994; Thijs, Robberecht, De Vos, & Sciot, 2003). Paquet et al. reported the case of a CADASIL patient, who developed rapidly progressive cognitive decline 3 years before death, showing characteristic arteriolar changes associated with abundant amyloid-beta (Aβ) deposition throughout the cerebral cortex, frequently periarteriolar, with rare amyloid plaques and minimal tau pathology. Aβ accumulation could result from abnormal synthesis or impaired elimination due to the arteriolar changes in CADASIL. This case raises the question that besides the classical, purely subcortical form of CADASIL, a "cortical" form with numerous lacunar infarcts and Aβ deposition in the cerebral cortex may occur and be difficult to differentiate clinically from Alzheimer's disease (Paquet et al., 2010).

7.1.4 Treatment

No effective treatment is available for CADASIL. Since evidence of cholinergic deficit was previously observed (Keverne et al., 2007; Mesulam et al., 2003), an international multicenter trial in 168 patients was performed to examine the efficacy of the cholinesterase inhibitor donepezil in the disorder. Donepezil showed no improvement in the primary outcome; change on the vascular AD assessment scale cognitive subscale (V-ADAS-cog). Still, improvements were noted on several measures of executive function, but the clinical relevance of these findings was not clear (Dichgans et al., 2008). Depression should be treated by antidepressant drugs, though further studies are required to determine the benefit of pharmacotherapy for mood disorder in CADASIL.

Control of risk vascular factors is recommended. Because CADASIL is a vascular disorder responsible for cerebral ischemic events, different clinicians prescribe aspirin for secondary prevention, but its benefit in the disease has not been demonstrated. The presence of microhemorrhage in 31–69% of CADASIL patients and the occurrence of intracerebral hemorrhage in few cases raise questions about the use of antiplatelets as prevention and suggests that anticoagulant therapy may be dangerous (Maclean et al., 2005; Ragoschke-Schumm et al., 2005; Rinnoci et al., 2013).

Some drugs are useful in relieving specific symptoms during the course of CADASIL. However, for migraine, vasoconstrictive drugs such as ergot derivatives and triptans are not recommended during the course of the disease. Cortical oligemia has been reported in asymptomatic patients (Chabriat, Tournier-Lasserve, et al.,

1995; Chabriat, Vahedi, et al., 1995). Also, the blood–brain barrier is possibly altered because of the vascular lesions (Ruchoux et al., 2002). Therefore, treatment of migraine should be restricted to analgesic agents and nonsteroidal anti-inflammatory drugs.

As reported for other ischemic diseases, rehabilitation procedures are crucial, particularly when a new ischemic event occurs. If stroke occurs at an early stage of the disease, recovery is often complete.

Finally, psychological support for the patient and family is of upmost importance, due not only to the psychological consequences of the neurological deficits but also to those related to the hereditary nature of CADASIL. The diagnosis of this familial disorder may have major consequences within the family and modify relationships among close relatives. Genetic testing raises important ethical problems similar to those encountered in families with Huntington disease, particularly for asymptomatic members at risk of having the deleterious mutation. Therefore, genetic counseling and testing should be performed only at specialized centers that have the necessary experience (Reyes, Kurtz, Herve, Tournier-Lasserve, & Chabriat, 2012).

7.2 MELAS

Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-like episodes (MELAS) is one of the most important encephalomyopathies related to mitochondrial dysfunction and is another inherited disease leading to vascular lesions. The acronym refers to a particular clinical syndrome described in 1984 by Pavlakis, Phillips, DiMauro, De Vivo, and Rowland (1984) that may be associated with different mutations in the mitochondrial DNA. In most cases, the enzymatic defect is a complex I respiratory chain deficiency and, to a lesser degree, a complex IV deficiency. The enzyme abnormality is associated with a point mutation at np3243 in the tRNA Leu (UUR) region, which accounts for 80% of the patients with MELAS (Goto, Nonaka, & Horai, 1990). About 20% of patient's positive for this "MELAS mutation" present with a different clinical syndrome.

In the MELAS syndrome, the onset of symptoms usually occurs before age 40 years. The main symptoms (as summarized by the acronym) include stroke, seizures, lactic acidosis, and exercise intolerance. Additional clinical manifestations include cognitive impairment, limb weakness, short stature, recurrent migraine-like headaches, hearing loss, and diabetes. Patients with mitochondrial disorders can present with psychiatric symptoms, including mood disorders, psychosis, and anxiety and may be more frequent in MELAS than in other mitochondrial diseases (Anglin, Garside, Tarnopolsky, Mazurek, & Rosebush, 2012). Psychiatric symptoms, such as schizophrenia-like clinical presentation, have been reported (Thomeer, Verhoeven, van de Vlasakker, & Klompenhouwer, 1998). The clinical expression is

highly variable. It ranges from asymptomatic to severe disability and may overlap with other mitochondrial syndromes, such as progressive external ophthalmoplegia (Damian et al., 1995) or with a syndrome associating diabetes mellitus and deafness (Maassen et al., 1996).

Stroke-like episodes are characteristic of the MELAS syndrome and are not observed in the MERRF syndrome (Myoclonic Epilepsy with Ragged Red Fibers), another mitochondrial disorder. These stroke-like episodes are often associated with headache and nauseas followed by visual symptoms (such as hemianopia or cortical blindness), aphasia, and psychosis. The pathogenesis of these episodes is not fully understood. Morphologic evidence of mitochondrial dysfunction has been demonstrated in the capillary endothelium of the small cerebral blood vessels in autopsies of patients with MELAS suggesting that the neurological manifestations are related to a "mitochondrial angiopathy" (Ohama et al., 1987).

The characteristics of the cognitive profile associated with MELAS have been poorly described in the literature. There may be no specific pattern of cognitive impairment in the MELAS, since both cortical and subcortical regions can be affected with focal or diffuse lesions. Sartor et al. reported one case without dementia but with marked alterations of visuospatial abilities and executive functions. After a 4-year follow-up, a progressive deterioration was detected in the absence of stroke-like episodes (Sartor, Loose, Tucha, Klein, & Lange, 2002). In childhood, the disease can lead to mental retardation.

The most common radiological finding of patients carrying the MELAS mutation is basal ganglia calcification, which is progressive and symmetric. Other abnormalities include focal lesions most commonly involving cerebellum and gray matter of parietal and occipital lobes. Cortical and cerebellar atrophy are also present in severe cases (Sue et al., 1998).

In 2003, Iizuka et al. described the MRI features of stroke-like lesions in four patients with MELAS (Iizuka, Sakai, Kan, & Suzuki, 2003). In all patients, diffusion-weighted imaging demonstrated a slow progression of stroke-like lesions with a moderate decrease of diffusion and involvement of different cortical regions distinct from ischemic stroke. Moreover, they observed that clinical and electrophysiological epileptic activities were associated with these events. These authors suggested that stroke-like episodes may be non-ischemic neurovascular events characterized by focal neuronal hyperexcitability related to the "mitochondrial angiopathy." Another characteristic of these stroke-like lesions is their preferential localization to the occipital and parietal lobes, but the exact mechanism of this posterior predilection remains to be elucidated.

Current treatment approaches in MELAS are based on the use of antioxidants, respiratory chain substrates, and cofactors in the form of vitamins. However, no consistent benefits have been observed using these treatments (Scaglia & Northrop, 2006).

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Chapter 8
Carotid Artery Disease

Brajesh K. Lal, Randolph Marshall, and Ronald M. Lazar

8.1 Introduction

Atherosclerosis with carotid plaque-induced luminal narrowing causes asymptomatic carotid artery stenosis (ACAS) in ~10% of older adults and the vast majority remain undetected (de Weerd, Greving, de Jong, Buskens, & Bots, 2009; O'Leary et al., 1992). Medical advancements in recent decades have increased life expectancy substantially, leading to an increased incidence of carotid disease, since the prevalence of carotid stenosis increases steeply with advanced age (Fairhead & Rothwell, 2006). The advent of new imaging modalities such as computed tomography angiography (CTA), magnetic resonance angiography (MRA), cerebral angiography, and carotid Doppler ultrasound (CDUS) made it possible to diagnose patients with carotid disease prior to the onset of symptoms. In a large population-based study, the prevalence of carotid stenosis 35% or greater was found in 3.8% of men and in 2.7% of women: prevalence increased with age in both genders (Mathiesen, Joakimsen, & Bønaa, 2001). Others have reported the prevalence of asymptomatic carotid stenosis of 50% or greater detected by ultrasonography to be 6.4% among people aged 50–79 (Mineva, Manchev, & Hadjiev, 2002). Rates of internal carotid artery stenosis >40% are higher among Type II diabetics and

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_8

increase with advancing age from 5.0% at 50–59 years to 7.3% at 60–69 years and 9.5% at 70–79 years (Park, Kim, Kim, Park, & Baek, 2006).

The detection of ACAS identifies individuals at higher risk of cardio- and cerebrovascular events. Although stroke occurs in only 2% of ~eight million patients with ACAS, its prevention is the main focus of treatment (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study, 1995; Ricotta et al., 2011). The notion that carotid artery disease can produce cognitive impairment was first proposed by Dr. Fisher in 1951, based on a necropsy case (Fisher, 1951). He postulated that carotid occlusive disease can produce a dementia state, and proposed that restoration of blood supply could reverse the condition. This stimulated the first carotid reconstruction (Carrea, Molins, & Murphy, 1955) and carotid endarterectomies (CEA) (DeBakey, 1975; Eastcott, Pickering, & Rob, 1954) on patients with stroke and internal carotid artery (ICA) stenosis, thereby introducing CEA as an important procedure in the management of stroke. Subsequently, stroke was recognized as a leading cause of death in the United States with about 20% attributable to atheroembolization from carotid artery stenosis (American Heart Association, 2003; Lal & Hobson, 2000). Stroke prevention has therefore become the primary focus of carotid revascularization.

The possibility that revascularization of carotid stenosis could also alter cognitive function has only recently received attention again but has been approached only in the form of nonrandomized case series. No randomized clinical trial has ever addressed the question.

By 2030, 20% of the US population will be 65 years of age or older. Cognitive dysfunction is the most frequently reported disability in this age group, prevalent in ~20% (Courtney-long & Carroll, 2015), and often progress to falls, frailty, loss of functional independence, dementia, disability, and death (Forman-Hoffman et al., 2015; Fried et al., 2001; Guralnik, Ferrucci, Simonsick, Salive, & Wallace, 1995; Hardy, Kang, Studenski, & Degenholtz, 2011; Hirvensalo, Rantanen, & Heikkinen, 2000; Houles, Canevelli, van Kan, & Cesari, 2012; Hugo & Ganguli, 2014; Stalenhoef, Crebolder, Knottnerus, & Van Der Horst, 1997; Stanaway et al., 2011). Older age and male sex (Alzheimer's Association, 2017), genetic factors (e.g., ApoE) (Verghese et al., 2013), silent brain infarctions (Vermeer et al., 2003), white matter hyperintensities (Rosano, Naydeck, & Kuller, 2005), and microbleeds (Ding et al., 2017) are known non-modifiable risk factors associated with cognitive decline. Although vascular risk factors—hypertension, diabetes, dyslipidemia, cigarette smoking, and obesity—respond to aggressive pharmacological and lifestyle modifications, long-term compliance remains challenging due to recidivism. The possible causative relationship between carotid disease and cognitive impairment suggests that restoration of blood supply could restore cognitive functions. The aim of this chapter is to review the current state of knowledge about the nature, severity, and course of cognitive deficits as well as the possibility of surgical means for reversing dysfunction in patients with stenosis or occlusion of the carotid arteries.

8.2 Measuring the Extent of Narrowing in the Carotid Artery

8.2.1 Angiography

Cerebral Angiography is an X-ray of the vasculature in the neck and brain. Normally, arteries are not visible in an X-ray, for this reason a contrast dye is injected via a catheter placed into an artery leading into the carotid circulation. Cerebral angiography is the gold standard for cerebrovascular imaging to evaluate patency and degree of stenosis in the carotid artery in the neck and in intracranial vessels (Ricotta et al., 2011). It permits classification of carotid lesions into one of the three groups: (1) nonsignificant stenosis (<50%) that does not impede blood flow, (2) severe stenosis (70–99%) that may induce hypoperfusion, and (3) complete occlusion. It also provides information about tandem atherosclerotic disease and collateral circulation. For instance, the coexistence of intracranial atherosclerotic disease in patients with moderate carotid stenosis of 50–70% may identify a subgroup of patients that are more susceptible to hypoperfusion and hence, more likely to benefit from a revascularization procedure (Fairhead & Rothwell, 2006; Lal, Beach, & Sumner, 2011). Cerebral angiography for assessment of the cerebral vasculature has to be considered in the context of its high cost, invasive nature, and most importantly, risk of neurological complications. A review of eight prospective and seven retrospective studies using cerebral angiography showed the likelihood of inducing a disabling stroke is 1% (Hankey, Warlow, & Sellar, 1990). These limitations render angiography a better test when an intervention is being planned, and not for screening purposes.

8.2.2 CTA and MRA

CT Angiography (CTA) requires specially designed X-rays and intravenous contrast to evaluate anatomic details of the blood vessels whereas MRA is a type of magnetic resonance imaging (MRI) scan that uses a magnetic field and intravenous contrast to image the structure of blood vessels. Both techniques image flowing blood noninvasively and provide static 3D anatomic information on the entire carotid system. They do not evaluate the hemodynamic status of the vascular network, which is possible on cerebral angiography. MRA and CTA have a sensitivity and specificity for evaluation of carotid stenosis in the range of 88% and 84% and 77% and 95%, respectively (Fig. 8.1) (Ricotta et al., 2011).

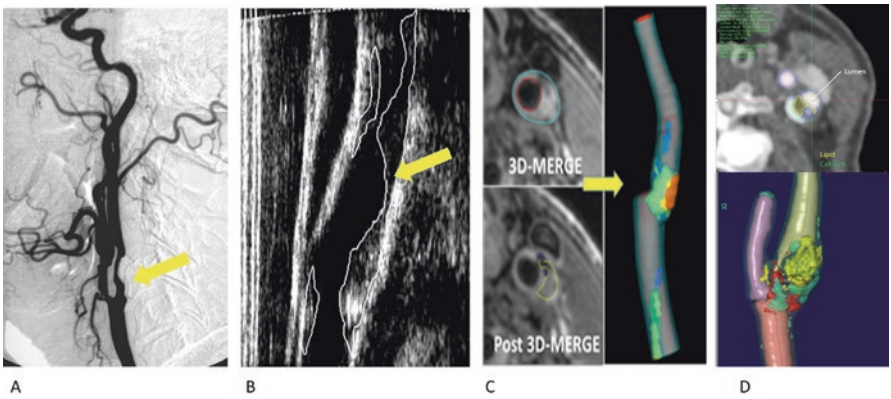

Fig. 8.1 Angiogram, duplex ultrasound (DUS), magnetic resonance angiography (MRA), and computed tomography angiography (CTA) from a patient with right internal carotid artery (ICA) stenosis. (**a**) Cervical angiogram with arrow pointing to ICA narrowing at the carotid bifurcation; (**b**) DUS of the carotid bifurcation and ICA showing the lesion outlined, (**c**) MRA of the carotid artery bifurcation showing the lesion (two axial sections with the plaque outlined are to the left; 3D reconstruction of serial axial images is on the right with different plaque constituents shown in color), (**d**) CTA of the carotid bifurcation showing the lesion (one axial section is on the top; the 3D reconstruction of serial axial images is at the bottom

8.2.3 Duplex Ultrasound (DUS)

Duplex ultrasonography is a noninvasive diagnostic tool that uses ultrasound to view plaques or other blood flow abnormalities in the carotid artery. Currently, DUS is the primary screening test for carotid artery disease because it is noninvasive, relatively accurate, and cost-effective (Ricotta et al., 2011). Most clinicians use DUS as the single preoperative evaluation diagnostic test, essentially avoiding the risk and the cost of preoperative cerebrovascular angiography (Ricotta et al., 2011). Peak blood flow velocity is the parameter used to measure the severity of stenosis. Increases in blood flow velocity detected in the narrowed portion of the carotid lumen is proportional to the severity of obstruction. DUS has the added advantage of being able to evaluate the surface and the composition of the atherosclerotic plaque. Areas of intraplaque hemorrhage and increased fat deposition show up as hypoechoic areas on DUS and represent areas of plaque vulnerability rendering patients at higher risk of suffering a stroke (Cires-Drouet, Mozafarian, Ali, Sikdar, & Lal, 2017). A meta-analysis comparing CDUS with intraarterial cerebral angiography for the diagnosis of high-grade carotid stenosis (70–99%) showed that CDUS had a sensitivity of 89% and specificity of 84% (Ricotta et al., 2011). DUS does have some limitations. It is not capable of providing a global perspective of cerebral vasculature since only the cervical portion of the carotid and vertebral arteries can be examined in detail. Furthermore, it has limited use in patients with calcified carotid lesions or tortuous carotid arteries. Another serious draw back, the diagnostic accuracy of DUS relies heavily upon the technical skills and expertise of

the operator. Other sources of variability include the difference in equipment, and measurement threshold properties. Since these variations are clinically significant, physicians will often repeat DUS studies performed elsewhere and rely on data obtained from a trusted ultrasound laboratory.

8.2.4 Transcranial Doppler (TCD)

TCD measures blood flow velocity and direction in the major intracerebral arteries distal to the carotid arteries (Edmonds Jr., Isley, Sloan, Alexandrov, & Razumovsky, 2011). TCD can be used in conjunction with DUS to evaluate the intracranial hemodynamic consequence of high grade carotid stenosis. Several TCD findings have been highly associated with critical carotid stenosis, for example, absence of ophthalmic artery and carotid siphon TCD signals, reduced MCA flow velocity, decreased pulsatility index, and diminished flow acceleration (Christou et al., 2001). Furthermore, development of collateral flow patterns is a common finding in the setting of severe carotid stenosis. For instance, reversed flow in the ipsilateral anterior cerebral artery (ACA) or augmented flow velocity in the contralateral ACA suggests collateral flow from the contralateral ICA. Also, reversed flow in the ipsilateral ophthalmic artery implies collateral flow from the external carotid artery (ECA) to the ICA (Guan, Zhang, Zhou, Li, & Lu, 2013). The use of TCD can also be extended to detect MCA micro emboli stemming from the heart or carotid artery.

8.3 Pathophysiologic Mechanisms for Cognitive Decline in Carotid Disease

Symptomatic carotid disease is primarily associated with stroke and TIA through embolism of thrombotic material and additionally from hypoperfusion secondary to stenosis with insufficient collateral compensation, “watershed infarction” (Fisher et al., 2005; Hu, Michael De Silva, Chen, & Faraci, 2017). Fisher’s classic papers, regarded as the earliest evidence proposing hypoperfusion-mediated cognitive impairment, were the groundwork from which investigators developed this field of research (Fig. 8.2). In stroke-free patients, hypoperfusion (De La Torre, 2012) and showering of atheroemboli (Fisher et al., 2005) may be important factors leading to cognitive decline in patients with carotid artery stenosis or occlusion.

Chronic diseases common to the elderly such as intracranial vasculopathy, hypertension, and cardiac failure, are associated with cerebral hypoperfusion, cerebral hypometabolism, and cognitive dysfunction (Daulatzai, 2017; Ruitenberg et al., 2005; Wolters et al., 2017; Zuccalà et al., 1997). Similarly, balloon occlusion or clamping of the carotid artery leads to attentional deficits proportionate to the reduction in cerebral blood flow (Marshall, 2004; Marshall et al., 1999). Narrowing

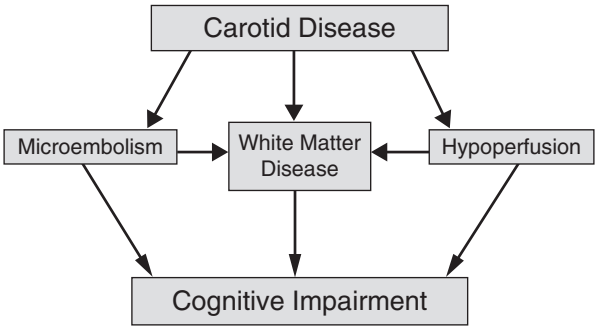

Fig. 8.2 Carotid disease is implicated in cognitive impairment through three direct mechanisms: (1) Microembolism (2) White Matter Disease and (3) Hypoperfusion. Microembolism and hypoperfusion have a further contribution to cognitive impairment by increasing the burden of white matter disease. Reprinted from Chmayssani, Festa, & Marshall, Chronic ischemia and neurocognition. Neuroimaging Clinics of North America 17(3):317, August 2007, with permission from Elsevier

of the carotid artery in ACAS may also be associated with hypoperfusion with attendant reduced cognition (Lal et al., 2017; Sasoh et al., 2003). Cerebral hypoperfusion results in brain (neuronal) glucose hypometabolism measurable as reduced uptake of 2-[18F]fluoro-2-deoxy-D-glucose (FDG) on positron emission tomography (PET) (Daulatzai, 2017) that is associated with cognitive decline and progression to Alzheimers' disease (Landau et al., 2010).

As with all arterial stenoses in multiple vascular beds across the body (coronary, renal, mesenteric and lower extremity), cerebral hypoperfusion can occur progressively as an initial pressure drop across a carotid artery narrowing, followed by flow failure at rest.

1. ***Net pressure drop*** is a measure of pressure gradient across a stenosis plus the effect of collateral compensation. When carotid arteries of rats are ligated to produce chronic cerebral hypoperfusion, they demonstrate poor performance on water maze memory tests (de la Torre, Fortin, Park, Pappas, & Richard, 1993). Restoration of carotid blood flow within 1 to 2 weeks restores cerebral blood flow (CBF) and memory performance. Revascularization at 3 weeks or later does not improve CBF or memory function, likely as a result of irreversible brain infarction from the chronic ligation of the artery. This indicates that neuronal ischemia with manifestations of behavioral deficits is potentially reversible for a period of time if CBF is improved by reversing the flow restriction.

   In 24 patients with ACAS, 22% had reduced flow in the middle cerebral artery (MCA) on transcranial Doppler (TCD) at baseline. After CEA, flow and attentional performance improved in these patients (Ghogawala et al., 2013). This suggests that in ACAS patients with stenosis-related pressure drop and consequent hypoperfusion, CEA may improve perfusion and cognition.

   Our computer circuit modeling shows that carotid artery narrowing results in a pressure gradient that can be compensated for by collateral circulation from the

opposite hemisphere via the Circle of Willis (COW) (Lal et al., 2011). The COW is, however, incomplete in half of the population (Alpers, Berry, & Paddison, 1959), consistent with our finding that at least half of ACAS patients have brain hypoperfusion (Lal et al., 2017). Therefore patients with a large pressure gradient across a tight stenosis, and inadequate collateral compensation, are at higher risk for cerebral hypoperfusion (Deweese, May, & Lipchik, 1970; Lal et al., 2011; Warwick, Sastry, Fontaine, & Poullis, 2009; Young, Cholvin, & Roth, 1975).

2. ***Flow failure*** (Marshall & Lazar, 2011). If net pressure drop across the stenosis is large enough, as might occur in severe chronic ACAS, the intracranial arterioles become maximally dilated in an effort to maintain brain perfusion. They may fail to dilate further (flow failure) when challenged by CO_2 (e.g., by breath-holding) that is manifested by reduced vasoreactivity on TCD testing (Balestrini et al., 2013; Markus & Harrison, 1992). This impaired cerebrovascular vasoreactivity from flow failure should recover after CEA since it is related to the stenosis-induced pressure drop (Sfyroeras et al., 2006).

In the Rotterdam scan study, silent infarcts in healthy elderly people at baseline doubled the risk of dementia and decline in cognitive function on follow-up (Vermeer et al., 2003). These findings were confirmed by the Atherosclerosis Risk In Communities study (Mosley Jr. et al., 2005) and the Cardiovascular Health Study (Longstreth Jr. et al., 1998). Furthermore, people with pre-existing infarcts are at a higher risk for additional silent or symptomatic infarcts during follow-up (Bernick et al., 2001) and cognitive decline occurs more often in these patients (Vermeer et al., 2003). Similarly, the cerebrovascular burden of new procedural microinfarction may worsen or accelerate Alzheimer's Disease progression (O'Brien et al., 2003). These observations are mirrored in experimental studies where injection of 50 μm microspheres into rat carotid arteries resulted in cerebral injury and reduced attentional performance (Craft, Mahoney, DeVries, & Sarter, 2005). Surgical (Braekken, Russell, Brucher, Abdelnoor, & Svennevig, 1997; Grocott et al., 1998) or catheter/guidewire (Braekken, Endresen, Russell, Brucher, & Kjekshus, 1998) manipulation of the aorta during cardiac procedures also results in microembolic brain injury. While its etiology is multifactorial, postoperative cognitive decline in patients undergoing coronary artery bypass procedures has also been correlated with silent microembolic cerebral injury (Braekken, Reinvang, Russell, Brucher, & Svennevig, 1998; Sylivris et al., 1998).

The clinical impact of microembolism due to carotid disease remains unclear. Although Droste et al. (1997) reported up to 142 embolic signals per hour in patients with carotid stenosis and recent transient attacks, symptoms manifested at a surprisingly low rate (Crawley et al., 1997). Furthermore, several studies found no correlation between T2-weighted MRI examinations and induced microemboli during carotid artery stenting (CAS) procedures (Poppert et al., 2004). Investigators have attempted to attribute specific infarcts to silent areas of the brain but no firm conclusion has been reached (Jayasooriya, Thapar, Shalhoub, & Davies, 2011; Norris & Zhu, 1992). Therefore, several mechanisms have been suggested to explain why

microemboli occur without overt clinical manifestation or MRI evidence: (1) the human cortex contains extensive collateral vasculature that wash out the emboli; (2) there is a size threshold for acute ischemic events such that the likelihood of an emboli causing symptoms is proportionally related to the size of the emboli (Rapp et al., 2000); and (3) mild transient symptoms are not appreciable when patients experience microembolization during sleep or sedation. Finally, the sequelae of microemboli may be more prominent over the long term if embolic fragments induce an inflammatory process that results in cellular infiltration and fibrosis leading ultimately to neuronal death and development of scar tissue. The latter could explain the late worsening in cognition that is commonly witnessed in patients following coronary artery bypass surgery (Newman et al., 2001).

8.4 Relationship Between Cerebral Hypoperfusion and Cognitive Function

Major evidence highlighting the effects of chronic cerebral hypoperfusion on cognitive functioning stems from the cardiac literature. End-stage heart failure constitutes a state of global ischemia of the brain (Georgiadis et al., 2000) where 35–50% of patients have suboptimal cognitive functioning (Leto & Feola, 2014). Following implantation of a left ventricular assist device or after transplantation for heart failure, these patients experienced neuropsychological improvement (Bhat, Yost, & Mahoney, 2015; Deshields, McDonough, Mannen, & Miller, 1996) that was coupled with significant increases in cerebral blood flow and middle cerebral artery (MCA) mean flow velocity (Gruhn et al., 2001). The enhanced cerebral perfusion offers a physiological explanation for these improvements. Cognitive dysfunction resulting from large infarctions in cortical areas supplied by the carotid artery is well established. The unsettled component is the unclear causative relationship between carotid disease and cognitive impairment in the absence of stroke. The key question is whether carotid atherosclerosis is the cause of cognitive impairment or is a marker for underlying risk factors and vascular disease that are themselves the cause for cognitive decline. In a manner analogous to congestive heart failure, hypoperfusion due to carotid stenosis/occlusion may result in cognitive dysfunction.

With the refinement of new imaging techniques in the 1990s, it became possible to evaluate the impact of hypoperfusion on neuronal metabolism and cognitive derangement. Tatemichi et al. reported a case of a 55-year-old man with bilateral internal carotid artery (ICA) and unilateral vertebral artery occlusions presenting with behavioral and cognitive changes suggesting frontal lobe deficits. A baseline PET scan showed a 40–50% reduction in blood flow and metabolism. Following a revascularization procedure, there was improvement on neuropsychological testing, particularly executive functioning, that was coupled with increases in CBF and metabolism (Tatemichi et al., 1994). Similarly, by means of SPECT, Tsuda et al. reported on a patient with cognitive dysfunction attributed to extensive hypoperfu-

sion in the left anterior-parietal and parietotemporal cortex secondary to left ICA occlusion (Tsuda et al., 1994).

Increasingly, cross-sectional studies have demonstrated a positive correlation between carotid plaques and neuropsychological dysfunction. In an early study, the relationship was examined in a small subset of patients with high-grade (>75%) left (n = 32) ICA stenosis from among 4006 patients from the Cardiovascular Health Study (Johnston et al., 2004). After adjusting for other vascular risk factors, the authors found that carotid stenosis was associated with low scores on the Mini Mental State examination (MMSE). Bakker et al. conducted a comprehensive review of the literature evaluating the impact of carotid occlusive disease on cognitive function (Bakker, Klijn, Jennekens-Schinkel, & Kappelle, 2000). In patients with carotid disease, cognitive impairment was apparent even in the absence of neurological deficits (stroke or TIA). Among those studies, two noted a generalized cognitive impairment (Benke, Neussl, & Aichner, 1991; Sissel, Jack, Christian, & Boysen Gudrun, 1986), three documented focal deficits for memory (Hamster & Diener, 1984; Nielsen, Højer-Pedersen, Gulliksen, Haase, & Enevoldsen, 1985), learning (Nielsen et al., 1985), psychomotor speed (Hamster & Diener, 1984), and problem solving (Naugle, Bridgers, & Delaney, 1986; Nielsen et al., 1985), and two did not specify the nature of cognitive deficits (Baird et al., 1984; Hemmingsen, Mejsholm, Boysen, & Engell, 1982). Another study enrolled 39 consecutive patients, not necessarily surgical candidates, with carotid occlusion, who had ipsilateral cerebral and retinal TIA but no stroke on MRI (Bakker et al., 2003). Cognitive impairment was demonstrated in 44% of the patients though deficits were mild and nonspecific in nature. In a prospective study of 73 consecutive patients with TIA or minor stroke who had an occlusion of the ICA, high lactate levels on H-MR spectroscopy (^{1}H-MRS) in non-infarcted white matter correlated with a decline in nonverbal intelligence, executive functioning, reaction time, motor speed, as well as verbal learning and memory (Bakker et al., 2003; Bakker, Klijn, van der Grond, Kappelle, & Jennekens-Schinkel, 2004). At baseline, 70% of patients with strokes and 40% of patients with TIAs were cognitively impaired. At 1-year follow-up, improvement in cognitive functioning was witnessed in patients who had no lactate at baseline and who did not experience recurrence of a neurological deficit. In the Trømso study, Mathiesen et al. compared 189 patients with carotid stenosis to 201 healthy controls (Mathiesen et al., 2004). Patients with carotid disease had significantly lower scores on tests of attention, psychomotor speed, memory, and motor function than controls. In the Framingham Offspring Study, participants (n = 1975) without dementia or history of stroke but with a carotid stenosis, demonstrated reduced cognitive performance and indices of cerebral ischemia on MRI (Romero et al., 2009).

Recent longitudinal studies have also identified a relationship between stenosis and deteriorating cognitive function. Balestrini et al. found that severe unilateral carotid stenosis was associated with increased rates of cognitive deterioration in 210 patients with asymptomatic carotid artery stenosis during a 3-year follow-up study (Balestrini et al., 2013). At follow-up, patients with severe unilateral ACAS were more likely to show cognitive deterioration compared to controls. Comparably, a

3-year follow-up study examined cognitive performances in 159 patients with asymptomatic bilateral carotid stenosis (70–99%). Patients with bilaterally impaired cerebrovascular reserve (CVR) at baseline had the highest levels of cognitive decline as assessed by the mini mental state examination (MMSE) at 36 months (Buratti et al., 2014).

Several studies have failed to demonstrate a direct relationship between carotid stenosis and cognitive dysfunction (Boeke, 1981; Kelly, Garron, Javid, & Javid, 1980; van den Burg et al., 1985). Using tests of set shifting, verbal memory, visual memory, verbal fluency, and the MMSE Iddon et al. failed to demonstrate impairment in cognitive function as compared to controls (Iddon, Sahakian, & Kirkpatrick, 1997). Similar findings were also observed by King et al. when testing verbal IQ (King, Gideon, Haynes, Dempsey, & Jenkins, 1977). However, these studies did not include long-term follow-up and there was a selection bias among the patient population, given that 67% of the studies were designed to evaluate the outcome after surgery (CEA and bypass); therefore, only surgical candidates were enrolled. A further limitation of these studies is that they often included both patients with carotid occlusion and carotid stenosis, precluding the exact characterization of distinct neurobehavioral syndromes.

8.5 Cognitive Changes After Carotid Artery Revascularization

Given that carotid disease may be associated with cognitive dysfunction, an emerging hypothesis is that revascularization procedures could potentially improve or preserve cognitive function. Though the prophylactic effect of revascularization procedures against neurological deficits has been indisputably established in large randomized trials, the impact of vascular reconstruction on cognitive performance remains inconclusive. The underlying mechanisms for anticipated cognitive improvement can be the cessation of repeated embolic episodes and/or the restoration of blood flow.

Several periprocedural mechanisms may impact cognitive function following revascularization, some patient specific and others procedure specific (Fig. 8.3) The former include plaque morphology (Stary, 2000), severity and extent of cerebral ischemia (Chmayssani, Festa, & Marshall, 2007), baseline neuronal injury, and the presence of *APOE*-ε4 allele, which is associated with a worse outcome following CEA (Heyer et al., 2002, 2005). The procedure specific mechanisms include the perioperative complications: new cerebral infarction, intraoperative ischemia (Heyer et al., 2002), and postoperative hyperperfusion (Ogasawara et al., 2005). The net outcome of cognition following revascularization procedures is therefore a result of both patient- and procedure-related mechanisms.

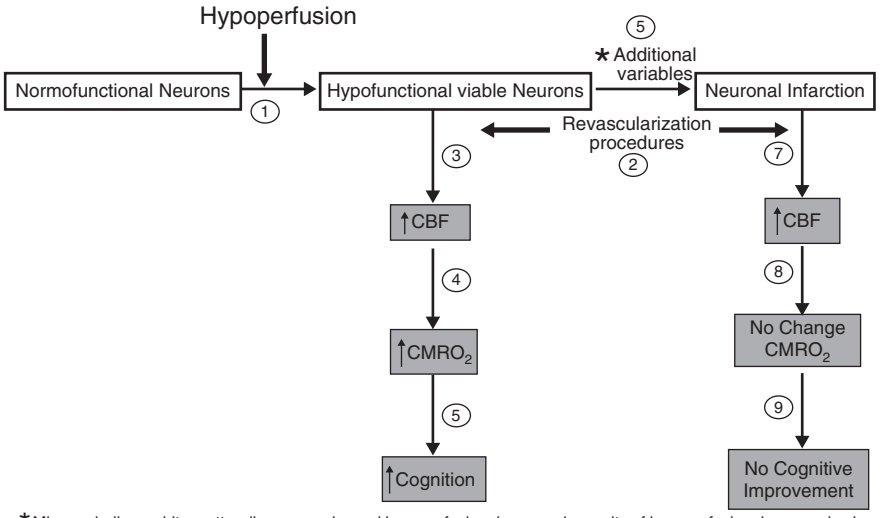

Fig. 8.3 The scheme illustrates the natural history of neurons subjected to chronic ischemia. A mild hypoperfusion (1) shifts cells into a hypofunctional but viable state. If a revascularization procedure (2) is performed at that point, a resultant increase in CBF (3) leads to a concomitant increase in neuronal metabolism (4), and this manifests in improved cognitive performance (5). Alternatively, if the hypoperfusion state is prolonged, increased in severity or volume, or coexists with either microemboli or white matter disease, infarction occurs and revascularization (6) will result in CBF restoration (7) that does produce increased neuronal metabolism (8) or consequently cognitive improvement (9)

8.5.1 Carotid Endarterectomy and Cognition

Carotid endarterectomy (CEA) is in widespread use to treat carotid stenosis; between 80,000 and 100,000 CEAs have been performed for Medicare patients per year in the United States since 1985 (Hsia, Moscoe, & Krushat, 1998; Lichtman et al., 2017). Frequent studies spanning several decades have explored the impact of CEA on cognitive functioning. The first formal study was conducted in 1964 (Williams & McGee, 1964). In reviews by Irvine et al. and Lunn et al. in the late 1990s, 16 of 28 (57%) studies reported cognitive improvement following CEA, others showed no change (39%), and still others demonstrated cognitive deterioration (4%) (Irvine, Gardner, Davies, & Lamont, 1998; Lunn, Crawley, Harrison, Brown, & Newman, 1999). The inconsistent findings were attributed to the fact that the vast majority of these publications suffered from poor methodology. Most studies lack appropriate controls and therefore, cannot account for several potential confounds such as practice effects, preoperative heightened anxiety and depression, and perioperative effects. Another limitation of these studies is the wide variation in retest

intervals (3 days to 8 months). Without long-term follow-up, it is impossible to account for the effects of surgery and anesthesia and to monitor any long-term benefit on cognitive performance. An additional complicating factor is the wide range of patient characteristics that can affect cognitive functioning including age, education, IQ, and presence of comorbid cerebrovascular disease. Inclusion of patients suffering major strokes makes firm conclusions about cause and effect more difficult. For instance, cognitive improvement witnessed in those patients might be confounded by the natural recovery of stroke; alternatively, an absence of improvement can be attributed to permanent neurological damage that would hinder any cognitive improvement. The studies include outcomes from a broad range of neurocognitive tests rendering results and conclusions across studies to be less comparable.

Several subsequent studies have included surgical controls with unrelated disease yet highly similar demographics to correct for the influences of anesthesia, surgery, and practice effects on cognition. Sinforiani et al. and Fearn et al. found a benefit of CEA on cognitive functioning with respect to verbal memory and attention (Fearn et al., 2003; Sinforiani et al., 2001). In contrast, Heyer et al. reported a decline in visuospatial organization on the Rey Complex Figure copy task 1 month after CEA (Heyer et al., 2002). In addition, Bossema et al. and Aleksic et al. reported no restorative effect on cognitive functioning.

Only a few studies have evaluated both CBF and cognition following CEA. Fukunaga et al. reported improvement in frontal lobe functions as reflected in improved categories achieved as well as reductions in loss of set and perseverations on the Wisconsin Card Sorting Test, particularly for those with severe stenosis or reduced cerebral perfusion prior to surgery (Fukunaga, Okada, Inoue, Hattori, & Hirata, 2006). When compared to controls, another study found improved performance on a block design test in patients with the highest degree of stenosis and impaired vasomotor reactivity preoperatively (Kishikawa et al., 2003).

Some studies investigated the influence of surgical laterality on cognitive functioning, based on the premise that hemodynamic impairment would be more beneficial to cognitive functions associated with the hypoperfused hemisphere. This argument is supported by pre- and postoperative MRI studies showing that carotid stenosis induces ipsilateral white matter changes, which were shown to regress following CEA (Soinne et al., 2003). Others have shown significant improvement in spatial memory and copying drawing in right stenosis patients as compared to left stenosis patients (Sinforiani et al., 2001). However, laterality was not demonstrated in several other studies (Fearn et al., 2003; Fukunaga et al., 2006; Heyer et al., 2002; Kishikawa et al., 2003).

8.5.2 Carotid Artery Stenting

Carotid artery stenting is an increasingly performed revascularization technique that offers patients a less-invasive approach to treating carotid stenosis. One randomized controlled trial comparing CAS and CEA has demonstrated equivalence between

the two approaches with respect to a composite outcome measure that includes stroke, myocardial infarction, and death (Brott et al., 2010). This study as well as others have however found an increased periprocedural risk for stroke with CAS compared to CEA, and this has resulted in CAS being preferentially performed at most institutions for patients with anatomic or physiologic contraindications to CEA (Brott et al., 2010; Mas et al., 2006). For this reason, the impact of CAS on cognitive functioning has not been elucidated, but it is presumed to have the potential to improve cognition in a manner similar to CEA by restoring cerebral hypoperfusion and/or reducing chronic microembolization.

Carotid artery stenting represents a rapidly evolving technique, therefore special attention should be given to reviewing studies addressing stroke and cognitive outcomes following CAS procedures, as the published outcomes often lag behind current advancement in the field. The first reported study compared cognitive outcome in 20 patients randomized to carotid artery balloon angioplasty without stenting to 26 patients undergoing CEA (Crawley et al., 2000). At the two postoperative follow-ups, 6 weeks and 6 months, there were no significant group differences in cognitive function at either of the follow-up intervals, though five patients in each group suffered equivalent decline in cognitive performance. CAS methodology has since evolved and currently includes stenting, and Lehrner et al. reported no significant cognitive changes in 20 stroke free patients—nine symptomatic with TIA and 11 asymptomatic—undergoing unilateral carotid stenting (Lehrner et al., 2005). Another study aimed to test cognitive changes after CAS with concurrent use of a proximal protection device to reduce thromboembolic events. The most common form of protection used is a filter deployed in the distal ICA prior to treating the stenosis at the carotid bifurcation. Ten patients assessed 48 h post-op demonstrated significant improvement in executive function (sequential tracking using the Number Connection Test) and new learning and memory (verbal list learning task from the Word List Learning test of the Consortium to Establish a Registry for Alzheimer Disease [CERAD] battery) on post-testing conducted 2 days after CAS. A trend for improvement was seen on another executive function test, the Animal Fluency test. However, no comparisons were made with CEA, and the absence of a control group makes it impossible to determine the relative contributions of simple practice effects and treatment-specific gains (Grunwald et al., 2006). Moftakhar et al. examined cognitive outcomes in a retrospective, uncontrolled study of 20 consecutive patients who had undergone CAS, 3 to 10 months previously (Moftakhar et al., 2005). The main outcome was self-reported change in daily function on the IQ-CODE (a structured questionnaire of competence in daily activities used in dementia studies (O'Brien et al., 2003)). Respondents were the patients themselves ($n = 5$) or "close contacts" ($n = 15$). A total of 16/19 respondents reported a "positive change." The results should be viewed cautiously as all ratings were made retrospectively, at a single point in time, by non-blinded raters who may have been prone to a positive attribution bias. Chen et al., compared 34 patients with asymptomatic carotid stenosis, who underwent CT perfusion scans to measure CBV, CBF, and a cognitive assessment at baseline and 3 months post-procedurally (Marshall et al., 2012). Patients who demonstrated cerebral ischemia at baseline,

improved their perfusion status with successful stenting. In this particular group alone, cognitive function improved after revascularization thereby providing strong evidence for the cognitive impairment in carotid stenosis being related to impaired cerebral hemodynamics. In a nonrandomized prospective study, we tested multiple cognitive domains at baseline and 6 months post carotid revascularization in patients undergoing CEA (n = 25) and CAS (n = 21) for high-grade asymptomatic carotid stenosis (Lal et al., 2017). Cognitive tests included TMT-A & B, Processing Speed Index, Boston Naming Test, Working Memory Index, Controlled Oral Word Association Test, and Hopkins Verbal Learning Test. A composite score was generated for each patient at baseline and follow-up, and change scores between the two time points were used as the primary outcome. A secondary analysis compared change scores for each individual test. We found that the composite cognitive score improved significantly after both procedures, with notable improvements in learning/memory, motor speed/coordination/executive function, language/naming, verbal fluency and processing speed, compared to baseline.

8.5.3 EC-IC Bypass

Cerebral hypoperfusion in the setting of ICA occlusion has been implicated in intellectual decline, with revascularization as a possible therapeutic option. EC-IC bypass provides an opportunity to study the behavioral parameters of surgical therapy for cerebral ischemia. It should be noted that CEA carries a significant advantage over EC-IC bypass, since EC-IC bypass restores blood flow across the carotid bifurcation without reducing the incidence of showering of atheremboli leaving the distal end of the carotid artery as a continued potential source of emboli (Fig. 8.4) (Xu et al., 2018).

In patients with a total occlusion, CEA cannot be performed. In such patients, the efficacy of EC-IC bypass was pursued initially in case studies that suffered major design limitations and yielded an array of conflicting results. For example, Nielson et al. found that among 33 patients undergoing EC-IC bypass, only the 23 with left carotid occlusive disease had a presurgical performance that was significantly worse than controls on mental sequencing (Trail Making Part B, Digit Span) and word learning and memory (Nielsen et al., 1985). Postoperatively, the left-occlusive patients did not perform worse than controls. However, two other controlled studies have yielded less promising results after an EC-IC bypass. Binder et al. compared 12 EC-IC bypass patients to 7 patients treated medically (Binder, Tanabe, Waller, & Wooster, 1982). Although limited by a small sample size, both the surgical and medical groups had improved comprehension and verbal memory at the 2-month follow-up. In another case series of 38 patients undergoing EC-IC bypass, Drinkwater et al. reported minor improvements in aspects of memory and processing speed but no prominent global improvement (Drinkwater, Thompson, & Lumley, 1984). Other investigators evaluated CBF using ^{133}Xe inhalation in a series of 44 patients undergoing EC-IC bypass (Younkin et al., 1985). Despite generalized

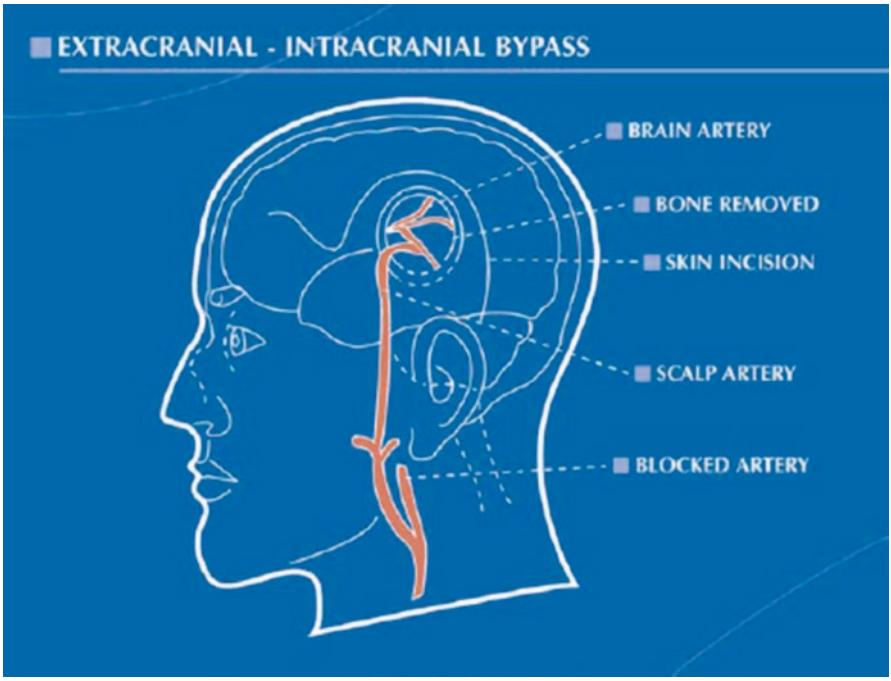

Fig. 8.4 Reprinted with permission from William J. Powers, MD Principle Investigator, Carotid Occlusion Surgery Study

improvement in cognitive function at 3- and 9-month follow-ups, the authors proposed that the clinical improvements were due to natural recovery from stroke deficits, since there was no concomitant increase in CBF measures and those with the greatest improvements had a recent CVA. Reports of chronic CBF changes following EC-IC bypass using the old imaging tools conflict. With refinement of imaging techniques, it has become possible to decipher the physiological interactions among EC-IC bypass, subsequent hemodynamic changes, and cognitive functioning. By means of SPECT, Tsuda et al. reported on a patient with occlusion of the left ICA siphon, where improvement in CBF and neuronal metabolism was associated with general cognitive improvement that was sustained over a 3-year follow-up. Sasoh et al. used PET to perform pre- and post-bypass CBF and metabolism assessment in 25 patients with chronic cerebral ischemia due to ICA occlusion (Sasoh et al., 2003). They showed that elevated OEF (oxygen extraction fraction) and reduced $CMRO_2$ (cellular metabolism) was related to cognitive dysfunction. Post-operatively, there was normalization in hemodynamic factors: OEF, CMRO2, CBF, and CVR (cerebrovascular reactivity) and improvement in WAIS-R IQ scores.

These valuable contributions to the literature highlight the efficacy of EC-IC bypass in patients with stage II hemodynamic failure and were the basis for initiating the randomized clinical trial, Randomized Evaluation of Carotid Occlusion, and Neurocognition (RECON) an ancillary study of the Carotid Occlusion Surgery

Study, a randomized trial intended to test the question of whether EC-IC bypass when added to best medical therapy can reduce subsequent ipsilateral ischemic stroke at 2 years in patients with symptomatic ICA occlusion and stage II hemodynamic failure. We have found impaired cognitive function in patients with carotid occlusion and asymmetric OEF confirming that hemodynamic failure is independently associated with cognitive impairment in patients with carotid occlusion (Marshall et al., 2012).

8.6 Conclusion

Since the early days of C. Miller Fischer, investigators have continued to report increasingly convincing evidence of an association between carotid disease and the development of cognitive impairment. More recently, studies have attempted to control for the multiple patient- and procedure-related confounders to evaluate potential cognitive benefits of carotid artery revascularization. These studies point to the strong possibility that both CEA and CAS may reverse hemodynamic abnormalities associated with carotid artery narrowing with subsequent improvements in several cognitive domains. Unfortunately, these studies suffer from several limitations that warrant cautious interpretation. For instance, patient heterogeneity particularly with respect to other causes of cognitive impairment such as congestive heart failure or severe systemic atherosclerosis, inconsistent study design including variable timelines and control groups, and finally, a lack of standardized cognitive testing. A randomized trial that is adequately powered, includes asymptomatic otherwise healthy patients, and uses standardized cognitive testing is currently underway to provide a more definitive answer to this important clinical problem (Marshall et al., 2018).

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Chapter 9
Cardiac Arrest

Chun Lim and Michael Alexander

9.1 Introduction

The human brain is dependent upon the delivery of oxygen and glucose and the removal of waste products for normal activity with the interruption of this cycle resulting in tissue injury. A reduction of oxygen content within the brain parenchyma is the state of anoxia, while the cessation of blood flow is ischemia. There are many different etiologies of anoxia including a reduction in blood flow—stagnant anoxia; lack of oxygenation—hypoxic anoxia; insufficient oxygen transport—anemic anoxia; and a disturbance in the intracellular oxygen transport—histotoxic anoxia. In adults the most common cause is a combined hypoxic and ischemic injury caused by cardiac arrest.

For a neurological disease state with such high prevalence, surprisingly little is understood about the precise patterns of impairment or about the natural history of recovery. There are robust early predictors of outcome of anoxic-ischemic coma (Nolan et al., 2015; Wijdicks, 2006), but the outcome has rarely been specified beyond good, poor, and death.

This chapter is designed to examine the etiology, pathology, neurological sequelae, treatment, and outcome of patients who survive a cardiac arrest.

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_9

9.2 Epidemiology and Clinical Burden

Cardiac disease has been the leading cause of death in the United States since 1921, currently accounting for 30% of all deaths (Minino & Smith, 2001). In 1998 in the United States, 456,076 deaths, or 63% of all cardiac disease deaths were caused by cardiac arrest (Zheng, Croft, Giles, & Mensah, 2001)—a 7% increase over the previous 10 years. The average age of the cardiac arrest patients is approximately 65 years (Eisenburger et al., 1998; Kuilman, Bleeker, Hartman, & Simoons, 1999). Estimates of short-term survival from large population surveys of patients who have undergone resuscitation for cardiac arrest vary from 1.4% (Becker, Ostrander, Barrett, & Kondos, 1991; Lombardi, Gallagher, & Gennis, 1994) up to 20%(Fischer, Fischer, & Schüttler, 1997; Kuisma & Maata, 1996; Sedgwick, Dalzeil, Watson, Carrington, & Cobbe, 1993; Waalewijn, de Vos, & Koster, 1988). The best survival rate in the United States of about 15–20% comes from a suburban community in Washington State (Cummins, Ornato, Thies, & Pepe, 1991; Rea, Eisenberg, Becker, Murray, & Hearne, 2003), while the worst is the urban communities (Gaieski et al., 2017; Lombardi et al., 1994). With a mean survival rate of 8% (Chan, McNally, Tang, Kellermann, & CARES Surveillance Group, 2014), there would be 36,500 survivors of cardiac arrest every year in the United States alone. The long-term survival of these patients has been reported as 70–85% at 1 year (Chan et al., 2016; Fischer et al., 1997; Graves et al., 1997; Kuilman et al., 1999; Sedgwick et al., 1993), 66% between 2 and 5 years (Ladwig et al., 1997), 52% at 3.5 years (Earnest, Yarnell, Merrill, & Knapp, 1980), 44–77% at 5 years (Graves et al., 1997; Kuilman et al., 1999), 73% at 7 years (1999), and 18% at 10 years (Graves et al., 1997). Improvement in medical care has resulted in a steady increase in survival (Rea, 2003; Smith, Andrew, Lijovic, Nehme, & Bernard, 2015; Wong et al., 2014) and neurological outcomes (Chan et al., 2014) over time.

Chart reviews (Graves et al., 1997), telephone interviews (Ladwig et al., 1997), and neuropsychological testing (Roine, Kajaste, & Kaste, 1993) on patients who have survived a cardiac arrest have shown that one-quarter to two-thirds of all survivors have neurological deficits, and one-half of all survivors have cognitive or motor deficits of a magnitude that requires a major lifestyle change (Bergner, Hallstrom, Bergner, Eisenberg, & Cobb, 1985; Earnest et al., 1980; Graves et al., 1997).

Based on the reported rates for survival and impairment, we would estimate a yearly incidence of approximately 5/100,000 (12,000) survivors of cardiac arrest who will have persistent neurological deficits and a rolling prevalence of 50,000 impaired survivors in the United States. This is roughly equivalent to the number of patients diagnosed with multiple sclerosis in the United States every year (National Multiple Sclerosis Society, 2005). These numbers are increasing with the improvement of the "chain of survival" concept (Cummings et al., 1991), implementation of disease modifying therapy (The Hypothermia after Cardiac Arrest Study Group, 2002), and further refinement of the implantable defibrillator (Hlatky, Saynina, McDonald, Garber, & McClellan, 2002). This improvement also reflects an

improvement in neurological outcomes (Chan et al., 2014). For example, a nationwide study in Japan (Kitamura et al., 2012) demonstrated a near doubling (from 1.6% to 2.8%) of favorable neurological outcomes in 2009 compared to 2005.

9.3 Neuropathology

During a cardiac arrest, brain tissue can survive for about 4–5 min without oxygen and blood before irreversible damage occurs (Bass, 1985). The severity of brain damage is dependent upon the duration of ischemia, the degree of ischemia, the core temperature, and the blood glucose level (Auer & Benveniste, 1994). Even though cardiac arrest causes global ischemia and hypoxia, neuronal injury is maximal in specific focal regions, a concept known as selective vulnerability. For reasons still not entirely understood, the small- and medium-sized neurons of the striatum, the Purkinje cells of the cerebellum, the layer III neurons of the cerebral cortex, and thalamic neurons are the first areas to show degenerative changes (Auer & Benveniste, 1994; Kuroiwa & Okeda, 1994). The pyramidal neurons of the hippocampal formation may not show the earliest damage but undergo delayed neuronal death (Horn & Schlote, 1992; Petito, Feldmann, Pulsinelli, & Plum, 1987). The etiology of this delayed neuronal death is unknown, but factors thought to play a role include the intracellular formation of oxygen free-radicals and excessive neuronal excitability because the hippocampal pyramidal neurons are at the end of a major excitatory pathway (Auer & Benveniste, 1994; Murayama, Bouldin, & Suzuki, 1990).

There have been several studies on the temporal sequences of cell death after anoxia. Horn and Schlote (Horn & Schlote, 1992) examined the brains of 26 cardiac arrest patients and found the earliest damage occurring in cortical layers three, five, and six, appearing within the first few days. Purkinje cell necrosis was observed up to day 6. Rapid hippocampal pyramidal neuronal cell death was seen from days 4 to 7. Petito et al. (1987) found a similar pattern in their review of 14 cases and concluded that the cortex and basal ganglia suffered early damage (occurring within the first 18 h) while the hippocampus suffered delayed necrosis at greater than 24 h.

The pathology literature is dominated by patients who suffered a severe anoxic injury and early death. Little is known about possible regionally specific brain pathology in patients suffering less severe anoxia. Although selective vulnerability is the accepted theory to account for the patterns and distribution of neuronal damage and patterns of clinical impairment, the precise relationship between pathology and clinical signs is incompletely understood.

Hypoxic–ischemic damage to specific regions of the brain is, nevertheless, certainly responsible for the diverse, specific neurological deficits. Immediate (hours to days) complications of cardiac arrest include death, coma (Levy et al., 1985; Yarnell, 1976), severe encephalopathy (Sawada et al., 1990), seizures (Madison & Niedermeyer, 1970), myoclonus (Lance & Adams, 1963), and cortical blindness

(Sabah, 1969). Long-term complications include persistent vegetative state (Sazbon, Zabreba, Ronen, Solzi, & Costeff, 1993; Yarnell, 1976), diffuse injury (Parkin, Miller, & Vincent, 1987), amnestic syndrome (Volpe & Hirst, 1983), frontoexecutive dysfunction (Armengol, 2000; Reich, Regestein, Murawski, DeSilva, & Lown, 1983), visuospatial dysfunction (Howard, Trend, & Ross Russell, 1987; Kase, Troncoso, Court, Tapia, & Mohr, 1977), pyramidal tract weakness (Allison, Bedford, & Meyer, 1956), extra-pyramidal disorders (Hawker & Lang, 1990), ataxia (Lance & Adams, 1963), spinal cord infarct (Silver & Buxton, 1974), and other very rare disorders. The frequency of each of these complications and whether they co-occur in any particular pattern are not known. Whether the course of recovery or specific outcome conditions (other than death) is tightly related to the severity of the hypoxic–ischemic event is unknown. It is also unknown if any pattern of early deficits is systematically linked to long-term sequelae.

For the clinician, there are several levels of importance: (1) predicting acute survival as a basis for judgment about intensive support, (2) managing and predicting short- and long-term recovery among survivors, (3) recognizing the range of residual deficits and the implications for specific vulnerability, and (4) working knowledge of the utility of proposed treatments.

9.4 Acute Prediction of Survival and Quality of Recovery

The bulk of outcome prediction research was collected before the advent of targeted temperature management (TTM). While targeted temperature management improved survival (Bernard et al., 2002; The Hypothermia after Cardiac Arrest Study Group, 2002), it was initially unclear how it affected outcome prediction (Nielsen et al., 2013). Pooled data suggests that TTM incurs a survival and neuroprotective benefit (Schenone et al., 2016). It has also become clear that it impacts the prognostic utility of clinical examination and laboratory testing. TTM may alter or delay the course of neurological recovery, and hence, the timing of assessing prognosis remains unknown. Validated protocols for assessing outcomes following TTM are rare, biased by withdrawal of care (Gold et al., 2014; Mulder et al., 2014), and in the absence of a standard consensus protocol, continue to rely on pre-temperature management data.

9.4.1 Examination

There is no measure of injury that has proven uniformly informative about severity. Duration of anoxia, time to CPR and defibrillation, or cause of cardiac arrest accurately does not predict the outcome (Wijdicks, 2006), although one study showed

that >99% of patients with favorable outcomes, defined as cerebral performance category[1] (CPC) of 1–2, had CPR of less than 35 min (Goto, Funada, & Goto, 2016).

Only about 25% of out-of-hospital cardiac arrest patients survive to hospital admission (McNally et al., 2011), with approximately 25% awake (Longstreth, Inui, Cobb, & Copass, 1983). Relying on the level of consciousness to predict outcome, Longstreth et al. (1983) found that of those patients who awakened after 24 h, 73% had cognitive or motor deficits. After 4 days of coma, no patient ever fully recovered. This predictive method may not apply to those who have not received targeted temperature therapy because several recent studies have found that over 80% of patients who received targeted temperature therapy who awakened after 72 h were discharged with a CPC 1–2 (Gold et al., 2014; Grossestreuer et al., 2013). While this may not be a true discrepancy since CPC of 1 includes patients with minor neurological deficits, there are reports of patients in coma for greater than 7 days, who received TTM, with good outcomes (Greer, 2013; Grossestreuer et al., 2013). Other studies confirmed that the early awakeners generally have good outcomes with only between 13% and 23% having any motor or cognitive deficits compared to 52% and 73% of the patients awakening after 12 h having deficits (Earnest, Breckinridge, Yarnell, & Oliva, 1979; Snyder et al., 1980). Sazbon et al. (1993) and others (Estraneo et al., 2013) followed patients with a history of 30 days or more of unconsciousness for at least 5 years and found that not a single patient recovered to a state of moderate disability or better.

The most straightforward and predictively useful applied evaluation is the clinical examination. The critical aspects of the acute, clinical examination are description of the depth of coma and the status of the critical vegetative brainstem functions. Assessment of coma may be complicated by intensive care management. The reliance on using the neurological examination to predict neurological outcome was initially based on the work by Levy et al. (1985). They and others (Edgren, Hedstrand, Kelsey, Sutton-Tyrrell, & Safar, 1994; Zandbergen et al., 2006) have shown that the absent pupillary light reflex after 24 h has a 100% positive predictive value (PPV) for a poor outcome. The sensitivity of this test is only around 20%. Subsequent to TTM, there have been reports of patients who did not have one or more brainstem reflexes at day 3 (Bouwes et al., 2012; Dragancea et al., 2015; Rossetti, Oddo, Logroscino, & Kaplan, 2010) with good outcomes (CPC 1–2). An automated pupillometry approach may ultimately have the best predictive value in assessing outcomes (Solari et al., 2017).

Absent motor response to painful stimuli at 72 h is a more sensitive test (around 60%) with two pre-TTM class I studies (Edgren et al., 1994; Levy et al., 1985) having a PPV of 100%, but (Zandbergen et al., 2006) five out of 105 patients with absent motor responses at 72 h were awake after 1 month in the most recent class I

[1] Cerebral performance category: CPC of 1 indicates good cerebral performance but may have minor psychological or neurological deficits. CPC of 2 indicates moderate cerebral disability typically resulting in impairment of activities of daily living. CPC of 3 is severe cerebral disability with dependence upon others for daily support. CPC of 4 is coma or vegetative state, and CPC of 5 is death.

study. The motor response appears to have been most affected by TTM (Al Thenayan, Savard, Sharpe, Norton, & Young, 2008; Dragancea et al., 2015; Rossetti et al., 2010) and is no longer felt to be a useful predictor of poor outcome.

9.4.2 Laboratory Studies

Prolonged cardiac arrest results in metabolic cell death with the release of intracellular contents, and recent studies have explored the utility of assays of brain enzymes as a potential marker of injury severity and outcome. Studies have focused on serum neuron-specific enolase (NSE) (Karkela, Bock, & Kaukinen, 1993; Schoerkhuber et al., 1999; Zandbergen et al., 2006), serum astroglial S100 (Pfeifer et al., 2005; Zandbergen et al., 2006), brain-type creatine kinase isoenzyme (Karkela et al., 1993; Karkela, Pasanen, Kaukinen, Morsky, & Harmoinen, 1992), and CSF lactaid (Edgren, Hedstrand, Nordin, Rydin, & Ronquist, 1987). These studies indicate that serum NSE levels >33 μg/L between days 1 and 3 following cardiac arrest most accurately predicts poor outcome with a PPV of 100% and sensitivity around 50%, but again, its predictive value has diminished post-TTM with debates on the cutoff value and timing (Bouwes et al., 2012; Oksanen et al., 2009; Rundgren et al., 2009; Tiainen, Roine, Pettilä, & Takkunen, 2003). One small study showed that abnormal serum astroglial S100 levels at day 3 was associated with low test performance in attention, memory, and executive function (Prohl, Bodenburg, & Rustenbach, 2009).

Recently, an offshoot of the Targeted Temperature Management study (Nielsen et al., 2013) used a novel assay to detect serum levels of axonal injury maker tau in 689 cardiac arrest patients (Mattsson et al., 2017). They found that at 72 h, serum tau levels above 72.7 ng/L had a PPV of 100% in predicting poor outcome (CPC 3–5) with a sensitivity of 42%. Reducing the cutoff to 13.4 ng/L brought up the sensitivity to 65% with a false-positive rate of 1%. Tau did not appear affected by TTM, and low levels or decreasing levels from 24 h to 72 h may predict a good outcome (CPC 1–2), although sensitivity and specificity were not discussed.

Serum tau has the potential to be a more practical test because it may have utility in other disease such as traumatic brain injury (Liliang et al., 2010; Ost et al., 2006) and dementia (Shekhar et al., 2016). These tests currently offer little practical utility because many hospitals cannot provide rapid turnover of these test results.

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9.4.3 Electrophysiology

Electroencephalography (EEG) and somatosensory evoked potentials (SSEP) supplement the clinical examination and laboratory tests as predictive measures of poor outcome. Generalized suppression, burst suppression, or generalized periodic

complexes on a flat background EEG patterns within the week of admission almost invariably resulted in death or vegetative state (Edgren et al., 1987; Rothstein, Thomas, & Sumi, 1991; Scollo-Lavizzari & Bassetti, 1987), although in a single study, two patients with malignant EEG had a good recovery (Chen, Bolton, & Young, 1996). TTM has likely altered the predictive value (or timing) of EEG because the most recent large group analysis demonstrated a false-positive rate of 1.5% (Rossetti et al., 2017) in patients with highly malignant EEGs.

Specific seizure types can also portend a grim prognosis. Initially, several controlled studies have shown that the presence of myoclonic status epilepticus within the first 24 h has grim prognosis (PPV of 100%) (Wijdicks, Parisi, & Sharbrough, 1994; Zandbergen et al., 2006), although there has been a case report of a survivor of myoclonic status epilepticus (Arnoldus & Lammers, 1995). A lack of a clear standard definition of myoclonic status epilepticus continues to cloud prognostication, as some papers have relied on the clinical presence of sustained myoclonus (Arnoldus & Lammers, 1995; Wijdicks et al., 1994) regardless of EEG correlation. When outcomes were examined in post-TTM patients with myoclonus with or without EEG evidence of seizures, those patients with corresponding poor EEG (suppression-burst background with spike-wave discharges in lockset with myoclonic jerks) had a much poorer prognosis (Elmer et al., 2016), but even with these stricter criteria, 1% of these patients have good outcomes (Seder et al., 2015).

Absent SSEP within the first week was also predictive of poor recovery. The only class I study (Zandbergen et al., 2006) and six class III studies (Bassetti, Bomio, Mathis, & Hess, 1996; Berek et al., 1995; Chen et al., 1996; Gendo et al., 2001; Logi, Fischer, Murri, & Mauguiere, 2003; Madl et al., 2000) observed that no patient with bilaterally absent N20 response ever recovered. A single class III study (Young, Doig, & Ragazzoni, 2005) had a false-positive rate of 6%. A meta-analysis of these eight studies (Wijdicks, 2006) demonstrated a PPV of 99.3% with a sensitivity around 50%. Post-TTM studies have generally supported SSEP as a highly specific predictor of poor outcomes (Bisschops, van Alfen, van der Hoeven, & Hoedemaekers, 2011; Bouwes et al., 2009; Leithner, Ploner, Hasper, & Storm, 2010; Rossetti et al., 2010; Tiainen, Kovala, Takkunen, & Roine, 2005) with a few controversial good outcomes (Bouwes et al., 2012; Dragancea et al., 2015).

An earlier meta-analysis and recent comparative, prospective study by a group in the Netherlands (Zandbergen et al., 2006; Zandbergen, de Haan, Stoutenbeek, Koelman, & Hijdra, 1998) evaluating various early prediction of poor outcome, including clinical examination, brain enzymes, and electrophysiology, demonstrated that absence of SSEP at any time within the first week was the most useful predictor of poor outcome. This has been validated (Geocadin et al., 2006) showing that this was the clinical parameter most relied upon by neurologists to estimate prognosis.

9.4.4 Neuroimaging

Imaging is frequently obtained in survivors of cardiac arrest, but to date, there is no datum on the utility of these modalities to predict outcome in survivors of cardiac arrest. While highly informative, the subjective interpretation and day-to-day variability in abnormalities (Greer et al., 2011) has diminished imaging's utility as a reliable outcome prognosticator. Early CT findings of comatose patients revealed diffuse cerebral edema and occasional low densities in the basal ganglia, thalamus, or watershed distributions (Fujioka, Okuchi, Sakaki, Hiramatsu, & Iwasaki, 1994; Kjos, Brant-Zawadzki, & Young, 1983). MRI in comatose cardiac arrest patients using fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted (DW) imaging demonstrated early signal abnormalities in the cerebral cortex, cerebellum, thalamus, and hippocampus (Wijdicks, Campeau, & Miller, 2001), and in the cerebral white matter (Chalela, Wolf, Maldjian, & Kasner, 2001). (See Fig. 9.1 for a representation of images of a comatose survivor of a cardiac arrest who died 3 days later.)

Not surprisingly after a direct metabolic injury to neurons, there is a significant reduction in brain metabolic activity in patients with acute cardiac arrest. Mean cerebral glucose utilization in vegetative or comatose subjects is reduced by 38% (Roine et al., 1991) to 50% (DeVolder et al., 1990), compared to a 25% reduction in conscious patients. The reduction is in the watershed distributions of the cerebral cortex, the basal ganglia, and the thalamus. Progressive decline of oxygen metabolism may foretell prolonged coma (Edgren, Enblad, Grenvik, & Langstrom, 2003).

Although non-randomized and non-prospective, these imaging studies do offer some useful markers of a bad outcome (death or severe disability): brain swelling on CT scan on day 3 (Morimoto, Kemmotsu, Kitami, Matsubara, & Tedo, 1993), extensive abnormalities on MRI DWI and FLAIR images (Wijdicks et al., 2001), and >50% perfusion deficits of the supratentorial brain on SPECT scan (Roine et al., 1991). The converse is less useful: structural imaging may be normal in patients who will survive with substantial neurological deficits (Alexander, 1997; Carbonnel, Charnallet, David, & Pellat, 1997; De Renzi & Lucchelli, 1993; Rupright, Woods, & Singh, 1996; Speach, Wong, Cattarin, & Livecchi, 1998).

More recently the use of quantitative image analysis at around day 3 can be used as adjunctive information to improve diagnostic accuracy in predicting poor outcome while maintaining specificity using CT measurements (Kim et al., 2013; Wu et al., 2011) or DWI analysis (Hirsch et al., 2016; Kim et al., 2016; Wijman et al., 2009; Wu et al., 2009). Analysis of thresholds remains variable and subjective; thus, its use as a stand-alone prognosticator has not been demonstrated. The advent of resting-state functional connectivity MRI analysis may hold promise because preliminary studies have demonstrated a reduction in the default mode connectivity, maybe associated with poor outcome (Koenig et al., 2014; Norton et al., 2012).

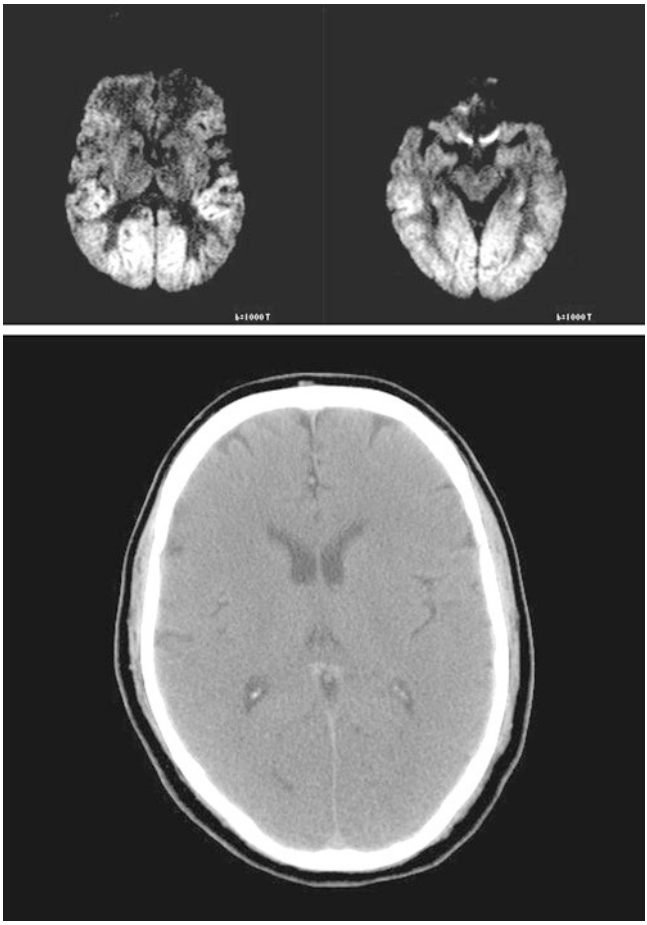

Fig. 9.1 Diffusion-weighted MRI images (**a**, **b**) and CT image of a 53-year-old man who suffered a 30-min cardiac arrest. Diffusion images reveal areas of restricted diffusion within the entire cerebral cortex. CT scan shows evidence of gross edema with effacement of sulci and loss of grey/white matter junction

9.4.5 Summary

The recent study by the Netherlands group (Zandbergen et al., 2006) also examined whether the predictive values of various tests and clinical findings were additive in increasing sensitivity. They found that the combination of the SSEP and NSE raised the sensitivity to 66% and the addition of EEG (burst suppression or worse pattern) increased it to 71% while maintaining 100% PPV.

The current recommendations from the American Academy of Neurology (Wijdicks, 2006), updated by the European Resuscitation Council (Nolan et al., 2015) involves a decision tree using the variables pupillary light reflex, corneal

reflex, motor response to pain, myoclonic status epilepticus, NSE, and SSEP to aid in the prediction of outcome in survivors of cardiac arrest. This algorithm involves the near certain prognosis of a poor outcome with absent brainstem reflexes (pupillary and corneal reflexes) or absent N20 responses on the SSEP after 72 h, and the likely prognosis of a poor outcome with the presence of status myoclonus, unreactive burst suppression or worse on EEG, or elevated serum NSE after 72 h. Even with the adoption of this algorithm, the sensitivity remains poor.

There remains no clinical finding or test result that reliably predicts a good outcome.

9.5 Course of Recovery

Caronna and Finklestein (1978) have proposed that patients in coma for less than 12 h suffer from a reversible encephalopathy and usually make a rapid and complete recovery, whereas the more severe hypoxic–ischemic patients are in coma for longer than 12 h and suffer structural damage to specific brain regions. In regard to time to awakening, several studies (Earnest et al., 1979; Longstreth et al., 1983; Snyder et al., 1980) found that 15–27% were awake upon arrival to the hospital and 20–43% of survivors would awaken after 12 h. The most common recovery pattern was of early in-hospital awakening to a confusional state to clearing of cognitive deficits (at least overt ones) during the hospitalization (Levy et al., 1985; Longstreth et al., 1983; Snyder et al., 1980). This has been supported by anecdotal case reports of patients progressing from coma to reportedly normal within 24 h (Sabah, 1969) and of isolated amnestic syndromes recovering over 10 days (Finklestein & Caronna, 1978).

As outlined above, there is a fairly inviolate relationship between duration of coma and the quality of recovery. For coma greater than 4 days, the probability of a good outcome falls dramatically (Longstreth et al., 1983). Patients who present comatose who do not wake up will progress to brain death or vegetative state, a state of wakefulness without detectable awareness (Jennett & Plum, 1972). A vegetative state present 1 month after brain trauma is defined as a persistent vegetative state (Multi-Society Task Force on PV, 1994). Among all nontraumatic causes, 53% die, 32% remain in persistent vegetative state, and 15% recover consciousness (1994). Of those who awoke, only 1 out of 15 had a good outcome, but the underlying etiology of that one patient was not clarified. The remaining 14 were severely disabled, many with minimal communication at best and all dependent (Higashi et al., 1981). Estraneo et al. (2013) followed 43 anoxic patients for 2 years after entering persistent vegetative state and found only 9 awoke, all with severe disabilities. Thus, contrary to traumatic brain injury, all patients who remain unresponsive for more than 1 month following anoxic brain injury have poor outcomes.

For those who awaken, the course of recovery is, however, similar for all injuries, except for the severe injuries—slower and incomplete. All patients awaken, that is,

their eyes open, marking the end of coma in the narrowest sense. More mildly injured patients progress almost immediately into a confusional state. More severely injured patients remain vegetative—eyes open, random eye movements without fixation, and without any directed responsiveness—before moving into a confusional state.

Confusional states are conditions of impaired attention with or without impaired arousal. They are characterized by reduced ability to sustain attentional focus, easy distractibility, poor registration of new information, and defective recall of experience. Patients are often agitated. Sleep is often disrupted. Over hours to weeks, depending on severity, confusion clears, that is, attention improves. Only when confusion has cleared, can the nature and severity of residual deficits be judged.

Determination of the overall distribution of severity of residual deficits will be influenced by the timing and setting of patient accrual, and by the measure of severity. One prospective study of patients in coma for at least 12 h (Caronna & Finklestein, 1978) demonstrated 3-month mortality of 60%, severe disability or vegetative state of 20%, moderate disability of 8%, and good recovery of 12% (30% of all survivors). Differences in "moderate" and "mild" probably reflect differences in measures used. Another prospective study included patients who had already survived at least 3 weeks and were medically stable enough to be evaluated for definitive cardiac management. The percentages with good recovery was 28% at initial (3 weeks) evaluation, 43% at about 2 months, and 71% at 6 months (Sauve, Doolittle, Walker, Paul, & Scheinman, 1996). This study suggests that there exists a subgroup of patients who will have some late recovery. In a retrospective, population-based chart review, Graves et al. (1997), using the poorly sensitive cerebral performance category (CPC), revealed that after 1 year 29% of patients in CPC3 and 77% of patients CPC2 improved by at least one performance category. Case reports also mention severely impaired patients who make remarkable recovery within the first 1–3 months of injury (Goh, Heath, Ellis, & Oakley, 2002; Kam, Yoong, & Ganendran, 1978; Kaplan, 1999). Contrary to the above studies, Kim et al. (2016), also relying on the CPC, showed that only 4% of their patients improved from CPC 3 to CPC 2 over the first 6 months, and none improved after 6 months.

Patients admitted to rehabilitation centers will be the ones with persistent significant deficits once medically stable, but not such severe deficits that they cannot participate in therapies. The point of initial assessment will usually be 2–4 weeks after arrest. Fertl, Vass, Sterz, Gabriel, and Auff (2000) observed that 35% of their patients, all with CPC of 3, improved one performance category and 10% improved two categories during the 3-month rehabilitation. They also noted an improvement of the mean Barthel index of all their patients from 28 to 61. At time of discharge from rehabilitation hospital, 35% had moderate and 55% had severe deficits. Roine et al. (1993) traced cognitive recovery, albeit with a very coarse instrument for this purpose, the Mini Mental State Exam, and found very little change after 3 months. Others have noted no improvement after 4 months (Groswasser, Cohen, & Cosfeff, 1989) or 8 months (Drysdale, Grubb, Fox, & O'Carroll, 2000). We prospectively

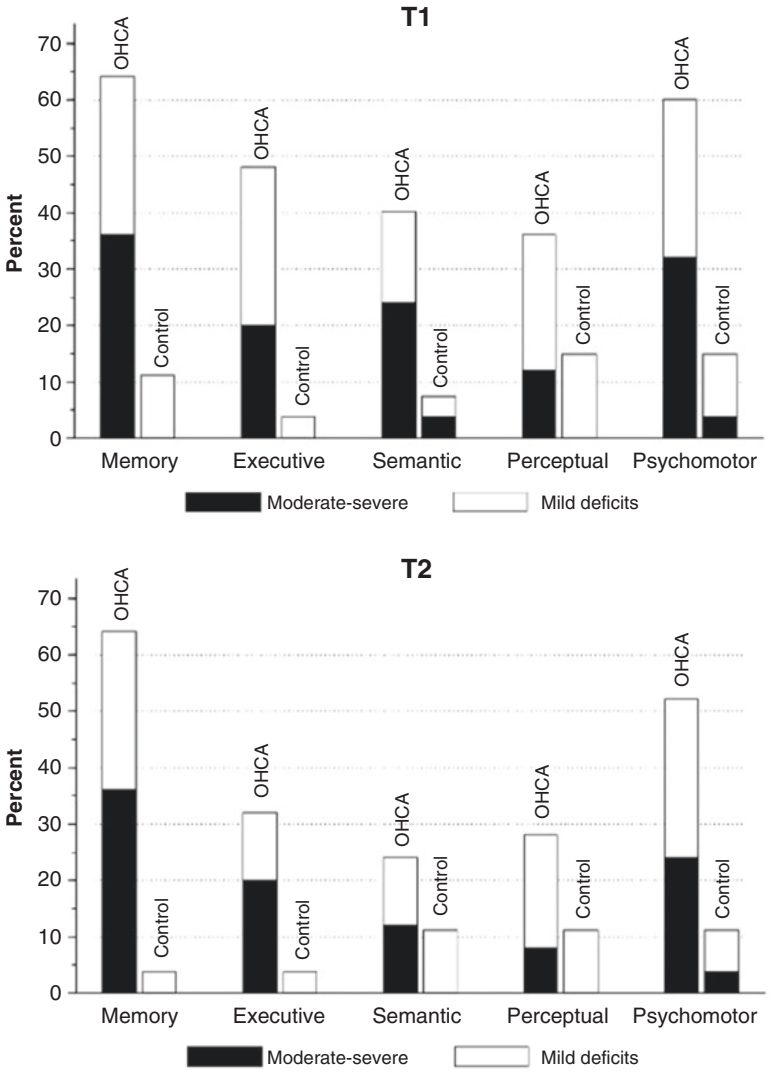

Fig. 9.2 Neuropsychological deficits at 3 months (T1) (**a**) and 12 months (T2) (**b**) post-injury. Percentage of out-of-hospital cardiac arrest (OHCA) and control patients with mild (z-scores between −1 and −2) or moderate-severe (z-scores ≤−2) deficits in each domain

followed 25 survivors for 1 year and noted (1) the bulk of the recovery occurred within 3 months, (2) there was no further recovery of memory function after 3 months (see Fig. 9.2), (3) memory performance predicted quality of life (Lim, Verfaellie, Schnyer, Lafleche, & Alexander, 2014).

9.6 Residual Deficits

The focus of this discussion will be on the cognitive deficits because those are almost universally most limiting. The majority of the literature consists of case reports motivated by interest in the cognitive impairment rather than the range of neurological consequences of cardiac arrest. Some investigators were indifferent to the etiology of the hypoxic event. Most group studies followed the same approach, with only a few examining the patterns, frequency, and natural history of the survivors of cardiac arrests. In some reports, there was a broad latitude in the diagnosis of a hypoxic event, and in others, multiple etiologies of hypoxia were considered together without isolating the cardiac arrest patients from other etiologies. We will describe the specific persistent cognitive impairments that have been reported as well as where those impairments fit into the more common characterization of arrest outcomes by severity.

The case reports examining some aspects of cognition after cardiac arrest do offer some insight into the nature of possible impairments. We found 22 case reports with 39 patients who suffered an uncomplicated cardiac arrest (Table 9.1). There were two cases presenting with virtually unique clinical syndromes, one with loss of semantic knowledge (Alexander) and the other with delayed dystonia (Boylan). There were three cases with cognitive deficits in a single domain, with two amnestic (Cummings and Volpe) and one with visual perceptive problems (Rizzo). Based on the clinical description of the cases, we arbitrarily divided the patients into three categories: mild, moderate, or severe. One case had no deficits, nine cases had multiple deficits of moderate severity, and 12 cases had severe deficits. The remaining 12 cases had insufficient clinical or neuropsychological information to categorize. A large number of case reports did not have an isolated cardiac arrest.

The patients in the moderate-injury category presented with a very wide range of signs and symptoms. Coma duration ranged from 15 min to 1 week. Some awoke with no initially reported neurological abnormalities (Reich, case 6), and others were confused and disoriented (McNeill). All patients had deficits in more than one domain.

Of the 12 severe cases, eight reported coma duration, and all were comatose for more than 24 h. Two other cases were confirmed to have been in coma, but the duration was not provided. All four patients whose emergence from coma was described had a severe confusional state. All patients had deficits in every domain tested, although not all domains were tested or discussed in each case report.

The group studies, in contrast to the case reports, offer population-based information, but often lack detailed neuropsychological evaluations and frequently involved a mixed population. Roine et al. (1993) observed that the most common deficits among 68 consecutive survivors of cardiac arrest at 3 months were disorders of memory (49%), visuoconstructive dyspraxia (43%), and dyspraxia (42%), followed by problems with motivation (37%), depression (35%), programming of activity (34%), and dyscalculia (31%). Language disorders were uncommon (3%). The high frequency of memory disturbances has been confirmed by others, with

Table 9.1 Summary of case reports of survivors of isolated cardiac arrest

Study	Case	Age/ sex	Time to testing	Coma	Category	M	FE	VS	EPS	MO	C	S	L
Alexander		43/M	1 month	5 days	Severe	++	−	+		+			+
Allison	5	41/M		Yes	Severe		+	+					+
	6	19/M			Mod			+		+			+
Armengol	2	45/M	13 months	42 hours	Severe	++	++	++		+			
	5	47/M	15 months	15 days	Severe	++	++	++		+			
Barnes		46/F	1 year	24 hours	Mov	+			++				
Bengtsson	1	54/M	3 years		N/A	+		+					
	2	78/M	3 years		N/A	+	+	+					
	3	70/M	3 years		N/A	+	+	+					
	6	60/M	2.5 years		N/A	+		+					
	9	54/F	2 years		N/A	+	+	+					
	11	73/F	1.5 years		N/A	+	+	+					
	12	58/M	1 year		N/A	+	+	+					
	13	74/M	1 year		N/A	+	+	+					+
	15	81/F	10 months		N/A	+	+						
	18	63/F	7 months		N/A		+						
Boylan		50/M	2 years		N/A				++	+			
Bruni		56/M	1 month	4 days	Severe		+		+	+	+		
Carbonnel		55/M	1 year	1 week	Severe	+		++					+
Cummings		53/M	3 months		Amn	++	+	−		+			−
Dalla Barba		57/F	5 months	6 hours	Mod	++	++						−
Feve	4	34/M	1 month	1 week	Mod			+	++	−			
Lance	1	64/F	8 years	4 days	N/A				+		+		
	2	62/M	4 years	3 days	Mod	+			+		+		
McNeill		49/F	6 years		Mod	++	+	−		+			
Norris	4	49/M	6 months	5 days	Mild								
	5	41/M	11 months	Days	Severe		+	+	+	+	+		+
Parkin		43/F	1 year	16 days	Severe	+	+	+	+		+		+
Reich	1	48/M	2 years	Hours	Mod	++	+						
	2	41/M	2 years	15 months	Mod	++	+						
	3	39/M	2 years	20 hours	Mod	++	+						
	6	56/M	6 months	24 hours	Mod	+	+						
Rizzo	1	65/M			Vis	−		++					
Ross		58/M	3 years	Yes	Severe	++	++	+					+
Rupright	1	40/M	2 years		Severe	+	+	+					
	4	31/F	1 month		Severe			+					
Silver	5	54/M	2 months	24 hours	Severe	+						+	
Szlabowicz		43/M	1 month	8 days	Severe								
Volpe	2	42/M	18 months		Amn	++	−	−		+			−

Abbreviations: *M* memory deficit, *FE* frontoexecutive deficit, *VS* visuospatial deficit, *EPS* extrapyramidal deficits, *MO* motor deficits, *C* cerebellar deficits, *S* spinal deficits, *L* language deficits, *Mod* moderate, *Diff* diffuse, *Amn* amnestic syndrome, *Vis* isolated visuospatial deficit, *Mov* isolated movement disorder

+ Neurological deficit by report or mild deficit verified by neuropsychological testing

++ Substantial neurological deficit verified by neuropsychological testing

− No neurological deficit by report or verified by single neuropsychological testing

−− No neurological deficit verified by two or more neuropsychological tests

ranges from 80% (Grubb et al., 2000) to 100% of patients examined (Kotila & Kajaste, 1984; Pusswald, Fertl, Faltl, & Auff, 2000). Visuospatial impairments have also been common, occurring in 30–100% of these patients. None of these studies specifically examined executive functions.

Wilson (1996) performed neuropsychological assessments in 18 survivors of cerebral hypoxia to explore for consistent cognitive profiles. Equipped with an unusually balanced battery of neuropsychological tests for this literature, she identified five distinct patterns: (1) an amnesic syndrome; (2) memory and executive deficits; (3) memory, executive, and visuospatial deficits; (4) isolated visuospatial impairments; and (5) widespread cognitive deficits. With the analysis restricted to survivors of cardiac arrests, there were three profiles: (1) memory and executive deficits; (2) memory, executive, and visuospatial deficits; and (3) widespread cognitive deficits. There were no isolated amnesic or visuospatial syndromes in her pure cardiac arrest patients, which seemed to occur more frequently from other causes of anoxia. Her patient population was small, but if isolated cognitive deficits occur after cardiac arrest, they must be at a very low frequency.

Volpe, Holtzman, and Hirst (1986) has reported the largest series of patients with isolated amnesia after cardiac arrest. These six patients had memory quotients at least 20 points below full-scale IQ, with normal performance on Ravens Progressive Matrices, the Wisconsin Card Sort task, and the Controlled Oral Word Association test. Clinical data, raw scores, and measures of motor control, mood, or behavior were not reported, but these patients appear to represent a pure amnestic syndrome.

It would seem likely that chronically amnestic patients might have hippocampal atrophy, and more diffusely impaired patients might have cortical atrophy. This hypothesis has been explored, although there are limitations because so many of the arrest survivors have implanted defibrillators now and cannot have an MRI. Grubb et al. (2000) compared MRI-brain volume in memory impaired and memory intact survivors of cardiac arrest. They did not find selective hippocampal atrophy in their memory impaired patients. Reduction in whole brain volume significantly correlated with memory impairment. Hopkins and colleagues have done MRI volumetric on a number of anoxic patients. In a series of papers comparing anoxic patients to controls, they (Hopkins & Kesner, 1995) found a reduction in hippocampal areas but not temporal lobe or parahippocampal gyrus volume. Another study (Hopkins et al., 1995) did suggest a relationship between morphological abnormalities with performance on cognitive testing, but was limited to three patients. The largest study comprised 13 patients, of whom only five had had a cardiac arrest, showed a strong correlation between performance on anterograde memory tests with both hippocampal and regional gray matter volume residuals (Allen, Tranel, Bruss, & Damasio, 2006).

We had the opportunity to study 11 cardiac arrest patients under the age of 80 years who were referred to a memory disorder clinic for persistent memory deficits (Lim, Alexander, LaFleche, Schnyer, & Verfaellie, 2004). Using standardized neuropsychological tests, we assessed their memory, executive function, perception, language and, motor function (see Table 9.2). Ten of our patients had moderate to severe memory impairment, and five had severe executive impairments. There

Table 9.2 Neuropsychological testing domains of 11 patients who has suffered an isolated cardiac arrest: mean *z*-scores or number of tasks on which performance was abnormal

Patient	Memory (*z*-score)	Executive (*z*-score)	Boston naming (*z*-score)	Perceptual impairment	Motor (*z*-score)
1	0.4	0.5	0.9	0/3	−1.0
2	−2.6	−0.6	0.1	0/3	−3.3
3	−2.5	−0.5	0.2	1/3	−2.1
4	−3.3	−1.8	−0.1	1/3	−5.0
5	−3.3	−1.2	−1.4	0/3	−2.1
6	−2.0	−1.2	0.8	0/3	−3.8
7	−3.2	−2.8	−1.2	0/3	−2.9
8	−6.5	−2.9	−2.4	0/3	−8.0
9	−3.1	−4.8	−5.1	3/3	−10.0
10	−3.5	−2.6	−9.5	2/3	−1.3
11	−3.6	−3.1	−2.7	1/3	−2.8

was only one patient impaired in lexical-semantic function and only one with perceptual difficulties. Nine patients had moderate to severe impairments in motor function. We performed a k-means cluster analysis which produced a three-cluster solution that yielded a cluster with no impairments (patient 1), a second cluster with memory and motor impairments and variable executive dysfunction (patients 4–6), and a third cluster with impairments in all domains (patients 7–11). No patient had an isolated neurological disorder.

Our patient 1 and the small number of case reports with no deficit or only subtle deficits presumably exemplify the largest outcome group of survivors of cardiac arrest. These patients with good recovery usually emerge early from coma. Whether the neural injury was entirely transient and reversible, or simply too mild to cause lasting deficits is unknown. As with our patient, there may be relative decrements in performance that are obscured by arbitrary cutoffs on tests, or functional deficits that are not detectable by neuropsychological testing. These patients are likely to be underrepresented in the literature.

Patients in our cluster 2, the four patients reported in the Wilson's study with memory and executive deficits (Wilson, 1996), and several of the case reports reviewed above uniformly had intermediate outcomes. The relationship between duration of coma and outcome is quite variable. We propose that these patients have not suffered permanent widespread cortical damage and may have damage restricted to the selectively vulnerable brain regions. To our knowledge, this hypothesis has not been directly addressed in any autopsy or adequately sensitive anatomical study. Our patients all had memory and motor impairments. We believe that executive deficits would also consistently have been detected if this group had been evaluated sooner after emergence from coma and confusion.

The patients in our cluster 3 and many of the patients whom we categorized as severe from case reports have similarly poor outcomes. These patients usually have long periods of coma (>24 h). In addition to memory and executive impairments,

language and visuospatial functions are disturbed, suggesting that the injury likely involved cortex as well as the more vulnerable subcortical and hippocampal regions. Motor deficits might have been prominent if they had been consistently assessed.

Neither the results from our patient group nor a critical review of the literature support the notion that isolated disorders of visual perception or memory occur frequently following cardiac arrest. Thus, the evidence that classic, abrupt CA results in isolated damage to the hippocampus and produces long-standing isolated amnesia is much weaker than commonly assumed. This is not to conclude that it cannot happen because there are descriptions of amnesia following cardiac arrest. We propose, however, that the residual deficits in most patients who survive cardiac arrest will fall along a continuum reflecting the severity of injury to those electively vulnerable sites. Impairment will range from no or subtle impairments to a mix of executive, learning, and motor control deficits to such severe executive deficits that all cognitive functions are impaired—a virtual, chronic confusional state. Intermixed within these patterns are the rare cases of isolated memory or visuospatial deficits, or unusual presentations such as semantic memory loss or delayed dystonia.

9.7 Treatment

9.7.1 Temperature Management

In 2002, two studies showed that 24 h of therapeutic hypothermia (TH) within the first 4 h of a cardiac arrest will improve overall outcome and survival (Bernard et al., 2002; The Hypothermia after Cardiac Arrest Study Group, 2002). The improved outcomes may not be the result of hypothermia, rather the avoidance of hyperthermia (Gebhardt et al., 2013; Nielsen et al., 2013; Zeiner et al., 2001), although the general evidence still supports the use of TH (Arrich, Holzer, Havel, Müllner, & Herkner, 2016; Schenone et al., 2016). Current consensus guidelines advocates for the maintenance of temperature between 32 and 36 °C, now known as targeted temperature management (Nolan et al., 2015).

There are several distinct epochs of management, each with its own treatment imperatives. There are few therapeutic interventions that directly affect the outcome of survivors of out-of-hospital cardiac arrest. Pharmacological interventions that have proven to be ineffective include nimodipine (Roine et al., 1993), thiopental (Brain Resuscitation Clinical Trial I Study Group, 1986), magnesium and/or diazepam (Fatovich, Prentice, & Dobb, 1997; Longstreth, Fahrenbruch, & Olsufka, 2002), sodium bicarbonate (Vukmir & Katz, 2006), and amiodarone and lidocaine (Kudenchuk et al., 2016).

As described above, patients emerge from coma into vegetative states or confusional states. There are no clinical studies of potential treatments for vegetative state after cardiac arrest. Confusional state is usually a transient condition during recovery, and in milder injuries, it may be rapid enough that no treatment issues emerge.

If there is a treatment concern, it is usually agitation. There are no controlled studies of treatment of agitation in this condition. Most adequately controlled studies are in the dementia literature. There are a few basic clinical observations that may assist management of confusion/agitation.

First, confusion and agitation are not synonymous. Treatment of confusion is probably limited to control of the environment around the patient—avoidance of over-stimulation, readily observed orientation material (calendars, clocks, pictures), and vigorous regularization of sleep phases. These should be implemented in every patient. Treatment of agitation should be modulated to the level of distress or inadvertent danger of injury that the patient presents. When possible, use of distractions may be sufficient—visits from family members, opportunities to converse with anyone on staff, recreational activities such as playing cards with a volunteer, watching sports on TV, etc. When the patient is very distressed, possibly becoming in inadvertent danger of injury or disruption of essential medical care, then supervision, passive restraints, and medications are required.

Second, the treatment targets of sleep onset and maintenance and of agitation reduction are not the same. Reduction of agitation should not produce excessive sleep or else sleep phases will become abnormal, probably worsening agitation. Second-generation antipsychotics such as quetiapine and olanzapine probably offer the best proportion of tranquilizing without excess sedation. Sleep onset is a separate problem, probably best addressed with standard hypnotics such as trazodone and short half-life benzodiazepines, but these medications will fail at sleep onset in a patient who is agitated, so they may require a preparatory dosage of antipsychotic to achieve a calm enough state that the hypnotic will be effective. Hypnotics should not be repeated too late at night or there will be further disruption of sleep phases due to daytime somnolence. Thus, management may require both treatments, each targeted at a specific factor.

For patients with significant residual deficits, there is at present little direct treatment. We could not identify any controlled studies or even large case reports of late rehabilitation interventions. We are aware of the off-label use of cholinesterase inhibitors, stimulants, and dopaminergic medications but with minimal sense of success and no reported claims of success. To judge by the reports of Grosswasser and Wilson described above—both reports coming from respected cognitive rehabilitation centers—there is little optimism that the fundamental deficits can be treated behaviorally. Whether patients with executive impairments after cardiac arrest might respond to some of the behavioral strategies that have been implemented in patients with trauma or focal frontal lesions is unknown.

There are many obstacles to the construction of useful interventions for these patients. We are not entirely clear about the nature of the residual deficits. Are they fundamentally executive function deficits? If so, there is a reasonable possibility of importing useful behavioral and medication treatments from the larger literature on treatment of trauma and focal lesions. When do they stabilize? How malleable are they over the post-acute epoch? Or do the patients who do not recover quickly also always have true memory system (hippocampal) injury as well? If so, behavioral treatments are likely to be insufficient to achieve any functional improvement. Until

treatments become more effective or until acute management discovers a biological intervention that prevents acute cell death and apoptosis, there will be a growing population of inadequately treated patients at risk for poor quality of life.

9.8 Quality of Life

Impairment does not necessarily lead to disability and handicap, but the reported effects on quality of life have been variable. We found that coma duration of greater than 3 days or presence of memory impairment at 3 months were associated with reduced quality of life (Lim et al., 2014). Cardiac arrest survivors fare significantly worse in all categories of their QOL compared to a random control population (Bergner, Bergner, Hallstrom, Eisenberg, & Cobb, 1984), and when compared to survivors of myocardial infarcts (Bergner et al., 1985; Lim et al., 2014). de Vos, de Haes, Koster, and de Haan (1999) showed that the quality of life of their cardiac arrest survivors were worse than an elderly control population, but better than that of patients with strokes. An 8-year follow-up of cardiac arrest patients found that the quality of life in patients was considered good (Kuilman et al., 1999), but the study lacked age-matched controls.

Evaluating the number of patients able to live independently or return to work may be the most sensitive markers of impairment, disability, and handicap. As many as 30–75% of survivors who awaken early are able to return to their previous level of employment (Bergner et al., 1985; Earnest et al., 1980; Graves et al., 1997; Kragholm et al., 2015; Sauve, 1995; Sunnerhagen, Johansson, & Herlitz, 1996). On the other hand, only 25% of patients who remain in coma for greater than 12 h return to work (Lim et al., 2014), while in those admitted to rehabilitation hospitals, fewer than 10% return to work (Groswasser et al., 1989; Howard et al., 1987). Approximately one-half of all survivors achieve full independence in all aspects of daily living (Earnest et al., 1980; Howard et al., 1987; Sunnerhagen et al., 1996) although many require substantial supervision and assistance for instrumental activities, finances, and social activities (Sauve, 1995). There is no datum on return to driving.

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Chapter 10
Cardiac Surgery and Cognition: Etiologies and Assessment Considerations

Jeffrey N. Browndyke and Benjamin J. Edner

10.1 Introduction

Over half a century of research substantiate that some individuals are at increased risk for perioperative neurological injury and postoperative cognitive dysfunction (POCD) following cardiac surgery (see Berger et al., 2018 for review; Lewis, Maruff, & Silbert, 2004). Perioperative neurovascular damage associated with cardiosurgical intervention ranges from overt stroke to covert embolic injury (Lansky, Messe, Brickman, & Dwyer, 2017), while other perioperative complications confer additive or additional risks (e.g., hypoperfusion, neuroinflammation, etc.; Krenk, Rasmussen, & Kehlet, 2010). While cardiosurgical procedures (both simple and complex) carry inherent risks for a myriad of potential neurological and systemic complications, the full panoply of causal mechanisms and their interaction producing POCD remain elusive (Berger et al., 2018; Gottesman, Hillis, Grega, & Borowicz, 2007; Jildenstål, Rawal, Hallén, Berggren, & Jakobsson, 2014). Noncardiac surgery has been associated with similar patterns of POCD (Grape, Ravussin, Rossi, Kern, & Steiner, 2012; Monk et al., 2008), but several lines of research demonstrate that both early and late onset rates of POCD are considerably higher among those who underwent cardiac compared to noncardiac surgery (Grape et al., 2012; Lewis, Maruff, & Silbert, 2004). While cardiac surgery is associated with higher rates of POCD and neurological complications, the presence of POCD in noncardiac surgical interventions suggests that there are shared general surgical

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_10

factors contributing to POCD onset and severity. The putative physiological correlate of both cardiac and noncardiac-related POCD primarily involves neuroinflammatory processes (Cibelli et al., 2010; Terrando et al., 2010; van Harten, Scheeren, & Absalom, 2012), while additional variability in POCD onset and severity maybe ascribed to perioperative and postoperative factors, such as embolic load and alteration in cerebral perfusion yielding changes in cerebral autoregulation (Berger et al., 2018).[1] The relationship between POCD and these underlying pathological processes will be discussed throughout this chapter, as well as broad discussion regarding the clinical assessment of POCD and the reliable measurement of cognitive change from pre- to postoperative recovery.

10.2 Cognitive Dysfunction Following Cardiac Surgery

Cognitive deficits following cardiac surgery may manifest through acute onset postoperative delirium (POD) or occur more gradually over the post-acute period, up to and in some cases beyond 3-months recovery[2] (i.e., postoperative cognitive dysfunction; POCD). Both POD and POCD are distinguishable from dementia. Dementia is a more pervasive and chronic decline in cognitive functions, with distinct etiology from POD and POCD (Tsai, Sands, & Leung, 2010), though it is understood that POD is associated with increased risk for later dementia (Cortese & Burger, 2017; Lingehall et al., 2017; Sprung et al., 2017). In contrast, POCD has not shown to reliably predict the onset of dementia (Steinmetz et al., 2012), although it is important to note that in a few longer-term longitudinal studies, POCD does appear to be associated with increased dementia risk following cardiac surgery (Evered, Silbert, Scott, Maruff, & Ames, 2016).

POD is an acute medical crisis manifest as significant and sudden disturbances in attention, arousal and awareness from baseline functioning (American Psychiatric Association, 2013), which is hypothesized to reflect an acute breakdown in brain network connectivity (Sanders, 2011). Symptom onset usually occurs within hours to a few days after surgery and typically presents with general disorientation and pronounced deficits in memory, language, visuospatial ability, and/or perception (APA, 2013). Rates of POD following cardiac surgery range from 14% to 50% (Rudolph et al., 2009; Sauer et al., 2014), but these rates likely underrepresent the true prevalence of delirium given significant variability in how delirium has been assessed and inconsistent clinical awareness of the syndrome (Berger, Browndyke, & Mathew, 2015).

POCD typically presents as subjective cognitive complaints and mild-to-moderate decline in a wide array of cognitive functions when compared to

[1] Refer to Berger et al. (2018) for comprehensive review of these mechanisms and their relation to postoperative delirium and postoperative cognitive dysfunction.

[2] FDA guidelines consider events attributable to intervention to be within 30 days, or any time during the surgical admission.

preoperative cognitive functioning (Lewis et al., 2004; Swartz, 2017; Tsai et al., 2010). Declines in cognitive domains of attention, working memory, processing speed (Krenk et al., 2010; Tsai et al., 2010), language comprehension, abstract thinking, social integration (Grape et al., 2012), and executive functioning (Tsai et al., 2010) have been described. POCD has been shown to be transient for a majority of patients, with symptoms lasting approximately three months and resolving within a year of initial symptom onset (Abildstrom et al., 2000; Ancelin et al., 2001). A considerable number of patients, however, may experience POCD symptoms for years (Newman et al., 2001; Selnes et al., 2001). Higher rates of POCD symptoms have been reported among older patients (Johnson et al., 2002; Monk et al., 2008; Postler, Neidel, Günther, & Kirschner, 2011) with age moderating POCD symptom severity (Swartz, 2017). While data indicate that POCD occurs frequently, incidence rates of POCD vary widely, due to a lack of formal criteria with respect to assessment and diagnosis (Wang et al., 2014), paucity of an international definition of the symptom clusters constituting POCD, as well as differing methods of data acquisition (Krenk et al., 2010).

POCD is typically conceptualized as having a 7- to 14-day delayed onset after surgery (Swartz, 2017), but this interval is largely borne from the notion that more acute postoperative cognitive changes are related to other postoperative factors (e.g., opioid analgesia, postoperative mobility/frailty, etc.; Morrison et al., 2003; Graham, 2017) or even sub-syndromal delirium (i.e., partial delirium features or mild dysfunction suggestive of an underlying deliriogenic process; Meagher, Adamis, Trzepacz, & Leonard, 2012). Research indicates that POCD occurs in approximately 15–20% of patients following surgical procedures (Bryson & Wyand, 2006) and is present in 30–40% upon hospital discharge (Monk et al., 2008).

There are no consistent or firm etiological bases upon which to pin the end of acute operative medical factors on cognition and the start of the traditionally viewed delayed onset of POCD. Indeed, depending upon how POD and POCD are assessed and defined, it has been demonstrated that both conditions may be present or serially interchangeable during the inpatient acute recovery period (Youngblom, DePalma, Sands, & Leung, 2014). The mutability of POD and POCD during the acute recovery period, as well as shared core cognitive characteristics (e.g., general cognitive dysfunction or decline in attention and executive skill domains), suggest that POD and acute POCD may reflect different points along a syndromal spectrum (Deiner & Silverstein, 2009). Indeed, it is now appreciated that POD is a significant risk factor for POCD during the later recovery period and even longer-term cognitive decline (Cortese & Burger, 2017; Devore et al., 2017). This chain of association suggests that both POD and POCD may share, in part, certain physiological and/or neurological determinants. It is known that preoperative cognitive dysfunction (particularly executive and attention deficits) and depression are risk factors for both conditions (Bekker et al., 2010; Greene et al., 2009; Jankowski et al., 2011; Leung, Sands, Mullen, Wang, & Vaurio, 2005; Smith, Attix, Weldon, Greene, & Monk, 2009), reinforcing the likelihood of broadly shared neurological substrates. Limited evidence from functional neuroimaging studies of POD and POCD suggest that one shared link may be found in brain regions associated with the “default

mode" network (Browndyke et al., 2017, 2018; Choi et al., 2012; Huang et al., 2018; Kyeong et al., 2017); a highly distributed and prominent cortical network involved in the mediation of internal state and task-oriented resource allocation (Raichle, 2001, 2015). POD and POCD disruption of this network central to consciousness and external attentional engagement may explain, in part, common cognitive deficits resulting from peri- and postoperative pathophysiological processes on top-down cognitive control.

10.3 Pathophysiologic Processes and Perioperative Iatrogenic Factors

10.3.1 Neuroinflammation

Neuroinflammation has been proposed as one etiological basis for POD (Cerejeira, Firmino, Vaz-Serra, & Mukaetova-Ladinska, 2010; Cortese & Burger, 2017; Vasunilashorn et al., 2015), POCD (Cibelli et al., 2010; Li, Wen, Zhao, Hang, & Mandell, 2013; Vacas, Degos, Feng, & Maze, 2013) and Alzheimer's disease (Cunningham & Hennessy, 2015; Heneka et al., 2015; Tang, Eckenhoff, & Eckenhoff, 2011). The invasive nature of surgery triggers damage-associated molecular patterns (DAMPs; Zhang et al., 2010) that lead to broad release of pro-inflammatory cytokines, microglia activation, and chemokines into both the periphery and central nervous system (CNS; Berger, Burke, Eckenhoff, & Mathew, 2014; Steinberg, Sundman, Terrando, Eriksson, & Olofsson, 2016). DAMPs trigger neuroinflammation by activating mast cells, triggering microglia activation and neuronal damage (Zhang, Dong, Li, et al., 2016). Wan et al. (2010) found that surgery in older rodents provoked astrogliosis, beta-amyloid accumulation, and tau phosphorylation. These processes in combination with peri- and postoperative partial breakdown of the blood–brain barrier (BBB; Reinsfelt et al., 2012; Zhang, Dong, Zhang, et al., 2016) can result in systemic inflammation entering the CNS (Terrando et al., 2010) without necessarily showing biochemical signs of neuronal damage (Reinsfelt et al., 2012). Within rodent models, migration of macrophages into the hippocampal regions via tumor necrosis factor-alpha (TNFα) following peripheral surgery yields BBB disruption (Rosczyk, Sparkman, & Johnson, 2008). For cardiac patients, cardiopulmonary bypass surgery has been found to increase BBB permeability as well as generate microemboli, both of which were shown to negatively impact cognitive functioning (Lund et al., 2003). Merino et al. (2013) found BBB dysfunction in 50% of cardiac surgery patients. The intensity and location of BBB disruption correlate more strongly with POCD than perioperative microembolic load (Abrahamov et al., 2017).

Anesthetic drug administration can also impact neuroinflammatory responses (Avramescu et al., 2016). Research indicates that anesthesia during cardiac surgery can modulate postoperative neurocognitive functioning (Berger et al., 2014). Such

modulation could occur via the impact of anesthetic agents on inflammation or synaptic function. Further, neuroinflammation could possibly stimulate a positive feedback loop, augmenting initial neuroinflammatory responses (Berger et al., 2018) due to increased neuronal sensitivity caused by anesthetic drugs (Avramescu et al., 2016).

Neuroinflammation can deleteriously impact cognition, memory, behavior, and mood (Capuron & Miller, 2011; Najjar, Pearlman, Alper, Najjar, & Devinsky, 2013). In humans, it appears to be associated with cognitive impairment without domain-specific deficits (Hovens et al., 2012), while in rodent models it is associated with more specific deficits in spatial learning and memory (i.e., hippocampal dependent cognition; Hovens et al., 2014). These possible distinctions between human and rodent cognitive impairment patterns, however, may be due to the limited range of cognitive domains amenable to rodent behavioral assessment (e.g., maze-type learning paradigms, matching-to-sample, etc.) and the aforementioned association of POD and POCD with the default mode network, where network dysfunction is more likely to impact a broad spectrum of cognitive abilities through impaired attentional allocation and task engagement (Browndyke et al., 2018). Despite initial recovery and/or functional improvements after cardiac surgery, peri- and postoperative neuroinflammation can accelerate cognitive decline and lead to increased dementia risk (Scott, Evered, & Silbert, 2014). The link between peri- and postoperative neuroinflammation and cognitive dysfunction is best illustrated by recent intervention studies. By blocking neuroinflammation, Terrando et al. (2011) demonstrated reduced memory deficits in postoperative rodent models, while Mittal et al. (2016) found cognition improvements in patients with autoimmune encephalitis. However, it is important to note that several clinical trials using anti-inflammatory agents did not prevent POD or POCD following cardiac surgery (Mathew et al., 2004, 2010, 2013), suggesting a more complex relationship between neuroinflammation and POD/POCD than can be addressed through simple prophylaxis.

10.3.2 Cerebral Embolic Injury

Peri- and postoperative cerebral embolic injury can deleteriously impact cognitive function depending on the eloquence or strategic importance of the affected brain regions (Selnes & Gottesman, 2009). Cerebral infarction can be focal or multifocal embolization, which can occur during cardiosurgical instrumentation or manipulation (Lansky et al., 2017). Cardiac surgery often disrupts atheromatous plaque due to direct aortic manipulation (Berger et al., 2018), and "silent" ischemic cerebral infarcts are common after a wide range of procedures (Bonati et al., 2010; Messé et al., 2014).

Intraoperative microemboli can be detected by a host of methods, including Doppler ultrasound (Dobler, 2004) with postoperative effects on diffusion-weighted magnetic resonance imaging (DWI-MRI; Mirow et al., 2011). However, "clinically covert strokes" (McDonagh et al., 2014) can occur when microemboli evade

detection due to lack of association with neurologic abnormalities during clinical examination and are associated with an increased risk of cognitive decline, Alzheimer disease, and stroke (Mirow et al., 2011). Embolic load may also be associated with altered brain activity during cognitive task performance (Abu-Omar et al., 2006).

Emboli can vary in size, with solid and gaseous compositions. Chaudhuri and Marasco (2011) point out that gaseous emboli are common during open cardiac cases. Gaseous microemboli can complicate interventional strategies to minimize embolic injury and by extension cognitive decline. Mack et al. (2017) found that patients undergoing surgical aortic valve replacement (SAVR) with embolic catchment devices did not reduce the risk of CNS infarction at 7 days post-surgery compared to the placement of standard aortic cannula. While embolic catchment devices in SAVR and transfemoral valve replacement approaches capture microemboli with solid composition (sometimes to a startling degree), the absence of a mitigating effect on stroke and cognition could be due to gaseous microemboli permeating through these devices. Despite a firm lack of efficacy in these catchment devices, the FDA has approved their use with the reasoning that any reduction in microembolic load must confer at least some cerebral protection benefit over standard procedures.

10.3.3 Cerebral Blood Flow and Autoregulation

Cardiosurgical procedures can impair autoregulation in up to 20% of patients with "pressure passive" cerebral blood flow (Ono et al., 2012), and patients with impaired autoregulation demonstrate increased rates of perioperative stroke (Joshi et al., 2010). While perfusion pressure during cardiopulmonary bypass (CPB) surgery is often kept at levels lower than physiologic mean arterial pressure (MAP), maintenance of MAP within a higher range of 80–90 mmHg—compared to 60–70 mmHg—has been associated with reduction in POD, as well as postoperative mini mental status exam (MMSE) scores more commensurate with preoperative performance (Newman et al., 1994; Siepe et al., 2011). The relationship between lower MAP values and POD rates could, in part, result from cerebral venous oxygen desaturations, compromising cerebral oxygen delivery (Croughwell et al., 1994). Intraoperative cerebral oxygen desaturations are more likely to yield POD and POCD in cardiac surgery patients both at 7 and 30 days following surgery (de Tournay-Jette et al., 2011; Schoen et al., 2011; Slater et al., 2009). In contrast, MAP exceeding optimum levels has also been associated with disrupted cognitive functioning. For example, Hori et al. (2016) found that excursions above the optimal MAP, as well as maintaining blood pressure above the upper limit of cerebral autoregulation, is associated with POD rates (Hori et al., 2015, 2016). Together, these results suggest that perioperative deviations from MAP in cardiac surgery are associated with cognitive dysfunction and delirium severity.

Metabolic rate of cerebral oxygen utilization is closely regulated by temperature (Berger et al., 2018). Reduction in temperature (i.e., hypothermia) may lower cerebral metabolic rate of oxygen utilization, which in turn can reduce brain oxygen deprivation from neurocognitive injury during periods of reduced oxygen delivery (Berger et al., 2018). As such, avoiding hyperthermia during rewarming following cardiosurgical procedures may help optimize postoperative cognitive function (Boodhwani, Rubens, Wozny, Rodriguez, & Nathan, 2006). For example, Grocott et al. (2002) found that maximum postoperative temperature following cardiosurgical procedures was related to cognitive dysfunction 6 weeks after surgery. However, use of temperature management during cardiac surgery is still hotly debated (Cook, 2009; Grocott, 2009).

10.3.4 Extracorporeal Circulatory Management

Rates of POCD in patients undergoing coronary artery bypass graft (CABG) surgery have been reported to be around 75% at discharge and 33% at six months post-surgery (Newman et al., 2001). After 5 years post CABG, Newman et al. (2001) found that cognitive decline occurs with high prevalence following a pattern of early improvement with subsequent decline. This onset of later cognitive impairment could in turn be predicted by the presence of early postoperative cognitive dysfunction (Newman et al., 2001). As previous discussions in this chapter have highlighted the unique contribution of cardiosurgical procedures on cognitive dysfunction, several lines of research have examined possible surgical management iatrogenic factors, most notably the impact of on-pump versus off-pump cardiac surgery (Berger et al., 2018).

While the impact of on- versus off-pump cardiac surgery on postoperative cognitive functioning has been debated, evidence regarding the superiority of one procedure over the other is mixed, with many studies elucidating no statistical differences (e.g., Selnes et al., 2012; Shroyer et al., 2009). While the differences that have been found are typically variable, studies have suggested less cognitive dysfunction using off-pump procedures (e.g., Bucerius et al., 2004; Kok et al., 2014). In contrast, other studies indicate that off-pump cardiac surgery has been associated with poorer cognitive outcomes at one year post-surgery (Kok et al., 2014).

However, these possible differences in postoperative cognitive functioning outcomes between on-pump *versus* off-pump procedures appear to be short-lived. Prior differences appear to be mitigated by improvement in surgical procedures, implementation of embolic protection devices and better appreciation of perioperative risk factors for POD and POCD. For instance, van Dijk et al. (2002) found in the OCTOPUS Trial that patients undergoing off-pump cardiac surgery exhibit a small trend toward less cognitive dysfunction at three months post-surgery. However, differences in cognitive functioning between patients receiving off-pump versus on-pump surgery resolved after 12 months post-surgery (van Dijk et al., 2007). The

results of the Randomized On/Off Bypass (ROOBY) Trial failed to elucidate any differences in cognitive functioning outcomes for patients undergoing on-pump versus off-pump cardiac surgery (Shroyer et al., 2009). Similarly, Farhoudi et al. (2010) found no postoperative cognitive differences between on- and off-pump groups at two months post-surgery.

While these extracorporeal techniques likely activate differing physiological mechanisms affecting cortical structures in various ways—e.g., increases in central venous pressure and arterial hypotension resulting from surgical manipulations in off-pump patients may yield reductions in cerebral perfusion pressure (Berger et al., 2018)—such differences do not appear to dramatically impact overall cognitive outcomes. The differences that do arise likely stem from residual confounds, such as age, location, hospital, surgical complexity, and disease severity. With the implementation of new, less invasive cardiosurgical techniques (e.g., transcatheter aortic valve replacement; TAVR), postoperative cognitive outcome differences are likely to be minimized further.

10.4 Assessment of Cognitive Change Following Cardiac Surgery

Appropriate measurement of change, progression, and/or reversibility of cognitive status requires consistent serial assessment within prespecified timeframes (Lansky et al., 2017). Cognitive assessment during the acute, in-hospital recovery period, as discussed earlier, is likely to be confounded by possible residual POD symptoms and other treatment factors (e.g., pain medications, inflammation, etc.), in which case, it is recommended that assessments occur between 30 days to 3 months following surgery (Grape et al., 2012). While there is clear evidence of the impact of cardiac surgery on neurocognitive functioning, the criteria to define "clinically meaningful" change has been an area of contention among neuropsychologists and medical practitioners (Berger et al., 2015). Some research has designated a 1-standard deviation (1-SD) reduction from baseline functioning as constituting a significant change (Newman et al., 2001), while other studies have designated a 2-SD drop as representing meaningful change (Ottens et al., 2014). The inconsistent use of diagnostic and statistical criteria has obscured professional and scholarly consensus on how to empirically determine POCD. For example, studies utilizing a -1.0 SD post-surgery cognitive change have reported POCD rates up to 40% (Mathew et al., 2013; Newman et al., 2001), while studies using -2.0 SD criteria have resulted in rates of approximately 10–16% (Evered, Scott, Silbert, & Maruff, 2011; Ottens et al., 2014). This discrepancy highlights the need to employ measurement theory and advanced statistical methods to detect postoperative cognitive change following cardiac surgery.

10.4.1 Psychometric Methods and Considerations

Cognitive change that is generally considered "meaningful" following cardiac surgery occurs when the observed difference between scores at two separate time points exceeds the measurement error around the mean (Andrew, Baker, Bennetts, Kneebone, & Knight, 2001; Attix et al., 2008; Lehrner et al., 2005; Lewis, Maruff, Silbert, Evered, & Scott, 2006). Given the inconsistent use of diagnostic methods and classification of POCD, it is difficult to precisely account for the notable variability in cognitive loss occurring after cardiosurgical procedures (Grape et al., 2012; Tsai et al., 2010). To provide clear indication of the requisite cognitive change required for diagnosing POCD, pre- and postoperative assessment is necessary (Grape et al., 2012; Rundshagen, 2014). From a statistical standpoint, determining change on a single measure is relatively straightforward. However, determining change across multiple cognitive domains that do not statistically aggregate to a single composite score is more challenging and necessitates more robust quantitative methodologies (Lewis et al., 2004).

The trend toward using more refined statistical techniques to evaluate performance is strongly recommended for practitioners (Crawford & Garthwaite, 2007; Crawford, Garthwaite, Denham, & Chelune, 2012; Frerichs & Tuokko, 2006). While numerous evidence-based statistical methods are available, they vary in sophistication and validity. While a more in-depth discussion of these methods is beyond the scope of this chapter, Table 10.1—adapted from Duff (2012)—provides an outline of the formulas, advantages, and disadvantages of the aforementioned statistical methods. Briefly, of the more straightforward and modest statistical methods, the Simple Discrepancy method is the easiest to calculate (Duff, 2012). However, this method neither controls for test-retest reliability, practice effects, nor regression to the mean, which limits the validity of the method and requires extensive psychometric knowledge of the neuropsychological measures. Similar to the Simple Discrepancy method, the Standard Deviation method is easy to calculate and has the advantage of providing a more precise estimation of change (Duff, 2012). While these methods are simple and straightforward, more complex statistical methods are being utilized with increased frequency (Crawford & Garthwaite, 2006; Crawford & Garthwaite, 2007). For example, Reliable Change Index (RCI) and Regression-Based Change formulas serve as the most accurate and sensitive methods of POCD detection and increase confidence in determination of "clinically meaningful" change (Duff, 2012; Duff et al., 2016; Frerichs & Tuokko, 2006; Lewis et al., 2006).

In addition to using these differing change measurement techniques, the process of capturing accurate and representative data is impacted by sources of error, which can be grouped into three domains. Duff (2012) outlines these domains as: (1) variables associated with the selected measure; (2) variables associated with the testing environment; (3) and variables associated with the individual patient being evaluated. With respect to measure selection, there are numerous psychometric

Table 10.1 Statistical techniques for evaluating postoperative cognitive change in cardiac surgery patients

Simple discrepancy	Formula	$T_2 - T_1$
	Advantages	– Easiest to calculate
	Disadvantages	– Clinician requires access to normative data of discrepancy scores of a certain sample – No control for test reliability, practice effects, or regression to the mean – The method is generally a one-size-fits-all approach
Standard deviation	Formula	$T_2 - T_1/S_1$
	Advantages	– Easy to calculate – Provides a more precise estimate of relative change than the simple discrepancy
	Disadvantages	– No control for test reliability, practice effects, or regression to the mean – The method is generally a one-size-fits-all approach
Reliable Change Index (RCI)	Formula	$T_2 - T_1/\text{SED}$ $\text{SED} = \sqrt{2(S_1[\sqrt{(1 - r_{12})}])^2} = \sqrt{2S_1^2(1 - r_{12})}$
	Advantages	– A more precise estimate of relative change and control for the test's reliability
	Disadvantages	– Does not correct for practice effects or variability in Time 2 scores – The method is generally a one-size-fits-all approach
RCI + Practice effects	Formula	$(T_2 - T_1) - (M_2 - M_1)/\text{SED}$ $\text{SED} = \sqrt{2(S_1[\sqrt{(1 - r_{12})}])^2} = \sqrt{2S_1^2(1 - r_{12})}$
	Advantages	– A more precise estimate of relative change and control for the test's reliability – Controls for practice effects
	Disadvantages	– Practice effects correction is uniform
Regression-based change formulas	Formula	$T_2' = \beta T_1 + c$ $\text{RCI}_{\text{SRB}} = T_2 - T_2'/\text{SEE}$ $\beta_{\text{est}} = S_2/S_1$ $c_{\text{est}} = (M_2 - [\beta_{\text{est}} M_1])$ $\text{SEE}_{\text{est}} = \sqrt{(S_1^2 + S_2^2)(1 - r_{12})}$
	Advantages	– Provides a more precise estimate of relative change – Corrects for practice effects and test-retest reliability – Corrects for variability in Time 2 scores – Potentially incorporate additional clinically relevant variables (e.g., age, education, retest interval) into the prediction
	Disadvantages	– Typically need access to the actual data of relevant control samples to generate the regression analyses, which may be a challenge in most clinical trial designs

Table adapted from Duff (2012). Notes: T_1 = score at Time 1; T_2 = score at Time 2; S_1 = standard deviation at Time 1; S_2 = standard deviation at Time 2; r_{12} = correlation between Time 1 and 2 scores; M_1 = control group mean at Time 1; M_2 = control group mean at Time 2; β = slope of the regression model; c = intercept of the regression model (constant); SEE = standard error of the estimate of the regression model; T_2' = predicted score at Time 2 based on the regression model; SED = standard error of the difference; SRB = standardized regression-based formula

considerations to keep in mind when selecting and interpreting appropriate objective assessments, the primary factors being patient demographics, practice effects, floor and ceiling effects, and regression to the mean (Duff, 2012).

10.4.2 Cognitive Screen and Testing Battery Selection

"Meaningful changes" can only be truly determined by analyzing the relationship between postoperative changes on cognitive measures and everyday tasks that patients perform (Keith, Puente, Malcolmson, Tartt, & Coleman, 2002). While the parameters of what is considered "meaningful change" are heavily debated, diagnostic criteria for POCD are generally characterized as diminished scores on objective performance measures of memory and executive functioning post-surgery (Tsai et al., 2010).

POCD manifests in several cognitive domains (Swartz, 2017). In a meta-analysis of neuropsychological tests used to evaluate post-cardiac surgery patients, Swartz (2017) reported effect sizes (i.e., Hedge's *g*) of pre- and post-surgery outcomes across cognitive domains. The Mini Mental Status Examination (MMSE) showed the largest difference between pre- and postoperative performance (.89). Following the MMSE, cognitive domains showing the largest pre- to postoperative differences included measures of delayed recall (.63); language (.55); processing speed (.51); visual processing (.39); attention and memory (.38); motor performance (.32); executive functions (.32); and learning and recall (.28). While research shows that POCD presents with deficits across these cognitive domains, results suggest that measures of general neurocognition (i.e., composite index of multiple cognitive areas), delayed recall, language, and processing speed may be the most sensitive in detecting cognitive change post cardiac surgery (Swartz, 2017).

While cognitive screening measures are appropriate (Hachinski et al., 2006), Gunstad, Mueller, Stanek, and Spitznagel (2012) recommend obtaining comprehensive neuropsychological testing prior to surgery and cognitive screening postoperatively. Measures used for this aim should be brief, repeatable, produce data that is not pigeonholed by range restriction (Collie, Darby, Falleti, Silbert, & Maruff, 2002), and provide a continuous rather than dichotomous outcome variable (Lewis et al., 2004). In fact, it has been recommended that diagnostic classification of POCD be graded on a continuum rather than dichotomously "yes or no" (Grape et al., 2012). In this case, a score of 0 could equal no postoperative change in cognitive status, whereas a score of 100 could mean a definitively observed change—the continuum serving as the range between extremes. This approach has advantage in providing a broader baseline across cognitive domains. A limitation of this approach however, is that it fails to address the severity of change, only indicating the degree of certainty that change has occurred.

Several recommendations have been offered pertaining to neurocognitive test selection for evaluating both POD and POCD. The American Delirium Society (ADS) has compiled numerous delirium screening measures available for medical professionals. Descriptions of these measures can be found in Table 10.2. The Society of Thoracic Surgeons provided a Statement of Consensus on Assessment of Neurobehavioral Outcomes After Cardiac Surgery (Murkin, Newman, Stump, & Blumenthal, 1995) outlining testing considerations and measure selection, evaluating the cognitive domains of learning and memory, executive functioning, and fine-motor dexterity. The National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards

Table 10.2 Recommended neuropsychological screening measures for postoperative delirium

Scale type	Measure name	Description
Screening for delirium	4 A's Test for Delirium Screening (4AT)	– Screening instrument for rapid assessment of cognitive impairment and delirium – Administration time: 2 min
	4-item Abbreviated Mental Test (AMT4)	– Brief assessment for mental impairment in the elderly – Administration time: 2 min
	Months of the Year Backwards (MOTYB)	– Attention/working memory task requiring patient to name months of the year in reverse order – Administration time: 1 min
Confusion Assessment Method (CAM)	CAM (Original)[a]	– Screening of delirium: symptom onset, attention, organization of thought, and level of consciousness – Administration time: <5 min
	CAM-ICU	– Simple attention task and four simple yes/no questions and a command – Limited sensitivity in non-intubated patients[b] – Administration time: 1 min
	Brief CAM (b-CAM)	– Months of the year backwards and four simple yes/no questions and a command – Administration time: 1–3 min
	3D-CAM	– Digit span tasks (forward and backward) and months of the year backwards – Administration time: 3 min
Extended delirium screening	Cognitive Test for Delirium (CTD)	– 9-Item performance measure evaluating orientation, attention span, memory, comprehension, vigilance – Administration time: 10–15 min
	Delirium Rating Scale-Revised-98 (DRS-R-98)[c]	– 16-Item screening of delirium symptom severity: 3 diagnostic items and 13 severity items – Administration time: 20–30 min

[a]Inouye et al. (1990) [b]Kuczmarska et al. (2016) [c]Trzepacz et al. (2001)

(Hachinski et al., 2006) provided recommendations for neurocognitive test batteries with multiple durations; three test batteries with durations of 60, 30, and 5 min, respectively. Lansky et al. (2017) proposed standardized neurological endpoints for cardiovascular clinical trials including neurocognitive test recommendations within the domains of overall cognitive status, pre-morbid intellectual status estimation, attention, memory, language, executive function, and visuospatial function. In addition, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) has developed and evaluated clinical and neuropsychological test batteries to capture cognitive decline (Fillenbaum et al., 2008). The neurocognitive measures within the aforementioned recommendations have been consolidated and are provided in Table 10.3.

Table 10.3 Recommended neuropsychological measures for evaluating pre- and postoperative cognitive functioning

Cognitive domain	Performance measures	Core cognitive skill
Premorbid cognitive status	Word Reading subtest: Wide Range Achievement Test (WRAT-4 or WRAT-5)[a]	– Word decoding through letter identification and word recognition – Administration time: <5 min
	Wechsler Test of Adult Reading (WTAR) or Wechsler Test of Premorbid Functioning (TOPF)[a]	– Decoding of words with atypical grapheme to phoneme translations – Administration time: <10 min
	Vocabulary subtest: Wechsler Adult Intelligence Test (WAIS-IV)[a]	– Word knowledge and verbal concept formation – Administration time: 10–20 min
Global neurocognition screening estimates	Mini Mental Status Examination (MMSE)[b,c,d]	– Screening of cognitive impairment and tracking of cognitive changes that occur over time – Administration time: 5–10 min
	Modified Mini Mental Status Examination (3MS)	– Broader screening of cognitive impairment and changes that occur over time – Administration time: 5–10 min
	Montreal Cognitive Assessment (MoCA)[a]	– Detection of cognitive impairment – Administration time: 5–10 min
	Repeatable Battery for Neuropsychological Status (RBANS)[a]	– Screening of cognitive domains and tracking of cognitive changes – Administration time: 30 min – Three alternative forms available

(continued)

Table 10.3 (continued)

Cognitive domain	Performance measures	Core cognitive skill
Language/Lexical retrieval	1-Letter Phonemic Fluency subtest (MoCA)[e]	– Spontaneous word production restricted to a particular letter (Phoneme): 1 trial – Administration time: 60 s
	Boston Naming Test, 2nd Edition (BNT-2)[b,d]	– Visual naming ability using black and white drawings of common objects – Administration time: 10–20 min
	Category Fluency[a,b,c,d]	– Spontaneous word production restricted to a particular category (i.e., Animals) – Administration time: 60 s
	Controlled Oral Word Association Test (COWAT)[a,b,c,d]	– Spontaneous word production restricted to a particular letter (Phoneme): 3 trials – Administration time: 3 min
Visuospatial perception	Hooper Visual Organization Test (VOT)[a]	– Visuospatial processing and integration – Administration time: 15 min
	Rey-Osterrieth Complex Figure Copy (RCFT)[a,b]	– Visuospatial processing and visual-motor integration ability – Administration time: ≤5 min
Motor performance	Grooved Pegboard Test (GPT)[f]	– Hand–eye coordination, motor speed, and fine motor dexterity – Administration time: 5 min

(continued)

Table 10.3 (continued)

Cognitive domain	Performance measures	Core cognitive skill
Learning and memory	5-Word Memory Task (MoCA)[e]	– Single-trail verbal list-learning task with short and delayed recall and recognition – 5-Word list – Administration time: <5 min
	Brief Visuospatial Memory Test-Revised (BVMT-R)[a]	– Multi-trial visuospatial learning, delayed memory, and recognition – Six simple geometric figures – Administration time: 45 min; 20 min of testing; 25 min of delay
	California Verbal Learning Test (CVLT-2 or CVLT-3)[a]	– Multi-trial verbal list-learning, delayed memory, and recognition – 16-Word list – Interference trial – Optional forced choice task – Administration time: 35 min; 15 min of testing; 20 min delay – One alternate form available
	Hopkins Verbal Learning Test, Revised (HVLT-R)[a,b,c]	– Multi-trial verbal list-learning, delayed memory, and recognition – 12-Word list – Administration time: 25–30 min; 5–10 testing minutes; 20-min delay – Six alternate forms available
	Rey Auditory Verbal Learning Test (RAVLT)[f]	– Multi-trial verbal list-learning, delayed memory, and recognition – Interference trial – Optional forced choice task – 15-Word list – Administration time: 30–35 min; 10–15 testing minutes; 20-min delay – Three alternate forms available
Attention/ Concentration	Conners Continuous Performance Test (CPT 2 or CPT 3)[a]	– Focal and sustained visual attention, impulsivity, and vigilance – Administration time: 14 min
	Digit Span subtest (WAIS-IV)[a]	– Auditory/verbal working memory capacity – Administration time: 10 min
	Digit Symbol-Coding (WAIS-III) or Coding (WAIS-IV)[a,b,c]	– Graphomotor and information processing speed – Administration time: 2 min
	Trail Making Test (TMT): Trails A[a,b,c,f]	– Visual scanning and detection speed – Administration time: ≤5 min – Norms available for both paper and pencil and oral formats

(continued)

Table 10.3 (continued)

Cognitive domain	Performance measures	Core cognitive skill
Executive functioning/ Activation	Matrix Reasoning (WAIS-IV)[a]	– Nonverbal reasoning and problem solving – Administration time: <15 min
	Ruff Figural Fluency Test (RFFT)[a]	– Fluid and divergent thinking, speed, and mental flexibility – Administration time: 5 min
	Similarities (WAIS-IV)[a]	– Verbal reasoning and development of concepts – Administration time: 10 min
	Stroop Color-Word Test (SCWT)[a]	– Cognitive flexibility and verbal response inhibition – Administration time: 5 min
	Trail Making Test (TMT): Trails B[a,b,c,f]	– Divided attention, speed, and mental flexibility – Administration time: 5 min – Norms available for both paper and pencil and oral formats
Mood and affect	Center for Epidemiological Studies Depression Scale (CES-DS)[b,c]	– Severity of depression symptoms within past 7 days including day of examination – Informant rating scale – Contains 20 items
	Neuropsychiatric Inventory Questionnaire (NPI-Q)[b]	– Screening for dementia-related behavioral and affective symptoms – Informant rating scale – Contains 12 items
Behavioral functioning	Behavior Rating Scale for Dementia (BRSD)[d]	– Behavioral abnormalities in demented and cognitively impaired patients – Informant rating scale – Contains 46 items – 17-Item short form available
	Clinical Dementia Rating Scale[d]	– Functional performance with six cognitive domains – Clinician administered interview – Uses a 5-point rating system
	Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQOCDE)	– Screening for dementia symptomology – Informant rating scale – Contains 16 items

[a]Included in the NeuroARC neuropsychology battery recommendations (Lansky et al., 2017; Nasreddine et al., 2005)
[b]Included in *60-min battery* of the Vascular Impairment Harmonization Standards (Hachinski et al., 2006)
[c]Included in *30-min battery* (Hachinski et al., 2006)
[d]Recommended by the Consortium to Establish a Registry for Alzheimer's Disease (Fillenbaum et al., 2008)
[e]Included in *5-min battery* (Hachinski et al., 2006)
[f]Recommended in the Statement of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery (Murkin et al., 1995)

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Chapter 11
Cognitive Outcomes in Patients Undergoing Coronary Interventions and Transcatheter Aortic Valve Replacement

Alexander Ghanem, Timm Ubben, Hendrik Wienemann, and Tobias Spangenberg

11.1 Introduction

Non-focal neurological deficits are very common following cardiovascular procedures and are dreaded as independent predictors of morbidity and mortality (Maniar et al., 2016). Despite this, postoperative cognitive decline (POCD) is not reported systematically as a safety endpoint in cardiovascular interventional trials (Kappetein et al., 2012). Objectification and quantification of POCD is complicated, since deficits predominantly impair distinct domains (e.g., attention, psychomotor speed, and memory). However, POCD is often defined as a decrease of global cognitive function (e.g., >1 SD decline from baseline) after a cardiovascular intervention (Ghanem et al., 2010). Based on observational trials, the most conceivable mechanisms of cerebral injury and POCD are hemodynamic causes: cerebral embolism and hypoperfusion (Edmonds, 2000; Newman, Wilkinson, & Royse, 2014). However, neither embolization nor hypoperfusion demonstrate distinct morphological defects or functional deficits; therefore, a monocausal hemodynamic model for a very specific cognitive deficit profile is unlikely. Besides hemodynamics, further independent risk factors for mental impairment can be individual risk factors for cognitive decline.

Previously, we discussed the increasing risk of cerebral injury based on risk assessment of kidney injury criteria: *R*isk, *I*njury, *F*ailure, *L*oss, and *E*nd-stage disease (RIFLE; Ghanem, Naderi, Frerker, Nickenig, & Kuck, 2016). Most contributors of cerebral injury are in the subclinical risk and injury stage and therefore below clinical threshold. To depict this, we propose an "iceberg model of risk" (see Fig. 11.1). However, each RIFLE-criterion is independently associated with adverse

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_11

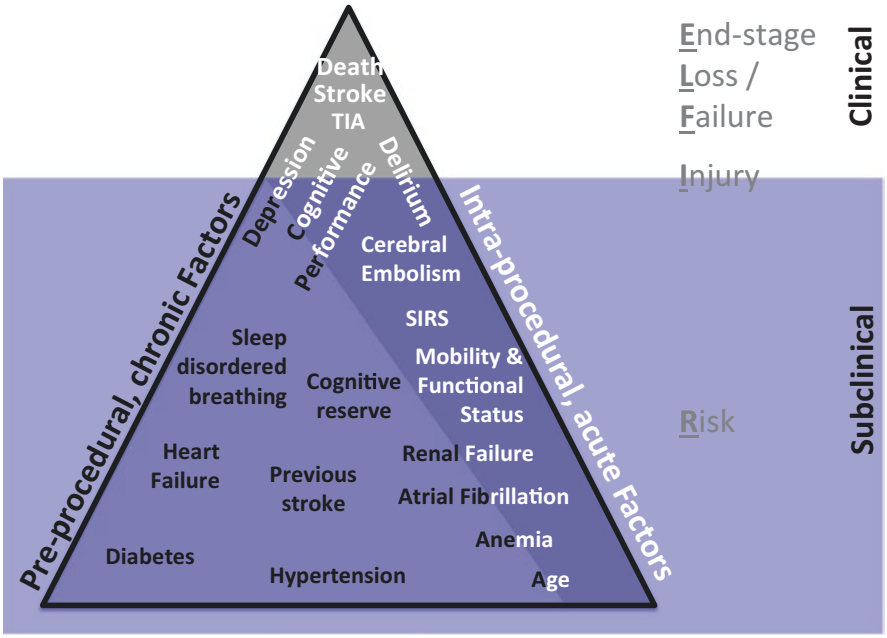

Fig. 11.1 Iceberg model of cognitive outcomes in the periprocedural context after TAVR. Cognitive outcomes are impacted by pre-, intra- and post-procedural factors in an interdependent and complex fashion. *TAVR* transcatheter aortic valve repair, *SIRS* systemic inflammatory response syndrome, *TIA* transitory ischemic attack

outcome and therefore of great clinical value, at least for renal injury. A different approach for the assessment of cognition is the time-dependent trajectory of performance with several variables (e.g., the procedure itself or consecutive hemodynamic alteration). This model is multifactorial and instructive, since an improvement of cognitive performance is also depicted, and quantified (Hogan, Shipolini, Brown, Hurley, & Cormack, 2013; Selnes et al., 2012). Both approaches integrate individual risk, pre-, intra- and post-procedural cerebral injury and their individual time courses, and are therefore valuable but abstract risk models. However, data on valid and independent risk factors of POCD after cardiovascular interventions are not available yet. Retrospectively, the available datasets from eligible studies did not address whether age, baseline cognitive function, prior stroke or transient ischemic attack (TIA), baseline cardiovascular disease severity, hypertension, diabetes, or depression modify the association between cardiovascular procedures and intermediate- or long-term cognitive outcomes in older adults. Furthermore, evidence exists linking chronic brain hypoperfusion induced by numerous cardiovascular disorders (e.g., atrial fibrillation, thrombotic events, hypertension, hypotension, heart failure, high serum markers of inflammation, coronary artery disease, low cardiac index, and valvular pathology) to the cognitive impairment preceding Alzheimer's disease (De La Torre, 2004). Hence, POCD holds a critical role and is an active target in

assessing postoperative recovery following cardiac interventions, as well as longer term outcomes and disease risks.

11.2 Coronary Interventions

Atherosclerosis is principally associated with an increased risk for silent stroke and cognitive impairment (Giele, Witkamp, Mali, & Van Der Graaf, 2004; Van Exel et al., 2002). As left heart catheterization and coronary angiography (CA) frequently lead to cerebral embolism, its impact on focal neurological deficits and cognitive performance are of utmost interest. Omran et al. (2003) found 22% of patients undergoing a retrograde catheterization of the aortic valve present with focal diffusion-weighted imaging (DWI) abnormalities in a pattern consistent with acute cerebral emboli. Three percent of these patients demonstrated focal neurological deficits. Patients without transvalvular passage were without evidence of cerebral embolisms (Omran et al., 2003). In contrast, in a later study of 46 patients with aortic valve stenosis undergoing CA including transvalvular passage, the incidence of new ischemic lesions was 2.2% and no patients presented with focal deficits (Hamon et al., 2006). Hamon et al. (2012) reported no significant impact of access route (femoral vs. radial) on the incidence of cerebral embolism. Putting this finding into perspective, Jurga et al. (2016) collected Montreal Cognitive Assessment (MoCA) test results and monitored intraoperative cerebral emboli by transcranial Doppler. The MoCA screening results were not significantly altered following the procedure, nor were there any significant correlations between MoCA change from pre- to postoperative recovery and the number of cerebral microemboli or any association with surgical access site. However, one-third of the patients presented with mild cognitive impairment with a baseline MoCA result <26 (Jurga et al., 2016).

With respect to focal neurological deficits related to percutaneous coronary intervention (PCI), Hoffmann, Altiok, Reith, and Brehmer (2014) elaborated on the neuroimaging patterns, ischemic mechanisms, and functional outcomes of ischemic strokes over a 16-year period. Infarctions were subclassified by radiological pattern and arterial territory as embolic, small subcortical, or hemodynamic. Modified Rankin Scale scores were used to assess functional outcome at 3 and 6 months and while PCI-stroke was radiologically confirmed in 35 patients, 91% of the strokes were of embolic pattern (9% subcortical). No watershed strokes were identified, although almost one-fifth of the patients experienced periprocedural hypotension. Functional outcomes among survivors of PCI-stroke were typically favorable in those who had single rather than multiple vascular territory involvement (Hoffmann et al., 2014). Concerning cognition, the Tilburg Health Outcome Registry of Emotional Stress after Coronary Intervention (THORESCI) study investigated 384 patients undergoing PCI and assessed impaired concentration and attention, mood and fatigue at baseline, 1-month and 12-month follow-up. In addition to poor perceived cognition outcomes, the authors found an association with poorer health-related quality of life (HRQL; Duijndam, Denollet, Nyklíček, & Kupper, 2017). In

regard to the long-term cognitive outcomes in patients undergoing PCI, Sauër et al. (2013) compared cognitive performance 7.5 years following off-pump coronary artery bypass surgery and PCI. Cognitive performance was assessed through a neuropsychological battery of nine tests that were summarized into a combined performance *Z*-score. After multivariable adjustment for potential confounders, no significant differences were observed (*Z*-score difference 0.14, 95% confidence interval −0.01 to 0.29, $p = 0.08$), though these seemingly negative results are difficult to interpret as a baseline measurement of cognitive function was lacking (Sauër et al., 2013).

11.3 Transcatheter Aortic Valve Replacement

Throughout the last decade, the numbers of structural heart interventions, such as transcatheter aortic valve replacement (TAVR) have increased (Eggebrecht & Mehta, 2016; Mylotte et al., 2013). The most recent clinical outcome data of TAVR are compelling, although some complications limit broad application (e.g., neurological complications; Leon et al., 2010; Smith, Leon, Mack, Miller, & Moses, 2011). The risk of procedural stroke in TAVR has decreased over time and has come to 1.5% in recent studies and this is notable since mortality after TAVR-related stroke is 50% (Mack et al., 2019; Popma et al., 2019; Stortecky, Wenaweser, & Windecker, 2012). To date, various studies have sought to clarify the interdependence of cardiovascular procedures, cerebral injury due to embolism and hypoperfusion, and cognitive performance, but root causes have not been consistent (Vermeer, Longstreth, & Koudstaal, 2007). In particular, the clinical impact of perioperative diffusion-weighted imaging (DWI) cerebrovascular embolism remains to be fully elucidated, whereas, the sequelae of clinically "silent" brain infarctions are well characterized (Vermeer et al., 2003). Observational studies reveal a strong relationship among these silent brain infarctions, cognitive decline and dementia in long-term and large-scale Rotterdam Scan Study participants (Vermeer et al., 2003). In contrast, DWI-detected emboli were neither related to loss of self-sufficiency or mortality (Ghanem, Muller, et al., 2013), nor to a decline in cognitive function testing for up to 2 years (Ghanem et al., 2010). Although POCD largely resolves within 1 year, its early occurrence appears to accelerate cognitive deterioration with an increased risk for future stroke (odds ratio: 2) and conversion to overt dementia (odds ratio: 3). Moreover, early cognitive dysfunction after cardiovascular interventions is independently related to a three-fold increase of mortality after 1 year (Maniar et al., 2016). Estimation of the overall risk for POCD and late cognitive outcomes is critical. But since these factors interact with each other in an unknown manner, and each has specific impact on distinct cognitive domains over time, the cumulative risk of POCD after TAVR remains elusive.

The incidence of POCD is reported with up to 50% within the first week after (surgical or transcatheter) aortic valve replacement, with gradual resolution between

3 months and 1 year (Ghanem, Kocurek, et al., 2013; Knipp et al., 2005). Cognitive deficits in short- and mid-term intervals were observed rarely after TAVR (<5%). Patients undergoing TAVR without extracorporal circulation and general anesthesia had an acceptable incidence of POCD, well below 10% throughout a 2-year follow-up (Ghanem, Kocurek, et al., 2013). Cognitive assessment of patients at baseline and 4 months post-TAVR using a cognitive battery that included tests of verbal-learning, delayed recall and recognition, an estimate of global cognition (i.e., Mini Mental State Examination, MMSE), and executive function (i.e., Trail Making Test, Clock-Drawing Test) revealed an improvement of immediate recall during follow up. Furthermore, among patients with lower presurgical cognitive abilities, MMSE and immediate memory recall were both significantly improved after TAVR. Though prevalent in the early phase (61%), procedural DWI lesions were observed only in a minority of patients at long-term follow-up (6.5%). The procedural DWI lesions did not impact the trajectory of white matter hyperintensities or cerebral atrophy. Functionally, these TAVR-associated perioperative DWI lesions did not significantly affect early postoperative cognitive function, but there was a trend toward cognitive deterioration at long-term follow-up. Interestingly, only a fraction of lingering white matter hyperintensities evolved from procedural DWI lesions (22.2%). The authors concluded that acquired white matter hyperintensities after TAVR, but not perioperative DWI lesions per se were associated with functional impairment after TAVR (Ghanem et al., 2017).

Numerous pre-procedural conditions are risk factors for POCD and accelerated cognitive decline. Cardiovascular risk factors, such as age, diabetes, smoking, and hypertension are known contributors to cognitive deterioration (De Galan et al., 2009; Knecht et al., 2008; Nash & Fillit, 2006; Plassman, Williams, Burke, Holsinger, & Benjamin, 2010; Roberts et al., 2008). Further, heart failure, sleep disordered breathing and depression are known risk factors for cognitive decline (Garcia et al., 2011; Gruhn et al., 2001; Zuccalà et al., 1997). A possible indicator of a valvular cause for decreased cerebral perfusion in aortic stenosis is resolution of central sleep apnea syndrome immediately after TAVR (Linhart et al., 2015).

From the mechanistical perspective, cerebral embolism may be the most accepted etiological cause of POCD following cardiac surgery. First, cerebrovascular etiologies have been posited as major contributors to clinical deterioration in neurodegenerative disease states (De La Torre, 2004; Van Oijen et al., 2007). Additionally, cognitive deterioration was shown to be based on cumulation of white matter hyperintensities over the period of 3–4 years (Vermeer et al., 2003). However, the application of this deductive approach on procedural lesions seen in DWI neuroimaging data remains controversial. In a comprehensive meta-analysis, perioperative DWI lesions were not associated with cognitive decline in six out of seven trials after open-heart surgery and TAVR (Kruis, Vlasveld, & Van Dijk, 2010). Notably, the trials investigated patients after cardiac surgery and not catheter-based procedures. Further, no systematic cognitive decline was seen after cardiovascular procedures in a recent review article by Fink et al. (2015) investigating 7802 patients with a maxi-

mum follow-up of 72 months. In particular, recent small-scale observational studies of TAVR demonstrate a low incidence of POCD (see Table 11.1). However, the relationship among individual risk, cerebral embolism and cognitive outcome following TAVR is not yet understood and is further complicated by the use of various neuroprotection devices meant to capture particulate matter during surgery.

Neuroimaging studies demonstrate a high embolic risk during the TAVR procedure (Astarci et al., 2011; Fairbairn et al., 2012; Ghanem et al., 2010; Kahlert et al., 2010, 2012; Rodés-Cabau et al., 2011). Almost every patient undergoing TAVR incur lesion events as detected by DWI. Functionally, though, only a small amount demonstrate focal neurological deficits following TAVR. Morphologically, only a small fraction of procedural lesions seen with DWI were visible as white matter hyperintensities on fluid-attenuated inversion recovery (FLAIR) MRI at mid-term follow-up (Ghanem et al., 2010), demonstrating a rather complex and yet not fully elucidated chronological relationship of cerebral morphology and function after TAVR. This discrepancy may additionally be explained by a paucity knowledge regarding the factors contributing to the longitudinal complexity of lesion and cognitive performance patterns, as depicted in Fig. 11.1. Besides thrombotic embolism, hypoperfusion is another conceivable mechanism of post-procedural onset or maintenance of POCD. More than mild aortic regurgitation leads to decay of diastolic perfusion pressure and impaired renal perfusion with excessive increase of renal artery resistance index (Sinning et al., 2014). This change in renal artery resistance index, in turn, could lead to cerebral hypoperfusion (Sinning, Scheer, et al., 2012). Additionally, systemic inflammatory response syndrome (SIRS) is a known hypoperfusion syndrome, often associated with patients with residual aortic regurgitation and is an independent predictor of adverse outcomes (Sinning, Hammerstingl, et al., 2012).

A prospective trial investigating cognitive function in a cohort of 229 patient years using the MMSE before and 6 months after TAVR found a cognitive deterioration in 12.7% overall, but no independent predictor thereof. However, patients with POCD revealed specific post-interventional traits, such as post-procedural stroke, progressive renal failure, progressive heart failure, or delirium as possible causes (Schoenenberger et al., 2016). Delirium is a known risk factor for POCD (Saczynski et al., 2012). It was found to be as frequent as 44% after TAVR (CARDELIR-Trial), but still significantly lower in comparison to surgical aortic valve replacement (e.g., 66%; Eide et al., 2015). This is of particular interest, since the onset of delirium is an independent predictor of mid-term cognitive deterioration (Saczynski et al., 2012). In a small-scale observational study ($n = 44$), no delirium cases were observed after TAVR (Erdoes et al., 2012). Wilbring and associates studied 508 patients in a case-control study and post-procedural delirium was present in 11.5% and 28.3% after TAVR and conventional surgical aortic valve replacement, respectively. These results suggest significantly less post-procedural delirium in TAVR relative to conventional surgical replacement (i.e., $p = 0.046$; Wilbring et al., 2013) and indicate possible neuroprotective superiority of TAVR. This hypothesis is further corroborated by a recent study of Maniar et al. (2016), who report on a decreased mortality in TAVR as compared to the surgical approach based on the association of delirium and mortality (Maniar et al., 2016).

Table 11.1 Observational data on cognitive performance after TAVR

Protocol			Cognitive domains									Outcome: Cognitive deficit								
Intervention/ Control	Tests	Included subjects (*n*)	MS	VMC	AT	SCW	SCL	VC	SASA	IP	AF	3 months-FU (*n*)	Loss-to-FU 3 months *n* (%)	Reasons *n* (%)	<7 days *n* (%)	≤3 months *n* (%)	>3 months *n* (%)	>12 months *n* (%)	Potential Min./ Max. PPCD incidence % (*n*)	Ref.
TAVR/SAVR	MMSE	51/NA	TAVR – SAVR +	TAVR + SAVR +	TAVR + SAVR +	TAVR + SAVR +	TAVR – SAVR +	TAVR – SAVR +	TAVR – SAVR +	TAVR – SAVR +	TAVR – SAVR +	32/21	19 (37%)	Death: 3 (6%), PPM: 5 (10%), Contraindication for MRI 9 (17%), refused: 2 (4%)	+ (0%)	+ (0%) (0/32)	–	–	Min 0% (0/50)/ Max 37% (19/50)	Kahlert et al. (2010)
TAVR/–	MMSE	81	–	+	+	+	–	–	–	–	–	60/–	21 (26%)	Death: 5 (6%), PPM: 6 (7%), refused: 6 (7%), hemodynamic or respiratory instability: 3 (4%), abortion of the procedure: 1 (1%)	+ (0%)	+ (0%) (0/60)	–	–	Min: 0% (0/81)/ Max: 26% (21/81)	Rodés-Cabau et al. (2011)
TAVR/–	MMSE, MoCA	204/–	+	+	+	+	+	+	+	+	–	73/–	131 (64%)	Death 10 (5%); unsuitable for transcranial Doppler : 107 (52%), refused: 14 (7%)	+ (0%)	+ (0%) (0/73)	–	–	Min 0% (0/204)/ Max 64% (131/204)	Kahlert et al. (2012)

(continued)

Table 11.1 (continued)

Protocol			Cognitive domains									Outcome: Cognitive deficit								
Intervention/ Control	Tests	Included subjects (*n*)	MS	VMC	AT	SCW	SCL	VC	SASA	IP	AF	3 months-FU (*n*)	Loss-to-FU 3 months *n* (%)	Reasons *n* (%)	<7 days *n* (%)	≤3 months *n* (%)	>3 months *n* (%)	>12 months *n* (%)	Potential Min./ Max. PPCD incidence % (*n*)	Ref.
TAVR/SAVR	MMSE+[a] (TAVR), STB (SAVR)	27/37	TAVR − SAVR +	TAVR + SAVR +	TAVR + SAVR +	TAVR − SAVR +	TAVR − SAVR +	TAVR − SAVR +	TAVR + SAVR +	TAVR − SAVR +	TAVR − SAVR +	18/34	TAVR: 9 (33%)/ SAVR: 3 (8%)	TAVR: Death: 7 (26%), refused 2 (7%)/SAVR: not reported: 3 (8%)	+ (TAVR: 18% (4/22) SAVR: 46% (17/37)	+ (TAVR: 28% (5/18) SAVR: 6% (2/34)	–	–	TAVR: Min 18% (5/27)/ Max 51% (14/27) SAVR: Min 5.4% (2/37)/ Max 13.5% (5/37)	Knipp et al. (2013)
TAVR/–	MMSE, RBANS	125/.	+	+	+	+	+	+	+	+	+	102	23 (18%)	Death: 10 (8%), post-procedural complications 13 (10%)	+ 6/111 (5%)	+ 7/102 (7%)	+ 7/86 (8%)	+ 4/32 (12%)	Min 4.8% (6/125)/ Max. 24% (30/125)	Ghanem, Kocurek, et al. (2013)

Abbreviation: *TAVI* transcatheter aortic valve implantation, *SAVR* surgical aortic valve replacement, *NA* not available, *n* number, *MS* motor skills, *VMC* verbal memory capacity, *AT* attention, *SCW* speed and capacity of working memory, *SCL* speed and capacity of long-term memory, *VC* visuospatial capacity, *SASA* selective and sustained attention, *IP* information processing, *AF* alternate forms of the tests, *MRI* magnetic resonance imaging, *PPM* permanent pacemaker, *MMSE* mini-mental state examination, *RBANS* repeatable battery for the assessment of neuropsychological status, *MoCA* Montreal Cognitive Assessment, *NIHSS* National Institutes of Health Stroke Scale, *STB* standardized testing battery consisting of 11 neuropsychological tests (digit span forward/backward, Corsi block tapping forward/backward, Horn test no. 3/9, Reitan Trail making A/B, Verbal Learning Test—immediate recall/ delayed recognition, Zimmermann divided attention test)

[a]Digit span subtest, wordlist test, Regensburg verbal fluency test

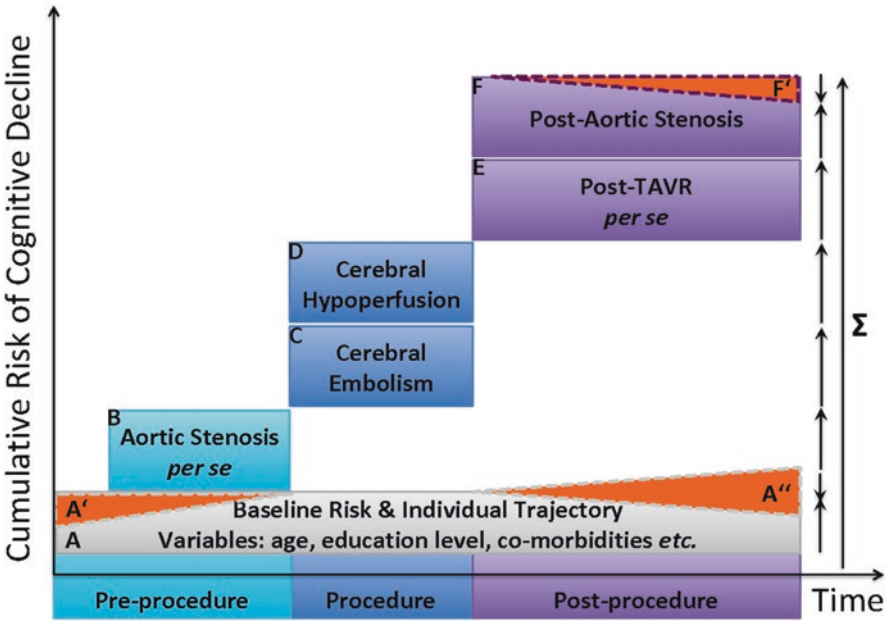

Fig. 11.2 Risk model of cumulative risk of cognitive decline in the periprocedural context. The cumulative risk of post-procedural cognitive decline over time is the integration of a complex interplay of six contributing factors with individual trajectories: baseline risk and individual trajectory (**A**) is attributed to the patient age and co-morbidities, pre- and postprocedural trajectories are individually variable and depicted as first and second derivative of (**A**), (**A′**), and (**A″**), respectively. With the onset of hemodynamic impairment based on the underlying disease of aortic stenosis until the time of treatment, the second component contributes to cognitive performance integrating the interplay with pharmacological hemodynamical effects, e.g., vasodilators commonly used in patients with hypertension and mild-to-moderate aortic stenosis (**B**). Periprocedural components of postoperative cognitive decline comprise cerebral embolism (**C**) and hypoperfusion (**D**), based on procedural dislodgement of valvular debris and rapid pacing runs, respectively. The postprocedural phase is characterized by a high-risk period of embolism, based on new-onset of atrial fibrillation and/or valvular thrombosis, each individually contributing to postprocedural cognitive decline. Ultimately, post-TAVR patients are also "post-stenosis" patients with improved cerebral hemodynamics (**F**). Despite age and comorbidities, cognitive trajectory might be beneficially affected (**F′**). Hence, cognitive performance after TAVR over time is the integrative sum (**Σ**) of these variables and/or derivatives

In patients undergoing TAVR, several factors contribute to the complexity of long-term longitudinal investigations of cognitive performance: (1) the individual, cerebral risk of the patient prior TAVR; (2) the chronic, hemodynamic contribution of the underlying disease aortic valve stenosis (e.g., low cardiac output and low cerebral perfusion); (3) acute, hypoperfusion during the TAVR procedure due to rapid pacing and/or anesthesia; (4) cerebral embolization during the procedure from valve positioning and deployment and/or post-dilatation, and (5) specific significant post-procedural risks (e.g., bleeding, SIRS, valve leaflet thrombosis, new-onset of atrial fibrillation; see Fig. 11.2). On the one hand, estimation of the overall risk for

POCD and late cognitive outcome is necessary. But, each of the factors above interact with the other in an unknown manner (additive? exponential?), and each has specific impact on distinct cognitive domains over time. As a result, the absolute risk and root etiologies of POCD after TAVR remain elusive. Complicating our ability to understand these risks and etiologies, no systematic cognitive declines were observed after cardiovascular procedures in a recent review article by Fink et al. (2015), who investigated 7802 patients with a maximum follow-up of 72 months. Additionally, after TAVR recent small-scaled observational studies demonstrate a low incidence of POCD (see Table 11.1). Ultimately, patients with and without DWI lesions demonstrate similar cognitive outcome for up to 2 years after TAVR (Ghanem, Kocurek, et al., 2013). Further, neuroimaging patterns differ in their impact on cognitive performance. While DWI lesions had no impact on survival, stroke rate and cognitive function in long-term observations, the incidence of FLAIR-positive lesions was associated with cognitive decline. Interestingly, FLAIR-positive white matter hyperintensities in long-term follow-up rarely result from procedural DWI lesion events. In all, the relationship of individual risk, timing of cerebral embolism and cognitive outcome is not fully elucidated in TAVR.

With respect to preventive measures, three trials (PRO-TAVI C, DEFLECT III, CLEAN-TAVI) investigated the impact of embolic protection devices (EPDs) on cerebral embolic burden during TAVR in a randomized, controlled clinical trials (Haussig et al., 2016; Lansky et al., 2015; Rodés-Cabau et al., 2014). In PRO-TAVI C, the Embrella™ deflection device failed to reduce the embolic burden during TAVR. In DEFLECT III trial, the investigators stated they found reduction of embolic burden and improvement of cognitive performance in patients undergoing TAVR protected by the Triguard™ device. However, besides other significant limitations, conclusions on the development of POCD were precluded in a study protocol with short-term follow-up. In CLEAN-TAVI trial, Haussig et al. (2016) observed a reduction in embolic burden with the Montage™ device, a dedicated distal embolic filter system. In a second trial, the use of cerebral embolic protection reduced the rate of disabling and nondisabling stroke significantly from 4.6% to 1.4% ($p = 0.03$). Furthermore, the rate of stroke-free survival compared with unprotected TAVR was significantly higher when the Montage™ System was utilized (Seeger, Gonska, Otto, Rottbauer, & Wöhrle, 2017). A prior meta-analysis of four randomized clinical trials ($n = 252$) showed that EPDs were associated with a lower total lesion volume ($p = 0.002$) on MRI, a smaller number of new ischemic lesions ($p = 0.03$), a trend toward lower risk for deterioration in National Institutes of Health Stroke Scale score at discharge ($p = 0.09$), as well as a higher post-procedural MoCA scores ($p = 0.03$). The risk for overt stroke and all-cause mortality, however, was nonsignificantly lower in the EPD group (Giustino, Sorrentino, Mehran, Faggioni, & Dangas, 2017). The assumption of EPD utility is further fueled by the findings of Pagnesi, who found EPDs to be associated with a significant reduction in total ($p = 0.02$) and single ($p = 0.0001$) lesion volume after TAVR. However, the number of new lesions per patient and the number of patients with new lesions were not significantly reduced (Pagnesi, 2016).

These EPD results seem encouraging, but have limitations. Firstly, imaging endpoints have been based on embolic burden with a skewed distribution pattern integrating micro- and macroembolic embolism. Inconsistently, the embolic burden has been lower in all vascular territories, a coincidental finding without causal context to the devices. Secondly, the devices themselves may be thrombogenic and positioning EPDs is capable of dislodging atherosclerotic debris leading to cerebral embolization. Imaging and clinical data on the safety and efficacy of EPDs lack controls undergoing sham procedure with a filter-free device. Thirdly, a significant number of patients with an overt stroke have not been subjected to post-procedural imaging protocols. Hence, the data on the reduction of embolic burden does not encompass the complete intention-to-treat cohort for which the studies were powered. But as TAVR shifts to younger and lower-risk patients, the prevention of procedure-related cerebral injury remains a significant but yet unmet clinical need (Latib & Pagnesi, 2017). It will be critical to further investigate the impact of these EPDs and post-procedural pharmacological management on neuroprotection in clinical trials with long-term follow-up.

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Chapter 12
The Neuropsychology of Pulmonary Disease and Lung Transplantation Complications

Patrick J. Smith and Jeffrey N. Browndyke

12.1 Epidemiology of Pulmonary Disease

Pulmonary disease, including chronic obstructive pulmonary disease (COPD), is the third leading cause of public health expenditures in the United States and is projected to continue representing a leading public health concern due to a lack of available treatments. In addition to COPD, other advanced pulmonary conditions including idiopathic pulmonary fibrosis and cystic fibrosis are also common, associated with significant disability, and remain limited by a narrow range of treatment options. COPD is the third leading cause of mortality in the United States and a significant cause of disability, with estimated direct and indirect cost of $32 billion (Mannino, 2002). Cognitive deficits are prevalent among individuals with COPD, affecting 77% of COPD patients with hypoxemia (Dodd, Getov, & Jones, 2010) and are a significant source of disability and mortality (Antonelli et al., 2006; Fix, Daughton, Kass, Bell, & Golden, 1985).

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_12

12.2 Types of Pulmonary Diseases

Although COPD represents one of the most common and well-studied pulmonary condition, accounting for the most public health expenditures within pulmonary diseases, there are numerous other types of pulmonary diseases with distinct pathophysiology, clinical progression, and neurobehavioral consequences.

12.3 Cognitive Impairment in Pulmonary Disease

In addition to the impact of advanced pulmonary disease on quality of life, morbidity, and mortality, an emerging light of research suggests that advanced pulmonary conditions are associated with an increased risk of cognitive dysfunction (Dodd, 2015). Although transient causes of impairing cognition are well-known, including hypoxia, studies over the past few years have suggested that long-term, subclinical hypoxemia and other associated risk factors confer risk of long-term cognitive impairment above and beyond their transient impact (Thakur et al., 2010). In addition, due to the increasing number of older adults in the Baby Boomer generation and improvements in the treatment of cardiovascular disease and cancer, the burden of cognitive impairment associated with advanced pulmonary disease is projected to increase (Lopez-Campos, Tan, & Soriano, 2016).

Epidemiological studies have consistently reported associations between poorer lung function and greater incidence of cognitive impairment, although the magnitude of association and domains impaired have varied substantially (Dodd, 2015). For example, in the Atherosclerosis Risk in Communities (ARIC) Study, poorer lung function was associated with increased risk of dementia hospitalization (Pathan et al., 2011). A similar association was reported in the Age, Gene/Environment and Susceptibility—Reykjavik Study, in which lower midlife pulmonary function predicted worse processing speed and executive function, as well as the development of adverse clinical outcomes including the mild cognitive impairment (MCI) and dementia over a 23-year follow-up (Vidal et al., 2013). In addition, the MRC National Survey of Health and Development study found that lower midlife pulmonary function predicted cognitive decline over a 10-year follow-up (Richards, Strachan, Hardy, Kuh, & Wadsworth, 2005). Other cohort studies have reported similar findings (Anstey, Windsor, Jorm, Christensen, & Rodgers, 2004; Carroll, Batty, Mortensen, Deary, & Phillips, 2011; Chyou et al., 1996; Emery, Finkel, & Pedersen, 2012; Weuve et al., 2011).

Among pulmonary diseases, COPD has received the most attention for its deleterious effects on neurobehavioral outcomes (Dodd et al., 2010, 2012; Dodd, Charlton, van den Broek, & Jones, 2013). Epidemiological data suggest that the presence of COPD is associated with substantially increased risk of neurodegenerative conditions. For example, in a recent case–control study of 8640 older individuals, the presence of COPD was associated with increased risk of Alzheimer's disease (AD)

and Parkinson's disease, after matching for age, gender, and comorbidities (Liao, Ho, Ko, & Li, 2015). A subsequent meta-analytic study reported nearly identical risk estimates, demonstrating an approximately 72% increased odds of cognitive dysfunction among individuals with COPD relatively to matched control groups (Zhang et al., 2016).

In addition to the association between COPD and dementia in later life, point estimates suggest that a substantial number of individuals with COPD have cognitive impairment. Estimates for the prevalence of cognitive impairment among individuals with COPD vary widely, with studies suggesting that between 20% (Torres-Sanchez et al., 2015) and 60% of individuals may experience impairments (Dodd, 2015; Dodd et al., 2010). Impairments appear to be most closely associated with disease severity, with more severe COPD conferring the greatest cognitive impairment (Torres-Sanchez et al., 2015). For a significant subset of individuals with COPD, neurocognitive deficits are comparable in severity to those observed in Alzheimer's disease (Incalzi et al., 1997). In addition to impacting quality of life, poorer neurocognitive function among individuals with chronic medical illness is an important predictor of medical adherence (Stilley, Bender, Dunbar-Jacob, Sereika, & Ryan, 2010), is associated with greater disability (López-Torres et al., 2014), and may even be predictive of mortality (Antonelli et al., 2006; Smits, Deeg, Kriegsman, & Schmand, 1999).

Despite the frequency and impact of cognitive impairment, the pattern and nature of cognitive deficits in COPD remains poorly understood (Dodd et al., 2010). Patterns of neuropsychological deficit provide important information on the brain structures impacted by chronic disease (Libon et al., 2008) and on the prognosis of neurocognitive impairment (Reid et al., 1996). In addition, different patterns of neurocognitive dysfunction have varying implications for patient management: deficits in verbal memory, for example, have been associated with poorer medication adherence among COPD patients (Incalzi et al., 1997). Perhaps the most common deficits observed among advanced pulmonary patients are on tests of executive function and learning (Cleutjens et al., 2017; Torres-Sanchez et al., 2015). Previous studies have reported deficits in memory, executive function, attention, motor function, and global cognitive function (Dodd et al., 2010), but it remains unclear whether these deficits are due to underlying deficits in processing speed or whether these represent a pattern of frontal-lobe dysfunction, specifically, which has been suggested by prior perfusion-imaging studies (Ortapamuk & Naldoken, 2006).

12.3.1 Other Pulmonary Conditions

In addition to COPD, a small body of work has suggested that children with asthma exhibit subtle neurocognitive decrements relative to their peer counterparts (Irani, Barbone, Beausoleil, & Gerald, 2017). For example, a recent meta-analytic review including 2017 individuals with asthma and 2131 healthy controls found small- to medium-sized differences on neurocognitive outcomes, including academic perfor-

mance, global cognitive performance, executive functioning, processing speed, attention, visuospatial functioning, language, learning, and memory. Although these effects were persistent after controlling for multiple background characteristics, children from lower socioeconomic backgrounds appeared to be impacted the most.

Similarly, a closely related comorbidity impacting numerous individuals with pulmonary disease is obstructive sleep apnea (OSA; Lal, Strange, & Bachman, 2012). Although a comprehensive review of OSA is beyond the scope of the present chapter, the pattern and magnitude of deficits observed in OSA is similar to that reported in COPD, with impairments occurring particularly often on tests of executive functioning, memory, and learning (Lal et al., 2012). In addition, regional gray matter reductions have been reported in multiple brain areas, including the hippocampus, anterior cingulate, and several additional prefrontal and parietal regions. Functional and metabolic brain markers show a similar pattern of dysfunction, with decreased brain activation and evidence of excitotoxicity noted across most of these regions.

12.4 Neuroimaging Correlates of Pulmonary Disease

Numerous studies have examined the correlates of cognitive impairment among individuals with pulmonary disease. Although these data are somewhat distinct from behavioral markers of brain function, such as cognition, they provide important information on central nervous system mechanisms underlying the behavioral impairments commonly observed among individuals with advanced pulmonary disease. In addition to the data described below, a large body of evidence has demonstrated that smokers exhibit reduced brain volume in multiple brain regions, particularly in the prefrontal cortex, as well as cerebral atrophy (Domino, 2008; Swan & Lessov-Schlaggar, 2007). Given the substantially increased risk of stroke among smokers, it is not surprising that cerebrovascular disease has also been widely implicated among individuals with pulmonary disease (Lahousse, Tiemeier, Ikram, & Brusselle, 2015). For example, epidemiological studies have shown that worse pulmonary function is associated with greater incidence of white matter lesions and cerebral microbleeds after accounting for demographic and clinical risk factors, including cardiovascular risk factors (Liao et al., 1999). In addition, individuals with pulmonary disease have been shown to have increased carotid arterial plaque burden, as well as increased risk of plaque rupture (Barr et al., 2012; Iwamoto et al., 2009; Lahousse et al., 2013).

Similar findings have been reported among individuals with clinical pulmonary disease conditions, with a higher prevalence of white matter hyperintensities observed among individuals with COPD compared to healthy controls (Dodd et al., 2012; van Dijk et al., 2004). The majority of available neuroimaging studies have utilized case–control methodologies, comparing individuals with stable lung disease to matched controls. In one of the larger studies available, individuals in the Rotterdam study with COPD exhibited a greater frequency of cerebral microbleeds,

as well as a substantially elevated risk of developing deep/paratentorial microbleeds, compared with matched controls (Lahousse et al., 2013). Examination of volumetric differences between COPD patients and controls has consistently demonstrated reduced regional and global gray matter patterns. For example, in one case–control study, hippocampal volume was significantly smaller in COPD patients and was associated with lower oxygen saturation, blood oxygen levels, and global cognition (Li & Fei, 2013). In a similar study (Zhang et al., 2013), COPD patients were found to have reduced global gray matter volume, which was associated with both disease duration and performance on a test of visual memory. In addition to these structural differences, emerging data suggest that subtle, microvascular dysfunction is observable in COPD patients using sensitive neuroimaging modalities, such as diffusion tensor imaging. For example, in one smaller case–control series, the authors found reduced gray matter density and increased fractional anisotropy in patients with COPD (Zhang et al., 2012).

12.5 Mechanisms of Cognitive Impairment in Pulmonary Disease

There are several, interrelated mechanisms that have been suggested to underlie the greater incidence of cognitive impairment among individuals with pulmonary disease, including hypoxia, hypercapnia, hypoperfusion, microvascular dysfunction/cerebrovascular disease, physical activity, systemic inflammation, and oxidative stress. COPD, for example, is a complex medical illness, and multiple interrelated medical factors have been suggested as mechanisms explaining the COPD and neurocognition relationship. These mechanisms include poorer pulmonary function, physical inactivity, greater vascular comorbidities, more extensive smoking history (Dodd et al., 2010), and increased inflammation (Borson et al., 2008).

Perhaps the most widely studied mechanism explaining cognitive impairment in pulmonary disease is hypoxia (Brown & Thore, 2011; Nielsen et al., 2017). Although the magnitude of association varies widely across studies, multiple studies have demonstrated an association between greater levels of hypoxia and poorer cognitive performance (Fix, Golden, Daughton, Kass, & Bell, 1982; Grant, Heaton, McSweeny, Adams, & Timms, 1982; Prigatano, Parsons, Wright, Levin, & Hawryluk, 1983; Stuss, Peterkin, Guzman, Guzman, & Troyer, 1997), particularly on speed-dependent outcomes (Parekh et al., 2005). Although the precise nature of this relationship has yet to be elucidated, available evidence suggests that chronic, low-grade levels of hypoxia are equally if not more important to the development of cognitive impairments compared with acute, short drops in oxygenation levels (Gao, Long, Zhao, & He, 2011; Schega et al., 2016; Thakur et al., 2010). A closely related determinant of central oxygenation is hypercapnia, conventionally operationalized as arterial carbon dioxide tension (Incalzi et al., 1993). Worsening levels of oxygenation, particularly among lung transplant candidates, have been associ-

ated with poorer cognition (Incalzi et al., 1997; Parekh et al., 2005). Although the impact of low peripheral oxygenation may be mitigated by efficient baroreceptor and cerebrovascular reactivity response, central hypoxia ultimately triggers a number of potentially deleterious mechanism, including anaerobic metabolism, release of a pro-inflammatory cytokine cascade, microglial cell activation, and neuronal death (Mukandala, Tynan, Lanigan, & O'Connor, 2016). Although few studies have examined cerebrovascular reactivity (CVR) among individuals with pulmonary disease specifically, greater duration of CVD risk factors and endothelial dysfunction have been shown to impair cerebrovascular compensatory response (Farkas & Luiten, 2001; Ficzere et al., 1997; Lavi, Gaitini, Milloul, & Jacob, 2006), suggesting the possibility that CVR is impaired in many pulmonary patients, particularly those with COPD. CVR is a critical compensatory function supporting cerebral hemodynamics, helping to maintain a constant supply of blood to the brain (Schwertfeger et al., 2006) and has been found to be pathologically altered in the presence of CVD risk factors (Manolio, Olson, & Longstreth, 2003) and neurodegenerative diseases (Girouard & Iadecola, 2006).

Poorer pulmonary function has been associated with neurocognitive dysfunction in several studies. Etnier and colleagues (Etnier et al., 1999) found that FVC was associated with working memory performance in a sample of older patients with mild COPD, and another cross-sectional study among COPD patients with hypoxemia found that FEV_1 was associated with poorer memory performance. Similarly, two prospective studies examining the relationship between FEV_1 and neurocognition found that poorer FEV_1 predicted worse MMSE performance (Incalzi et al., 1998), as well as poorer performance on measures of attention, visual-motor function, and perception (Fix et al., 1982). One of the largest studies to date, conducted among healthy adults aged 60–64 years, found that FEV_1 was strongly related to reduced levels of brain atrophy and white matter hyperintensities (Sachdev et al., 2006), as well as better performance on several measures of neurocognition. In addition, the authors found that FEV_1 and FVC were associated with lower ventricle-to-brain ratio after controlling for demographic factors, physical activity, and smoking, suggesting an independent association. Another recent prospective study found that poorer pulmonary function at baseline was a predictor of poorer cognitive function and increased rates of dementia-related hospitalization in a 10-year study of nearly 11,000 individuals participating in the Atherosclerosis Risk in Communities study (Pathan et al., 2011). Interestingly, poorer pulmonary function did not predict cognitive decline over time, suggesting an indirect association. Finally, previous studies have suggested that lower PCO_2 and higher PO_2 were associated with better neurocognitive function among a group of end-stage lung patients listed for transplantation (Parekh et al., 2005). Despite several studies suggesting a relationship between pulmonary function and neurocognitive outcomes, at least four other studies among COPD patients utilizing similar neurocognitive measures have failed to find a relationship between pulmonary function and neurocognition (Dodd et al., 2010), suggesting that pulmonary function may be indirectly associated with neurocognitive outcomes. Similar inconsistent findings have been reported for measures of hypercapnia and hypoxemia (Dodd et al., 2010), suggesting that although these

factors are commonly associated with neurocognitive deficits, their relationship may not be direct.

The CNS effects of hypoxia overlap substantially with those observed in hypoperfusion (Brown & Thore, 2011; Di Marco, Farkas, Martin, Venneri, & Frangi, 2015), which has been reported in some pulmonary samples (Antonelli Incalzi et al., 2003). Reduced cerebral perfusion has been associated with a greater risk of cognitive impairment and dementia, independent of stroke (Wolters et al., 2017). Lower cerebral perfusion may impact brain outcomes through several mechanistic pathways. Numerous studies have suggested that hypoxia induces transcription factors leading to increased expression of pro-inflammatory cytokines (Bartels, Grenz, & Eltzschig, 2013; Eltzschig & Carmeliet, 2011) and subsequent microglial activation (Heppner, Ransohoff, & Becher, 2015). Lower perfusion has also been associated with reduced β-amyloid clearance in animal models, as well as correlated with amyloid burden in human samples (Mattsson et al., 2014). Hypoperfusion has also been implicated in the pathogenesis of small-vessel, microvascular disease (Clark et al., 2017; de la Torre, 2000) as well as endothelial dysfunction (Di Marco et al., 2015) and increased blood–brain barrier permeability (Chakraborty, de Wit, van der Flier, & de Vries, 2017; Nielsen et al., 2017; Yew, Nation, & Alzheimer's Disease Neuroimaging, 2017).

Cerebrovascular risk factors may partially explain the relationship between neurocognitive dysfunction and COPD. Vascular disease is common among individuals with COPD, occurring in 50% of hospitalized patients (Royal College of Physicians London British Thoracic & British Lung, 2008), and is a well-established risk factor for neurocognitive dysfunction in other patient populations (Cohen et al., 2009). In epidemiological studies, cardiovascular disease and stroke are also more common among COPD patients relative to the general population (Curkendall et al., 2006). Furthermore, smoking, which is highly prevalent among individuals with COPD, is a major risk factor for stroke (Colditz et al., 1988). Smoking may negatively impact neurocognitive functioning through both its influence on cerebrovascular structures (Lindenstrom, Boysen, & Nyboe, 1993) and increasing the risk of dementia and Alzheimer's disease (Ott et al., 1998). In addition, we have recently shown that greater cerebrovascular risk factors and recency of smoking cessation are significantly associated with poorer neurocognition in a sample of non-smoking, end-stage pulmonary patients awaiting lung transplantation at Duke after accounting for background characteristics, pulmonary function, and fitness level (Smith et al., 2011).

As noted above, one common pathway by which pulmonary disease may confer cognitive dysfunction is elevated neuroinflammation (Najjar et al., 2017). Many pulmonary diseases, including COPD, are characterized by chronically elevated inflammatory levels (Borson et al., 2008; Cleutjens et al., 2017; Lahousse et al., 2015), which have been widely implicated in the pathogenesis of neurodegenerative conditions (Di Marco, Venneri, et al., 2015; Toth, Tarantini, Csiszar, & Ungvari, 2017). Although few studies have examined this directly, several small COPD samples have reported associations between elevated inflammation and poorer neurobehavioral functioning (Cleutjens, Ponds, et al., 2017). Borson et al. (2008), for example, demonstrated that elevated levels of inflammation were associated with

poorer cognitive performance and MRI markers of cerebrovascular disease among individuals with COPD. Other studies have failed to replicate these associations, however (Klein, Gauggel, Sachs, & Pohl, 2010). Greater inflammation is thought to have an independent and adverse impact brain function through a number of biochemical processes (Dziedzic, 2006), including microglia activation, local upregulation of central cytokine expression, and subsequent beta-amyloid deposition (Dziedzic, 2006). Greater levels of circulating inflammatory markers have also been associated with all the aforementioned risk factors for neurocognitive dysfunction, including poorer lung function (Engstrom et al., 2002), increased rates of vascular disease (Jialal, Devaraj, & Venugopal, 2004), smoking (Gan, Man, & Sin, 2005), and hypoxia (Eltzschig & Carmeliet, 2011). In addition, in all cases, inflammation has been suggested to have an independent association and does not appear to be indirectly associated through other comorbidities, providing additional evidence that inflammation may be an important mechanism of neurocognitive deficits among COPD patients, similar to other populations (Etminan, Gill, & Samii, 2003).

12.6 Lung Transplantation

Lung transplantation remains the only viable treatment to extend survival for many individuals with advanced pulmonary disease (Christie et al., 2010). In addition, the number of potential transplant candidates has increased dramatically over the past two decades (Christie et al., 2012) and is projected to continue rising as advanced pulmonary diseases such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) continue to increase, with few treatment options to slow their progression (Akgun, Crothers, & Pisani, 2012; Lowery, Brubaker, Kuhlmann, & Kovacs, 2013). In addition, implementation of the Lung Allocation System (Egan et al., 2006; Gries et al., 2010) has resulted in the prioritization of IPF patients, who tend to be older and clinically decompensated, systematically contributing to a more vulnerable transplant recipient population to adverse clinical outcomes (Kozower et al., 2008). Accordingly, improvements in clinical end-points have remained far worse when compared with other solid organ transplant groups, despite the increasing rate of transplantation and pool of candidates (Abecassis et al., 2012). For example, estimates by the International Society for Heart and Lung Transplantation registry (ISHLT) suggest a median survival time of only 5–6 years posttransplant, with only one fourth of patients surviving up to 10 years (Trulock et al., 2007; Yusen et al., 2013). Moreover, current estimates suggest that one in five patients dies within the first year after transplantation (Trulock et al., 2007; Valapour et al., 2013), with the highest mortality rates among older recipients (Valapour et al., 2013). Despite the high level of mortality among lung transplant recipients, lung transplantation remains one of the most expensive and burdensome medical procedures in the United States healthcare system, with surgical costs alone exceeding $1 million in many cases (Hanson, 2014; How much does a transplant cost?, 2016) and total medical costs within the first year approaching $2 million (Hanson, 2014).

12.7 Neurological Events Following Lung Transplantation

These findings suggest that perioperative neurological events, particularly posttransplant delirium, are relatively common following lung transplantation affecting nearly half of patients undergoing lung transplantation and are predictive of subsequent clinical outcomes (Mateen, Dierkhising, Rabinstein, van de Beek, & Wijdicks, 2010; Sher, Mooney, Dhillon, Lee, & Maldonado, 2017; Shigemura et al., 2013). These findings extend previous evidence suggesting that a substantial subset of patients experience significant neurological complications following transplant (Shigemura et al., 2013), although the predictors of neurologic events and clinical implications have not been thoroughly examined (Mateen et al., 2010; Sher et al., 2017). For example, Mateen and colleagues (Mateen et al., 2010) found that 92% of lung transplant recipients experienced a neurological complication when followed up to 10 years after transplant.

Previous studies have reported that the overall presence of neurological events among lung transplant recipients is high, occurring in as many as 80% of some cohort studies (Mateen et al., 2010), and that significant neurological complications (e.g., stroke) were associated with greater mortality (Mateen et al., 2010; Shigemura et al., 2013; Smith et al., 2014). Although most of the previous studies had examined severe neurologic changes, recent studies from our group (Smith et al., 2015) and others (Sher et al., 2017) have suggested that between 36 and 44% of patients exhibit postoperative delirium, which is associated with worse short-term clinical outcomes. Although delirium has frequently been associated with mortality in geriatric and other critical care samples (Zhang, Pan, & Ni, 2013), ours is the first to demonstrate an association between delirium and subsequent mortality. Of note, although previous studies have generally suggested that delirium is associated with worse 6-month (Ely et al., 2004) and 12-month mortality (Aliberti et al., 2015), our findings suggest that the association between NSE (which was primarily delirium) and posttransplant mortality increased over time, rising to its greatest magnitude between 2 and 3 years postoperatively. Although the reasons behind the timing of this association are unclear, it is possible that impaired cognition, which is one of the primary long-term effects of severe delirium, leading to nonadherence to medical regimen or to more debilitated state, could explain this association (Pandharipande et al., 2013).

Neurological sequelae and impaired cognition are increasingly recognized as an important consideration among lung transplant recipients (Diamond & Mikkelsen, 2014), in large part because of the increasing age of all solid organ transplant recipients (Hajduk, Kiefe, Person, Gore, & Saczynski, 2013; Mapelli et al., 2011; Schulz & Kroencke, 2015). Although originally envisioned as a treatment for younger patients, the average age of transplant recipients has steadily increased as the number of patients with IPF has risen, increasing from an average age of approximately 45 years in the 1980s to nearly 60 years of age at present (Yusen et al., 2014). Indeed, patients aged ≥65 years constitute approximately one third of all recipients (Singer et al., 2015; Singer et al., 2016; Valapour et al., 2013), who experience com-

paratively lower QoL improvement relative to younger recipients (Singer et al., 2016).

Although the mechanisms by which lung transplant affects NSE are unknown, it is likely that a combination of individual patient risk factors and perioperative events together contribute to risk. In the present study, we found a tendency for PGD to be associated with greater delirium risk, similar to our prior study (Smith et al., 2016). In addition, individual risk factors are the strongest predictor of postoperative NSE (Raats, van Eijsden, Crolla, Steyerberg, & van der Laan, 2015), with greater age, poorer cognition, and medical acuity all increasing risk (Smith et al., 2015). This is consistent with the finding that greater LAS predicted risk of delirium in the present study. In addition to diagnosed NSE, many more patients will likely experience undiagnosed, subclinical neurological changes following surgery (Bendszus & Stoll, 2006), suggesting that neuroimaging assessments could provide critical insights into how the brain is affected following lung transplantation (Bendszus & Stoll, 2006). Indeed, available evidence suggests that greater microvascular disease and systemic dysregulation of multiple brain networks are the key contributors to postoperative neurobehavioral impairments among pulmonary patients but may only be detected using sensitive neuroimaging approaches (Dodd et al., 2012).

Taken together, available evidence suggests that neurological events are common among lung transplant recipients, although few studies have examined mechanisms underlying these frequently observed complications. Mechanistic studies could have important implications, as emerging data have linked intraoperative characteristics (Smith et al., 2016) and postoperative neuroimaging biomarkers to clinical outcomes (Browndyke et al., 2017), providing an opportunity to more comprehensively elucidate NSE mechanisms following transplant.

12.8 Posterior Reversible Encephalopathy Syndrome

One neurological event that is overly represented among transplant recipients is posterior reversible encephalopathy syndrome (PRES; Rosso et al., 2012). PRES is a rare neurological sequelae characterized by focal neurological deficits, visual changes, headache, seizures, and an acute spike in blood pressure. Originally described 20 years ago (Hinchey et al., 1996), PRES is still poorly understood, which can be reflected in the various names considered to describe this clinical phenomenon including APPLE (acute predominantly posterior leukoencephalopathy syndrome) and RPLS (reversible posterior leukoencephalopathy syndrome; Hinchey, 2008). Interestingly, there are a wide range of clinical groups for which PRES has been described, although the most common groups include transplant recipients, pregnant women, and young women with kidney disease. In lung transplant recipients, PRES is an important perioperative complication, as it typically results in the changing of immunosuppressive therapeutic regimen to another class of medications, with subsequent symptom resolution. However, because most indi-

viduals are changed to suboptimal medication regimens the long-term implications of PRES are significant, given the median survival among lung transplant recipients remains approximately 6 years.

Several case series have described the clinical presentation of PRES within lung transplant recipients (Rosso et al., 2012). In their case series of four lung transplant recipients (5.7% of patients in their total clinical sample), Rosso et al. (2012) found that all patients who experienced PRES were female, between 16 and 43 years of age, and three of four had cystic fibrosis as their native disease. Three out of four also required extracorporeal support (ECMO). As is the case in other case series, administration of calcineurin inhibitors (CNI) was associated with the development of PRES and suspension of cyclosporine or tacrolimus resulted in improvement in symptoms. In a separate case series, the onset of PRES preceded CNI administration (Arimura et al., 2014), suggesting that this is only one component of a more complex pathophysiological process.

Indeed, multiple mechanisms for PRES have been suggested (Bartynski, 2008), although considerable speculation remains (Hinchey, 2008). There are two major hypotheses that predominate the current literature (Chen et al., 2016): (1) severe hypertension leading to transient impairment in autoregulation and (2) neurotoxicity and hypertension-induced hypoperfusion with resulting ischemia and edema. Related to both of the prevailing theories above, increased blood–brain permeability ("leakiness") and endothelial dysfunction have also been widely implicated in the pathophysiology of PRES and are consistent with the characteristic posterior vasogenic edema common in clinical presentation. Although PRES tends to be characterized by posterior edema, the pattern of neuroimaging abnormalities is likely much more varied in actuality, and recent review papers have suggested that the majority of PRES cases also present with frontal lobe abnormalities, with a substantial subset showing additional abnormalities in the temporal lobes and cerebellar hemispheres (Bartynski & Boardman, 2007).

In a recent case series from our institution, we found that approximately 4% of recipients developed PRES postoperatively (Bottiger et al., 2018). All seven PRES patients were female, younger, and more likely to have cystic fibrosis relative to recipients who did not experience neurological sequelae. In addition, relative to a matched control group of female cystic fibrosis patients of similar age, patients who developed PRES had longer transplant surgery times (10.2 vs. 7.2 h, $P = 0.04$), greater 24-h peak lactate levels (5.3 vs. 3.0 mmol/L, $P = 0.045$), and longer post-transplant length of stay.

12.9 Delirium

One of the most common neurological events following transplantation is delirium, occurring in between one third and half of recipients (Sher et al., 2017; Smith et al., 2015). For example, in a retrospective study of 136 lung transplant recipients, Sher et al. (2017) demonstrated that 36% and 44% of patients developed early- and ever-

onset delirium postoperatively. In their study, obesity and benzodiazepine use were associated with greater incidence of delirium, which was in turn associated with longer ICU and total hospital LOS. Our group reported similar findings in a prospective study of 67 patients (Smith et al., 2015) and a subsequent, retrospective study of 276 transplant recipients (Smith et al., 2018). A nearly identical incidence of delirium was found, with 37% in our prospective study (Smith et al., 2015) and 40% in our retrospective cohort (Smith, Stonerock, et al., 2018). Similar to other studies, delirium was associated with longer LOS and tended to be predictive of 3-year survival independent of background and clinical characteristics. Moreover, the increased risk of mortality appeared greatest between 2 and 3 years following transplantation ($P < 0.01$ for interaction), suggesting that this association was not driven by perioperative outcomes (Smith, Stonerock, et al., 2018).

In closer examination of our prospective cohort, several interesting findings were noted suggesting that the risk factors and clinical consequences of delirium following lung transplant may be similar to previous reports among geriatric patient samples. First, consistent with prior studies in other populations (Greene et al., 2009; Smith, Attix, Weldon, Greene, & Monk, 2009), cognitive performance was one of the only preoperative predictors of postoperative delirium (Smith et al., 2015). Second, the presence of delirium influenced the trajectory of cognitive change following transplantation (Khadka, McAlinden, & Pesudovs, 2012). Specifically, although the majority of patients experienced a recovery in cognitive performance following transplantation, patients who became delirious experienced further deterioration during 3-month follow-up assessments (Smith et al., 2014). Finally, although no studies had previously examined mechanisms of posttransplant delirium, studies from cardiac samples suggested that alterations in cerebral perfusion and autoregulation may underlie the development of postoperative delirium changes (Hori et al., 2014). We were able to assess this association in our own prospective sample of lung transplant recipients, examining minute-to-minute cerebral perfusion pressure (CPP) levels and subsequent development of delirium (Smith et al., 2016). We found that lower CPP during transplant was associated with greater incidence, duration, and severity of postoperative delirium, with every 10 mmHg lower CPP associating with nearly twice the odds of delirium and a nearly 2-day longer duration of delirium.

12.10 Cognitive Changes Following Lung Transplantation

Neurocognitive function is increasingly recognized as an important consideration among lung transplant recipients (Diamond & Mikkelsen, 2014), in large part because of the increasing age of all solid organ transplant recipients (Hajduk et al., 2013; Mapelli et al., 2011; Schulz & Kroencke, 2015). Although originally envisioned as a treatment for younger patients, the average age of transplant recipients has steadily increased as the number of patients with IPF has risen, increasing from an average age of approximately 45 years in the 1980s to nearly 60 years of age at

present (Yusen et al., 2014). Indeed, patients aged ≥65 years constitute approximately one third of all recipients (Singer et al., 2016; Singer, Chowdhury, et al., 2015; Valapour et al., 2013), who experience comparatively lower QoL improvement relative to younger recipients (Singer et al., 2016).

Accordingly, there has been an increased interest in the potential impact of POCD on quality of life (QoL) and clinical outcomes, which represent the two primary treatment targets of transplantation. Neurocognitive impairments are common among advanced pulmonary patients (Dodd et al., 2010), including pretransplant patients, and have been associated with worsening physiological function, such as poorer gas exchange (Parekh et al., 2005). Preliminary data from our group (Hoffman et al., 2012; Smith, Rivelli, et al., 2014) and others (Cohen et al., 2014) have demonstrated that POCD is common following lung transplantation, affecting more than half of recipients (57–67%; Cohen et al., 2014; Smith, Rivelli, et al., 2014). Although many transplant recipients exhibit at least mild impairments preoperatively (Hoffman, Blumenthal, Carney, O'Hayer, et al., 2012; Parekh et al., 2005; Smith et al., 2015), cognitive function often worsens following transplant, with up to 86% of patients exhibiting at least mild levels of impairment, depending on the definition of POCD used (Hoffman, Blumenthal, Carney, O'Hayer, et al., 2012; Smith, Rivelli, et al., 2014). Available evidence suggests that impairments are most commonly observed on tests of executive function, attention, and working memory, suggesting an important role for prefrontal and subcortical brain structures (Grieve, Williams, Paul, Clark, & Gordon, 2007). In addition, older age and mild preoperative neurocognitive impairment appear to be associated with the increased risk of POCD following transplant (Hoffman, Blumenthal, Carney, O'Hayer, et al., 2012; Smith et al., 2015), consistent with data from other surgical populations (Berger et al., 2015; Monk et al., 2008). Importantly, although older age is perhaps the strongest risk factor for POCD, available evidence suggests that younger patients, such as those with cystic fibrosis, are also at risk (Chadwick et al., 2016; Smith, Rivelli, et al., 2014). These data suggest that identification and improved management of vulnerable patients may be possible.

12.10.1 Neurocognitive Function and Clinical Events

Data from our laboratory (Smith, Blumenthal, et al., 2014) and others (Jha et al., 2016) suggest that poorer neurocognitive functioning is predictive of long-term mortality following lung transplantation, similar to the relationship observed in other patient populations, including advanced COPD (Raffaele et al., 2006), renal transplant (Sharma et al., 2016), heart failure (Pressler, Kim, Riley, Ronis, & Gradus-Pizlo, 2010), and in the general population (Sachs et al., 2011; Stump, Callahan, & Hendrie, 2001). For example, memory dysfunction, psychomotor slowing, and lower executive function have been shown to predict subsequent mortality in heart failure patients (Pressler et al., 2010). Similar to other published cohort studies (Pressler et al., 2010; Sharma et al., 2016), the association between neuro-

cognitive impairment and mortality appeared strongest for the executive function and memory domains (Smith, Blumenthal, et al., 2014). We have recently reported similar data from long-term assessments of participants from the INSPIRE study of lung transplant candidates (Smith, Blumenthal, et al., 2014).

We previously found that pretransplant executive function and memory were predictive of posttransplant, long-term mortality (Smith, Blumenthal, et al., 2014). In addition, recent data from this cohort demonstrated that poorer postoperative cognitive function was associated with greater mortality in several domains (Executive Function: HR = 0.52 [0.28, 0.97], Processing Speed: HR = 0.58 [0.36, 0.95]), and greater risk of CLAD (Memory: HR = 0.54 [0.29, 1.00]) (Smith, Blumenthal, Hoffman, Davis, & Palmer, 2018). Examination of individual tests suggested that performance on measures of executive function (Stroop Color-Word Test: HR = 0.39 [0.20, 0.75]; Verbal Fluency: HR = 0.65 [0.40, 1.04]) and attention/working memory (Digit Span: HR = 0.37 [0.17, 0.80]) were most strongly predictive of survival, consistent with other clinical cohorts (Pressler et al., 2010; Sharma et al., 2016; Stilley et al., 2010). Moreover, as noted above, recent data from our group suggest that patients who experience early neurological sequelae (NSE; e.g., delirium within the first postoperative week) have an 86% increased risk of mortality after accounting for relevant medical predictors (Smith, Stonerock, et al., 2018). Interestingly, the risk of subsequent mortality was greatest 2–3 years following transplantation, suggesting that this association was not due to early postoperative complications.

Despite the prevalence of POCD in lung transplant recipients and its association with clinical events, no studies, to our knowledge, have examined the association between POCD, health behaviors, and QoL. Health compliance behaviors, including medication adherence, appointment attendance, physical activity, and home spirometry, are critical to posttransplant survival, with lung transplant recipients often having to accurately manage a regimen of 10–12 medications and up to 30 pills per day. Non-adherence to immunosuppression medications after transplant is the most common, preventable cause of mortality (Castleberry et al., 2017), and even modest levels of non-adherence have been associated with a sevenfold increase in the odds of graft failure in some populations (Butler, Roderick, Mullee, Mason, & Peveler, 2004). Indeed, medication adherence is not only a critical component of posttransplant management but is one of the strongest predictors of long-term survival in transplant patients (De Geest, Dobbels, Fluri, Paris, & Troosters, 2005; Wainwright & Gould, 1997).

Levels of adherence vary widely among lung transplant recipients, with some estimating that more than 40% of recipients exhibit clinically significant non-adherent behavior within the first few years of receiving a transplant (Korb-Savoldelli et al., 2010). Despite the frequency of non-adherence, strikingly few risk factors are consistently predictive of subsequent non-adherent behaviors among transplant recipients (Dew et al., 2008). In other healthy populations, observational studies have consistently found an association between neurocognitive function and adherence (Stilley et al., 2010). For example, greater working memory function has been shown to predict subsequent medication adherence among older primary care

patients (Stoehr et al., 2008) as well as in three studies examining cardiovascular medication adherence (Stilley et al., 2010), in which attention, mental flexibility, and working memory were consistently predictive of adherence behaviors. Multiple studies among other medical populations have suggested that neurocognitive deficits in executive function, memory, and working memory are associated with poorer medication adherence (Becker, Thames, Woo, Castellon, & Hinkin, 2011; Ettenhofer, Foley, Castellon, & Hinkin, 2010; Hayes, Larimer, Adami, & Kaye, 2009; Stilley et al., 2010), including patients with HIV (Ettenhofer et al., 2009, 2010; Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009), cardiovascular disease (CVD; Stilley et al., 2010), and even among healthy older adults (Hayes et al., 2009). Indeed, lower cognitive function has been associated with nearly fourfold greater risk of medication non-compliance in older adults (Hayes et al., 2009). Although no studies have systematically examined neurocognition and QoL, neurocognitive symptoms (trouble remembering and concentrating) are prevalent and one of the most distressing symptoms reported among lung transplant candidates (Lanuza et al., 2012). Indeed, neurocognitive dysfunction is one of the most stressful health concerns in the broader U.S. population, as many patients would prefer to diagnoses of cancer or heart disease than experience neurocognitive impairment (Alzheimer's, 2010).

Determining clinical predictors of psychological QoL after transplant is particularly important, as changes in psychological indices after transplant have rarely been studied (Seiler et al., 2016). In contrast, multiple studies suggest large and robust improvements in health-related QoL among lung transplant recipients (Seiler et al., 2016; Singer et al., 2015). Despite HQoL improvements, the impact of lung transplantation on mental/psychological QoL is far less clear, and prior data from our research team suggests that psychological QoL remains relatively unchanged after transplant, despite improved HQoL (Copeland, Vock, Pieper, Mark, & Palmer, 2012). In fact, a recent systematic review of QoL changes following lung transplantation concluded that "a considerable number of patients experience psychological distress and mental health problems," that "mental health appears to decline even if there are short-term improvements," and that "there are [few] data on predictors of mental health outcomes (Seiler et al., 2016)."

Although data on neurocognition and QoL in lung transplant patients is limited, data following patients undergoing CABG suggests that POCD diminishes improvements in QoL following surgery (Phillips-Bute et al., 2006; Rothenhausler et al., 2005). In their study of 732 CABG patients, the authors found that POCD limited QoL improvements, that changes in neurocognition were substantially correlated with changes in QoL, and that the most robust associations were observed with tests of complex attention/executive function (Phillips-Bute et al., 2006). Other investigators have found a similar pattern of QoL improvement following CABG when compared to lung transplantation: many patients do not experience improvements in mental/psychological QoL and neurocognitive function is a significant predictor of non-improvement (Le Grande et al., 2006). These associations appear to persist in long-term studies among both cardiac and non-cardiac samples, with data from large, multi-site, prospective studies, finding that POCD mitigates postoperative

QoL improvements and increases the likelihood of early retirement or withdrawal from the workplace (Newman et al., 2001; Steinmetz et al., 2009), as well as increased dependency for activities of daily living (Borges, Moreira, Moreira, Santos, & Abelha, 2016).

12.11 Mechanisms of Postoperative Cognitive Dysfunction

Although the mechanisms of POCD are not fully understood, retrospective studies suggest that neurological complications are highly prevalent following lung transplantation, affecting up to 90% of recipients (Mateen et al., 2010). Neurological complications are most commonly due to cerebrovascular events and posttransplant encephalopathy, although posterior reversible encephalopathy syndrome (PRES) is also common (Shigemura et al., 2013). Of note, available evidence consistently demonstrates an increased risk of poorer clinical outcomes following transplantation among individuals who experience a neurological event, including mortality (Mateen et al., 2010; Shigemura et al., 2013; Smith, Blumenthal, et al., 2014). Because many more patients will likely experience undiagnosed, subclinical neurological changes following surgery (Bendszus & Stoll, 2006), neuroimaging could provide critical insights into how the brain is affected following lung transplantation (Bendszus & Stoll, 2006). Indeed, available evidence suggests that greater microvascular disease and systemic dysregulation of multiple brain networks are the key contributors to POCD among pulmonary patients, but may only be detected using sensitive neuroimaging approaches (Dodd et al., 2012).

Mechanisms underlying POCD in lung transplant recipients are also informed by a wealth of data from other transplant and cardiothoracic surgical populations (Rudolph et al., 2010; Selnes & Gottesman, 2010), in which occult white matter damage and alterations in resting state functional connectivity (Browndyke et al., 2017) have been suggested to underlie postoperative cognitive changes (Gupta et al., 2016; Tarumi et al., 2014; Wee et al., 2012). Among CABG patients, sensitive imaging assessments reveal that approximately 33–50% of patients experience occult cerebrovascular changes that are clinically undetectable (Barber et al., 2008; Bendszus & Stoll, 2006; Cook et al., 2007; Gerriets et al., 2010). Although the effects of coronary surgery on the brain are likely multifactorial, the primary postulated mechanisms include microembolic showers, regional metabolic abnormalities, neuroinflammatory changes, intraoperative hypoxia, and ischemia (Royter, Bornstein, & Russell, 2005). In addition, over the past decade, it has become clear that several patient characteristics are consistently predictive of posttransplant POCD, including older age (Hoffman et al., 2012), greater cerebrovascular disease, and preexisting neurocognitive weaknesses (Kadoi & Goto, 2006; Kozora et al., 2010). This same cluster of risk factors appears predictive in lung transplant recipients as well (Smith et al., 2015, 2016; Smith, Rivelli, et al., 2014), although this will be the first study to examine this systematically.

12.12 Summary

In conclusion, cognitive dysfunction is common among individuals with pulmonary disease and is associated with worse clinical outcomes and QoL. Although the mechanisms of cognitive dysfunction are multifactorial, inflammation is increasingly identified as a potential factor underlying the higher prevalence of cognitive impairments across pulmonary populations. Cognitive dysfunction, delirium, and POCD may be particularly important among lung transplant recipients, for whom cognitive function has important implications for medication adherence and post-transplant mortality.

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Chapter 13
Diabetes and Hypertension

Clinton Wright and Michelle Caunca

13.1 Introduction

Cognitive impairment and dementia are very prevalent conditions in people 60 years and older. Estimates of people with a mild level of cognitive impairment (MCI) vary widely depending on the definition of MCI and the sample (Panza et al., 2005), but in community-based studies, it is estimated to be at least twice the overall prevalence of dementia. Many people with cognitive impairment go on to develop dementia, which doubles in prevalence and incidence every additional 5 years of age (Lobo et al., 2000). Between 65 and 85 years and older, the prevalence of dementia increases from about 3% to approximately 32% of the population (Hebert, Weuve, Scherr, & Evans, 2013), and the number of new cases that develop increases from 2 per 1000 people to 37 per 100 people (Hebert, Beckett, Scherr, & Evans, 2001).

Vascular disease is also highly prevalent in older individuals. Hypertension represents a very large public health problem with a US prevalence rate estimated at 32%, based on the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2014 (Whelton et al., 2017). With the new guidelines that have lowered blood pressure targets to ≥130/80 mmHg, this prevalence increases to 46% (Whelton et al., 2017). Similarly, the worldwide prevalence of hypertension is estimated as about 31% as of 2010 (Mills et al., 2016). In the elderly at greatest risk of dementia, the prevalence of hypertension can be as high as 78% (Whelton et al., 2017). Type 2 diabetes (T2D) is also rapidly emerging as a global epidemic and challenge to the public health system (Amos, McCarty, & Zimmet, 1997; Passa,

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_13

2002; Resnick, Harris, Brock, & Harris, 2000). Currently approximately 25% of older persons suffer from T2D (Centers for Disease Control and Prevention, 2017) and with the aging of the population, and as the increasing prevalence of the overweight and obese who are more prone to insulin resistance, this number is projected to increase (Boyle et al., 2001).

An increase in the prevalence of both hypertension and T2D has implications for vascular cognitive disorders due to the different mechanisms through which they may affect cognition. The major cerebral consequence of both hypertension and T2D has been macrovascular clinical stroke. However, advances in neuroimaging and growing availability of structural magnetic resonance imaging (MRI) data has increased the study of subclinical cerebrovascular disease and cognition. As a result, the inverse association between subclinical cerebral small vessel disease and cognitive function has been well-documented (Brickman et al., 2012; Dong et al., 2015; Poels et al., 2012; Vernooij et al., 2009; Wardlaw, Valdes Hernandez, & Munoz-Maniega, 2015). How vascular and neurodegenerative processes interact to affect cognition remains an important research area. Given that mixed dementia, defined as a combination of Alzheimer disease and other pathologies such as vascular damage, Lewy bodies, and others (Bennett, Schneider, Arvanitakis, & Wilson, 2012), is the most common cause of dementia, public health efforts to improve brain health through improvement of vascular health are currently under way (Gorelick et al., 2017; Iadecola et al., 2016).

In epidemiologic samples of older persons, where type 2 is the main type of diabetes, T2D has been associated with a higher prevalence of global cognitive impairment (Kalmijn, Feskens, Launer, Stijnen, & Kromhout, 1995) and a higher incidence of cognitive decline (Gregg et al., 2000). In the Cardiovascular Health Study (CHS) of persons over 65 years of age, T2D and high levels of glucose were significantly associated with a 7-year decline in cognitive function (Haan, Shemanski, Jagust, Manolio, & Kuller, 1999). Data from population-based studies also suggest that T2D is a risk factor not only for vascular dementia (Curb et al., 1999) but also for Alzheimer's disease (AD) (Leibson et al., 1997; Ott et al., 1999). Together, prospective cohort studies suggest diabetics have approximately two times the increased risk for AD, in particular, AD combined with cerebrovascular disease. This is a fairly robust finding, as studies are based on different ethnic/race/lifestyle groups, including Japanese–American men (Peila, Rodriguez, Launer, & Honolulu-Asia Aging, 2002), a mixed ethnic/race cohort (Luchsinger, Tang, Stern, Shea, & Mayeux, 2001), European Caucasian (Leibson et al., 1997; Ott et al., 1999), and religious order members (Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004).

Hypertension has also been associated with a greater risk of cognitive impairment (Kilander, Nyman, Boberg, Hansson, & Lithell, 1998) and dementia (Skoog et al., 1996), including the subtype of vascular dementia (Hofman et al., 1997). A relationship between blood pressure and AD has been found when BP was measured in mid-life (Kivipelto et al., 2001; Launer et al., 2000), but the relationship between Alzheimer's and blood pressure is inconsistent when measured close to the time of dementia onset (Morris et al., 2001; Posner et al., 2002). Other population-based studies have shown that elevated/high systolic blood pressure, if untreated,

was associated with cognitive impairment (Elias, Wolf, D'Agostino, Cobb, & White, 1993; Guo, Fratiglioni, Winblad, & Viitanen, 1997; Launer et al., 2000) and that treatment was associated with a lower risk of cognitive impairment (Murray et al., 2002).

Randomized double-blind clinical trials have not consistently shown treatment of hypertension to be protective against dementia, and the authors of a recent meta-analysis that included three such trials did not establish that treatment of hypertension prevents the development of cognitive impairment or dementia (McGuinness, Todd, Passmore, & Bullock, 2009). The Syst Eur trial did show a reduced risk of dementia in the group treated for hypertension, but 50% of the placebo group received active treatment, raising questions about the conclusions. However, the most convincing evidence to date comes from The large ($N = 8563$) Systolic Blood Pressure Intervention: Memory and Cognition in Decreased Hypertension (SPRINT MIND) trial where intensive systolic blood pressure lowering to <120 mmHg systolic was compared to standard blood pressure control of <140 mmHg. Study participants had a history of hypertension, no diabetes, and were at elevated cardiovascular risk, and while intensive blood pressure control did not significantly affect the primary outcome of probable dementia, significantly fewer participants in this arm developed MCI. Despite lack of statistical significance, the effect size was almost identical for probable dementia, with limited power and only half as many events, and these data are the first to show that intensive blood pressure control has a beneficial effect on cognitive outcomes at this early stage.(Sprint Mind Investigators for the SPRINT Research Group, 2019b). In this chapter, the pathophysiologic mechanisms that are hypothesized to contribute to the changes in brain function caused by hypertension and diabetes as well as characteristic neurobehavioral changes will be reviewed.

13.2 Neuropathology and Pathophysiology

Both hypertension and T2D are strong risk factors for arterial damage of large (>2 mm diameter) and small-sized (usually <0.8 mm diameter) vessels of the heart, systemic circulation, and other organs including the brain. As a result, the effects on cognition vary by the type of injury.

13.2.1 Large Vessel Disease

Hypertension and T2D can lead to ischemic heart disease (IHD) and atrial and ventricular chamber abnormalities that increase the likelihood of clot formation, embolization to the brain, and resulting ischemic stroke. Ruptured atherosclerotic plaque of the large vessels with distal embolization may have the same result. Both of these pathologic mechanisms most commonly result in damage to the brain territory of

one of the major intracranial vessels such as the middle, anterior, and posterior cerebral arteries and can result in cognitive deficits or frank dementia depending on the size, location, and number of lesions (see Chap. 3 for cognitive effects of stroke).

Aside from embolism to the brain, IHD can lead to heart failure (Chap. 11) and large vessel atherosclerosis with stenosis or occlusion of one or more vessels supplying the brain (e.g., the carotid artery, Chap. 9), resulting in severe reductions in blood flow that can cause cognitive dysfunction. Though there is some evidence that LVAD surgery may improve cognitive outcomes (Petrucci et al., 2009), cognitive decline is still common post-surgery (Dew et al., 2001; Fendler et al., 2015) and posttransplant (Burker et al., 2017).

13.2.2 Small Vessel Disease

Small vessel damage, or microangiopathy, is an important mediator of the effects of both hypertension and diabetes on cognition. Small vessel disease has been of great interest since Maxime Durand-Fardel described three common brain lesions associated with such damage, in the 1850s. The first of these, called "Atrophie interstitielle du cerveau" by Durand-Fardel, corresponds to modern day imaging findings of periventricular and deep white matter lucencies (on computed tomography (CT) scans) or hyperintensities (on magnetic resonance (MR) scans). Vladimir Hachinski coined the term "leukoaraiosis" for these changes to avoid *presuming* an etiology (Hachinski, Potter, & Merskey, 1987). However, pathological studies have found that leukoaraiosis often corresponds to ischemic damage of varying degrees that has been caused by injury to the small penetrating vessels that supply the basal ganglia and subcortical white matter (Fernando et al., 2006).

Small penetrating arterioles of the deep gray nuclei and white matter tracts are end-arteries without significant overlap with other vascular beds. As such, a key contributor to damage is the reduction in cerebral perfusion that accompanies arterial damage brought about by chronic hypertension and diabetes. Normally the brain is able to modulate the diameter of small "resistance" vessels in the brain parenchyma, dilating them to increase and constricting them to decrease the amount of cerebral blood flow to keep it within an acceptable range of perfusion pressures. However, chronic exposure to raised blood pressure damages vessels and reduces this "vasodilatory capacity." Resistance vessels are no longer able to constrict in the face of daily fluctuations in blood pressure, such as nocturnal dips, and adequate perfusion may not be maintained resulting in ischemic damage (Isaka, Okamoto, Ashida, & Imaizumi, 1994).

Based on autopsy studies, lacunae and leukoaraiosis are thought to result from four lesions—small vessel atherosclerosis, lipohyalinosis (complex small vessel disease), arteriolosclerosis (simple small vessel disease), and enlarged perivascular spaces—but their relationship to each other is not completely understood (Donnan, 2002). For example, to what extent is arteriolosclerosis a stage that precedes lipo-

hyalinosis? In addition, some lacunae are due to infarcts caused by thrombosis of a small vessel. In other cases, ischemic damage can also result from increased vascular permeability of damaged vessels causing chronic edema resulting in local hypoxia, or impaired nutrient supply to perivascular regions (Donnan, 2002).

Three subtypes of lacunae have been described pathologically and include the following: (1) incomplete infarctions in which not all cellular elements are damaged as well as complete infarctions that are gliotic cavitated lesions (type I); (2) lacunae with a large number of macrophages (type II); and (3) enlarged perivascular spaces (type III) (Fleury et al., 1984). Types I and II are very similar and probably represent different extremes rather than distinct entities. Type III lacunae may be due to disruption of the blood–brain barrier with damage to periarteriolar tissue or trauma to the brain tissue that surrounds small vessels due to high blood pressure. Thus, small vessel damage may first lead to ischemic demyelination in the deep white matter and, later, lacunar infarction (Fazekas et al., 1993).

13.2.3 Brain Atrophy and AD-Related Pathology

High blood pressure and T2D have also been associated with brain atrophy in addition to subcortical vascular lesions. Such reductions in brain volume may represent damage to the cortex that could have a detrimental effect on cognition. However, the importance of brain atrophy as a mechanism separate from microangiopathy is difficult to sort out because ischemic damage can cause reductions in brain volume as well (Goldstein, Bartzokis, Guthrie, & Shapiro, 2005; Schmidt et al., 2004; Wiseman et al., 2004). In addition, cortical volume loss can also be caused by AD, with hypertension or diabetes as important mediators. For example, midlife hypertension has been associated with greater brain atrophy and an increased burden of Alzheimer pathology in autopsied cases (Petrovitch et al., 2000). Consistent with these pathological data, vascular risk factors have been associated with thinner cortices in AD signature regions, greater tau deposition in the entorhinal cortex, and greater burden of amyloid beta deposition as measured by florbetapir positron emission tomography imaging (Gottesman et al., 2017; Vemuri, Knopman, et al., 2017; Vemuri, Lesnick, et al., 2017) in vivo. In the ARIC study of middle-aged and young-elderly men and women, T2D was associated with greater ventricular size, an indicator of general atrophy (Knopman, Mosley, Catellier, Sharrett, & Atherosclerosis Risk in Communities, 2005). Using a similar methodology, similar findings were reported for older men and women in the CHS (Longstreth Jr., Arnold, Manolio, Burke, & Fried, 2000). Other research (den Heijer et al., 2003) has also found that smaller hippocampal and amygdalar volumes, regardless of vascular pathology, were associated with T2D. Similarly, compared to non-diabetics, diabetics had smaller hippocampal volumes and more lacunas in a study of very old Japanese Americans followed as a part of the HAAS study (Korf, White, Scheltens, & Launer, 2006). In the HAAS study, there was evidence that insulin users had smaller hippocampi than

non-insulin using diabetics. In addition, results showed proportionately more brain pathology in those who have been diabetic for at least 20 years. In a multi-center MRI study of 65- to 75-year olds, an interaction between T2D and hypertension was noted: those with both conditions had an increased risk for brain atrophy that was greater than those having only one or neither of the conditions (Schmidt et al., 2004). These findings suggest that the amount of brain pathology may increase with disease severity, comorbidity, or duration. Experimental studies, which are less susceptible to bias and confounding compared to observational studies, have also been done to test the effects of blood pressure treatment in people with type 2 diabetes on cardiovascular and cognitive outcomes (Launer et al., 2011). In the Action to Control Cardiovascular Disease Risk in Diabetes Memory in Diabetes (ACCORD MIND) trial, intensive glycemic control was associated with significantly greater mean total brain volumes, but this did not translate into a significant effect on the primary cognitive outcome of mean Digit Symbol Substitution Test scores (Launer et al., 2011). These findings suggest that in type 2 diabetes, glucose lowering may have a positive impact on brain health. The lack of findings with cognitive outcomes may be explained by short follow-up in the clinical trial, a limitation of many trials in cognitive aging research. But, data from the SPRINT MIND trial recently showed that intensive blood pressure control reduced the risk of mild cognitive impairment (Sprint Mind Investigators for the SPRINT Research Group, 2019b). Further, those in the intensive blood pressure arm who underwent baseline and follow-up brain MRI scans in the intensive arm had less progression of white matter lesions but a greater reduction in brain volume than those in the standard arm (Sprint Mind Investigators for the SPRINT Research Group, 2019a).

13.3 Intermediary Metabolic, Inflammatory and Oxidative Mechanism: Hypertension

Studies suggest various pathways through which elevated BP or diabetes could alter the structure of the brain and cause cognitive impairment. Direct effects of high blood pressure on Alzheimer's disease pathology can be hypothesized. Endothelial damage caused by hypertension itself may lead to pro-inflammatory, pro-coagulant, and oxidative responses similar to those hypothesized to trigger the formation of neuritic plaques in Alzheimer's disease (Tanzi, Moir, & Wagner, 2004). Further, animal evidence suggests that hypertension may directly promote amyloid-related pathology by upregulating beta-secretase activity and increasing amyloid precursor protein processing (Faraco, Park, et al., 2016). Independent of endothelial damage, there is evidence in mouse models of hypertension that inflammatory processes mediated by resident perivascular macrophages contribute to neurovascular and cognitive dysfunction (Faraco, Sugiyama, et al., 2016).

13.3.1 Intermediary Physiologic Changes in Type 2 Diabetes

T2D is associated with oxidative stress, inflammation (Klein & Waxman, 2003), an increase in O-linked glycoprotein, and increased formation of advanced glycosylation end products (AGES) (R. Singh, Barden, Mori, & Beilin, 2001) that may have detrimental effects on cognition.

In addition to vascular damage, there has been considerable debate in the literature about whether those with T2D are at increased risk for Alzheimer disease (Forrester, 2004; Grossman, 2003; Halter, 1996; Hoyer, 1998). Several of the above mechanisms also contribute to neurodegeneration (Hardy & Selkoe, 2002). Other diabetes-related pathology, such as AGES, can contribute directly to neurodegeneration and the formation of neuritic plaques (NP) and neurofibrillary tangles (NFT). Consistent with these mechanisms, autopsy data based on the Honolulu Asia Aging Study (HAAS) cohort, shows a significant association of T2D to infarcts as well as hippocampal NFT and NP (Peila et al., 2002); another study, however, did not confirm this association (Arvanitakis et al., 2006). It is also likely that a vicious cycle develops with T2D and neurodegenerative processes. A hyperglycemic environment can lead to neuronal degeneration, and neuronal degeneration can lead to impaired glucose regulation. For example, there may be a direct effect of hyperglycemia on the calcium balance in hippocampal neurons that could lead to degeneration (McEwen, Magarinos, & Reagan, 2002). Such neuronal damage could interfere with the hippocampus role in regulating peripheral glucose (Gispen & Biessels, 2000; Magarinos & McEwen, 2000), as well as the synaptic plasticity in hippocampal neurons as demonstrated in animal studies (Klein & Waxman, 2003). It has also been suggested that hyperglycemia leads to increased vasopressin, which is part of a cascade that eventually results in the degeneration of hypothalamic neurons (Magarinos & McEwen, 2000) and impaired hypothalamic function. Since the hypothalamus is central to the regulation of many physiologic mediators, including vasopressin, leptin, ghrelin, insulin, and glucose (Elmquist & Marcus, 2003), changes in the neurons in this structure could lead to dysregulation of the pathways that depend on these metabolic products.

Diabetics are also at increased risk for hypoglycemic events, which disturb delivery of nutrients to the brain, may downregulate different markers of neuronal plasticity (P. Singh, Heera, & Kaur, 2003) and increase the amount of neurotoxic glutamate. Further, the brains of people with T2D are at risk for adverse sequela following repeated hypoglycemic events (Langan, Deary, Hepburn, & Frier, 1991; Perros, Deary, Sellar, Best, & Frier, 1997).

13.3.2 Hyperinsulinemia

In the brain, insulin modulates glucose availability as well as the activity of neurotransmitters and neuronal health (Craft & Watson, 2004). Central nervous system (CNS) insulin is derived mainly from the peripheral circulation (Schwartz et al.,

1991) and is proportionally related to plasma insulin levels (Schwartz, Figlewicz, Baskin, Woods, & Porte Jr., 1992). Under physiological conditions, a higher serum insulin level may reflect a higher level of brain insulin, and a low level could reflect an insufficient insulinization of the brain. In hyperinsulinemic conditions, the transport of insulin into the CNS is altered and insulin resistance can ensue (Bonora et al., 1998).

Insufficient insulinization in the brain could lead to multiple cerebral changes. Studies of the relatively acute effects of insulin in the brain have shown that insulin potentiates memory. It does this through several hypothesized pathways such as modulation of cellular glucose uptake, neurotransmitter levels, and long-term potentiation critical in the communication of memory-related impulses from neuron to neuron (Craft & Watson, 2004). Both peripheral and central levels of inflammatory markers and oxidative stress are also increased in hyperinsulinemic conditions. Metabolic dysregulation of insulin can cause endothelial damage and impair the health of the vasculature; it can also lead to phosphorylation of tau, disrupture of microtubles in the neuron, and neurofibrillary tangles, a hallmark of AD pathology (Hong & Lee, 1997). Greater insulin resistance has been associated with more amyloid deposition as quantified by Pittsburgh compound B PET imaging (Willette et al., 2015). These hypotheses have been examined in pilot clinical trials of testing the effects of regular and long-acting insulin on cognitive and AD biomarker outcomes (Craft et al., 2017).

Dysfunction of the insulin-degrading enzyme (IDE) may also provide a pathological link between neurodegeneration and T2D. This enzyme degrades insulin as well as β-amyloid, a major component of the extracellular plaques that characterize AD. In T2D, dysfunction of IDE leads to high levels of insulin and β-amyloid (Edbauer, Willem, Lammich, Steiner, & Haass, 2002; Qiu et al., 1998). In AD, hyperinsulinemia is more prevalent compared to controls, and the activity and amount of IDE is diminished (Cook et al., 2003; Perez, Morelli, Cresto, & Castano, 2000). Interestingly, IDE is located on chromosome 10; there is some evidence for genetic linkage of Alzheimer's disease on this chromosome (Bertram et al., 2000).

13.3.3 Diabetes and Genetic Susceptibility

Interactions between genetic susceptibility and T2D have been reported. Data from the Zutphen Study (Kalmijn, Feskens, Launer, & Kromhout, 1996) suggests that men who carry an Apolipoprotein E ε4 allele *and* have T2D had a higher risk for cognitive decline compared to those with no T2D or no Apo E ε4 genotype. Similarly, the HAAS study found that diabetics with an Apo E ε4 allele had a significantly higher risk for AD compared to those with none or one condition (Peila et al., 2002). An interaction of T2D and Apo E ε4 allele on the risk for dementia was also reported in the CHS (Irie et al., 2008). Recent evidence examining commonalities between T2D- and AD-related single nucleotide polymorphisms suggests a common genetic etiology between T2D and AD (Hao et al., 2015).

13.4 Characteristic Neurobehavioral Syndromes

The cognitive consequences of hypertension and diabetes depend on the mechanisms of damage noted in the preceding section. To review the cognitive deficits associated with specific lesion locations, such as with lacunar infarcts, is beyond the scope of this chapter (see Chap. 2). Infarcts in specific locations can result in cognitive deficits depending on the cognitive functions subserved by the area involved, although many cognitive processes are widely distributed. For example, thalamic infarcts can impair memory function, and infarcts in the frontal lobe often affect speed of processing and executive function (Vermeer et al., 2003). Multiple infarcts can likewise cause deficits in several domains.

Nineteenth-century authors, including Durand-Fardel and most famously Otto Binswanger, were the first to posit an effect of leukoaraiosis on cognition, but it was not until modern brain imaging with CT and MR that the issue has been addressed in large samples. The question is far from simple because leukoaraiosis is often seen incidentally on the brain scans of elderly individuals without dementia, and the amount required to cause cognitive problems is not known. In addition, elderly individuals with cognitive problems often have Alzheimer's disease in addition to hypertension and/or T2D, making the contribution of leukoaraiosis to the cognitive profile difficult to sort out. The above notwithstanding, leukoaraiosis has been associated with cognitive decline and dementia (Wardlaw et al., 2015).

The cognitive deficits associated with leukoaraiosis include psychomotor slowing and executive dysfunction and represent a typical subcortical pattern of injury (Prins et al., 2005; Sachdev, Wen, Christensen, & Jorm, 2005). Executive functions involve planning, decision-making, and cognitive flexibility. In order to explain how executive dysfunction might be caused by leukoaraiosis, microvascular damage has been posited to disrupt projections from cortical areas to subcortical structures (Cummings, 1993). Imaging studies of the topography of white matter hyperintensities in the coronal plane have shown that as the volume of damage increases, white matter damage extends further and further away from the ventricular wall in a uniform manner (DeCarli, Fletcher, Ramey, Harvey, & Jagust, 2005). In this way, frontal subcortical circuits adjacent to the ventricular wall might be progressively disrupted. This concept is supported by data showing that leukoaraiosis affects executive function regardless of the location (Tullberg et al., 2004). Another way leukoaraiosis may affect cognition is by slowing neural transmission since somatosenory and visual evoked potentials are delayed in the presence of leukoaraiosis (Kato, Sugawara, Ito, & Kogure, 1990; Shibata, Osawa, & Iwata, 2000).

The cognitive profile of chronic exposure to hypertension or diabetes independent of leukoaraiosis and lacunar infarction is difficult to sort out for the reasons mentioned earlier. Brain atrophy resulting from such exposure and not due to other causes such as Alzheimer's disease might have an effect on executive function as well. This is supported by data showing that men with higher systolic blood pressures had lower regional frontal lobe volumes (atrophy), and these lower volumes correlated with worse performance on tests of cognitive flexibility (executive

function) and working memory (Gianaros, Greer, Ryan, & Jennings, 2006). Experimental models of hypertension can also be helpful. Recent studies in Rhesus monkeys where blood pressure was increased to varying degrees experimentally have shown negative effects on abstraction and shifting set. Loss of neurons in the cortex and of myelin fibers in the white matter predominated in the forebrain, internal capsule, corona radiata, and cortex (Moore et al., 2002).

13.4.1 Diabetes: Special Considerations

13.4.1.1 Type 1 Diabetes

A recent systematic review and meta-analysis summarizing the literature on type 1 diabetes and cognitive impairment reported that disease duration, glycemic dysregulation, and complications from type 1 diabetes were associated with cognitive problems (Li, Huang, & Gao, 2017). The Diabetes Control and Complications Trial (DCCT) results on type 1 diabetic cases, however, did not demonstrate any differences in cognitive function between those in the intensive treatment arm and the conventional treatment arm (Diabetes Control and Complications Trial Research Group, 1996). The average age of type 1 patients in these studies is around 35 years. A recent study on a sample of relatively older type 1 diabetics (average age 60 years) and controls found only mild cognitive impairments in the diabetics compared to age-matched controls (Brands, Biessels, de Haan, Kappelle, & Kessels, 2005). The recent literature may not have considered the life course approach for this research question, however. For example, a recent study found significant associations between childhood-onset type 1 diabetes and cognitive outcomes in middle age (Nunley et al., 2015).

13.4.1.2 Type 2 Diabetes

Data in older individuals have been inconclusive regarding whether diabetes is associated with global cognitive impairment or impairment in specific domains. Part of the reason is the great variability in study design and test results that characterize this area of research. Small sample size, relatively young mean age, lack of control for confounders such as depression, and other cardiovascular risk factors characterize much of the literature (Coker & Shumaker, 2003; Cukierman, Gerstein, & Williamson, 2005; Musselman, Betan, Larsen, & Phillips, 2003; Stewart & Liolitsa, 1999). However, findings in several large-scale studies of people aged 60 years and older do suggest diabetics are cognitively impaired relative to those with no diabetes. Four studies (Fontbonne, Berr, Ducimetiere, & Alperovitch, 2001; Grodstein, Chen, Wilson, Manson, & Nurses' Health, 2001; Kalmijn et al., 1995; Sinclair, Girling, & Bayer, 2000) showed that, compared to non-diabetics, diabetics performed significantly poorer on tests of global cognitive function, such as the Mini-

Mental State Exam (MMSE), or equivalent (Folstein, Folstein, & McHugh, 1975; Teng & Chui, 1987). Several longitudinal cohort studies have found that T2D is associated with greater cognitive decline and greater risk of mild cognitive impairment (Mayeda et al., 2014; Mayeda, Haan, Kanaya, Yaffe, & Neuhaus, 2013; Mayeda, Haan, Yaffe, Kanaya, & Neuhaus, 2015; Rawlings et al., 2014; Roberts et al., 2014; Yaffe et al., 2012). A study of religious order members followed for a mean 5.5 years reported that diabetics declined significantly more than non-diabetics in tests of perceptual speed and semantic memory, marginally more in visuospatial ability, and did not differ in measures of working and episodic memory (Arvanitakis et al., 2004). In a study of three cognitive tests administered to participants in the Study of Osteoporotic Fractures, diabetic women 65 years and older demonstrated lower performance than those without diabetes on the Digit Symbol Substitution Test (a measure of psychomotor speed), the Trail Making Test Part B, a measure of executive function, and a modified version of the MMSE (Gregg et al., 2000)

Type 2 diabetes may interact with hypertension to increase the risk for cognitive impairment. A study based on the Framingham cohort suggests that persons with both T2D and hypertension are at a higher risk for impairment in verbal and visual memory, compared to those without these two conditions (Elias et al., 1997). Inconsistent findings in these studies may reflect the age of the subjects and therefore the balance and degree of neurodegeneration and vascular damage, non-comparable tests or the sensitivity of the cognitive tests in the specific populations, as well as the length of follow-up. Additional well-designed prospective studies on larger samples are needed to better identify cognitive domains that might specifically be impaired in diabetes and to identify other factors that interact with diabetes and lead to more impairment. In the ACCORD-MIND trial, the effects of intensive glycemic control on total cerebral volume and cognitive performance were tested controlling for assignment in the blood pressure or lipid intervention (Launer et al., 2011). Future studies should examine how these intensive diabetes and blood pressure treatments may interact to impact cognitive outcomes.

13.5 Plasma Glucose Dose Effects

Current studies provide a mixed picture as to whether the risk for cognitive disorders reflects an underlying linear increase with increasing glucose levels, similar to the linear increase in risk for stroke associated with increasing levels of blood pressure (MacMahon et al., 1990). Specifically, several investigators report no association between impaired glucose tolerance and performance on multiple cognitive tests (Fontbonne et al., 2001; Kanaya, Barrett-Connor, Gildengorin, & Yaffe, 2004). On the other hand, other studies have found that poor glucose control is associated with worse cognitive function (Yaffe et al., 2012). In a Finnish study, men and women with impaired glucose tolerance, compared to normoglycemic subjects, performed more poorly on the MMSE but not on the other tests of memory and frontal lobe function (Vanhanen et al., 1998). In a small study ($n = 30$) of glucose exposure

in non-diabetic middle age and older subjects, decreased general cognitive performance, memory impairment, and hippocampal atrophy were associated with reduced glucose tolerance measured with an i.v. 2-h glucose tolerance test (Convit, Wolf, Tarshish, & de Leon, 2003). Additional research is needed to explore the association of increasing levels of fasting glucose to cognitive impairment.

Severity or duration of disease may modify a diabetic's risk for brain aging. In the SALSA study of older Latinos, compared to subjects with no diabetic complications, diabetics with complications had a greater risk for a 2-year drop in global cognitive functioning (Wu et al., 2003); subjects with untreated diabetes as compared to those with treated diabetes had a higher risk of cognitive decline as well. Among those who were treated, those with more than 5 years of disease duration gained more cognitive benefit from treatment than those with less than 5 years duration of disease. Among those with more than 5 years disease duration, those receiving a combination of drugs had less cognitive decline than those receiving monotherapy. Similar associations of increased risk for cognitive decline associated with longer duration of disease and no treatment were reported for the Nurses' Health Study (Logroscino, Kang, & Grodstein, 2004). The Rotterdam Study (Ott et al., 1999) found the highest risk for AD in diabetics treated with insulin and also that insulin resistance is related to an increased risk of AD (Schrijvers et al., 2010), suggesting severity of the disease plays a role. Interestingly, in a case–control study of older type 1 diabetics and controls, no differences on MRI characteristics were noted. The authors conclude that these findings suggest changes in brain structure found in type 2 diabetics do not necessarily reflect only the effects of long-term exposure to hyperglycemia (Brands et al., 2006). Describing and understanding the aging process of type 1 diabetics will become of increasing importance as more of these patients are able to live longer.

13.6 Conclusion

There are an increasing number of population-based studies that provide evidence that hypertension and diabetes increase the risk of premature brain aging and cognitive disorders, either as a direct or indirect result of hyperglycemia and high BP levels or associated comorbidities of dyslipidemia and hyperinsulinemia. Current experimental and clinical data support the roles of hypertension and diabetes in the development of vascular lesions that can cause cognitive impairment or dementia. In addition, diabetes may have negative consequences separate from vascular disease. Finally, diabetes and to a lesser extent hypertension are associated with Alzheimer's disease pathology. Most of the research on brain outcomes and hypertension and diabetes is based on clinical and epidemiologic observational studies. Interpretation of these studies is limited by the possibility that unmeasured or unknown confounding factors may bias the results. For this reason, randomized trials are needed to know if controlling a risk factor is associated with a change in these outcomes of interest. In addition, further research is needed to determine whether specific cognitive functions or brain areas are impaired by these disorders.

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Chapter 14
Neurovascular Consequences of Systemic Disease: Lupus and Primary Hyperparathyroidism

Melissa Sum, Teja Kapoor, and Marcella Walker

14.1 Introduction

Systemic diseases can affect multiple organ systems including the neurovascular system. In this chapter, we will focus on the neurovascular consequences of two systemic diseases: systemic lupus erythematosus (SLE), a chronic rheumatological autoimmune inflammatory disorder, and primary hyperparathyroidism, a common endocrine condition.

14.2 Systemic Lupus Erythematous

14.2.1 Epidemiology

In the United States, the prevalence of SLE is approximately 130/100,000 (Danchenko, Satia, & Anthony, 2006). SLE has a tenfold higher prevalence in females than in males and 2.3-fold higher prevalence in blacks than in whites. There are significant racial disparities in SLE, with black and Hispanic SLE patients having an earlier age of onset, higher proportion of renal disease, and greater severity of SLE compared to their white counterparts. The prevalence of SLE in blacks is as high as 1 in 537 black females in some cohorts (Lim et al., 2009; Somers et al., 2014).

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_14

In 1999, the American College of Rheumatology (ACR) established case definitions for 19 neuropsychiatric syndromes that can occur in SLE patients and are collectively referred to as neuropsychiatric systemic lupus erythematosus (NPSLE) (see Table 14.1) ("The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes," 1999). The prevalence of nervous system involvement in SLE ranges from 6% to 91%, depending on the methodology of the study (Ainiala, Loukkola, Peltola, Korpela, & Hietaharju, 2001; "The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes," 1999; Brey et al., 2002; Cervera et al., 2003; Hanly et al., 2008; West, 2012). When using more restrictive case definitions that exclude solely subjective findings, the prevalence of NPSLE decreases to 12–30% ("The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes," 1999; Holliday and Brey, 2009).

Table 14.1 The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes (NPSLE) ("The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes," 1999)

NPSLE associated with central nervous system
Aseptic Meningitis
Cerebrovascular disease
Demyelinating syndrome
Headaches
Movement disorders (chorea)
Myelopathy
Seizure Disorders
Delirium (acute confusional state)
Anxiety Disorder
Cognitive Dysfunction
Mood Disorders
Psychosis
NPSLE associated with peripheral nervous system
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome)
Autonomic neuropathy
Mononeuropathy, single/multiplex
Myasthenia Gravis
Cranial neuropathy
Plexopathy
Polyneuropathy

14.2.2 Pathogenesis

The pathological mechanisms involved in NPSLE are multifactorial, but primarily involve inflammatory mediators, autoantibodies, microangiopathy, and atherosclerosis (Hanly, 2001). Brain histology in SLE patients reveals a wide variety of findings, including infarctions (both microinfarcts and gross infarctions), cortical atrophy, hemorrhage, and demyelination (Hanly, Walsh, & Sangalang, 1992).

14.2.2.1 SLE Vasculopathy

The vasculopathy in SLE involves primarily small vessels. The most common histological finding is a microvasculopathy attributed to immune-complex deposition and complement activation (Belmont, Abramson, & Lie, 1996). Histology of brain tissue reveals thickening of the innermost vascular lining (the intima) with a perilymphocytic infiltrate (Hanly et al., 1992). Functional neuroimaging with SPECT and MR spectroscopy in NPSLE patients has correlated with these findings, demonstrating diffuse cerebral ischemia and cerebral atrophy, which can occur in the setting of chronic changes in small vessels (Gonzalez-Crespo et al., 1995; Holliday and Brey, 2009; Karassa et al., 2000; Sibbitt Jr., Sibbitt, & Brooks, 1999).

14.2.2.2 Inflammatory Mediators, Cytokines, and Adhesion Molecules

Inflammatory mediators and cytokines have a central role in SLE disease activity, leading to an inflammatory response in the central nervous system (CNS) of NPSLE patients (Kelley & Wuthrich, 1999; Shovman, Gilburd, & Shoenfeld, 2006). Studies have demonstrated increased synthesis of interleukin-1α (IL-1α), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) molecules in both the cerebrospinal fluid and serum of NPLSE patients (Alcocer-Varela, Aleman-Hoey, & Alarcon-Segovia, 1992; Jara et al., 1998; Kozora, Laudenslager, Lemieux, & West, 2001; Maier, Goehler, Fleshner, & Watkins, 1998). These inflammatory cytokines do not readily cross the blood–brain barrier (BBB), thus it is thought that the cytokines act by (1) entering through more permeable circumventricular organs, (2) binding to endothelial receptors in the brain vessels which stimulate the release of inflammatory mediators into the brain parenchyma, or (3) activation of afferent neurons leading to neural activation in a separate location where the peripheral afferent neurons terminate (Holliday and Brey, 2009). Animal models demonstrate that these inflammatory cytokines lead to the clinical manifestations of fever, fatigue, malaise, memory impairment, and decreased pain thresholds (Holliday and Brey, 2009; Maier et al., 1998).

Adhesion molecules on endothelial cells, such as ICAM-1 (intracellular adhesion molecule 1) and E-selectin, are also upregulated in NSPSLE patients during periods of active disease. This allows for entry by lymphocytes, other leukocytes, and proinflammatory molecules into the CNS system (Holliday and Brey, 2009;

Zaccagni, Fried, Cornell, Padilla, & Brey, 2004). Studies show that once SLE disease activity decreases, serum and CSF levels of adhesion molecules also normalize (Baraczka et al., 1999; Egerer et al., 2000; Holliday and Brey, 2009; Matsuda, Gohchi, Gotoh, Tsukamoto, & Saitoh, 1994; Spronk, Bootsma, Huitema, Limburg, & Kallenberg, 1994; Zaccagni et al., 2004).

14.2.2.3 Autoantibodies

There are many autoantibodies associated with NPSLE, although only a few are commercially available for testing. These antibodies include antiphospholipid antibodies (aPL), anti-ribosomal antibodies, anti-neuronal antibodies, and *N*-methyl-D-aspartate receptor (NMDAR) antibody.

14.2.2.4 Antiphospholipid Antibodies

Antiphospholipid antibody syndrome (APS or aPL syndrome) is one of the most common forms of an acquired thrombophilia. Antiphospholipid antibodies are antibodies that bind to the negatively charged phospholipids of the cellular membrane. Detection of aPL antibodies involves the use of either lupus anticoagulant assays or ELISA assays to detect anti-cardiolipin antibody and β2-glycoprotein antibody. Other proteins such as prothrombin, thromboplastin, annexin A5, phosphatidylserine, protein C, and protein S have also been shown to bind phospholipids, but are much less common and are not part of the APS classification criteria (Miyakis et al., 2006; Miyakis, Giannakopoulos, & Krilis, 2004).

Manifestations of APS include arterial and venous thrombosis, recurrent pregnancy loss, and cognitive dysfunction. The classification criteria for APS (see Table 14.2) include a thrombotic event in the presence of moderate- to high-titer aPL antibodies that are present on at least two occasions at least 12 weeks apart. Other non-criterion manifestations include thrombocytopenia, Libman-Sacks cardiac valvular disease, and livedo reticularis. Thromboembolic vascular ischemia associated with aPL syndrome includes stroke, cerebrovascular venous sinus thrombosis, dementia, seizures, chorea, transverse myelitis, ocular ischemia, and sensorineural hearing loss (West, 2012). APS is classified as primary APS if it occurs in the absence of an underlying autoimmune disease, or secondary if it occurs in a patient with SLE or other autoimmune diseases (Miyakis et al., 2006).

The Euro-Phospholipid Project evaluated a large cohort of 1000 APS patients. In this cohort, 53.1% of the patients had primary APS. The remaining had secondary APS with 36.2% having SLE-associated APS and 10.7% had APS associated with other autoimmune diseases. The most common thrombotic manifestation was deep venous thrombosis (DVT) in 38.9% of the cohort. Cerebrovascular accident (CVA) was the most common arterial thrombotic manifestation in 19.8% of patients (Cervera et al., 1999). During the 10-year follow-up period, 16.6% of patients continued to have thrombosis during their first 5-year follow-up period and 15.3% in

Table 14.2 Revised classification criteria for antiphospholipid antibody syndrome (APS) classification criteria (Campbell et al., 1995)

APS is present if one or more clinical criteria and one or more laboratory criteria are present:
1. Clinical criteria
(a) *Vascular Thrombosis*: at least one clinical episode of arterial, venous, or small vessel thrombosis of any tissue or organ. (Thrombosis must be confirmed with appropriate unequivocal imaging studies or by histology without significant evidence of inflammation in the vessel wall.)
(b) Pregnancy morbidity: at least one or more of the following:
• Unexplained death in a morphologically normal fetus occurring at or beyond 10 weeks' gestation. (Normal fetal morphologic features should be documented by ultrasound or by the direct examination of the fetus)
• Premature birth of a morphologically normal neonate occurring before 34 weeks' gestation because of either:
1. Eclampsia or severe preeclampsia, as defined according to standard definitions.
2. Recognized features of placental insufficiency.
3. Three or more unexplained consecutive spontaneous abortions occurring prior to 10 weeks' gestation. Must exclude maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes.
2. *Laboratory criteria* (must be present in the plasma on two or more occasions, at least 12 weeks apart):
(a) *Lupus anticoagulant (LA)*: Detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies) (Brandt, Triplett, Alving, & Scharrer, 1995; Wisloff, Jacobsen, & Liestol, 2002).
(b) *Anticardiolipin (aCL) antibodies*: IgG and/or IgM isotype are present in the serum or plasma in medium or high titer (i.e., >40 GPL or MPL, or greater than the 99th percentile), as measured by a standardized ELISA.
(c) *Anti–β2 glycoprotein I antibody*: IgG and/or IgM isotype in serum or plasma (in titer greater than the 99th percentile) are present, measured by a standardized ELISA, according to recommended procedures.

ELISA enzyme-linked immunosorbent assay, *GPL* IgG antiphospholipid units, *MPL* IgM antiphospholipid units

their second 5-year follow-up period. The most common thrombotic events were strokes (affecting 5.3% of the entire cohort), transient ischemic attacks (4.7%), DVTs (4.3%), and pulmonary embolism (3.5%). There were a total of nine patients who developed catastrophic APS (CAPS), defined as thrombosis of at least three organs, systems, or tissues within 1 week with histopathological confirmation, in a patient with aPL antibodies. All cases of CAPS occurred in the first 5 years of the study, suggesting that CAPS is more likely to occur in the earlier stages of the disease course. When comparing primary to secondary APS patients, patients with SLE-associated APS had a higher rate of glomerular thrombosis (3.0% vs. 0.2%) and myocardial infarction (3.8% vs. 1.2%). Primary APS patients developed more superficial thrombophlebitis (1.9% vs. 0%) and obstetric complications such as premature birth (72.3% vs. 40%) and intrauterine growth retardation (51.5% vs. 1%) (Cervera et al., 2015).

Another European collaborative study, which focused on SLE patients, evaluated the morbidity and mortality of secondary APS. The European Working Party on SLE established a cohort of 1000 SLE patients, who were followed over a 10-year period. APS thromboses were the most common cause of death, secondary to strokes (11.8%), myocardial infarctions (7.4%), and pulmonary emboli (5.9%). Serologically, approximately 20% of the cohort had anti-cardiolipin IgG, 10.8% of the patients had anti-cardiolipin IgM, and 9.4% of the patients had lupus anticoagulant (Cervera et al., 2003).

When assessing the risk of strokes in younger versus older SLE patients, young SLE patients with persistently elevated aPL antibodies, especially with lupus anticoagulant, were at greater risk for ischemic strokes (Ainiala, Hietaharju, et al., 2001). In studies of older patients, other cerebrovascular risk factors (such as diabetes and hypertension) played a greater role compared to antiphospholipid antibodies in their risk for ischemic stroke (Brey, 2004).

Although the etiology of aPL antibodies is unclear, studies suggest that viral and bacterial infections may be involved in aPL pathogenesis. Studies by Gharavi and colleagues showed that normal mice who were immunized with viral protein fragments developed aPL antibodies and died from spinal cord infarction, thrombosis, and intrauterine fetal death (Gharavi, Pierangeli, et al., 1999; Gharavi, Chaimovich, et al., 1999; Gharavi & Pierangeli, 1998; Holliday and Brey, 2009). The prothrombotic effects by antiphospholipid antibodies involve activation of platelets and vascular endothelial cells. Using pathologic aPL antibodies from APLS patients, Campbell demonstrated a dose-dependent increase in the activation and aggregation of platelets (Campbell, Pierangeli, Wellhausen, & Harris, 1995; Holliday and Brey, 2009). Studies by Meroni and colleagues also suggest that β2-GP-1 may serve as a growth factor for vascular endothelial cells by being involved in lipid metabolism (Holliday and Brey, 2009; Meroni et al., 1998).

In addition to its role in thrombosis, aPL antibodies have been linked to cognitive dysfunction in SLE even in the absence of thrombosis. Compared to other SLE and NPSLE autoantibodies, antiphospholipid antibodies have the strongest association with cognitive dysfunction (Denburg, Carbotte, Ginsberg, & Denburg, 1997; Hanly, Hong, Smith, & Fisk, 1999; Menon et al., 1999). In a study by Erkan and colleagues, 60 patients with aPL syndrome demonstrated a linear relationship between aPL titers and the presence of cognitive dysfunction in the area of verbal fluency and complex attention, when matched to 60 gender-, age-, and education-matched controls (42% vs. 18%). The cognitive dysfunction was independent of any history of CVA or neurological involvement (Erkan, Barbhaiya, George, Sammaritano, & Lockshin, 2010). Longitudinal studies have also shown an association between elevated aPL antibodies and increased verbal memory deficits, decreased psychomotor speed, and decreased cognitive productivity on neuropsychological testing (Denburg et al., 1997; Hanly et al., 1999; Leritz, Brandt, Minor, Reis-Jensen, & Petri, 2002; Menon et al., 1999; Mikdashi & Handwerger, 2004). Menon et al. demonstrated a decrease in concentration, attention, and psychomotor speed observed on neuropsychological testing in SLE patients with persistently elevated cardiolipin IgG levels over a period of 3 years, compared to those without elevated titers. There was no

correlation with complement levels or anti-double-stranded DNA antibody levels (Menon et al., 1999). Similar findings were reported by Hanly et al. with cardiolipin IgG levels, in their longitudinal study of 51 SLE patients over 5 years. In addition, elevated cardiolipin IgA titers correlated with greater deficits in reasoning and higher executive functioning (Hanly et al., 1999). Other studies found similar relationships with β2-glycoprotein-1 antibodies and lupus anticoagulant (Denburg et al., 1997; Leritz et al., 2002; McLaurin, Holliday, Williams, & Brey, 2005). Though the mechanism of cognitive dysfunction by aPL antibodies is not clear, many experts believe the mechanism involves cerebrovascular endothelial dysfunction as described earlier, creating a disruption in the blood–brain barrier, allowing for pathogenic autoantibodies, inflammatory cytokines, and cells into the CSF, which ultimately leads to neuropsychiatric consequences (Ghirardello, Briani, Lucchetta, & Doria, 2010).

14.2.2.5 Other NPSLE antibodies

A number of other antibodies have been implicated in neuropsychiatric manifestations of SLE. NMDAR antibodies are a subtype of dsDNA antibodies that cross-react with NMDA receptors. They have been associated with cognitive dysfunction and emotional instability, especially when present in the CSF fluid (Faust et al., 2010). Anti-ribosomal antibodies are antibodies that target the cytoplasmic ribosomes. They are found in up to 16% of SLE patients, with a higher prevalence in Asians. Anti-ribosomal antibodies have been associated with severe cases of psychosis and depression with good specificity (80%) but with poor sensitivity (26%) in SLE patients. The poor sensitivity is thought to be due to the fluctuating nature of the antibody in the serum demonstrated in longitudinal studies (Ghirardello et al., 2010; Karassa et al., 2006).

There is a higher prevalence of anti-neuronal antibodies in CSF fluid of NPSLE patients (30–95%) compared to SLE patients without CNS involvement (11%). CSF neuronal antibodies were more closely associated with diffuse manifestations such as generalized seizures, encephalopathy, severe cognitive dysfunction, and psychosis compared to focal CNS manifestations of chorea or hemiparesis (West, 2012).

14.2.2.6 Atherosclerosis

Until recent years, atherosclerosis was thought to be the passive accumulation of cholesterol in arterial walls with progressive narrowing of the vessel lumen. Studies show that atherosclerosis and plaque rupture is a much more dynamic process, involving multiple inflammatory mediators (Hansson & Hermansson, 2011; Libby, 2001; Stoll & Bendszus, 2006). Hemodynamic stress (such as with hypertension) or exposure to inflammatory mediators such as ox-LDL, IL-1, or TNF-α molecules causes endothelial cell activation and promotes inflammatory changes in the vascu-

lar endothelium (Hansson & Hermansson, 2011). This leads to an increase in adhesion molecules and chemokines to attract monocytes. This results in a pro-inflammatory cascade that leads to monocyte and T-cell migration into the subendothelial space. Monocytes differentiate into macrophages and secrete collagenases which cause disruption of fibrous caps and promote plaque rupture. T-lymphocytes secrete γ-interferon, which inhibits collagen and elastin, molecules essential to fibrous cap formation (Stoll & Bendszus, 2006). Inflammatory mediators are therefore now thought to have a greater role in atherosclerosis than was previously understood.

Studies in systemic lupus erythematosus, as well as other chronic inflammatory autoimmune diseases such as rheumatoid arthritis, demonstrate that a chronic inflammatory state can lead to an accelerated atherosclerosis and premature cardiovascular and cerebrovascular events (Holliday and Brey, 2009). Mortality in early SLE may be due to SLE or infections. However, late mortality in SLE is caused by cardiovascular disease. Urowitz et al. described a bimodal pattern of mortality in a Toronto SLE cohort first recognizing cardiovascular disease as a significant cause of mortality in SLE patients (Urowitz et al., 1976). Compared to age-matched controls, SLE patients have a tenfold increased risk for cerebrovascular accidents (Ward, 1999) and a 50-fold increased risk of myocardial infarctions (Manzi et al., 1997). The risk of strokes in SLE patients aged 18–44 years was similar to the risk in elderly controls of women 65 years and older (Ward, 1999).

Studies show that the risk for cardiovascular events and cerebrovascular events persist despite controlling for traditional vascular risk factors, such as age, diabetes, hypertension, cigarette smoking, and hyperlipidemia (Esdaile et al., 2001; Ho et al., 2005), suggesting that SLE disease itself may increase the risk for cardiovascular disease. Roman et al. demonstrated that aggressive treatment of SLE with glucocorticoids, hydroxychloroquine, and cyclophosphamide was associated with decreased carotid plaque burden compared to age-matched controls. This suggests that treatment of the inflammation in SLE decreases atherosclerotic development in these patients (Roman et al., 2003).

14.2.3 Neuropsychiatric Manifestations in SLE

Neuropsychiatric manifestations can range from mild cognitive dysfunction to seizures. The most common manifestation is cognitive dysfunction (55–80%), headache (24–72%), mood disorders (14–57%), cerebrovascular disease (5–18%), seizures (6–51%), polyneuropathy (3–28%), anxiety (7–24%), and psychosis (0–8%) (Ainiala, Hietaharju, et al., 2001; Brey et al., 2002; Hanly, McCurdy, Fougere, Douglas, & Thompson, 2004; Hanly, Omisade, & Fisk, 2012; Sanna et al., 2003; Sibbitt Jr. et al., 2002). Neuropsychiatric manifestations can occur as a single event or multiple events during the course of SLE, even during periods in which serological SLE disease activity is quiescent (Rivest et al., 2000; Sibbitt Jr. et al., 1999). Approximately 40% of the NPSLE manifestations develop before the onset

of SLE or at the time of diagnosis. Approximately 63% of manifestations occur within the first year after SLE diagnosis (Rivest et al., 2000).

Cognitive dysfunction is a common feature in SLE patients, with a prevalence of ranging from 55% to 80% in SLE patients (Ainiala, Hietaharju, et al., 2001; Brey et al., 2002; Hanly et al., 2004; Sanna et al., 2003; Sibbitt Jr. et al., 2002). Cognitive impairment often involves the subcortical brain, causing difficulties with working memory as well as a reduction in information-processing and executive functioning, such as planning, organizing, or multi-tasking (Leritz, Brandt, Minor, Reis-Jensen, & Petri, 2000). The etiology of cognitive dysfunction in SLE is still under investigation, with current studies demonstrating that cognitive dysfunction cannot be fully explained by SLE disease activity or treatments or prior strokes (Brey et al., 2002; Rivest et al., 2000). Alternative explanations such as infection, malignancy, medication adverse effect (e.g., steroid-induced psychosis), and metabolic disturbances (e.g., uremia) need to be aggressively evaluated and excluded ("The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes," 1999; Futrell, Schultz, & Millikan, 1992; West, Emlen, Wener, & Kotzin, 1995). Studies have reported that as many as 66% of all neuropsychiatric events in SLE patients are attributable to non-SLE-related causes ("The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes," 1999; Hanly et al., 2004, 2007).

14.2.4 Laboratory and Radiological Findings

No specific test is diagnostic for NPSLE. In addition to a thorough history and physical examination, including a complete neurologic and rheumatologic evaluation, a wide variety of objective testing is necessary to diagnose NPSLE. Laboratory testing of serum and CSF fluid, neuroimaging, EEG, brain biopsy, and psychiatric and neuropsychological assessment are part of the clinical workup.

14.2.5 Laboratory Testing

NPSLE frequently occurs in settings when SLE is clinically and serologically active, and rarely as an isolated manifestation of SLE (Bertsias et al., 2010). SLE testing by a rheumatologist will include a complete blood count (to assess for cytopenias), serum complements C3 and C4, anti-dsDNA antibodies, Smith antibodies, U1RNP antibody, SSA (Ro) antibody, SSB (La) antibody, sedimentation rate (ESR), C-reactive protein (CRP), urinalysis (to assess urinary sediment and proteinuria), random urine protein, random urine creatinine, serum creatinine, serum albumin, and liver function tests. Blood work should also include testing for lupus anticoagulant, cardiolipin antibodies, β2-glyprotein-1 antibodies, anti-ribosomal P antibodies.

CSF analysis is necessary to evaluate central nervous system NPSLE manifestations. Anticoagulated patients may require short-term reversal of anticoagulation and thrombocytopenic patients who have less than 20,000 platelets/mm^3 may require platelet transfusions. CSF testing includes cell count with differential, protein, glucose, gram stain and culture, veneral disease research laboratory test (VDRL), India ink staining for *Cryptococcus*, polymerase chain reaction (PCR) for herpes simplex virus, varicella zoster virus, cytomegalovirus, JC virus, NMDAR antibodies, and anti-neuronal antibodies. Patients with NPSLE are likely to have pleocytosis, elevated CSF protein (70–110 mg/dL), normal to low CSF glucose with negative Gram stain, culture, and viral PCRs (West, 2012). Findings of pleocytosis, elevated protein (70–110 mg/dL), or low CSF glucose (<50 mg/dL) have poor sensitivity and are present in only about one third of patients. However, when present, these CSF findings are suggestive of CNS involvement in SLE patients. When immune-mediated CNS damage is ongoing during an SLE flare, the CSF IgG index or synthesis rate is often elevated in 80% of NPSLE patients, and an oligoclonal banding pattern is seen. In many patients, these abnormalities normalize when the flare resolves.

14.2.6 Neuroimaging

Brain imaging is an essential part of the diagnostic evaluation of NPSLE patients, although there is no specific finding on imaging diagnostic for NPSLE. CT scans may be helpful is assessing for cerebral atrophy, meningeal thickening, demyelination, a large CVA, and hemorrhage. Magnetic resonance imaging (MRI) is the test of choice and is more sensitive in detecting infarctions, more subtle demyelination, hemorrhages, edema, and other abnormalities.

In NPSLE, small focal lesions in periventricular and subcortical white matter make up 40–80% of brain imaging abnormalities. NPSLE can also develop cortical atrophy, dilation of the ventricles, diffuse white matter changes, and infarctions. MRI reveals multiple discrete white matter lesions in periventricular, cortical/subcortical junction, and frontal lobe more commonly in patients with past NPSLE manifestations compared to SLE patients without a history of NPSLE (Abreu et al., 2005; Holliday and Brey 2009; Karassa et al., 2006; Sibbitt Jr. et al., 1999). Large areas of white matter and Brey hyperintensities in the corpus collosum or periventricular areas are more characteristic of multiple sclerosis than SLE (Arnold & Matthews, 2002). In patients with primary or secondary APS, MRI can reveal small foci of high-signal scattered throughout the subcortical white matter (Csepany et al., 2003; Provenzale et al., 1994; Toubi, Khamashta, Panarra, & Hughes, 1995). These findings are non-specific and seen in many other conditions, including hypertension, arteriosclerosis, amyloid angiopathy, and vascular dementia (Pantoni & Garcia, 1995, 1997).

Although neuroimaging is necessary in the workup for NPSLE, patients with active NPSLE may have MRI findings similar to those without NPSLE or with inac-

tive NPSLE. This can cause diagnostic difficulties when trying to differentiate if neuroimaging findings are due to active SLE, non-SLE factors, or were the result of a previously active NPSLE that is now quiescent. Therefore, NPSLE diagnosis considers the clinical history, examination, laboratory data, in addition to neuroimaging, as a whole (Huizinga, Steens, & van Buchem, 2001; Sibbitt Jr. et al., 1999).

14.2.7 Neurofunctional Testing

Electroencephalogram (EEG) uses electrodes placed on a patient's scalp to detect electrical activity of the brain. EEG is useful in identifying seizure activity in SLE patients, which occur in 5% of SLE patients. The most frequent seizure in SLE patients are generalized tonic-clonic seizures and occur more commonly in SLE patients with aPL antibodies and prior CVAs (Bertsias et al., 2010; Glanz, Laoprasert, Schur, Robertson-Thompson, & Khoshbin, 2001).

Positron emission tomography (PET) detects elevated or low areas of glucose metabolism in the brain and is effective in detecting brain function abnormalities. PET-CT also provides a CT image of the brain to localize pathological abnormalities. White matter abnormalities in the prefrontal, anterior cingulate, and inferior parietal regions are helpful in differentiating acute from quiescent NPSLE (Komatsu et al., 1999). Low FDG-PET uptake in the bilateral parieto-occipital white matter regions was demonstrated in 60–80% of active NPSLE patients that previously had normal MR imaging (Otte et al., 1997; Weiner et al., 2000).

Magnetic resonance spectroscopy (MRS) provides information on the neurometabolic composition of brain tissue. It is often added to MRI, providing additional information on metabolic abnormalities in white and gray matter. Often, the abnormalities on MRS are suggestive of neuronal injury, neuronal loss, and demyelination. These changes are seen in both active and quiescent NPSLE (Chinn et al., 1997). Cerebral white matter changes on MRS have correlated with cognitive dysfunction in SLE (Kozora et al., 2005).

Cerebral angiograms, which are useful in assessing larger cerebral vessels, are usually normal in NPSLE, which tends to involve smaller vessels. CTA and MRA are alternative modalities to demonstrate pathology in medium and large vessels, but they too can be normal in NPSLE. In patients with thromboembolic strokes, carotid duplex and transesophageal cardiac echo are recommended to evaluate for an embolic source.

14.2.8 Neuropsychological Testing

While complaints of cognitive difficulties are common by SLE patients, objective testing is necessary to identify the degree of impairment. Studies have suggested that 11–54% of SLE patients may have subclinical cognitive dysfunction, which is evident

on neuropsychological testing (Denburg & Denburg, 2003). There are a number of different modalities that can be used for neuropsychological testing in SLE patients. The Cognitive Symptoms Inventory (CSI) is a questionnaire assessing a patient's ability to perform activities of daily living. High CSI scores suggest greater cognitive impairment (Hanly, Fisk, McCurdy, Fougere, & Douglas, 2005; Pincus, 1996). The ACR neuropsychological assessment involves a standardized battery of validated tests examining different domains of cognitive functioning, including memory, attention, visuospatial processing, language, problem-solving, speed, and executive functioning ("The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes," 1999; Kozora, Ellison, & West, 2004). However, background education and demographic factors may affect the results of the neuropsychological testing (Kozora, Ellison, & West, 2006). The Automated Neuropsychological Assessment Metrics (ANAM) is a set of computerized performance tests developed by the US military in the 1970s to test cognitive processing speed, complex attention, and visuospatial processing (Bleiberg, Garmoe, Halpern, Reeves, & Nadler, 1997; Bleiberg, Kane, Reeves, Garmoe, & Halpern, 2000; Reeves et al., 2006). ANAM has been validated against traditional neuropsychological tests of memory, attention, cognitive processing speed, and executive functions in patients with traumatic brain injuries (Bleiberg & Warden, 2005) as well as in SLE (Holliday et al., 2003; Roebuck-Spencer et al., 2006). ANAM was demonstrated to be a sensitive test in identifying cognitive deficits in SLE. ANAM demonstrated both good sensitivity (76.2%) and specificity (82.8%) in classifying SLE patients with probable versus no impairment on neuropsychological testing, even after adjusting for premorbid cognitive functioning (Roebuck-Spencer et al., 2006).

14.2.9 Treatment and Prognosis

Therapy depends on the severity and type of NPSLE manifestation. Mild NPSLE manifestations such as infrequent seizures, paresthesias, and mild cognitive dysfunction may only require pain medications, neuroleptic medications, neurocognitive therapy, and psychotropic agents. Immunosuppression is necessary in more severe cases of non-thrombotic NPSLE, such as psychosis, severe depression, transverse myelitis, and aseptic meningitis.

14.2.9.1 Treatment of Non-thrombotic Severe NPSLE

There is limited data regarding treatment of severe NPSLE. Data is largely limited to open-label clinical studies, small controlled trials, and anecdotal experience. Mok and colleagues led an open-label study in 13 NPSLE patients showing a favorable response after 6 months of treatment with oral cyclophosphamide, followed by maintenance therapy with azathioprine (Mok, Lau, & Wong, 2003). In another study, treatment with intravenous (IV) cyclophosphamide for up to 2 years was

compared to IV methylprednisolone in NPSLE patients. Patients treated with IV cyclophosphamide had a significantly greater response compared to methylprednisolone (95% vs. 54% respectively, $p < 0.03$), (Barile-Fabris et al., 2005). A majority of rheumatologists use a regimen of pulse intravenous methylprednisolone of 1000 mg for 3–5 days followed by prednisone 1 mg/kg/day along with intravenous cyclophosphamide (0.75–1 g/m^2) monthly in the treatment of severe NSPLE (Navarrete & Brey, 2000).

14.2.9.2 Treatment of Thromboembolic Disease in NPSLE

Appropriate therapy depends on the pathogenesis of the cerebrovascular insult in SLE patients. Most strokes in NPSLE are associated with thrombosis in the setting of antiphospholipid antibodies, rather than vasculitis, and require anticoagulation as the primary treatment (Brey, 2004; West, 2012). Initially, two retrospective studies had suggested that high-intensity warfarin treatment (target INR of 3.0 or greater) may be more effective than moderate-intensity warfarin (INR of 2.0–3.0) or aspirin in patients with antiphospholipid antibodies. Patients in these studies, however, did not have repeat antiphospholipid antibody testing to fulfill current criteria for APS (Khamashta et al., 1995; Rosove & Brewer, 1992).

A randomized, double-blind, controlled trial by Crowther and colleagues evaluated two warfarin treatment regimens in preventing recurrent thrombotic events in 114 patients with APS. Patients were followed for an average of 2.7 years with average INR value of 2.3 in the moderate-intensity warfarin group and 3.3 in the high-intensity warfarin group. Recurrent thrombosis occurred in 3.4% of moderate-intensity warfarin patients and 10.7% of high-intensity warfarin patients, but with no significant difference. There was no difference in major bleeding rates between the two groups. These results suggest that high-intensity warfarin treatment was no more effective than moderate intensity treatment in preventing recurrent thrombotic events in patients with APS, although the end point did not specifically address strokes (Crowther et al., 2003; Holliday and Brey, 2009). In patients with recurrent strokes refractory to low-intensity warfarin therapy, experts still recommend higher-intensity warfarin therapy (INR goal of 3.0–4.0) and/or combination therapy with antiplatelet agents (Ruiz-Irastorza, Hunt, & Khamashta, 2007).

The 13th International Congress on Antiphospholipid Antibodies recommends the use of the anti-malarial agent hydroxychloroquine for primary prevention of aPL-associated stroke (Ruiz-Irastorza et al., 2011). Hydroxychloroquine provides long-term mild anticoagulant effect in APLS patients in addition to reducing SLE disease activity (Jung et al., 2010). In patients with SLE with APLS, anti-CD20 therapy with rituximab has been reported to be successful in uncontrolled trials (Ramos-Casals, Soto, Cuadrado, & Khamashta, 2009). Data on oral anticoagulants such as dabigatran or rivaroxaban in APS are limited, with randomized control trials underway to compare oral anticoagulants to vitamin K antagonist (Cohen & Machin, 2010). Plasmapheresis may be of initial benefit as adjunctive

therapy for the removal of pathogenic antibodies along with intravenous immunoglobulin therapy. Additional therapy to limit the extent of damage to the ischemic tissue includes addition of antiplatelet agents, statins, and appropriate blood pressure management avoiding tight blood pressure control that may result in hypoperfusion (Navarrete & Brey, 2000). Cardiac echocardiogram should be performed to evaluate for Libman-Sacks endocarditis and valvular vegetation in APS-SLE patients.

14.2.9.3 Treatment of Cognitive Dysfunction in NPSLE

Before diagnosing NPSLE, secondary causes of cognitive dysfunction need to be excluded, including depression, thyroid disease, medication side effects, and sleep apnea. There is no definitive treatment for the cognitive dysfunction. Cross-sectional studies have shown no association between cognitive dysfunction and the use of glucocorticoids (Hay et al., 1992; Kozora, Thompson, West, & Kotzin, 1996; Shucard et al., 2004). SLE patients treated with aspirin were reported to have greater cognitive performance over 3 years, particularly in the subgroup that had concomitant diabetes (McLaurin et al., 2005).

Cognitive rehabilitation has been utilized in other neurological conditions, including stroke, dementia, and traumatic brain injury. A pilot study suggested that cognitive rehabilitation improved memory and cognitive function in SLE patients (Harrison et al., 2005). A randomized controlled trial using cognitive-behavioral stress management in SLE patients showed significant improvement in pain and psychological well-being, with continued effects during the 9-month follow-up period (Greco, Rudy, & Manzi, 2004; Holliday and Brey, 2009). As research continues in understanding the underlying pathophysiology of SLE cognitive dysfunction, novel treatment strategies may be available in the future.

14.3 Primary Hyperparathyroidism

14.3.1 Pathogenesis and Epidemiology

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by hypercalcemia and excessive parathyroid hormone (PTH) secretion. PTH is secreted by the four parathyroid glands. PTH tightly regulates serum ionized calcium via its direct stimulation of renal tubular calcium reabsorption and bone remodeling as well as its indirect effects to increase gastrointestinal calcium absorption by stimulating the formation of 1,25-dihydroxyvitamin D. Common clinical features of PHPT today include osteoporosis and hypercalciuria as well as vertebral fractures and nephrolithiasis, though the latter two features are often subclinical. In addition, PHPT is associated with neurological, cognitive, and psychiatric sequelae

that are less well-recognized than its skeletal and renal manifestations, but nevertheless clinically important.

Single parathyroid adenomas account for 80–85% of cases of PHPT (Bartsch, Nies, Hasse, Willuhn, & Rothmund, 1995; Ruda, Hollenbeak, & Stack Jr., 2005). The remaining cases arise from multiple adenomas or multiple-gland hyperplasia and rarely, from parathyroid carcinoma. In all cases, PHPT results from loss of normal feedback of elevated serum calcium to suppress PTH secretion, which is thought to be due to increased cell mass and/or a reduction in the number of calcium sensing receptors within adenomas or hyperplastic glands (Brown, 2013). The only curative treatment for PHPT is to remove the abnormal parathyroid gland or glands with parathyroidectomy (PTX).

Prior to the routine screening of serum calcium, PHPT was a relatively rare and symptomatic disorder. With the advent of the multichannel auto-analyzer and widespread screening of serum calcium in the early 1970s, cases of unrecognized, asymptomatic PHPT were identified, leading to an initial surge in the incidence of PHPT. The annual incidence is estimated to have increased from 16 per 100,000 person-years before the routine screening of calcium to 112 per 100,000 person-years several years later (Wermers et al., 2006). More recently, studies have estimated an incidence of PHPT of approximately 50 per 100,000 person-years in the United States between 1998 and 2010 (Griebeler et al., 2015; Yeh et al., 2013).

14.3.2 Clinical Manifestations

In the early twentieth century, the disease presentation was invariably symptomatic. Early descriptions of PHPT include patients with marked hypercalcemia, nephrolithiasis, nephrocalcinosis, polyuria, polydipsia, and renal dysfunction (Albright, Aub, & Bauer, 1934; Cope, 1966). Not uncommonly, patients presented with *osteitis fibrosa cystica,* a skeletal condition characterized radiographically by demineralization, fibrosis, brown tumors, and bone cysts as well as the clinical symptoms of bone pain and fractures (Albright et al., 1934; Cope, 1966). Gastrointestinal features of "classical PHPT" included anorexia, constipation, peptic ulcer disease, and pancreatitis, which were all attributed to the degree of hypercalcemia. There were clear neuromuscular consequences as well, including muscle weakness and atrophy. Muscle biopsies from patients with PHPT showed atrophy of both type I and type II muscle fibers, with type II fibers more extensively involved (Patten et al., 1974). Studies also indicated improvement in neuromuscular symptoms after PTX (Patten et al., 1974). Cognitive and mood changes were not uncommon and case series included descriptions of "mental disturbances," psychosis, fatigue, and lassitude (Albright et al., 1934; Cope, 1966; Petersen, 1968).

Today, in parts of the world where calcium is measured routinely, most patients with PHPT are "asymptomatic," a term that refers to those who lack the objective classic renal and skeletal manifestations of PHPT. While the neuromuscular atrophy and weakness described in classical PHPT are not seen today in the USA, some

"asymptomatic" patients do report nonspecific neuropsychological symptoms, such as generalized weakness, depression, intellectual weariness, loss of initiative, reduced memory and concentration, anxiety, irritability, and sleep disturbances (Silverberg, 2002). Indeed, at the Fourth International Workshop on the Management of Asymptomatic PHPT in 2013, experts agreed that "asymptomatic" PHPT was clearly associated with psychological and cognitive complaints (Silverberg et al., 2014). What was less clear were mechanisms underlying these manifestations and their reversibility with surgical correction of PHPT. The sections below summarize data regarding the neuropsychological manifestations of PHPT and potential underlying mechanisms.

14.3.3 Quality of Life (QOL) and Mood in PHPT

Most neuropsychological studies in the PHPT field have assessed QOL and mood. Many observational studies, but not all, suggest that there are psychological features of PHPT, including depression, anxiety, or impaired QOL, which improve after PTX (Brown, Preisman, & Kleerekoper, 1987; Burney, Jones, Christy, & Thompson, 1999; Caillard et al., 2007; Espiritu et al., 2011; Joborn et al., 1989; Pasieka & Parsons, 1998; Quiros et al., 2003; Walker, McMahon, et al., 2009; Weber et al., 2013). However, many investigations are limited by their non-randomized designs, small sample sizes, testing at short intervals after surgery, and in some cases failure to use objective assessment methods. Thus, conclusions regarding the causal association of such symptoms with PHPT and the benefit of PTX have remained uncertain. More rigorously designed trials have recently been published. Three randomized controlled trials (RCTs) assessing the effect of PTX vs. observation upon QOL and psychiatric symptoms in PHPT have been performed to date (Ambrogini et al., 2007; Bollerslev et al., 2007; Talpos et al., 2000). Despite similar designs and use of similar validated QOL and psychiatric assessment tools, all the three RCTs came to different conclusions regarding the presence of symptoms at baseline and improvement after surgery; one study found no QOL difference at baseline vs. normative values but suggested PTX prevents worsening of QOL and improves psychiatric symptoms (Talpos et al., 2000); a second study indicated reduced QOL at baseline but indicated no benefit of surgery and the third demonstrated improvement in QOL (Ambrogini et al., 2007; Bollerslev et al., 2007).

In summary, the majority of studies suggest the presence of depression, reduced QOL, or other psychological symptoms in patients with PHPT, but the improvement shown in observational studies contrasts with the lack of uniform benefit in larger RCTs. The lack of consistent improvement after PTX has called into question whether the association between PHPT and such symptoms is causal. Some have suggested that symptoms could be due to the burden of having a chronic condition, the anxiety related to anticipated surgical correction of PHPT, or selection bias (Walker & Silverberg, 2007). Similarly, the post-surgical improvements seen in observational studies could be due to baseline differences between groups or to biases introduced by nonrandomized designs.

14.3.4 Cognitive Dysfunction in PHPT

Fewer studies have investigated cognition in PHPT. Cross-sectional data have found that several aspects of cognition are reduced in PHPT compared to controls, though direct comparisons across studies is difficult as different aspects of cognition have been assessed with different tools in various studies (Babinska et al., 2012; Benge et al., 2009; Brown et al., 1987; Chiang et al., 2005; Lourida et al., 2015; Numann, Torppa, & Blumetti, 1984; Prager et al., 2002; Roman et al., 2005; Walker, McMahon, et al., 2009). In some studies, verbal memory and non-verbal abstraction improved after PTX while spatial learning improved in others (Babinska et al., 2012; Numann et al., 1984; Roman et al., 2005, 2011; Walker, McMahon, et al., 2009). Other studies have reported mixed results or no change (Casella, Pata, Di Betta, & Nascimbeni, 2008; Chiang et al., 2005; Goyal et al., 2001). Only one RCT of the effect of PTX vs. observation (n = 18) upon cognition has been performed (Perrier et al., 2009). Participants were studied with functional magnetic resonance imaging (fMRI) of the brain, sleep assessment, and a validated neuropsychological battery. Subjective sleepiness correlated with worse performance on executive function tests during fMRI. A reduction in serum PTH levels correlated with improved sleep as well as decreased neuronal activation on fMRI in the left precentral gyrus. This study suggested that PTX leads to decreased sleepiness, but is too small to draw definitive conclusions regarding cognition (Perrier et al., 2009).

A recent systematic review of PTH and cognitive function that synthesized data from 27 available studies relating parathyroid conditions to cognitive function noted considerable heterogeneity of study designs, populations, screening tools, sample size, and outcomes, rendering a quantitative synthesis of results difficult (Lourida et al., 2015). The review noted that 13 studies that compared PHPT patients before and after PTX provided mixed evidence for improvement in memory, though conclusions could not be drawn regarding other cognitive domains (Lourida et al., 2015). Overall, however, the review noted only mixed evidence supporting a "weak link between PTH, cognition and dementia due to the paucity of high quality research." Due to conflicting data regarding post-PTX improvement in cognitive symptoms, they are not currently considered a sole indication for PTX by most experts (Silverberg et al., 2014).

14.3.5 Possible Mechanisms of Neuropathology and Neuropathophysiology

The biochemical hallmarks of PHPT, increased serum calcium and PTH concentrations, could both underlie changes in cognition and mood in PHPT. Calcium plays a key role in regulating neurotransmitter release at synaptic junctions, and hypercalcemia could interfere with that process. Marked hypercalcemia of any cause is clearly associated with altered cognition, delirium, and encephalopathy in multiple

disorders (Inzucchi, 2004; Shane & Dinaz, 2006). Additionally, several studies have also noted an association between mild hypercalcemia and depression in patients with mild PHPT (Espiritu et al., 2011; Petersen, 1968). Data in the elderly without PHPT indicate that higher serum calcium levels within the normal range are associated with more rapid cognitive decline in a population-based study (Schram et al., 2007). One potential mechanism may be that increased extracellular calcium ion concentrations cause increased diffusion across the blood–brain barrier, leading to increased levels of calcium in the cerebrospinal fluid. This may enhance calcium influx into neurons during signaling when calcium channels are opened, leading to excess calcium "overload," neuronal signaling disruption, or atrophy in hippocampus (Toescu & Vreugdenhil, 2010). While rare, calcium deposits in the brain have also been observed in those with frontal-subcortical dementia in association with basal ganglionic calcification in hyperparathyroidism (Margolin, Hammerstad, Orwoll, McClung, & Calhoun, 1980).

On the other hand, it is also possible that PTH mediates the relationship between cognitive and mood symptoms and PHPT. Some studies have suggested that PHPT patients with the largest decline in PTH post-PTX had the greatest improvement in cognition (Roman et al., 2005, 2011). Such changes could be mediated by PTH's known vascular effects. The vascular effects of PTH were first shown by Collip in the early twentieth century with experiments demonstrating that dogs and rats injected with PTH(1–34) had a drop in mean arterial pressure (Collip & Clark, 1925). Intermittent exposure to exogenous PTH, as well as endogenous PTH and PTH-related peptide, has subsequently been shown to induce vasodilation by binding to PTH receptors on vascular smooth muscle and/or endothelial cells, the latter of which leads to nitric oxide production (Lutteke et al., 2005; Musso, Plante, Judes, Barthelmebs, & Helwig, 1989; Noonan, Qian, Stuart, Clemens, & Lorenz, 2003; Ogino, Burkhoff, & Bilezikian, 1995; Prisby, Menezes, & Campbell, 2013; Raison et al., 2013; Roca-Cusachs, DiPette, & Nickols, 1991; Suzuki, Lederis, Huang, LeBlanc, & Rorstad, 1983). Indeed, in 1983, Suzuki et al. showed that brief in vitro exposure to synthetic PTH led to vasorelaxation of human middle cerebral arteries obtained from subjects who had undergone temporal lobectomy (Suzuki et al., 1983). In contrast, sustained PTH elevations, as occurs in PHPT and secondary hyperparathyroidism, are thought to potentially desensitize the vasculature to PTH receptor signaling (Friedman & Goodman, 2006; Massfelder et al., 1996; Nyby et al., 1995). Towler et al. note "the vasculopathy of PHPT and secondary hyperparathyroidism" may be due to continuously elevated PTH downregulating PTH receptor signals that would otherwise maintain and protect vascular tone (Thompson & Towler, 2012).

There are abundant and consistent data to suggest that vascular tone is, indeed, compromised in patients with PHPT and related to PTH. Several studies indicate that vascular stiffness is increased in PHPT and that higher PTH levels are associated with higher carotid and aortic stiffness in patients with PHPT (Rosa et al., 2011; Rubin, Maurer, McMahon, Bilezikian, & Silverberg, 2005; Schillaci et al., 2011; Smith et al., 2000; Walker, Fleischer, et al., 2009). In one study, the presence of PHPT was a stronger predictor of elevated aortic stiffness than traditional cardio-

vascular risk factors (Rubin et al., 2005). There is evidence for other possible cardiovascular effects of PHPT, including increased left ventricular mass, increased carotid intima-media thickness, carotid atherosclerosis, and impaired endothelial function, though data regarding their presence in PHPT tend to be conflicting (Iwata et al., 2012; Kosch et al., 2000; Nuzzo et al., 2002; Piovesan et al., 1999; Stefenelli et al., 1993, 1997; Walker et al., 2010; Walker, Fleischer, et al., 2009; Walker & Silverberg, 2008). These studies have variably associated such abnormalities with PTH vs. calcium, and it is certainly possible that hypercalcemia, in addition to PTH, underlies some vascular effects in PHPT.

Few studies have specifically assessed the cerebral vasculature or cerebral blood flow in PHPT, but PTH-dependent changes in cerebral hemodynamics, similar to those observed in the aorta or carotid, could compromise cerebral blood flow and autoregulation, the process by which the brain maintains stable perfusion by vasoconstriction or vasodilation. PTH does indeed cross the blood–brain barrier, and PTH receptors are present in the human brain (Khudaverdyan & Asratyan, 1996). Two studies have assessed cerebral perfusion in PHPT using SPECT with Tc99-labeled hexamethylpropylenamine-oxime (HMPAO). The first study was uncontrolled and suggested that pathologically reduced regional cerebral blood flow was present in 87.5% (14 of 16) of PHPT patients and reversible with PTX (Mjaland, Normann, Halvorsen, Rynning, & Egeland, 2003). This study found no association between blood flow and depression or biochemical hallmarks of PHPT (Mjaland et al., 2003). In a second study, elevated PTH levels in patients with PHPT were associated with reduced regional cerebral blood flow compared to non-PHPT controls. Several of the affected cortical regions are known to be involved in memory and learning (Cermik et al., 2007). However, the latter study did not assess if such reductions in blood flow were associated with reduced mood or cognition.

Altered cerebral hemodynamics has, however, been associated with cognitive impairment in other conditions such as vascular dementia, carotid disease, carotid occlusion, and heart failure (Alosco et al., 2014; Balestrini et al., 2013; Judd et al., 1986; Marshall, 2012; Marshall et al., 2012). For example, a recent study indicated that those who had cerebral hypoperfusion, measured by positron emission testing, due to carotid atherosclerosis had worse cognition than those without hypoperfusion but similar degrees of carotid occlusion (Marshall et al., 2012). There were no differences in demographic, clinical, or radiologic characteristics between the two groups, yet significant differences in age- and education-adjusted neurocognitive scores were observed. As such, cerebral hemodynamic failure was found to be independently associated with cognitive impairment.

These data suggest that a similar mechanism is plausible in PHPT. Impaired cerebrovascular function or blood flow could underlie the altered cognition observed in PHPT, though no studies have specifically assessed if this or other cardiovascular mechanisms underlie altered cognition and mood in PHPT. Data in the general population do, however, support a link between PTH and cognition. In a community-based study, each 1 standard deviation increase in log PTH increased the risk for vascular dementia by 41% adjusted for cardiovascular risk factors, calcium, and vitamin D. Further, PTH accounted for 18.5% of the attributable risk for vascular

dementia, exceeding all other risk factors. In this study, higher PTH levels were also associated with more ischemic changes on MRI (Hagstrom et al., 2014). Moreover, a recent epidemiological study identified elevated PTH as a risk factor for cognitive decline in elderly patients without PHPT independent of calcium levels or renal function (Bjorkman, Sorva, & Tilvis, 2010). As such, the elevation in PTH may very well play a role in the altered cognition observed in PHPT.

Another factor that may contribute to the cognition and mood changes in PHPT is vitamin D deficiency. Vitamin D deficiency, defined as a serum 25-hydroxyvitamin D <20 μg/L, is common worldwide and thought to be more common in PHPT than the general population (Boudou, Ibrahim, Cormier, Sarfati, & Souberbielle, 2006; Grey et al., 2005; Moosgaard et al., 2005). In a recent longitudinal multiethnic cohort study of 382 older adults without PHPT, rates of decline in episodic memory and executive function among vitamin D-deficient participants were greater than those with adequate status after controlling for age, gender, education, ethnicity, body mass index, season of blood draw, vascular risk, and apolipoprotein E4 genotype (Miller et al., 2015) though notably the results did not control for PTH level. Indeed, a recent review emphasized the need to consider the potential contributions of calcium and PTH in the relationship between vitamin D and neurological function given their close interplay (Littlejohns, Kos, Henley, Kuzma, & Llewellyn, 2016). Although the exact mechanisms linking dementia risk to low vitamin D levels have not been fully elucidated, low vitamin D status has been associated with increased white matter hyperintensities (Annweiler, Annweiler, Bartha, et al., 2014) and enlarged ventricular volumes (Annweiler, Annweiler, Montero-Odasso, Bartha, & Beauchet, 2014); higher serum 25-hydroxyvitamin D has also been associated with decreased levels of β-amyloid 1–42 in cerebral spinal fluid, a recognized risk factor for dementia (Hooshmand et al., 2014).

Several direct and indirect mechanisms are possible. There is data to suggest that low vitamin D increases inflammation and activates the renin–angiotensin system. For example, vitamin D has been shown to have direct antioxidant effects (Bao, Ting, Hsu, & Lee, 2008) and upregulates production of neurotrophic factors that enhance survival, development, and function of neurons (Fernandes de Abreu, Eyles, & Feron, 2009; Schindowski, Belarbi, & Buée, 2008). Vitamin D deficiency is also thought to stimulate atherogenesis. Vitamin D receptors are present in endothelial cells, which express 1-alpha-hydroxylase to convert 25-hydroxyvitamin D to 1,25-dihydroxyitamin D. 1,25-Dihydroxyitamin D acts as a direct transcriptional regulator of nitric oxide in endothelial cells (Menezes, Lamb, Lavie, & DiNicolantonio, 2014). Vitamin D deficiency may lower the bioavailability of nitric oxide, which is known to regulate vascular tone, prevent platelet aggregation, and inhibit vascular smooth muscle proliferation. Vitamin D also inhibits proinflammatory cytokine release, proliferation, and migration of vascular smooth muscle cells, mitigating the pathway toward intimal and medial artery calcification (Zittermann, Schleithoff, & Koerfer, 2007). Furthermore, lower vitamin D levels have been associated with increased activity of the renin angiotensin system, as shown in a cross-sectional study of 184 normotensive subjects. In this study, vitamin D deficiency was associated with higher levels of angiotensin II and trend toward higher renin

activity (Forman, Williams, & Fisher, 2010). Indeed, in vitro models have shown that vitamin D suppresses renin gene expression via a vitamin D response element (Li et al., 2002, 2004). Animal data suggests activation of the renin–angiotensin system is associated with cognitive impairment, perhaps due to a decrease in cerebral surface blood flow and an increase in oxidative stress (Inaba et al., 2009). Indirect effects of vitamin D are also possible via an inverse association that has been demonstrated between 25-hydroxyvitamin D and PTH levels in PHPT patients in multiple studies (Rao et al., 2002; Silverberg, 2007) leading to higher PTH levels in PHPT patients with vitamin D deficiency. Such heightened PTH elevations could worsen vascular tone as described above.

14.4 Summary and Future Directions

In summary, PHPT is associated with anxiety, depression, impaired QOL, and altered cognitive function. Whether such symptoms are causally related to PHPT has remained unclear due to lack of data regarding mechanisms and conflicting information about improvement with surgical correction of PHPT. Several potential mechanisms mediated by calcium, PTH, or vitamin D may underlie the psychological and cognitive manifestations of PHPT. There is abundant data to indicate that PHPT is associated with vascular pathology, most consistently increased vascular stiffness. This provides a plausible mechanism by which cerebrovascular blood flow and function may be affected, thereby causing mood and cognitive effects of PHPT. This mechanism has been demonstrated to affect cognition in other disorders. Well-designed prospective studies using novel approaches to reliably assess cerebrovascular disease and its relationship to mood and cognition as well as biochemical indices in PHPT are needed.

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Chapter 15
Depression and Neurovascular Disease

Abhishek Jaywant and Faith M. Gunning

15.1 Introduction

Depression is a significant global health concern because of its relationship to psychological well-being, quality of life, disability, medical comorbidity, and mortality. Epidemiological statistics from the World Health Organization suggest that over 300 million individuals across the world suffer from depression, making it the leading cause of disability worldwide (World Health Organization, 2017). In older adults with vascular disease, depression is common, both in individuals with chronic microvascular disease and following a cerebrovascular accident (stroke). In this chapter, we will summarize the seminal work in this field together with an emphasis on the most recent findings as they pertain to the pathophysiology, assessment, and treatment of depression within the context of cerebrovascular disease. The research in depression and cerebrovascular disease comes both from individuals with late-life depression and concurrent small vessel disease ("vascular depression") and individuals who develop depression following a stroke (post-stroke depression or PSD). There is much overlap between these patients, and as will be discussed below, between the clinical characteristics, pathophysiology, and treatment approaches.

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_15

15.2 Vascular Depression

15.2.1 Clinical Expression of Vascular Depression

Research on vascular depression has focused on the identification of a specific clinical phenotype. Age and a history of vascular risk factors such as hypertension are associated with vascular depression (Krishnan et al., 2004). In a comparison of individuals with vascular depression and non-vascular depression, Alexopoulos and colleagues (Alexopoulos, Meyers, Young, Campbell, et al., 1997; Alexopoulos, Meyers, Young, Kakuma, et al., 1997) defined vascular depression clinically based on a rating scale of vascular burden (Cumulative Illness Rating Scale-Geriatrics) and the occurrence of the first depressive episode at age 60 or older. Their comparison indicated that vascular depression was a distinct entity neuropsychologically and clinically: compared to non-vascular depression, those with vascular depression had greater psychomotor slowing, greater overall cognitive impairment on the Mattis Dementia Rating Scale, less agitation, fewer feelings of guilt, and a greater lack of insight. This clinical profile has been replicated and extended. For example, relative to depressed individuals without vascular risk factors, depressed individuals with vascular risk factors exhibit greater loss of energy, slowed initiation (lassitude), and greater physical disability (Naarding et al., 2007).

Executive dysfunction and slowed psychomotor processing speed commonly co-occur with vascular depression, suggesting that this neuropsychological profile may be a core feature of vascular depression (Pimontel et al., 2013; Reinlieb et al., 2014). Neuropsychological tasks that assess complex attention, initiation/perseveration, cognitive flexibility, and response inhibition, and that depend on the integrity of frontostriatal circuitry and rapid performance under time constraints, appear to be the most sensitive in differentiating vascular depression from non-vascular depression, and are significantly associated with cerebrovascular disease as seen on magnetic resonance imaging (MRI) (Sheline et al., 2008). Further, symptoms of depression and executive dysfunction are both associated with reduced cerebral blood flow velocity and arterial perfusion integrity (Puglisi et al., 2018).

Within the domain of executive dysfunction, response inhibition, as assessed using the Stroop task, is frequently impaired in vascular depression and associated with the burden of cerebrovascular disease (Pimontel et al., 2013). In a sample of 51 depressed older adults that used diffusion tensor tractography to assess white matter integrity, the Stroop color-word interference condition was significantly associated with the integrity of white matter fibers adjacent to the anterior and posterior cingulate cortex, prefrontal cortex, insular cortex, and parahippocampal region (Murphy et al., 2007). These findings suggest that depressed mood and executive dysfunction commonly co-occur in vascular depression and may have a common neural substrate in the disruption of frontostriatal white matter tracts. Though not specific to vascular depression, the presence of executive dysfunction appears to be a core feature of the syndrome.

15.2.2 Pathophysiology

Early observations of the high prevalence rates of depression in older adults with vascular disease (Rabkin, Charles, & Kass, 1983), and of the frequent occurrence of white matter hyperintensities (WMH) on MRI in depressed older adults (Krishnan et al., 1988), led to the conceptualization of vascular depression as a distinct entity and subtype of late-life depression. This "vascular depression hypothesis" proposed that cerebrovascular disease "predisposes, precipitates, and perpetuates" depression in aging, older adults (Alexopoulos, Meyers, Young, Campbell, et al., 1997). The model as summarized by Alexopoulos and colleagues (Alexopoulos, 2005; Taylor, Aizenstein, & Alexopoulos, 2013) posits that microvascular ischemic disease—visualized as WMH on MRI—progressively disrupts neural pathways in frontal, subcortical (striatal), and limbic regions, resulting in a disconnection of frontostriatal and limbic regions. Behaviorally, this disconnection may then heighten the experience and salience of negative emotions through excessive activation of limbic regions such as the subgenual cingulate (Aizenstein et al., 2011). This hyperactivation is accompanied by decreased top-down ability of prefrontal regions such as the dorsolateral prefrontal cortex and dorsal anterior cingulate cortex to regulate emotions and exert cognitive control over emotional experiences.

In support of the initial description of the vascular depression hypothesis, WMH burden has been shown to be significantly greater in depressed older adults compared to non-depressed age-matched individuals (Gunning-Dixon et al., 2010; Taylor, MacFall, et al., 2003; Wang, Leonards, Sterzer, & Ebinger, 2014). Ischemia in the deep white matter of the dorsolateral prefrontal cortex is significantly greater in elderly depressed versus non-depressed individuals on post-mortem evaluation (Thomas et al., 2003). Post-mortem studies have also demonstrated that deep WMH are more frequently of vascular origin (cerebral ischemia) and are more commonly located in the dorsolateral prefrontal cortex in elderly depressed patients (Thomas et al., 2002) relative to non-depressed older individuals. A data-driven approach using latent variable modeling also found support for vascular depression as a distinct entity separate from non-vascular depression, with deep white matter hyperintensity emerging as the greatest predictor of vascular depression (Sneed, Rindskopf, Steffens, Krishnan, & Roose, 2008). In addition to WMH, cerebral microhemorrhages or "microbleeds," particularly in deep infratentorial regions, are also associated with depressive symptoms (Direk et al., 2016; Wang, Liu, Ye, & Yan, 2018).

The location of microvascular ischemic lesions in frontal, subcortical, and limbic regions may be especially relevant for the emergence of depression and its clinical symptoms in late life. In depressed older adults, there is decreased integrity in white matter adjacent to dorsolateral and dorsomedial prefrontal cortex, anterior and posterior cingulate, thalamus, and peri-amygdalar and insular cortex (Gunning-Dixon et al., 2008; Hoptman et al., 2009). Lacunar infarcts are associated with depression in older adults, implicating disruption to frontostriatal pathways (Direk et al., 2016). White matter lesions in specific fiber tracts including the fronto-occipital fasciculus,

uncinate fasciculus, superior longitudinal fasciculus, and inferior longitudinal fasciculus have also been associated with late-life depression (Sheline et al., 2008). Further evidence for the specificity of white matter lesions is suggested by the finding that lesions in ventromedial prefrontal cortex may result in disconnection of different circuits from those in the dorsolateral prefrontal cortex, resulting in a depressive episode characterized by mood lability and disinhibition (Manning, Gunning, McGovern, Kotbi, & Alexopoulos, 2015).

WMH may not just co-occur with depression but may play a causal role in the emergence of depression and maintenance of symptoms. There is an association between vascular disease burden (hypertension, diabetes, cardiac disease) in midlife and emergence of depression symptoms in late life (Scott & Paulson, 2018). In a longitudinal analysis of individuals in the Framingham Heart Study, a baseline assessment of WMH was associated with an increase in depressive symptoms and an elevated risk for severe depressive symptoms at a mean follow-up interval of 6.6 years (Qiu et al., 2017). Over a four-year period, the progression of deep white matter lesion volume predicts increased depression symptoms (Chen, McQuoid, Payne, & Steffens, 2006), and over 2 years greater progression of WMH is associated with a failure to sustain remission of depression (Taylor, Steffens, et al., 2003).

Taken together, the research to date has demonstrated some evidence for a vascular depression subtype with distinct clinical, neuroanatomic, and neuropsychological features. However, additional etiological pathways likely exist to depression and executive dysfunction in older adults. In addition and related to ischemia, hypoperfusion and loss of arterial structural and functional integrity (e.g., arterial stiffness) are common in late-life depression (Greenstein et al., 2010; Tiemeier, Breteler, van Popele, Hofman, & Witteman, 2003). Inflammatory processes such as prolonged pro-inflammatory states and immune responses may contribute to the onset and maintenance of depression in older adults (Alexopoulos & Morimoto, 2011). Chronic stress and altered hypothalamic-pituitary-adrenal axis dysfunction have been implicated in depression (Pariante, 2009) and may play a causal role in late-life depression. Genetic factors, including polymorphisms of APOE (involved in maintenance of myelin and metabolism of beta-amyloid), BDNF (synaptic plasticity), and SLC6A4 (serotonergic function), are also associated with late-life depression (Tsang, Mather, Sachdev, & Reppermund, 2017). These pathways to depression are interrelated and likely interact in the emergence of depression in late life (Taylor et al., 2013).

15.2.3 Assessment

When evaluating patients in the clinic for a possible depressive disorder, clinicians should be mindful of factors that are suggestive of the presence of vascular depression. MRI can allow the clinician to quantify the burden of chronic microvascular ischemic disease, in particular the presence of deep white matter hyperintensities, which are strongly associated with vascular depression. A comprehensive medical

history can elucidate the presence of vascular risk factors. Clinically, individuals with vascular depression may present with symptoms of psychomotor slowing, poor initiation, loss of energy, lack of guilt, and poor insight. Further, a history of non-response to antidepressant treatment may suggest the presence of vascular depression. As part of the assessment process, a brief neuropsychological screening evaluation—with measures sensitive to frontal network dysfunction such as the Trail Making Test and Stroop Test—can provide additional supporting evidence for the presence of vascular depression with co-occurring executive dysfunction.

15.2.4 Treatment

Following the assessment and diagnostic process, the question of how to treat a patient most effectively becomes most pressing. Unfortunately, vascular depression and associated cognitive deficits can confer resistance to treatment and perpetuate a depressive episode, as originally hypothesized (Alexopoulos, Meyers, Young, Campbell, et al., 1997; Taylor et al., 2013). In a study of 42 elderly depressed individuals who were treated with 10 mg of escitalopram daily for 12 weeks, those individuals who failed to achieve remission as assessed by the Hamilton Depression Rating Scale (HDRS) had a significantly greater burden of ischemic white matter disease than did those individuals whose depression remitted following treatment (Gunning-Dixon et al., 2010). Similar results have been found in a comparative trial of nortriptyline and sertraline, where WMH in the deep white matter and periventricular regions both significantly decreased the odds of achieving remission (Sneed et al., 2011). Further, in a prospective trial of sertraline for vascular depression, non-remitters had significantly poorer performance on measures of processing speed, executive function, episodic memory, and language (Sheline et al., 2010).

Ensuring adequate management and treatment of vascular risk may confer some benefit. For example, in elderly depressed individuals, obstructive sleep apnea is associated with increased deep WMH burden and cognitive impairment (Kerner et al., 2017; Kerner & Roose, 2016). Therefore, ensuring optimal treatment of a risk factor such as sleep apnea may limit the behavioral and physiologic changes associated with vascular depression, although the relative efficacy of such an approach remains an open question for further research. Pharmacologic management of hypertension, hyperlipidemia, diabetes, and cardiac disease is also important in preventing the worsening of depression symptoms given the association between advancing WMH burden, depression severity, and treatment non-response.

Augmentation of antidepressant medication with cardiovascular-specific medication may be another avenue for targeting vascular depression. Augmentation of fluoxetine with a calcium channel blocker (nimodipine) has been found to lead to a greater remission rate compared to augmentation with a placebo (54% vs. 27%), which the study researchers hypothesized may be due to the reduction of calcium influx into neurons or nimodipine's vasodilatory effects on arterioles that can protect against ischemia and hypoxia (Taragano, Bagnatti, & Allegri, 2005). Further,

augmentation of antidepressant medication with methylphenidate has demonstrated efficacy in the treatment of late-life depression broadly (Lavretsky et al., 2015; Lavretsky, Park, Siddarth, Kumar, & Reynolds, 2006), although evidence for the efficacy of this combination approach in the vascular depression subtype has been limited to a study using a retrospective chart review method (Mantani, Fujikawa, Ohmori, & Yamawaki, 2008). The literature in this area is relatively sparse, however, and further research is necessary to understand the optimal pharmacologic treatment strategy in patients with vascular depression.

15.2.5 Non-pharmacologic Approaches

One promising treatment avenue is the use of noninvasive brain stimulation techniques such as transcranial magnetic stimulation (TMS). TMS generates a magnetic field and can be used to enhance or inhibit neural activity and, when done repetitively (repetitive TMS or rTMS) can increase the excitability of stimulated regions (Rossini & Rossi, 2007). TMS targeting aspects of the cognitive control network such as the dorsolateral prefrontal cortex may have antidepressant effects by enhancing the ability of frontal regions to regulate emotions and control behavior (Dubin, Liston, Avissar, Ilieva, & Gunning, 2017; Lantrip, Gunning, Flashman, Roth, & Holtzheimer, 2017; Liston et al., 2014).

rTMS demonstrates positive effects in treating depression in older adults with vascular disease. An early study that compared active versus sham rTMS over the left dorsolateral prefrontal cortex in individuals with vascular depression found greater response rates and remission rates in those receiving active stimulation compared to the sham (Jorge, Moser, Acion, & Robinson, 2008). A recent systematic review of TMS interventions for vascular depression and post-stroke depression found five studies that met inclusion criteria for the review, all of which showed a significant benefit of rTMS in response rate (McIntyre, Thompson, Burhan, Mehta, & Teasell, 2016). These studies provide important, preliminary evidence for the efficacy of noninvasive brain stimulation as a treatment option in individuals with vascular depression.

Behavioral strategies that target both depression and comorbid vascular disease are also important methods of intervention for vascular depression. Care coordination approaches that incorporate psychoeducation, case management, and behavioral self-management strategies have demonstrated efficacy in improving depressive symptoms in older adults with comorbid vascular disease (Kastner et al., 2018). Psychotherapy that includes problem-solving therapy and behavioral activation delivered in the home significantly reduces depression symptoms in older adults with comorbid vascular disease (Gellis & Bruce, 2010). At-home interventions may be an especially important component to increase access to treatment for older adults with comorbid medical illness.

In sum, vascular depression is a complex and diagnostically and clinically unique subtype of late-life depression. With greater advances in imaging technology, the full relationship between cerebrovascular disease and depressed mood is now emerging. Vascular depression is a challenging disorder to treat, given that patients frequently show non-response and do not remit with traditional antidepressant therapy. Preliminary evidence suggests that pharmacologic augmentation and noninvasive brain stimulation are promising avenues to enhance treatment efficacy, though further research is needed in this regard.

15.3 Post-stroke Depression

15.3.1 Clinical Expression and Functional Consequences of Post-stroke Depression

A recent scientific consensus statement from the American Heart Association labeled post-stroke depression (PSD) as "underrecognized, underinvestigated, and undertreated" (Towfighi et al., 2016). Despite the paucity of research, PSD is common and disabling. Most prevalence estimates indicate that approximately 30% of stroke survivors meet criteria for a depressive disorder (Hackett & Pickles, 2014; Schottke & Giabbiconi, 2015). Like vascular depression, individuals with PSD have greater cognitive deficits than stroke patients without PSD (Tu, Wang, Wen, Xu, & Wang, 2018). Early post-stroke depressive symptoms have deleterious consequences for rehabilitation and recovery. In the acute inpatient rehabilitation setting, depression symptoms are significantly predictive of poor functional outcome at discharge (Ahn, Lee, Jeong, Kim, & Park, 2015) and at long-term follow-up (Kang et al., 2018; Parikh, Robinson, & Lipsey, 1990). PSD is also associated with poorer quality of life 1 year post-stroke (Kim et al., 2018).

Similar to the persistent symptoms of vascular depression, the presence of depressive symptoms in the inpatient rehabilitation period post-stroke is significantly predictive of a major depressive disorder at 6-month follow-up (odds ratio of 1.43) (Lewin-Richter, Volz, Jöbges, & Werheid, 2015). In another analysis, depressive symptoms in the subacute period (8 weeks post-stroke) were associated with depression at 6 months (Volz, Möbus, Letsch, & Werheid, 2016). The effects of PSD on mortality, disability, and quality of life are apparent even 5 and 10 years post-stroke (Ayerbe, Ayis, Crichton, Wolfe, & Rudd, 2014). These findings highlight the persistent nature of PSD and its effect on functional disability in the short term and long term.

15.3.2 Pathophysiology

Within a biopsychosocial framework, PSD can be conceptualized as resulting from damage to frontostriatal circuitry and a disconnection between frontal and limbic systems, together with a "psychosocial storm" due to the sudden, debilitating loss of function that often accompanies a stroke (Alexopoulos et al., 2013). PSD is associated with reductions in gray matter volume in the lateral and medial prefrontal cortex and limbic system (Shi et al., 2017a), as well as reduced overall brain perfusion, increased cortisol, and decreased brain derived neurotrophic factor (Noonan, Carey, & Crewther, 2013). Similar to the findings noted above in vascular depression, infarcts affecting the frontostriatal circuitry may lead to depression (Douven et al., 2017) as well as depression with executive dysfunction (Vataja et al., 2005).

Even in PSD, deep WMH are independently associated with depression (Tang et al., 2010) and lacunar infarcts in the basal ganglia, thalamus, and deep white matter are more strongly associated with PSD than larger macro infarcts (Santos et al., 2009). The onset of depression following stroke is also associated with the cumulative burden of cerebrovascular disease (Santos et al., 2009; Zhang et al., 2017), suggesting that the frontostriatal disruption that underlies PSD may result from both acute and chronic cerebrovascular processes. Recent meta-analyses have demonstrated conflicting results as to the relation between PSD and lesion laterality: one meta-analysis of 60 studies did not find that left hemisphere lesion location significantly increased the odds of depression (Douven et al., 2017), while a meta-analysis of 19 studies found increased relative risk of depression after a left hemisphere stroke (Mitchell et al., 2017).

Stroke onset may precipitate an abnormal interaction of functional cerebral networks involved in the experience of emotions, similar to that which occurs in major depressive disorder, with heightened limbic and default mode activity and decreased activity in cognitive control regions such as the dorsolateral prefrontal cortex. Individuals with PSD have significantly weakened EEG-derived functional connectivity between the left and right cerebral hemispheres, and decreased connectivity between frontal and parieto-occipital regions, which is associated with severity of depression (Sun et al., 2018). Increased resting state functional connectivity in the default mode network is associated with PSD (Vicentini et al., 2017) and correlates with PSD severity at 3 months post-stroke (Lassalle-Lagadec et al., 2012). In the subacute and chronic phase after stroke, increased connectivity between the default mode network and salience network is associated with depression severity (Balaev, Orlov, Petrushevsky, & Martynova, 2017). The anterior cingulate cortex (ACC)demonstrates increased functional connectivity with limbic regions such as the amygdala and insula, and decreased functional connectivity with lateral and medial prefrontal cortical regions implicated in cognitive control and emotion regulation (Shi et al., 2017a). PSD is also associated with decreased degree centrality (a measure of importance of a node within a brain network) in prefrontal regions and increased degree centrality in limbic regions (Shi et al., 2017b).

In the midst of this structural and functional neurobiological cascade, individuals with stroke are simultaneously left with a sudden and often catastrophic change in their daily functioning, which may overwhelm the ability to cope with the loss and life change associated with functional disability. This may be an especially vulnerable period for the emergence of negative cognitions, loss of self-esteem and self-efficacy, and a sense of hopelessness. Self-efficacy—or the belief in one's ability to exert control and influence over one's functioning—at 8 weeks post-stroke is associated with depressive symptoms at 6 months (Volz et al., 2016). This finding suggests that patients who experience a greater sense of uncontrollability may be most vulnerable to developing depression. Personality features such as a tendency towards neuroticism may also contribute to the emergence of PSD (Douven et al., 2018).

Following a stroke, the patient's family system is faced with significant life changes and modifications to their routine and goals, such that increased time is required to care for and support for the individual with stroke. The family may be unprepared to cope with the emotions that accompany such a life event, both within the patient and within caregivers (Alexopoulos et al., 2013). Additional risk factors for PSD include a past history of depression, stroke severity, functional deficits, and cognitive impairment (Luis Ayerbe, Ayis, Wolfe, & Rudd, 2013; De Ryck et al., 2013), although it should be noted that heterogeneity exists in findings likely due to methodological differences and patient characteristics across studies (De Ryck et al., 2014).

In terms of protective and resilience factors, social support has been identified as a possible protective factor. In the inpatient rehabilitation setting, social support from family members and caregivers was associated with fewer depressive symptoms (Ahn et al., 2015). Similarly, greater social support as assessed at 8 weeks post-stroke was associated with fewer depressive symptoms at 6 months (Volz et al., 2016). The implication of this finding for rehabilitation practitioners is that bolstering an individual's sense of confidence and gains through the rehabilitation process, and promoting contact with the patient's existing social support systems, may be fruitful avenues to prevent the emergence of depression.

15.3.3 Assessment

The diagnosis of PSD is complicated by the overlap of symptoms between depression and stroke. Common effects of stroke in the acute to subacute period include motor slowing, cognitive impairment, and fatigue/poor sleep, which overlap with the Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnosis of major depression's criteria of psychomotor retardation, poor concentration, and disrupted sleep. Further complicating the diagnosis is the presence of restricted affect, emotional lability, pseudobulbar affect, and poor initiation, all of which overlap with, and can be mistaken for, depression.

Certain behaviors characteristic of depression may be difficult to assess in the acute and subacute hospitalization period. For example, it can be difficult to determine whether a patient is anhedonic because patients may not have an opportunity to participate in valued, meaningful activities while hospitalized. Further, it can be expected that some degree of sadness is normative in the context of processing a significant loss and change in functioning. The point at which healthy and adaptive grieving for the loss of functioning and life change crosses into a depressive episode can be difficult to delineate. Thus, PSD poses a significant challenge for clinicians to separate what is a true mood disorder from a number of medical, neurologic, and psychological factors. Unsurprisingly, misclassification of post-stroke depression is common, particularly in the acute period (Kang et al., 2013).

Despite the challenges inherent to assessment and diagnosis of PSD, several studies have evaluated the accuracy of various diagnostic methods. The gold standard for a diagnosis of major depression is a structured or semi-structured interview, such as the Structured Clinical Interview for the DSM (SCID). In hospital settings, however, a lengthy clinical interview may not be feasible and therefore clinician-rated screening instruments and self-report screening measures are likely to be more practical and useful. Clinician- and patient-rated scales have the added advantage that they allow for the grading of depression symptoms and the quantitative monitoring of change over time. The HDRS and Montgomery Asberg Depression Rating Scale (MADRS) are two frequently used clinician-rated assessment tools that both have good internal consistency and excellent diagnostic accuracy in stroke (Kang et al., 2013; Meader, Moe-Byrne, Llewellyn, & Mitchell, 2013). Both the HDRS and the MADRS are therefore appropriate options for assessing depression and depressive symptom severity. Of note, however, is that the HDRS includes a greater number of somatic items as compared to the MADRS, which can result in higher misclassification (Kang et al., 2013).

In medical rehabilitation settings, even the feasibility of clinician-administered depression rating scales may be hampered by time constraints. Brief, self-report screening instruments can therefore be a viable alternative to assess for the presence of depressive symptoms. Recent systematic reviews and comparative studies have indicated that the Hospital Anxiety and Depression Scale-Depression (HADS-D) and the Center for Epidemiological Studies-Depression scale (CES-D) show relatively strong evidence for their sensitivity and specificity in identifying individuals with PSD in the acute inpatient rehabilitation setting (Burton & Tyson, 2015; Kang et al., 2013). In subacute to chronic stroke, additional screening measures such as the Geriatric Depression Scale (GDS), 15-item Geriatric Depression Scale (GDS-15), and the nine-item Patient Health Questionnaire (PHQ-9) also demonstrate relatively strong diagnostic accuracy (Burton & Tyson, 2015). A limitation of self-report is that cognitive impairment secondary to stroke may interfere with individuals' ability to complete and accurately report on their symptoms on the questionnaires described above.

In stroke patients with aphasia, the assessment and diagnosis of depression can become especially complicated. Individuals with comprehension difficulty may not understand verbal instructions and questions and may not be able to articulate their

inner mood states. Clinician-rated and self-report scales have been developed to screen for depression in individuals with aphasia. The Stroke Aphasia Depression Questionnaire (SADQ) is completed by clinicians and assesses the frequency of behaviors associated with depression including tearfulness, poor initiation, lack of smiling/laughing, participation, and perceived enjoyment and interest (Lincoln, Sutcliffe, & Unsworth, 2000). The Aphasic Depression Rating Scale (ADRS) is also clinician-rated and includes items that assess apparent sadness in facial affect, speech, and posture; slowness; fatigue/insomnia; somatic symptoms; hypochondriasis; and weight loss (Benaim, Cailly, Perennou, & Pelissier, 2004).

In contrast, the Visual Analogue Mood Scales (VAMS) is a self-report measure in which a patient is shown two emotional faces (e.g., a neutral and sad face) with a line between them and must select the point along the line that best represents his or her current mood (Stern, Arruda, Hooper, Wolfner, & Morey, 1997). In a recent systematic review (Van Dijk, Ginkel, Hafsteinsdóttir, & Schuurmans, 2016), the SADQ was found to have good internal consistency, variable construct validity, and poor test-retest reliability. The ADRS was found to have good content validity and moderately strong diagnostic accuracy, but poor test-retest and inter-rater reliability. The VAMS had positive internal consistency and construct validity, but was found to be limited by the requirement of comprehension of instructions. Overall, the individual studies that comprised the systematic review were graded as having poor methodological quality. Thus, while there is an emerging body of research on the utility of formal rating scales for depression in aphasia, further research is needed to validate these existing measures.

15.3.4 Treatment

Pharmacologic intervention using antidepressant medication is one option for treating PSD. In an early Cochrane review and meta-analysis of 16 controlled trials and 1655 individuals with PSD (Hackett, Anderson, House, & Xia, 2008), pharmacologic treatment for depression showed a small but significant effect of achieving remission from depression and in reducing the severity of depression symptoms. However, significant adverse effects on the central nervous system and gastrointestinal system were also found. More recent meta-analyses have also indicated benefit of doxepin, paroxetine, and nortriptyline for PSD (Qin et al., 2018). However, a recent large randomized controlled trial (n = 478) of escitalopram administered within 21 days of stroke onset to patients with and without depression symptoms found no significant effect of treatment on reducing moderate-severe depression symptoms, although there was a beneficial effect of treatment in individuals with only mild symptoms (Kim et al., 2017).

Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine have also demonstrated some evidence of efficacy for enhancing motor recovery after stroke (Chollet et al., 2011) although randomized controlled trials to date have included relatively small samples and larger trials are currently underway that are adequately

powered to detect possible adverse events (Mead et al., 2015). This is an important question for research as one barrier to the safety of pharmacologic intervention and SSRIs specifically in PSD is the risk for subsequent stroke (Wu, Wang, Cheng, & Gau, 2011) (Mead et al., 2013; Mortensen & Andersen, 2015).

15.3.5 Non-pharmacologic Approaches

Behavioral and psychotherapeutic interventions have emerged as a feasible and efficacious alternative, with the added advantage of limiting side effects as compared to pharmacotherapy. In a randomized controlled trial, community-dwelling stroke patients received a nine-session psychosocial support/behavioral intervention that augmented pharmacotherapy. The intervention ("Living Well With Stroke") was administered by nurses and focused on psychoeducation, problem-solving, and pleasant events scheduling (behavioral activation) (Mitchell et al., 2009). Compared to a treatment-as-usual control group, stroke patients in the active intervention had significantly fewer depression symptoms and greater percent remission immediately after treatment and at 12-month follow-up. This intervention provided preliminary support for problem-solving and behavioral activation as efficacious treatment strategies when used in conjunction with pharmacotherapy.

Behavioral activation also demonstrates efficacy in treating PSD in patients with aphasia. Thomas and colleagues developed a "Communication and Low Mood" intervention ("CALM") that focused on helping patients schedule and engage in pleasant events (Thomas, Walker, Macniven, Haworth, & Lincoln, 2012). The treatment process was tailored to accommodate language deficits by incorporating visual aids and other communication strategies. A 3-month course of behavioral activation demonstrated efficacy in terms of reducing depressive symptoms on the SADQ and VAMS, with the effects persisting at 6 months. Cognitive-behavioral therapy, both with and without concurrent antidepressant treatment, demonstrates positive effects in treating PSD (Wang et al., 2018) and a self-help relaxation training administered in the chronic phase of stroke was associated with decreased symptom severity on the HADS-D (Golding, Fife-Schaw, & Kneebone, 2018).

Building on their biopsychosocial conceptualization of PSD, Alexopoulos et al. (2013) developed a skills-based and action-oriented behavioral treatment called "Ecosystem Focused Therapy" (EFT). This treatment focuses on helping patients navigate the "psychosocial storm" of PSD by developing problem-solving and goal-setting skills, enhancing adherence to medication and rehabilitation regimens, coordinating care with rehabilitation therapists, providing psychoeducation, and modifying the environment. Critically, the treatment directly incorporates family members to help the patient and family restructure their goals according to the patient's new disability. In a 12-week, randomized pilot study comparing EFT to an active psychoeducation control condition, patients with PSD receiving EFT showed a greater decline in depressive symptoms over time, with a standardized effect size between groups of 0.83 at the conclusion of treatment. Sixty-seven percentage of

individuals in the EFT condition achieved remission compared to only 17% in the control condition. Moreover, EFT was associated with a significant decrease in physical disability. A larger randomized controlled trial is currently underway.

The results of these intervention studies highlight the importance of incorporating skills-based strategies such as behavioral activation and problem-solving concurrently with additional therapeutic approaches targeted to the unique psychosocial challenges resulting from stroke-related disability. Given the heterogeneity of deficits and symptoms following stroke, behavioral treatments likely require an idiographic approach that is tailored to the unique functional, cognitive, and social-emotional difficulties of individual patients. Such a framework allows for goal-setting that meets the patient where they are at the stage of their recovery.

In recent years, there has been increasing interest in noninvasive brain stimulation and neuromodulatory approaches for the treatment of PSD, similar to that described above in vascular depression. Compared to control (sham) conditions, rTMS over the left dorsolateral prefrontal cortex has shown efficacy in reducing depressive symptoms in chronic stroke survivors, including patients who previously did not achieve remission with pharmacotherapy (Gu & Chang, 2016; Jorge et al., 2004). A recent meta-analysis of 22 randomized controlled trials of rTMS for PSD found that rTMS led to overall reduction in depressive symptoms (mean change of 6.09 points on the HDRS), greater odds of achieving a response, and greater odds of achieving remission (Shen et al., 2017). This analysis also found rTMS to have beneficial effects on stroke-related disability and activities of daily living.

Another neuromodulatory approach that has gained increasing popularity is transcranial direct current stimulation (tDCS). tDCS applies a small current directly to the scalp and is thought to alter neuronal membrane potential and enhance cortical excitability (Filmer, Dux, & Mattingley, 2014; Romero Lauro et al., 2014). In (nonvascular) major depressive disorder, seven small randomized controlled trials of tDCS versus sham stimulation have demonstrated a small but statistically significant benefit of tDCS for reducing depressive symptoms (Hedges'g of 0.37), achieving a clinical response, and achieving remission (Shiozawa et al., 2014). In PSD specifically, a randomized controlled trial of 48 patients who were not on antidepressant medication showed a significant benefit of tDCS over the dorsolateral prefrontal cortex compared to sham stimulation in reducing depressive symptoms, achieving a clinical response, and achieving remission (Valiengo et al., 2016). tDCS may also be an efficacious treatment for patients with PSD and aphasia, as a small (uncontrolled) case series demonstrated that tDCS over the dorsolateral prefrontal cortex was associated with decreased depressive symptoms on the SADQ and ADRS (Valiengo et al., 2016).

One caveat to the treatment research on PSD is that it is aimed at intervening in the subacute to chronic phase of stroke. There is a dearth of information on evidence-based behavioral management in the acute, inpatient rehabilitation setting. Although intensive psychotherapy is likely not feasible in the hospital setting, brief interventions may still be useful in decreasing, or protecting against, emergent PSD. In light of research indicating that social support can be a protective factor against PSD,

encouraging patients with depressive symptoms to spend as much time as possible with caregivers, family, and friends may be clinically useful.

Similarly, increasing behavioral activation via therapeutic recreation, groups, music, and other activities may bolster mood and self-efficacy. A recent nursing-based intervention during acute hospitalization for PSD incorporated psychoeducation, enhancement of self-efficacy, promotion of social support, and guidance in finding meaning and support. The intervention was found to be feasible and acceptable, although no efficacy data were reported (Van Dijk, Hafsteinsdottir, Schuurmans, & De Man-Van Ginkel, 2018). Another group found that daily self-directed music listening that was initiated during inpatient hospitalization and continued after discharge for a 2-month period led to improved mood that was associated with change in activity in the subgenual anterior cingulate cortex (Särkämö et al., 2008, 2014); however, the intervention was not specifically targeted towards those with major depression. Further evidence for the efficacy of such brief psychotherapeutic interventions during stroke rehabilitation remains an important area for future scientific inquiry.

15.4 Summary

Since its original description and conceptualization in the literature, increasing evidence from clinical, neuropsychological, neuroimaging, and post-mortem studies has supported vascular depression as a distinct clinical entity and phenotype of late-life depression. Recent investigations have further elucidated predictors of vascular depression, including vascular disease burden earlier in life. Cognitive impairments, particularly in processing speed and executive functions, appear to be a core feature of vascular depression. Individuals with vascular depression are less likely to respond to traditional antidepressant treatment. Non-pharmacologic approaches including noninvasive brain stimulation are promising avenues for treating vascular depression.

Post-stroke depression is common, persistent, and predicts poor short-term and long-term functional outcome. Structural changes in the gray matter of prefrontal and limbic regions, as well as cerebrovascular processes such as WMH, have been implicated in the pathophysiology of PSD. Recent research has also indicated that altered functional connectivity between hemispheres, and within and between resting state networks such as the default mode network, may underlie PSD. Psychosocial changes associated with sudden functional disability are also critical to the emergence of PSD. The assessment and diagnosis of PSD, particularly in the acute period, remains challenging because of the overlap between symptoms of depression and stroke. Nonetheless, both clinician-rated and self-report screening measures demonstrate relatively strong diagnosis accuracy, and there is emerging research into the validation of depression assessments specifically for individuals with aphasia. Investigations into the efficacy of pharmacologic treatment for PSD have revealed mixed findings. Behavioral and skills-based psychotherapies that

incorporate psychoeducation, problem-solving, behavioral activation, and family support have demonstrated efficacy as alternative treatments. Both TMS and tDCS applied to the dorsolateral prefrontal cortex also appear to be promising avenues in treating PSD.

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Chapter 16
Pediatric Neurovascular Conditions: Developmental and Neuropsychological Implications

Robyn Westmacott and Ida Sue Baron

16.1 Introduction

Stroke and other cerebrovascular conditions are typically thought of as adult diseases. In fact, the incidence of ischemic stroke peaks twice throughout the lifetime—first in the perinatal period and later in older adulthood (Cardenas, Rho, & Kirton, 2011). Historically, what was referred to as "congenital hemiplegia" is now recognized to be ischemic stroke in the majority of cases (Kirton et al., 2016). Modern advances in neuroimaging and medicine have allowed for more accurate diagnosis and treatment of congenital heart disease, stroke, and other vascular conditions in childhood, including sickle cell disease and moyamoya disease (Dlamini & Kirkham, 2009). Consequently, the importance of screening for subclinical strokes in these populations is now recognized as viable and efficacious. As a result, there is also a growing interest in studying neuropsychological outcomes following vascular injury and disease in infancy, childhood, and adolescence. As for other medical conditions, etiology and outcomes may be vastly different in children than in adults with the same vascular diagnoses due, in part, to the strong influence of dynamic developmental factors and a child's evolving brain maturity. Despite the widely held belief that increased plasticity insulates the developing brain from the effects of injury and disease, there is considerable evidence that early onset neurovascular conditions are associated with significant neurological and neuropsycho-

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_16

logical morbidity (Dennis et al., 2013; Fuentes, Deotto, Desrocher, DeVeber, & Westmacott, 2014). This chapter summarizes the literature on congenital heart disease, ischemic and hemorrhagic stroke, sickle cell disease, moyamoya disease, and other vasculopathies in neonates, children, and adolescents. We also highlight important developmental considerations that are unique to pediatric populations in general, and to pediatric vascular conditions specifically.

16.2 Congenital Heart Disease

Epidemiology and pathophysiology: Congenital heart disease (CHD) is the most common structural birth defect in infants, with an incidence of 1 in 125 births. It includes a heterogeneous group of conditions. Simple septal defects of the ventricles or atria are much more common than complex deficits such as transposition of the great arteries (TGA), tetralogy of Fallot (TOF), and hypoplastic left heart syndrome (HLHS). The incidence of these more complex CHD syndromes is considerably lower, estimated at 6 per 1000 individuals (Marino et al., 2012), but they are associated with more neurological complications. Advances in the diagnosis, surgical treatment, and medical management of CHD have been substantial over the past several decades, with survival rates now exceeding 90%, compared with only 20 years ago. The increasing rates of survival for children with CHD are accompanied by a decrease in neurological complications and associated comorbid conditions, due to cardiological and surgical advances in diagnosis and treatment. CHD can even be detected by prenatal ultrasound (Marino, 2013), although complex CHD usually presents soon after birth. The effects of CHD may well persist over the individual's lifespan. Table 16.1 summarizes the most common CHD syndromes.

Newborns with CHD often present with cyanosis, hypotonia, lethargy, irritability, poor feeding, and poor temperature regulation. Approximately 30% of these infants are at high risk of mortality and require surgery in the neonatal period. Simpler forms of CHD may be asymptomatic initially, and only diagnosed later in childhood or even in adulthood (de los Reyes & Roach, 2014). Despite the dramatic improvement in rates of survival, neurodevelopmental and neuropsychological deficits commonly co-occur in children with CHD. The more complex syndromes are associated with especially high risk of such impairments due to intimate physiological interactions between the heart and brain (Ballweg, Wernovsky, & Gaynor, 2007), but even milder abnormalities may exert adverse effects.

CHD can disrupt cerebral circulation patterns and hemodynamic stability during gestation, and in utero investigations have revealed a number of abnormalities compared with unaffected infants. These include brain volume reductions and reduced *N*-acetyl-aspartate/choline ratios in affected fetuses (von Rhein et al., 2015). Fetal cerebral blood oxygen saturation is also significantly reduced in complex CHD syndromes such as HLHS and TGA (Sakazaki et al., 2014; Sun et al., 2015). Moreover, newborns with complex CHD have a 4–5 week delay in brain maturation compared with healthy newborns, and cerebral white matter abnormalities were documented

Table 16.1 Common congenital cardiac syndromes

Syndrome	Description of cardiac abnormality	Medical and neuropsychological outcomes
Simple congenital heart defects		
Atrial septal defect (ASD)	Abnormal blood flow between the atria (upper chambers of the heart); normally these are separated by the septum	Need for surgical intervention depends on size—Small defects may be asymptomatic and go unnoticed; large defects may require surgery to prevent damage to the heart and/or lungs. Neurodevelopmental outcome is generally good unless there are significant neurological complications
Patent foramen ovale (PFO)	A hole between the left and right atria of the heart. This hole exists in everyone before birth, but usually closes shortly after birth. When the hole does not close on its own after birth, it is called a PFO	Small PFOs are typically asymptomatic and go unnoticed. However, there is an increased risk of stroke. Surgical intervention is rarely required and neurodevelopmental outcomes are generally good
Ventricular septal defect	A hole in the wall (septum) that separates the ventricles (lower chambers of the heart) and allows blood to flow from the left to the right side	Need for surgical intervention depends on size—Small defects may be asymptomatic and go unnoticed; large defects may require surgery to prevent damage to the heart and/or lungs. Neurodevelopmental outcome is generally good unless there are significant neurological complications
Pulmonary stenosis	Obstruction of blood flow from the right ventricle to the pulmonary artery caused by narrowing (stenosis)	Mild to moderate pulmonary stenosis may not be associated with significant symptoms and may not require treatment. More severe pulmonary stenosis may require balloon valvuloplasty or open-heart surgery. Outcomes are generally good unless there are significant neurological complications
Complex congenital heart defects		
Coarctation of the aorta	Narrowing of the aorta (large blood vessel that branches off the heart), placing increased pressure on the heart to pump blood. Often occurs in combination with other cardiac anomalies	Common interventions include angioplasty and resection of severely stenosed regions of the vessel; neurodevelopmental outcome varies tremendously depending on neurological complications
Hypoplastic left heart	Severe underdevelopment of the left side of the heart, affecting blood flow through the entire organ	Multiple surgeries required; heart transplant may be needed; risk of stroke is high; neurodevelopmental disorders are common, even in those without neurological complications

(continued)

Table 16.1 (continued)

Syndrome	Description of cardiac abnormality	Medical and neuropsychological outcomes
Transposition of the great arteries	Abnormal arrangement (e.g., reversal) of any of the great vessels of the heart, including the superior and/or inferior venae cavae, pulmonary artery, pulmonary veins, and aorta	Arterial switch procedure commonly used as treatment; neurodevelopmental outcome varies depending on neurological complications
Tetralogy of Fallot	Typically this includes four anomalies: (1) Ventral septal defect, (2) pulmonary stenosis; (3) right ventricular hypertrophy (enlargement of right ventricle), and (4) overriding aorta (allowing blood from both ventricles to enter the aorta)	Requires open-heart surgery within the first year; surgical intervention is often multi-staged; long-term problems with irregular heart rate are common; risk of stroke is high and neurodevelopmental disorders are common
Atrioventricular septal defect	Holes between the chambers of the right and left sides of the heart; valves that control blood flow between the chambers may be underdeveloped	Treatment involves surgery to close atrial and ventricular septal holes and restore function of left atrioventricular valve. Neurodevelopmental outcome varies depending on neurological complications

using diffusion tensor imaging (DTI) (Licht et al., 2009; Miller et al., 2007). CHD also increases the risk of periventricular leukomalacia and other types of white matter injury postnatally following cardiac surgery (Galli et al., 2004; Miller et al., 2007; Von Rhein et al., 2014). In these respects, the brain morphology of a full-term baby with CHD (but no stroke) closely resembles the brain of a preterm infant in terms of cortical volume and white matter diffusion parameters (Wernovsky, 2006).

Individuals with CHD also are at high risk of embolic stroke. Indeed, CHD is the most common cause of cerebral embolism in children, accounting for approximately 20% of pediatric ischemic strokes (Dowling & Ikemba, 2011). Children who have only isolated septal defects or single valve abnormalities have a much lower risk of stroke than those children who are born with more complex cardiac anomalies.

16.2.1 Etiology and Risk Factors

Approximately 30% of individuals with CHD have a chromosomal disorder such as Down syndrome, 22q11.2 deletion syndrome, Turner syndrome, and Alagille syndrome (Marino, 2013; Masoller et al., 2016). These children often have structural brain abnormalities associated with their genetic syndrome (e.g., cortical dysplasia or migrational anomalies) that increase their likelihood of significant neurodevelopmental disability. Various maternal lifestyle factors are associated with CHD in their

offspring, including smoking, use of illicit drugs, and an elevated body mass index. Infants born to mothers exposed during their pregnancy to maternal illnesses such as rubella and Type 1/Type II diabetes are also at increased risk of CHD. However, in many instances, no specific cause or risk factor can be identified to explain the presence of CHD (de los Reyes & Roach, 2014).

16.2.2 Treatment and Rehabilitation

Approximately 30% of babies with complex CHD require life-saving surgery in the neonatal period (de los Reyes & Roach, 2014), and many more require medical or surgical interventions later in their development. Surgical treatment is often staged, with a primary surgery scheduled in the neonatal period and followed by subsequent procedures at specified points along the developmental trajectory. In addition to open-heart procedures, children with CHD may require single or repeated cardiac catheterization to diagnose, assess, and treat their condition. All of these procedures increase risk, including of paradoxical embolus when venous thromboembolism transits from right- to left-sided cardiac chambers, and compromised oxygen delivery to the brain (Wernovsky, 2006). Some children with severe CHD have compromised heart and lung function and require extracorporeal membrane oxygenation (ECMO) for cardiac and respiratory support. ECMO is a recognized life-sustaining intervention, and it is generally only maintained for a period of a few weeks (Abraham et al., 2016). Depending on whether a cardiac anomaly can be completely repaired, and a variety of other factors, many individuals with CHD must continue to take daily medications to support their heart function. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, and diuretics are often used to lower blood pressure and reduce stress on the heart. In severe cases, when medication and surgery are not sufficient, heart transplantation will be considered (de los Reyes & Roach, 2014).

16.2.3 Neurological and Neuropsychological Outcome

Neurodevelopmental delays and neuropsychological deficits are common in children with CHD. Their severity tends to be positively related with the complexity of the cardiac anomaly (Bellinger & Newburger, 2010; Marino et al., 2012). Although group averages for overall intellectual ability typically fall in the low-average to average range, there is significant individual variability depending on medical complexity, such complications as stroke and/or hypoxic-ischemic encephalopathy, and associated genetic syndromes (Wilson, Smith-Parrish, Marino, & Kovacs, 2015). Moreover, global estimates of intellectual ability generally fail to capture salient weaknesses in specific areas of neuropsychological function (Bellinger &

Newburger, 2010), emphasizing the relevance of obtaining comprehensive evaluations of brain–behavior relationships in order to best understand a child's strengths as well as weaknesses for early intervention planning.

Neuromotor delays in infancy are typically the first sign of neurodevelopmental morbidity. Deficits in attention, speech, language, and early concept formation often emerge during the toddler and preschool years. Gaynor et al. (2015) reported lower psychomotor and cognitive scores on the Bayley Scales of Infant Developmental (BSID-III) in toddlers aged 15 months who had CHD compared with controls, with low birth weight and neurological comorbidity contributing additional risk. However, the Bayley-III tends to under-identify children with developmental delay (Anderson & Burnett, 2016), making this report even more of a concern. Neuropsychological deficits can be expected to become more apparent over time in children with CHD, particularly when they have to master more challenging cognitive and academic tasks and integrate complex information. This phenomenon of emerging cognitive deficits is well documented not only in CHD but in other pediatric medical populations. It reflects the gradually unfolding neurodevelopmental consequences of early insult on the vulnerable and rapidly developing brain (Hövels-Gürich et al., 2002; Marelli, Miller, Marino, Jefferson, & Newburger, 2016).

Although researchers have attempted to identify modifiable factors pertaining to medical management and post-operative care that might predict neurodevelopmental outcome, the evidence to date suggests that patient medical characteristics (e.g., severity of cardiac lesion, presence of genetic syndrome and/or neurological comorbidities) are the most important determinants (Bellinger & Newburger, 2010). Research has also shown the adverse impact of CHD on white matter maturation later in childhood and adolescence, and the severity of this maturational disruption was associated with the magnitude of long-term deficits in overall intellectual ability, academic abilities, learning, memory, executive function, and visual-spatial ability (Panigrahy et al., 2015; Rollins et al., 2014). Socioeconomic status and maternal education are also found to impact the severity of neuropsychological deficits in children with CHD (Goldsworthy et al., 2016; Krueger, Brotschi, Balmer, Bernet, & Latal, 2015).

Children with CHD are vulnerable to experiencing a wide range of deficits involving cortical and subcortical regions, similar to children with other systemic medical conditions. The effects of CHD tend to be exhibited early, in speech and language delays, and to emerge later in complex verbal expression, social communication, and language pragmatics (Bellinger et al., 2003; Hemphill, Uccelli, Winner, Chang, & Bellinger, 2002). Broader challenges with respect to social cognition and theory of mind are also reported. Specifically, children with CHD performed worse than controls on first-order and second-order false belief stories (Calderon et al., 2010) and had greater difficulty decoding the emotions of others on the Reading Mind in Eyes Task-Revised (Bellinger et al., 2011). Deficits in early literacy skills such as phonological awareness, auditory analysis, and sight word recognition are reported, along with an increased incidence of poor academic

achievement (Hemphill et al., 2002; Ovadia, Hemphill, Winner, & Bellinger, 2000). Visual-spatial and visual-motor challenges are also common among children with CHD who have a high likelihood of white matter disruption and because these skills are particularly reliant on multi-modal integration of complex, higher order information as well as neuromotor performance. For example, Bellinger et al. (2003) found that children with CHD were impaired on the Rey–Osterrieth Complex Figure Test and tended to adopt a piecemeal and part-oriented approach, neglecting the overall Gestalt.

Impairments in attention and executive function (EF) are common in the CHD population. It is argued that they constitute the most important neurodevelopmental deficit in those without an associated genetic syndrome due to their impact on multiple aspects of adaptive function (Calderon & Bellinger, 2015). The incidence of Attention-Deficit/Hyperactivity Disorder (ADHD) is estimated to be 3–4 times greater among children with CHD than in the general population (Bellinger et al., 2011; Sistino et al., 2015), and subclinical attention problems are even more common (McCrindle et al., 2006). Challenges with multiple aspects of EF—attention regulation, inhibitory control, working memory, flexible thinking, organization, and planning—are also documented through standardized neuropsychological testing (e.g., Wisconsin Card Sorting Task, Delis–Kaplan Executive Function System) and a wide range of behavioral questionnaires completed by parents and teachers. A recent study by Cassidy and colleagues (Cassidy, White, DeMaso, Newburger, & Bellinger, 2015) indicated that over 75% of children with CHD exhibited significant deficits in EF, nearly twice as common as in their controls. Identification and early intervention for executive dysfunction in children with CHD are critical to reduce their risk of later academic and social difficulties.

Finally, children with CHD may also exhibit significant behavioral challenges, poor psychosocial functioning, and reduced quality of life. The likelihood of identifying such problems increases with age (Bellinger et al., 2009; Uzark et al., 2008). McCrindle et al. (2006) found that the incidence of anxiety, depression, learning deficits, or behavior problems was eight times greater in the CHD patient group than in a normative sample. Moreover, between 30% and 50% of children with CHD required academic accommodations and/or remedial support due to a combination of school absence and the cumulative effects of heart disease and its treatment (Bellinger et al., 2009; Shillingford et al., 2008). There is also evidence to suggest that those with academic difficulties are also more likely to exhibit problem behaviors (e.g., poor attention, behavioral dysregulation, peer difficulties) (Bellinger et al., 2009). Due to these complex and gradually unfolding neuropsychological deficits in children with CHD, long-term follow-up and careful longitudinal monitoring of development are strongly recommended. Finally, there is evidence to suggest an increased incidence of autism spectrum disorder among children with CHD, even in those without documented genetic syndromes (Marino et al., 2012; Razzaghi, Oster, & Reefhuis, 2015).

16.3 Pediatric Stroke

16.3.1 Epidemiology and Pathophysiology

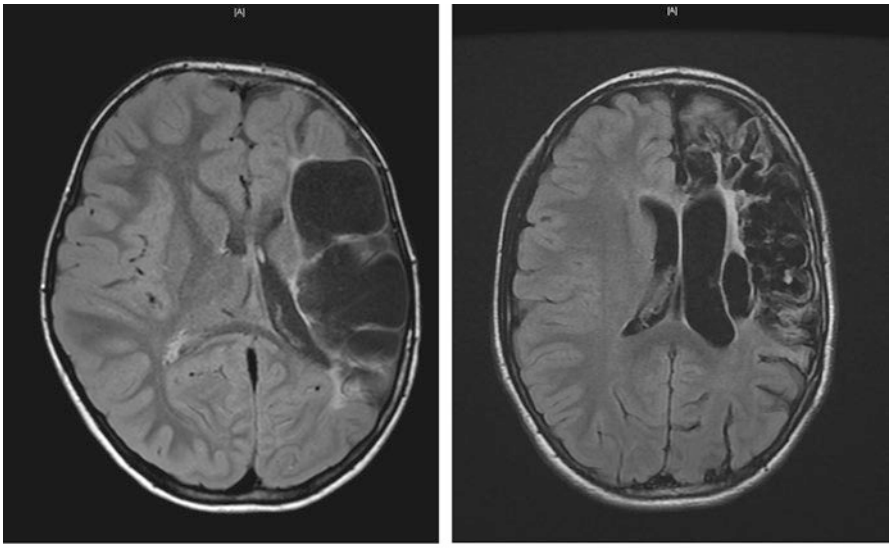
An *ischemic stroke* is a sudden, focal loss of neurologic function caused by a blocked blood vessel associated with acute infarction on brain imaging. Ischemic strokes are caused by disrupted blood flow in the arterial system (arterial ischemic stroke, AIS) or the venous system (cerebral sinovenous thrombosis; CSVT). There are two primary mechanisms of ischemic stroke. In the case of thrombosis, a blood clot forms on a blood vessel wall that causes that vessel to occlude. In the case of an embolus, a mass of material (e.g., blood clot, tissue, cholesterol, or amniotic fluid) detaches from its point of origin and travels through the circulatory system to occlude a blood vessel downstream (Kirton & deVeber, 2009). A *hemorrhagic stroke* refers to bleeding in the brain and may be classified as subarachnoid (SAH, bleeding into the subarachnoid space, between the pia mater and arachnoid membrane), intraventricular (IVH, bleeding into the cerebral ventricles), or intracerebral (ICH, bleeding into the brain tissue). Hemorrhagic and ischemic stroke are equally common in neonates and children, whereas the vast majority of adult strokes are ischemic in nature (Riel-Romero, Kalra, & Gonzalez-Toledo, 2009).

The distinction between perinatal stroke and childhood stroke is an important one, because they are very different in terms of clinical presentation, risk factors, and outcome. *Perinatal ischemic stroke* occurs between 20 weeks gestation and 28 days after birth, and has an incidence of approximately 1 in 2500 live births (Cardenas et al., 2011). The term *neonatal arterial ischemic stroke* (NAIS) is applied when the diagnosis of stroke is made acutely, usually because of focal seizures 12–24 h after birth. The term *presumed perinatal ischemic stroke* (PPIS) is used when a retrospective diagnosis of suspected stroke in the perinatal period is made, typically due to emerging hemiparesis between 4 and 8 months of age and findings of a remote infarct on brain imaging (Kirton & deVeber, 2009). *Childhood arterial ischemic stroke* is much less common, with a yearly incidence from 1.5 to 3 cases per 100,000 children (Amlie-Lefond, Sébire, & Fullerton, 2008). Presenting symptoms are similar to those in adults and typically involve acute-onset focal deficits that correlate with the location of the lesion, such as hemiparesis (70–80%), speech and language difficulties (40%), imbalance (20%), and seizures (20%) (Amlie-Lefond et al., 2008; DeVeber et al., 2017; Hartman, Lunney, & Serena, 2009).

As is true for adult stroke, most pediatric strokes involve the middle cerebral artery (MCA), whereas fewer involve the anterior cerebral artery (ACA) or posterior circulation (e.g., posterior cerebral artery (PCA), cerebellar arteries, basilar artery, and vertebral arteries). Posterior circulation strokes in children are rare and most often occur in the context of dissection—a tear in the blood vessel wall that allows blood to collect and separate the wall layers (Cardenas et al., 2011). Perinatal strokes are often large, involving both cortex and underlying subcortical structures (i.e., basal ganglia and/or thalamus), although they may be isolated and involve only cortical or subcortical regions. Perinatal strokes commonly involve the left hemi-

sphere, which has been attributed to differences between the left and right common carotid arteries (Cardenas et al., 2011). In contrast, childhood strokes are highly variable in terms of location, depending on etiology, and often involve basal ganglia and/or thalamus. Isolated cortical strokes during childhood are rare (Cardenas et al., 2011). Brain magnetic resonance imaging (MRI) of an acute neonatal stroke involving the left middle cerebral artery (MCA) is shown in Fig. 16.1a. Figure 16.1b shows a brain MRI of a left MCA stroke in a 10-year-old child. Several important definitions pertaining to pediatric stroke are outlined in Table 16.2.

Despite the focal nature of these symptoms, childhood stroke can be difficult to diagnose. One reason for this is that pediatric stroke remains under-recognized, even among health professionals—many cases are missed, diagnosed incorrectly, or diagnosed after a very long delay (Rafay et al., 2009). Braun, Kappelle, Kirkham, and Deveber (2006) found that 42% of the children in their sample who were eventually diagnosed with ischemic stroke were previously seen in an Emergency Department where the diagnosis was missed. Indeed, stroke is one of many possible diagnoses in children who present with focal neurological deficits—conditions such as epilepsy, hemiplegic migraine, brain tumor, meningitis, and vasculitis often present with stroke-like symptoms (Shellhaas, Smith, O'Tool, Licht, & Ichord, 2006). Moreover, the presence of severe headache, vomiting, and altered level of consciousness can make it difficult to detect focal neurological deficits in children and accurately attribute them to stroke (Steiinlin, 2013).



A B

Fig. 16.1 Left middle cerebral artery stroke sustained in the perinatal period (**a**) and in a 10-year-old child (**b**)

Table 16.2 Pediatric stroke definitions

Neonatal stroke	A cerebrovascular event occurring within the first 28 days of life
Presumed perinatal stroke	Retrospective diagnosis of suspected stroke in the perinatal period, usually made due to emerging hemiparesis and/or seizures between 4 and 8 months of age. An old lesion is observed upon neuroimaging
Childhood stroke	A cerebrovascular event occurring between 1 month and 18 years of age
Arterial ischemic stroke	Occurs when blood flow to a cerebral artery is suddenly blocked (e.g., due to embolism or thrombosis), resulting in death of affected brain tissue
Sinovenous thrombosis	Sudden blockage of the venous sinuses resulting in impaired blood drainage and death to affected brain tissue
Intraventricular hemorrhage	Hemorrhagic stroke caused by bleeding into the brain's ventricular system, which consists of fluid filled spaces containing cerebrospinal fluid
Subarachnoid hemorrhage	Hemorrhagic stroke caused by bleeding on the brain's surface, in the area between the arachnoid membrane and pia mater
Intracerebral hemorrhage	Hemorrhagic stroke caused by bleeding within the brain tissue
Thrombosis	Local coagulation (formation of a blood clot) inside of a blood vessel, resulting in obstruction of blood flow within the circulatory system
Embolism	The lodging of a blockage-causing piece of material (i.e., embolus) inside of a blood vessel. The embolus forms elsewhere in the body and travels throughout the circulatory system to occlude a vessel downstream. The blockage-causing material may consist of a blood clot, air bubble, tissue, plaque, bacteria, or amniotic fluid

CSVT, relatively uncommon in adulthood, is a frequent mechanism of infarction and hemorrhage in neonates. CSVT occurs when there is thrombosis of the veins or major venous sinuses in the brain. This often leads to hemorrhagic transformation (reperfusion of blood into ischemic tissue) and/or venous infarction involving subcortical and periventricular regions, although many instances of CSVT resolve successfully and without permanent damage to the brain. Approximately 25% of all pediatric cases of ischemic stroke involve the venous system, and lifetime incidence of CSVT is highest in the neonatal period (Kirton & deVeber, 2009). Neonatal CSVT typically presents with seizures, although diffuse neurological signs such as lethargy, irritability, and abnormal muscle tone may also be present. There is evidence to suggest that approximately 30% of neonates with IVH have underlying CSVT (Cardenas et al., 2011). CSVT is less common in children than neonates, and children who do develop CSVT are less likely than neonates with CSVT to sustain infarction.

Perinatal hemorrhagic stroke is the least well characterized of all pediatric stroke subtypes (Cardenas et al., 2011), with an incidence of approximately 6 per 100,000 live births (Armstrong-Wells, Johnston, Wu, Sidney, & Fullerton, 2009). Seizures and encephalopathy are the most common presenting symptoms, although many cases can be diagnosed on routine prenatal ultrasound. Childhood hemorrhagic stroke presents with nausea, vomiting, and headache in more than 50% of cases. Initial mortality rates are higher for hemorrhagic stroke than ischemic stroke, but survivors are less likely to have significant neurological or neuropsychological defi-

cits (Lo et al., 2008). It is important not to confuse primary perinatal hemorrhagic stroke with hemorrhagic conversion of ischemic strokes, as risk factors and outcome are different (Cardenas et al., 2011). Because ischemia affects the vascular bed in addition to brain tissue, hemorrhagic conversion arises from injured blood vessels.

Preterm infants are at an especially elevated risk of IVH due to the immaturity and fragility of the blood vessels in the germinal matrix that may rupture in the first few days of life. In Grade I or II IVH, blood remains contained in the ventricles and does not exert pressure on surrounding tissue, making it less likely that long-term neurological deficits will manifest compared with higher grade IVH. In Grade III IVH, bleeding is sufficiently extensive to obstruct the channels connecting the ventricles and may result in hydrocephalus. Grade IV IVH is significant bleeding that extends into the brain tissue, and is typically associated with hemorrhagic infarct in that region (Cardenas et al., 2011). Preterm infants who do not experience IVH may have age-appropriate neurocognitive and behavioral function (Baron, Ahronovich, Erickson, Gidley Larson, & Litman, 2009).

16.3.2 Etiology and Risk Factors

Risk factors for stroke in adults typically relate to lifestyle factors, such as elevated cholesterol, unhealthy diet, hypertension, Type II diabetes, and lack of exercise. These factors are rarely implicated in pediatric stroke. Indeed, there are many unanswered questions regarding risk and etiology of pediatric ischemic stroke, as up to one-third of cases are idiopathic (Armstrong-Wells et al., 2009; Kirton & deVeber, 2009, 2015), and as many as 50% are associated with multiple risk factors. Nonetheless, the pediatric stroke literature has expanded significantly over the past two decades, and a number of etiological factors have been identified. First, sex is a significant risk factor, with males accounting for approximately 60% of pediatric stroke samples across studies (Golomb, Fullerton, Nowak-Gottl, & Deveber, 2009). Males are more likely than females to experience both perinatal and childhood stroke, though the reasons for this are unclear. Second, a variety of maternal risk factors have been associated with perinatal ischemic stroke, including preeclampsia, gestational diabetes, advanced maternal age, autoimmune disease, twin gestation, low amniotic fluid, and infection (e.g., urinary tract infection, untreated Group B streptococcus, cytomegalovirus). Labor-related pediatric stroke risk is highest with emergency caesarian section, vacuum extraction, and birth trauma (Cardenas et al., 2011). Perinatal ischemic stroke is also attributed to emboli arising from the degenerating placenta around the time of birth, which enter the fetal circulatory system and occlude major cerebral arteries (most often the middle cerebral artery) (Coker, Beltran, Myers, & Hmura, 1988; Elbers, Viero, MacGregor, DeVeber, & Moore, 2011).

As noted above, CHD is a primary risk factor for both perinatal and childhood ischemic stroke, with the heart being the most common source of cerebral emboli

(Roach, Heyer, & Lo, 2012). Vascular anomalies (also called vasculopathies) have also been implicated and account for half of all arterial ischemic strokes in children (Amlie-Lefond et al., 2009). Blood disorders such as sickle cell disease increase the risk of blood clots within the vascular system, whereas vasculopathies, such as moyamoya, increase the likelihood of thrombi or emboli occluding the narrowed vessels. Arterial dissection of the carotid arteries is another prominent risk factor, accounting for approximately 20% of childhood ischemic stroke cases. Dissection may be spontaneous or related to trauma, and it occurs when a small tear forms in the arterial wall lining, increasing the risk for clotting and vessel occlusion. Organ transplantation and treatment for cancer are also associated with increased risk of childhood stroke, via an increased risk of blood clots and damage to vascular lining (Cardenas et al., 2011; Steiinlin, 2013). Finally, head and neck infections (such as sinusitis, otitis, and meningitis) may also co-occur with childhood stroke and are associated with emboli and infarcts via inflammatory immune response (Cardenas et al., 2011). The term *transient cerebral arteriopathy* (TCA) describes non-progressive, focal inflammation of a cerebral artery that increases the risk of stroke by occlusion of the vessel. TCA most often affects the supraclinoid internal carotid artery and its proximal branches, resulting in infarction of the basal ganglia region, and has been linked with infections such as varicella (Amlie-Lefond et al., 2009; Askalan et al., 2001; Dlamini & Kirkham, 2009).

In the case of primary hemorrhagic stroke, trauma is the most common risk factor among children in the United States. Hemorrhagic strokes that occur outside the context of trauma are most often due to arteriopathies, such as an arteriovenous malformation (AVM). AVM constitutes abnormal connections between the interfacing arterial system and venous drainage system, in which the interface lacks the normal branching structures that allow for a steady drop in blood pressure. Abnormal connections and high pressure of an AVM increase the risk of spontaneous hemorrhaging. AVMs can become symptomatic within the first few days of life. They account for a greater percentage of hemorrhagic strokes in children than in adults. Hemorrhaging can also result from small vessel disease, as seen in William's syndrome, where blood vessel walls become weaker and more prone to rupturing over time due to increased blood pressure within the narrowed cerebral arteries (Roach et al., 2012).

16.3.3 Treatment and Rehabilitation

Timely neuroimaging is essential for diagnosis and selection of hyperacute and acute treatments. Magnetic resonance imaging (MRI) of the brain with diffusion-weighted sequences and MR angiography are the imaging modalities of choice for the diagnosis of pediatric stroke. Management is based on early institution of neuroprotective measures and antithrombotic therapy (antiplatelet or anticoagulant). Neuroprotective measures aim to minimize the extent of ischemic injury to the brain, although most related research has been conducted using animal models. For

example, in animal models of stroke, hypothermia has been found to reduce infarct size, but this technique remains in the preclinical stage for humans (Rajah & Ding, 2017). Currently, no widely approved methods of neuroprotection are endorsed for children. The aim of antithrombotic therapy is to reduce the risk of recurrent thrombosis in childhood arterial stroke, neonatal cardioembolic arterial ischemic stroke, or thrombus propagation in CSVT (Kirton, Westmacott, & deVeber, 2007). In the acute post-stroke period, recombinant tissue plasminogen activator (rt-PA) is commonly used in adult ischemic stroke patients to facilitate the breakdown of blood clots, but its safety and efficacy in children is untested, and thus not recommended for use in pediatric patients. Immediate treatment with anticoagulant drugs such as aspirin, heparin, and warfarin is standard of care in pediatric ischemic stroke, especially when cardiac embolus or arterial dissection is present. However, there is considerable variability across medical centers with respect to acute post-stroke use of pharmaceuticals due to lack of evidence and limited drug trials in children. Medical guidelines suggest that extremely high intracranial pressure produced by hematoma can be alleviated by surgical evacuation, but its impact on outcome is unclear. The benefits of surgical intervention are more defined with progressive hydrocephalus caused by IVH, in which draining and, if indicated, later shunting is often necessitated (Roach et al., 2012).

Pediatric stroke remains under-recognized within the healthcare system and community organizations that provide rehabilitation. Pediatric rehabilitation services are largely allocated using the model of congenital/developmental disorders (e.g., genetic conditions, cerebral palsy), which may not adequately address the needs of children with acquired, focal lesions (Ganesan, 2013). Occupational therapy, physical therapy, and speech-language therapy make up the bulk of the intervention offered to children with stroke, but services are often discontinued or significantly reduced after the age of 5 or 6 years. For older children with stroke, it can be very challenging to find appropriate longer-term intervention services akin to what is offered as standard of care to adults. Access to cognitive intervention is particularly difficult for both children and adults, and the financial burden is significant. Many children with stroke receive specialized supports through the education system, including the development of an individual education plan, access to educational technology, academic accommodations, and/or assistance from an education assistant for physical needs. However, accessing these services can be challenging for children who do not have a psychological diagnosis recognized by the education system.

There is very little research on effective rehabilitative interventions for children with stroke. The importance of early assessment and intervention is recognized among clinicians, but there is little empirical support to distinguish between effective and ineffective therapies. Constraint-induced therapy improves motor outcomes by constraining the affected limb for a period of weeks in order to promote use and recovery of the affected limb (Gordon et al., 2007). Some newer research has also documented benefits of transcranial magnetic stimulation (TMS) on motor function for children with neonatal and childhood stroke (Kirton et al., 2016). TMS was also found to improve expressive language ability in a recent case study of childhood left

MCA stroke (Carlson et al., 2016). With respect to cognitive intervention, therapies targeting attention, working memory, processing speed, and EF are of interest because these are common areas of concern in the CHD population. The Cogmed working memory training program was utilized in studies of children with ADHD, and while it provided some preliminary support in children with stroke (Westerberg et al., 2007), a more recent study failed to find evidence supporting its effectiveness in children with acute ischemic stroke (Eve et al., 2016).

16.3.4 Neurological Outcome

Ninety percent of children with ischemic stroke survive, though this percentage drops to 60% in the case of childhood hemorrhagic stroke (Cardenas et al., 2011). Despite the much higher survival rates in children compared to adults, significant neurological morbidity is reported in more than half of pediatric stroke survivors (Cardenas et al., 2011). Recurrent stroke occurs in 10–30%, 30% develop seizure disorders, and 60–70% have persistent neurological deficits such as hemiparesis, spasticity, hemi-sensory loss, dystonia, and dysphasia (DeVeber et al., 2017; Ganesan, 2013; Steiinlin, 2013). In the case of hemiparesis, the upper extremities (i.e., hand, arm) are most frequently impacted, manifested as compromised finger dexterity and poor upper-limb movement planning. Perinatal stroke is the most common cause of congenital hemiplegic cerebral palsy, which is often marked by weakness, impaired dexterity, spasticity, apraxia, and a circumducting gait (Cardenas et al., 2011). Although lesions greater than 10% of total brain volume have been associated with increased risk of sensorimotor deficit, most studies have failed to demonstrate a clear relationship between lesion volume and specific neurological outcomes (Ganesan, Ng, Chong, Kirkham, & Connelly, 1999). One important predictive factor for long-term motor outcome following neonatal arterial ischemic stroke is acute Wallerian degeneration remote from the area of infarction, which appears as restricted diffusion MRI signal within descending corticospinal tracts during the acute and subacute phase. This has been correlated with poor motor outcome in neonatal ischemic stroke (Kirton, Shroff, Visvanathan, & DeVeber, 2007). The Pediatric Stroke Outcome Measure is a validated tool used for the standardized assessment of sensorimotor, language, behavioral, and cognitive outcomes following stroke in childhood (Kitchen et al., 2012). Functional status at 1 year post-stroke is strongly predictive of long-term outcome and when mental health issues are emerging as a significant area of need (Elbers, deVeber, Pontigon, & Moharir, 2013).

16.3.5 Neuropsychological Outcome

A substantial body of evidence indicates that individuals with a history of perinatal or childhood stroke experience difficulties in motor, cognitive, academic, and psychosocial functioning that emerge over the course of development (Fuentes et al., 2014), despite the persistent belief that the young brain is protected against neurological and neuropsychological deficits due to its plasticity. The literature on pediatric stroke highlights the extreme vulnerability of the developing brain, the long-term neuropsychological deficits that often result from early disruption of brain function and subsequent brain development, and the significant variability in outcomes seen across individuals. Heterogeneity in outcomes within the pediatric stroke population is linked to a range of clinical and demographic factors, including those related to the brain (e.g., lesion location, lesion size, and volume), the child (e.g., age at stroke, age at assessment, co-occurring neurological conditions, stroke etiology, genetic predispositions), and the environment (family stress/functioning, parent mental health, sibling interactions, educational support, rehabilitation therapy) (Fuentes et al., 2014). We are just starting to understand the complex interactions among these factors and their impact on neuropsychological outcome and resiliency following pediatric stroke. Outcomes following perinatal and childhood stroke across important cognitive domains are discussed below and summarized in Table 16.3.

16.3.6 Intellectual Ability

Children with perinatal and childhood stroke consistently score broadly within the average range on tests of overall intellectual ability, although statistically lower than the normative mean (Hajek et al., 2013; Studer et al., 2014; Westmacott, Askalan, Macgregor, Anderson, & Deveber, 2010). However, there is significant individual variability within this population, and it is challenging to identify determinants of outcome because many studies to date have included children with very diverse pediatric strokes who differ on many relevant factors (e.g., extent of lesion, presence of seizure disorder, age at stroke, age at test, and presence of neurological comorbidities). Nonetheless, several important themes have emerged from recent research.

First, there is considerable evidence that stroke early in childhood is more detrimental to overall intellectual ability than stroke later in childhood (Jacomb, Porter, Brunsdon, Mandalis, & Parry, 2016; Studer et al., 2014; Westmacott et al., 2010), highlighting the vulnerability of the immature brain. However, the relationship between age at stroke and intellectual outcome appears to be complex and mediated by other variables such as lesion location. For example, Westmacott and colleagues studied a large group of 145 children with arterial ischemic stroke (Westmacott et al., 2010) and found that subcortical lesions were most detrimental to intellectual outcome when they occurred in the perinatal period, whereas cortical strokes were

Table 16.3 Summary of notable neuropsychological outcomes and common difficulties following pediatric stroke

Domain	Notable neuropsychological outcomes
Intellectual ability	Generally low-average to average Poorer outcomes associated with larger lesions, younger age at stroke, and older age at assessment
Language	Delayed onset of language Slower rate of grammar acquisition Spared vocabulary and comprehension Word finding difficulties and simpler sentence structure
Visual-spatial ability	Left hemisphere injury = feature processing deficits Right hemisphere injury = pattern configuration deficits Mild to severe impairment that is persistent
Sensory motor	Deficits in stereoagnosis Hemiparesis in arm and hand contralateral to lesion Apraxia, weakness, spasticity, impaired dexterity Cerebral palsy in approx. 40% of perinatal cases Motor tracts capable of reorganization to compensate for motor loss. However, little plasticity in sensory cortex leads to persistent sensory deficits
Learning and memory	Verbal memory deficits (subtle, non-lateralized): Reduced encoding, less use of learning strategies to enhance recall, and reduced delayed free recall and recognition
Executive functioning and attention	Deficits in sustained attention, inhibitory control, working memory, and mental flexibility are particularly common
Academic achievement	Deficits in math, spelling, and reading are common Estimated 30% diagnosed with learning disability Left hemisphere injury linked to reading difficulties
Social-emotional functioning	Subtle deficits in facial affect recognition, especially with parietal lobe involvement Estimated 40% struggle with internalizing or externalizing problems Difficulty navigating social situations (making attributions and understanding the role of social context)

most detrimental to intellectual outcome when they occurred in early childhood (1 month to 5 years). Other studies have found a non-linear relationship between age at stroke and intellectual outcome. For example, Allman and Scott (2013) found that stroke in early childhood (1–5 years of age) resulted in a better intellectual outcome than stroke at earlier or later ages. Everts et al. (2008) reported peak intellectual resilience for those with stroke between 5 and 10 years of age. These conflicting findings likely reflect factors such as lesion size, age at assessment, and extent of neurological deficit that are not consistently accounted for across these studies. While there appears to be a general trend toward poorer overall intellectual outcome associated with earlier the age at stroke onset, the relationship is complex and multi-determined. Moreover, determinants of outcome may differ depending on the specific cognitive ability in question.

Another trend in the literature is that large lesions (i.e., encompassing multiple lobes), bilateral lesions, and lesions involving both cortical and subcortical struc-

tures are most likely to be associated with poor intellectual outcome at school age compared with outcomes of strokes classified as small, and strokes that are isolated to either subcortical or cortical structures (Ballantyne, Spilkin, Hesselink, & Trauner, 2008; Studer et al., 2014; Westmacott et al., 2010). Moreover, children with stroke and seizure disorders exhibit significantly poorer intellectual ability than those with stroke alone (Studer et al., 2014), and children with more severe neurological impairment tend to perform more poorly from a cognitive standpoint than those with milder neurological deficits.

Sex differences are also found. Males demonstrated poorer intellectual outcomes compared with females with similar strokes (Westmacott, Macgregor, Askalan, & Deveber, 2009). Finally, there is evidence of emerging deficits over time, with older age at assessment associated with poorer intellectual performance and slower than expected rates of skill development (Westmacott et al., 2009). However, other studies have suggested a significant amount of stability in intellectual ability over time (Ballantyne et al., 2008; Jacomb et al., 2016). Further investigation is warranted to explore the manner in which these factors interact to determine intellectual outcome following pediatric stroke.

16.3.7 Language

Left MCA strokes in the perinatal period do not typically result in persistent aphasic disorders, as commonly occur in adults. Early language milestones are often achieved more slowly for children with perinatal stroke, but equally so for those with left and right hemisphere lesions (Dennis, 1998). Moreover, core language skills, including vocabulary and comprehension, tend to be age-appropriate by school entry. The resilience of speech and language function in the event of early stroke has been attributed to enhanced plasticity of the young brain. However, there is growing evidence to suggest later-developing challenges with complex language skills, commonly found in verbal fluency and word retrieval, grammatical expression, discourse processing, and narrative expression, which are particularly pronounced in children with left hemisphere perinatal strokes (Reilly, Wasserman, & Appelbaum, 2013). In contrast, however, strokes impacting classic left hemisphere language areas later in childhood may result in acute aphasic deficits similar to that seen in adults. Because left hemisphere cortical lesions in later childhood are exceedingly rare, the nature and extent of the associated aphasic deficits are poorly understood. Although younger children do tend to recover more quickly from acute-stage language deficits than older children or adults, many go on to develop problems with more sophisticated language skills as they get older, such as narrative discourse, written expression, and verbal fluency (Reilly et al., 2013). An assumed enhanced plasticity of the young brain does not guarantee a more positive outcome is not explanatory, particularly if compensatory mechanisms are ineffective or disrupt the development of higher-level skills. The functional neuroimaging literature on language reorganization following pediatric stroke remains sparse. Increased

recruitment of right hemisphere regions during language task performance is reported, even greater to an extent than documented in similar studies of stroke outcomes in adults (e.g., Cao, Vikingstad, George, Johnson, & Welch, 1999; Ilves, Tomberg, Kepler, et al., 2014; Westmacott, Mcandrews, & de Veber, 2017). However, one study (Raja Beharelle et al., 2010) found a positive correlation between left frontal lateralization and language function in individuals with a history of left perinatal stroke, even though the group as a whole showed increased right hemisphere lateralization relative to controls. Thus, children with perinatal and early childhood stroke show a remarkable amount of cognitive resilience with respect to the development of core language skills, but higher-level verbal abilities are often negatively impacted, and there is evidence to suggest that persistent left hemisphere lateralization is associated with better outcome.

16.3.8 Visual-Spatial Ability

Research on visual-spatial processing carried out in children with perinatal stroke often finds that visual-spatial and visual-motor skills are more profoundly impacted than verbal abilities (Everts et al., 2010). Moreover, lateralized cerebral effects are more consistently documented in visual-spatial ability than in verbal ability. Stiles et al. (2008) reported a double-dissociation in visual-spatial processing, such that children with right hemisphere perinatal stroke exhibited deficits in global processing (i.e., the overall Gestalt), whereas those with left hemisphere perinatal stroke exhibited deficits in local processing (i.e., the details). These findings are consistent with the adult stroke literature showing lateralized effects in global and local processing. Children with early right hemisphere stroke also showed poorer strategy use and slower improvement with practice on an "impossible house" task of visual-spatial organization compared with children with early left hemisphere stroke. These data were interpreted as evidence for the limited capacity of the developing brain to reorganize visual-spatial processing following early right hemisphere injury (Stiles et al., 2008).

16.3.9 Learning, Memory, Attention, and Executive Function

Verbal learning and memory challenges follow pediatric stroke involving either cerebral hemisphere. High incidences of attention and working memory difficulties were documented following pediatric stroke (Fuentes, Westmacott, Deotto, deVeber, & Desrocher, 2016; Jacomb et al., 2016; Max et al., 2003). In a sample of 29 children with pediatric stroke, Max and colleagues (Max et al., 2003) found that 46% met criteria for a diagnosis of ADHD, and were associated with lesions of the ventral putamen and the mesial prefrontal and orbitofrontal cortex (Max et al., 2003). Interestingly, ADHD diagnosis was not associated with lesion size, laterality,

age at stroke, age at assessment, or family history. ADHD was associated with intellectual and academic deficits. More recently, a study involving a clinical sample of children with pediatric stroke found a much lower incidence of ADHD, but again demonstrated increased cognitive and academic deficits as compared to those with similar strokes but no ADHD. With respect to EF, deficits occurred frequently following pediatric stroke, both on psychometric measures and behavioral reports of everyday functioning (Roberts et al., 2016). Long and colleagues reported EF deficits in children with pediatric stroke independent of intellectual ability. There was a trend toward greater deficit following lesions that involved frontal and basal ganglia regions. This was consistent with the broader EF literature, but deficits were present even in those who had other brain lesions, and earlier age at stroke was associated with increased executive dysfunction (Long et al., 2011). Finally, given the important role of EF in academic performance, particularly in mathematics, it was of interest that academic ability was an area of particular vulnerability for children who had a stroke (Jacomb et al., 2016).

16.3.10 Social-Emotional Functioning

Quality of life is poor for many children with a history of pediatric stroke, though recent studies indicate that the majority do well with respect to social participation, mental health, and family relationships (Greenham et al., 2015; Neuner et al., 2016). Several risk factors for poor quality of life and social participation have been identified, including significant neurological deficit, low overall intellectual ability, sex (with females experiencing worse outcome than males), older age at stroke, and larger lesion size. Recent research has highlighted the critical importance of family functioning, parent mental health, and parent education in promoting social competence in children and reducing internalizing problems (Greenham et al., 2015).

16.4 Sickle Cell Disease

16.4.1 Epidemiology and Pathophysiology

Sickle Cell Disease (SCD) is genetic blood disorder with an autosomal recessive inherence pattern. It is most prevalent among those of African, Caribbean, and Mediterranean descent. There are several different subtypes of SCD, but all involve abnormalities in the hemoglobin molecule within red blood cells that is critical for oxygen transportation throughout the body. Abnormal hemoglobin results in polymerization of the red blood cells into an elongated, rigid, and sickled shape, making them less effective at carrying oxygen. Moreover, sickled red blood cells break down more quickly than they can be replaced and they tend to stick to the walls of

the blood vessels and each other, resulting in clots and narrowed blood vessels. As a result, the vascular system works less efficiently, placing the individual at elevated risk for hemolytic anemia, stroke, pain crises, chronic infections, and organ damage caused by vaso-occlusive episodes that can occur anywhere in the body (Ashley-Koch, Yang, & Olney, 2000; Hassell, 2010; Steiner & Miller, 2006). On average, individuals with SCD have one pain crisis per year, though this varies tremendously across individuals (Rees, Williams, & Gladwin, 2010).

In the United States, SCD has an estimated incidence of 2000 infants per year, including 1 of every 365 newborns of African descent (Hassell, 2010). Worldwide, the incidence is over 300,000 infants each year—the vast majority in Africa, India, and the Middle East. The most common genotypes of SCD in the United States are HbSS (sickle cell anemia, 65%), HbSC (sickle cell hemoglobin C, 25%), and HbSβ-thalassemia (sickle beta thalassemia, <10%). All subtypes have associated medical complications, though they tend to be less severe in the case of HbSC. Sickle cell trait (HbSA) is considered a carrier state, and occurs when an individual has only one affected allele. HbSA is not associated with increased risk for neuropsychological deficits, but may be associated with increased risk of stroke (Alexy et al., 2010; Daly, Kral, & Brown, 2008; Hassell, 2010). In North America and Europe, life expectancy for those with SCD has increased dramatically over the past 50 years due to universal screening of newborns and improvements in the safety and efficacy of medical management (e.g., blood transfusions, treatment of infections, screening for cerebrovascular disease). Subtypes and terminology related to SCD are outlined in Table 16.4.

Infants with SCD often do not manifest any symptoms in the first few months of life because they continue to produce an abundance of a fetal hemoglobin (HbF), which acts to protect the sickle hemoglobin. HbF can effectively transport oxygen through the body during these early months, preventing the later complications associated with the disease. However, HbF production begins to dwindle a couple of months after birth, and affected infants start to manifest symptoms such as anemia, infection, colic-like behaviors, and feeding problems. The majority of individuals with SCD experience medical complications throughout their lifespan including chronic pain, jaundice, and organ damage. Moreover, the risk of stroke is significantly elevated in children with SCD, and estimated to be more than 200 times that of unaffected children (Farber, Koshy, & Kinney, 1985; Ohene-Frempong et al., 1998). Indeed, SCD is the second most common cause of childhood stroke after CHD, and it is the most common cause for those of African descent. The HbSS genotype has the highest rate of stroke and other neurovascular complications, and overt strokes are most likely to occur in children between 2 and 5 years of age (1020 per 100,000) (Ohene-Frempong et al., 1998). After 10 years of age, strokes in the context of SCD are more likely to be hemorrhagic than ischemic. Even in the absence of overt clinical stroke, the rate of "silent" strokes (subclinical infarcts that are present on MRI but not associated with clinical symptoms or deficits) is extremely high. It is estimated that 27% of children with SCD have silent infarcts before 6 years of age (Kwiatkowski et al., 2009) and 37% before 14 years of age (DeBaun, Derdeyn, & McKinstry, 2006). Silent strokes often occur early in life and

Table 16.4 Sickle cell disease subtypes and terminology

Name	Description
Beta-globin	Protein needed to make normal hemoglobin (hemoglobin A); on chromosome 11
Hemoglobin	Molecule within red blood cells that carries oxygen. Individuals with SCD having abnormal hemoglobin (hemoglobin S)
Sickle cell anemia (HbSS)	Most common genotype of sickle cell disease; homozygous condition in which both alleles for beta-globin are abnormal
Sickle cell hemoglobin C (HbSC)	Heterozygous condition in which one allele codes for hemoglobin S and one allele codes for hemoglobin C (another type of abnormal hemoglobin). Symptoms are similar to HbSS though generally less severe
Sickle beta thalassemia (HbSβ)	Heterozygous condition in which the individual has one sickle allele and one beta thalassemia allele. Symptoms and treatment are similar to HbSS, though neurological and neuropsychological outcome tends to be more favorable
Sickle cell trait (HbSA)	Individual is a heterozygous (only one affected allele), meaning he/she is a carrier for SCD but not affected personally
Hemolytic anemia	Condition in which red blood cells are destroyed and removed from blood system before they can be replaced; common in SCD and associated with cognitive deficits
Fetal hemoglobin	Hemoglobin F—primary protein that transports oxygen in the fetus; persists until 6 months after birth, allowing babies with SCD to experience few symptoms in the early months
Silent stroke	Small infarcts present on MRI (usually impacting white matter) but not associated with overt neurological symptoms or deficits
Vaso-occlusive crisis	Sickled red blood cells obstruct blood flow and restrict blood flow to various organs in the body, leading to pain and possibly also ischemia or other organ damage
Chronic transfusion therapy	Regular (usually monthly) blood transfusions to increase the proportion of healthy red blood cells and decrease the proportion of sickled red blood cells. Used to reduce risk of stroke and other complications from SCD

the incidence decreases significantly after 10 years of age. In fact, one study reported that 13% of infants between 10 and 18 months of age had evidence of silent strokes on brain imaging. A brain MRI showing silent white matter infarcts in an adolescent with SCD is presented in Fig. 16.2. Silent infarcts typically involve the deep white matter of the frontal and parietal lobes, and although not associated with focal neurological deficits, they have been found to be associated with a variety of cognitive challenges (Daly et al., 2008; Schatz, Brown, Pascual, Hsu, & DeBaun, 2001; Schatz, Finke, Kellett, & Kramer, 2002). Interestingly, one study found evidence of reduced white matter integrity using diffusion tensor imaging in children with SCD, even when no silent infarcts were reported on traditional brain MRI. Moreover, reduced white matter integrity in the cerebellum and right frontal lobe was associated with poorer performance on tests of information processing speed (Scantlebury et al., 2011). In addition to cerebrovascular complications, lung function may be compromised in SCD. Individuals are at elevated risk for sleep apnea, which can

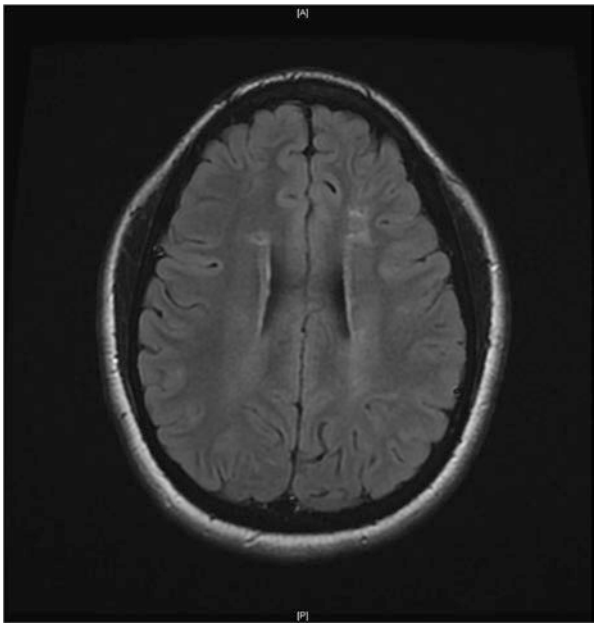


Fig. 16.2 "Silent" white matter strokes in a 16-year-old adolescent with sickle cell disease

result in reduced oxygen saturation, thereby increasing the risk of pain crises, acute chest syndrome, and stroke (Kirkham & Datta, 2006).

16.4.2 Treatment and Rehabilitation

Universal newborn screening for SCD is widespread across the United States and Canada, and this has transformed healthcare and significantly extended the expected lifespan for affected individuals. Diagnosis is made much earlier, allowing for more systematic monitoring and treatment of associated medical complications. Transcranial Doppler (TCD) monitoring, using duplex criteria, is used routinely to measure velocity of blood flow in the carotid and basilar arteries, and has been found to be a sensitive predictor of ischemic stroke in children between 2 and 16 years of age. TCD monitoring, however, does not appear to effectively predict the risk for silent infarction (Strouse, Lanzkron, & Urrutia, 2011). Abnormal TCD measurements lead to the initiation of chronic blood transfusions (usually on a monthly basis) to reduce the proportion of sickled cells, and this has been found to significantly reduce the risk of an initial stroke (Debaun & Kirkham, 2016). However, there is evidence to suggest that once a child has had one stroke, chronic transfusions do not reduce the risk of recurrent strokes (Debaun & Kirkham, 2016; Wang, 2007), and these children are usually placed on daily aspirin for secondary stroke prevention. Although most children with silent infarcts on MRI do not go on to have overt clinical strokes, they are at elevated risk compared to children with

SCD and normal MRIs (Debaun & Kirkham, 2016; Wang, 2007). In addition to chronic transfusion and stroke prevention, newer treatments for SCD include hydroxyurea medication to increase the proportion of hemoglobin F and stem cell transplants, which, in rare cases, can effectively cure this condition by intervening at the stage of cell production (Debaun & Kirkham, 2016).

16.4.3 Neurological and Neuropsychological Outcome

Even in the absence of overt stroke, children with SCD are at elevated risk for a variety of neuropsychological challenges (Wills, 2013). The Cooperative Study of Sickle Cell Disease (CSSCD) involved serial cognitive testing of children with SCD and normal MRIs, and revealed emerging deficits in verbal intellectual ability, psychomotor speed, and mathematics over a 5-year time period (Wang et al., 2001). This suggested that neuropsychological morbidity is a common manifestation of the physiological effects associated with disease presence. Other studies have found that chronic hemolytic anemia in children with SCD is associated with lower performance on measures of intellectual ability, academic ability, attention, and executive function as compared to controls (Ruffieux et al., 2013; Schatz, White, Moinuddin, Armstrong, & DeBaun, 2002; Steen et al., 2003a; Steen et al., 2003b), and severity of anemia (as measured by hematocrit levels) has been found to predict the extent of intellectual compromise (Hogan, Pit-ten Cate, Vargha-Khadem, Prengler, & Kirkham, 2006; Steen, Xiong, Mulhern, Langston, & Wang, 1999). Chronic brain hypoxia has been suggested as the likely mechanism by which anemia impacts neuropsychological function (Steen et al., 1999). Indeed, a recent meta-analysis found significantly reduced intellectual ability (7 points lower) in children with SCD and normal MRIs compared with controls (Kawadler et al., 2013). Moreover, nocturnal hemoglobin oxygen desaturation and sleep-disordered breathing has been associated with increased EF difficulties in children with SCD (Hollocks et al., 2012). The physiological process of vaso-occlusion in SCD also results in an inflammatory response that is chronic and systemic throughout the body (Manwani & Frenette, 2013; Rees et al., 2010). The combination of hemolytic anemia and chronic inflammation has been hypothesized to impact cognitive functioning, and specifically episodic memory, in SCD by disrupting hippocampal functioning (Iampietro, Giovannetti, & Tarazi, 2014). This hypothesis has support from the animal literature (de Deungria et al., 2000) and studies with adults who experience chronic hypoxia for other reasons (e.g., sleep apnea, high altitude exposure) (Ju et al., 2012; Virués-Ortega, Buela-Casal, Garrido, & Alcázar, 2004), but it has not been investigated directly in the SCD population.

Children who have evidence of silent infarcts on MRI tend to have more pronounced neuropsychological deficits than those with normal brain imaging, though less significant deficits than in those with overt clinical stroke (Armstrong et al., 1996; Brown, Armstrong, & Eckman, 1993). In addition to lower intellectual ability, children with silent infarcts have been found to have greater difficulty with

selective attention, sustained attention, and working memory (Schatz & Roberts, 2005; Schatz, White, et al., 2002). There is some evidence to suggest lateralized effects of silent infarcts, such that left hemisphere white matter density correlated with verbal IQ and right hemisphere white matter density correlated with performance IQ (Baldeweg et al., 2006). Other biological factors shown to be associated with poorer cognitive outcomes in SCD include growth delays, poor nutrition, and male sex (Knight, Singhal, Thomas, & Serjeant, 1995; Puffer, Schatz, & Roberts, 2010; Vichinsky et al., 2010). There is also some evidence to suggest worsening cognitive challenges over time, perhaps due to the cumulative effects of chronic brain hypoxia and school absences (Schatz, White, et al., 2002). However, findings have been mixed, with other studies failing to support the notion of emerging cognitive deficits in children with SCD and silent infarcts (Noll et al., 2001; Steen et al., 1999).

In addition to considering hematological and neurological factors that impact neuropsychological functioning, it is also imperative to recognize the importance of social and environmental factors (Wills, 2013). SCD is a chronic disease associated with frequent hospitalizations, pain crises, and medical appointments, which interferes with school attendance and social participations. In fact, chronic pain crises have been found to directly impact cognitive functioning (Moriarty, McGuire, & Finn, 2011). Children with SCD tend to perform more poorly than their peers in core academic areas, including reading, spelling, writing, and math, and they are frequently identified as having learning disabilities and even retained a grade in school (Kawadler et al., 2013). Moreover, the medical complications of the disease create significant emotional and practical stress for the child and family, resulting in a reduced emphasis on learning goals (Moskowitz et al., 2007). Low socioeconomic status, low parental education, and low levels of parental involvement are also frequently reported in the SCD population, and have been associated with poorer cognitive function among affected children (Boulet, Yanni, Creary, & Olney, 2010; Farber et al., 1985; King et al., 2014).

In light of these critical environmental factors, a major criticism of many studies has been the failure to use an appropriate control group for comparison. In order to draw meaningful conclusions about the impact of the disease on cognitive functioning, the study group and control group should be identical on all variables not under examination (Kawadler, Clayden, Clark, & Kirkham, 2016). It has been argued that sibling controls are ideal, as they share many of the critical environmental factors known to impact neuropsychological performance (e.g., socioeconomic status, parent education, genetics, etc.)., many studies rely on normative data from the Wechsler intelligence scales, which may not provide a fair comparison as they are not matched on these factors (Steen et al., 2003a; Steen et al., 2003b; White & DeBaun, 1998). However, deficits in intellectual ability, academic ability, visual-motor ability, attention, and executive function have been found even when appropriately matched control groups have been used (Hijmans et al., 2011).

16.5 Moyamoya Disease

16.5.1 Epidemiology and Pathophysiology

Moyamoya disease is a rare neurovascular disorder that involves progressive occlusion of the intracranial internal carotid arteries and their primary branches (Smith & Scott, 2010). Stenosis typically starts in the distal portion, progresses to involve the proximal anterior cerebral artery and middle cerebral artery, and later may also extend into the posterior circulation system. The primary mechanism of pathology involves endothelial hyperplasia, thickening of the intima, and tortuosity of vessels (Smith, 2009). Some newer research suggests that inflammatory processes may also be involved (Mejia-Munne, Ellis, Feldstein, Meyers, & Connolly, 2017). The term moyamoya comes from a Japanese expression meaning "a hazy puff of smoke," which was first used in 1969 to describe the characteristic appearance of abnormally dilated collateral vessels on cerebral angiogram or MR angiogram (Suzuki & Takaku, 1969). These moyamoya collaterals form in response to chronic ischemia in efforts to increase blood perfusion to brain tissue. Figure 16.3 depicts the chronic white matter ischemia in the border zone between the MCA and ACA territories, and the dilated collateral vessels typical of moyamoya disease.

Prevalence of moyamoya is highest in East Asia, with estimates of 1 in 100,000, and lower within Europe and North America (Kuriyama et al., 2008). It is twice as common in females compared to males (Nagaraja, Verma, Taly, Kumar, & Jayakumar, 1994). There is a bimodal age distribution, with peak periods of initial presentation in the first and fourth decades of life (Suzuki & Kodama, 1983). In most documented cases, moyamoya is idiopathic. However, a smaller proportion of cases occur in the context of some other medical condition or syndrome, such as neurofibromatosis type 1 (NF1), SCD, or Down syndrome. These latter cases are typically distinguished from idiopathic moyamoya disease and considered to be moyamoya syndrome. The neurological course and angiographic appearance of these two entities are extremely similar (Smith, 2009).

In children, the initial symptoms of moyamoya are most often recurrent transient ischemic attacks (TIAs, 80%), though 40% present with ischemic stroke (Rhee & Magge, 2011). TIAs may occur following episodes of crying, coughing, or hyperventilation because the already compromised cerebral blood flow is further reduced by vasoconstriction of vessels. TIAs tend to decrease in frequency a few years after disease presentation. Other presenting symptoms include headaches and seizures. Ischemic strokes are most common in children, whereas hemorrhagic strokes are most common in adults. Moyamoya typically involves both cerebral hemispheres. Some studies indicate approximately 18% of cases present with unilateral disease, though the majority of these progress to bilateral involvement with 1–2 years (Smith & Scott, 2010). For this reason, children with unilateral presentation are monitored carefully for progression.

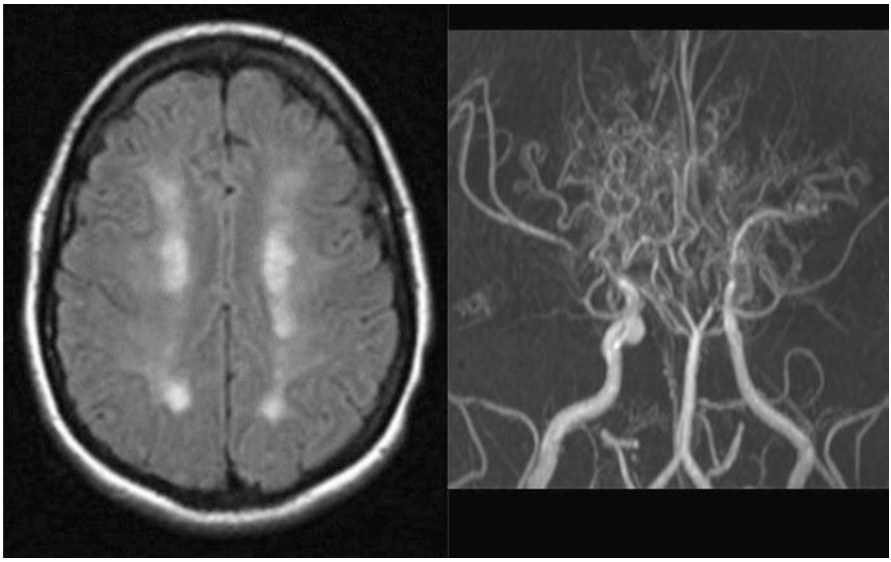


Fig. 16.3 Chronic ischemic deep white matter injury in a 12-year-old child, and extensive moyamoya vessels shown on magnetic resonance angiography

16.5.2 Etiology and Risk Factors

Much remains unknown about the etiology of moyamoya, but both genetic and environmental factors appear to play a role. The fact that the disease is particularly predominant among certain racial and ethnic groups suggests an important role for genetics, as do findings of familial occurrence (Søgaard & Jørgensen, 1975). There is also evidence from chromosomal linkage studies suggesting that the HLA gene on chromosome 6 may be linked with moyamoya disease. Moreover, there is a higher incidence of moyamoya disease among individuals with other genetically transmitted disorders, such as NF1, Down syndrome, SCD, and Fanconi anemia. Several acquired or environmental factors have also been associated with increased risk of moyamoya, including history of cranial irradiation for treatment of tumors involving the head and neck (e.g., optic glioma, craniopharyngioma, medulloblastoma), infectious illness, altered expression of mitogens, and angiogenic factors (Bitzer & Topka, 1995; Kestle, Hoffman, & Mock, 1993; Malek, Connors, Robertson, Folkman, & Scott, 1997).

16.5.3 Treatment and Neurological Outcome

Much about the natural course of moyamoya disease remains unknown but there appears to be significant individual variability in the rate of progression and severity of neurological complications. Some individuals exhibit very gradual disease pro-

gression, with few complications and periods of remission during which they are symptom-free. Others experience overt clinical strokes early in the disease and severe neurological deficits as a result. Little is known about the long-term prognosis of individuals with moyamoya. Prognosis appears to depend on the rate of disease progression (i.e., vascular occlusion), the effectiveness of the compensatory network of collateral vessels, age at presentation, severity of disease at diagnosis, and extent of cerebral infarction (Smith, 2009; Smith & Scott, 2010).

A minority of individuals with moyamoya remain in stable neurological condition without treatment, but most require neurosurgical intervention at some point during the progression of the disease. Several different surgical procedures have been developed to manage the disease and prevent major strokes, but there is currently no definitive treatment that permanently stops its progression and lifelong monitoring is generally required (Baaj et al., 2009). If the disease is diagnosed early, timely surgical intervention is often recommended as a prophylaxis rather than waiting until significant ischemic damage has occurred. However, for many individuals, the initial presentation is a clinical stroke, and permanent neurological deficits are common.

There are two main classes of revascularization surgery: indirect (non-anastomotic) bypass techniques and direct (anastomotic) bypass techniques. Indirect techniques are most often used in children and include pial synangiosis (connection of a scalp blood vessel to the surface of the brain), encephaloduroarteriosynangiosis (EDAS, the blood supply of the scalp is transferred directly to the brain), and encephaloduromyosynangiosis (EDMS, the blood supply of a muscle under the scalp is transferred directly to the brain). All of these procedures have been found to have a high rate of success, though like any surgical procedure involving the cerebrovascular system, they do carry a risk of stroke (Baaj et al., 2009). Moreover, it takes approximately 3–4 months following surgery for new collateral vessels to form and perfuse the brain, and the risk of stroke continues to remain elevated during this period. The most common direct procedure is extracranial-intracranial (EC-IC) bypass (connection of an artery that typically supplies the scalp to an artery that directly supplies the brain), though there are many different variants on this. Combinations of indirect and direct procedures are often used as well (Ibrahimi, Tamargo, & Ahn, 2010).

16.5.4 Neuropsychological Outcome

The neuropsychological literature on moyamoya is much less extensive than the other conditions discussed thus far, though with increased understanding of the underlying neuropathology there has been greater attention directed as studying cognitive outcomes in this population. Most of the research to date has focused on overall intellectual ability, with consistent evidence of moderately decreased average performance for children with moyamoya disease compared to healthy controls (Hogan et al., 2006; Hogan, Kirkham, Isaacs, Wade, & Vargha-Khadem, 2005;

Isono et al., 2002; Williams et al., 2012). Imaizumi, Imaizumi, Osawa, Fukuyama, and Takeshita (1999) followed a group of 38 children with moyamoya over time and found evidence of emerging intellectual challenges 5–10 years following the onset of symptoms, but performance stabilized thereafter. Similarly, Hogan et al. (2005)) found lower than expected verbal IQ and performance IQ in a group of 15 untreated children with moyamoya at the time of initial assessment, as well as significant standardized score declines (i.e., emerging deficits) when followed up over time. It has been suggested that chronic disruption of normal hemodynamic patterns is the most likely mechanism for the cognitive deficits seen in children with moyamoya who have not sustained cerebral infarction (Smith, 2009; Smith & Scott, 2010; Suzuki & Kodama, 1983).

A more recent study of 30 children with moyamoya who had not undergone surgery revealed lower overall intellectual ability in the patient group compared with the standardization sample, though the group mean still fell at the low end of the average range (Williams et al., 2012). Parent rating of executive function also indicated significantly greater difficulties in the patient group. Interestingly, depressed intellectual functioning and EF concerns were observed regardless of the presence or absence of associated medical conditions (e.g., NF1, SCD) or stroke. That is, children with moyamoya without any evidence of clinical stroke or silent infarction still showed intellectual and executive function deficits. Bilateral disease was found to be more detrimental to intellectual and executive functioning, and longer duration of moyamoya symptoms was associated with slower information processing speed.

The importance of early treatment has also been demonstrated in multiple studies. For example, Matsushima, Aoyagi, Nariai, Takada, and Hirakawa (1997) found that moyamoya disease with onset before 2 years of age was associated with poor cognitive outcome if left untreated. Those with onset between 2 and 5 years of age showed better outcome if they were treated before 9 years of age. A recent study of 65 children who underwent surgical treatment for moyamoya found generally age-appropriate intellectual performance prior to surgery and maintenance of this strong performance following surgery (Lee et al., 2011). Moreover, significant improvements were noted in post-operative performance on tests in which speed was a scoring criterion. Importantly, this study did not include a control group that would have made it possible to determine if intellectual performance was statistically significantly lower than a group of matched peers. Most other studies examining pre-surgical and post-surgical cognitive performance in children with moyamoya have involved small samples of case studies, and findings have been mixed regarding the stability of performance over time (Kuroda et al., 2004; Kuroda & Houkin, 2008; Matsushima et al., 1997). Centers that treat children with moyamoya are now starting to routinely collect pre- and post-surgical neuropsychological data, which will allow for systematic study of questions related to stability of cognitive performance and impact of treatment.

Finally, there has been little investigation of mental health outcomes in moyamoya, but a recent study by Ball, Steinberg, and Elbers (2016) reported poor quality of life in a group of 30 children. Chronic headaches were reported by 70% of chil-

dren with moyamoya and stroke, and 60% of those with moyamoya but no stroke. Educational support was received by 55 percent of those with stroke and 10% of those without. Furthermore, parent and child ratings indicated significantly decreased social participation and emotional health compared to healthy children. Ratings for children with moyamoya disease were similar to those for children with other types of chronic medical conditions. More research is needed to understand the impact of moyamoya disease on neurocognitive and psychosocial functioning. In particular, it would be of interest to investigate whether or not specific regional brain dysfunction can be more specifically detected using advanced neuroimaging techniques, and if these vulnerable regions could be associated with adverse neurocognitive and/or functional outcomes. In addition, studies could examine whether or not age at onset, disease severity, and/or parent and family coping styles influence psychosocial outcome in children and adolescents with moyamoya disease.

16.6 Developmental Considerations

A prediction of neuropsychological outcomes of any disease or disorder in a child or adolescent can be difficult. This is especially true for those with a neurovascular condition. The difficulty arises in relation to several independent yet interrelated factors. Heterogeneity is inherent across the many diagnoses of neurovascular disease making summary conclusions from group studies inappropriate in consideration of the outcome for any one individual. An intricate interplay occurs between factors such as the direct effects on brain structure and function, and the critically important influences of the socioenvironmental milieu, to determine how a child or adolescent will adapt and mature in the presence of an atypical course of development and in response to an underlying pathophysiology. Which brain regions are disrupted or damaged, the extent of morphological damage, age at onset, and duration of illness all contribute to outcome. These are further influenced by the treatment course, associated complications (e.g., seizures), effects of prescribed medications, associated symptoms such as pain and headache, secondary medical complications such as anemia, and any iatrogenic factors that may further interfere. This broad range of factors has the potential to adversely affect neuropsychological performance and complicate predictions about eventual outcome. As we show above, CHD, SCD, and moyamoya disease all increase the risk of stroke, yet each is defined by its own unique risk for neurocognitive deficit. Nonetheless, one unifying feature across these conditions may be hemodynamic failure that occurs consonant with an actively developing brain.

Neuropsychological assessment provides an objective foundation for understanding a child's cognitive and behavioral profile. It is a process that takes into account a child's personal and medical histories, and documents a recovery course that facilitates treatment planning and educational programming that is sensitive to prepotent developmental influences. Interpretation is based on patterns of data at a single time point that can be compared over multiple time points in order to monitor

a child's developmental trajectory and assist with prediction of long-term outcome (Baron, 2004; Dennis et al., 2014).

Several unique considerations arise in pediatric neuropsychological assessment. First, brain–behavior relationships evolve over a dynamic course of development, and assessment data must be interpreted in context with these changing dynamics. Second, the impact of an early focal lesion will evolve gradually over time, and this is not always predictable. Clinicians can help parents make the connection between their child's current struggles and the remote brain injury, while also educating parents, academic personnel, and other professionals who have the capacity to positively alter a child's trajectory with interventions, accommodations, and styles of interaction. Third, longitudinal follow-up is often essential in pediatric populations. An initial assessment can assist in documenting recovery of lost skills and providing a baseline for later follow-up, but the nuances of the child's cognitive profile often do not become clear until higher-level skills have started to develop (Dennis et al., 2014). Fourth, many children with neurovascular conditions have focal sensorimotor deficits that must be accommodated during an assessment and considered when findings are interpreted. A stroke impacting the dominant hand often results in switched hand dominance, the ramifications of which remain poorly understood (Kirton, Westmacott, & deVeber, 2007). Fifth, pediatric neurovascular conditions are under-recognized and poorly understood by the general population, and even within some healthcare settings (Rafay et al., 2009). The neuropsychologist must assist in educating family members and teachers about the impact of injury in the developing brain and advocate for access to services within the education system and the broader community. Finally, the transition to adult care can be challenging and overwhelming for patients and families. It may be difficult to find a neurologist working in adult disease who has experience working with young people impacted by neurovascular conditions, whose needs are quite different from older adults with similar medical conditions (Dyer, Yau, & Westmacott, 2009). Neuropsychological outcomes in pediatric vascular conditions highlight the vulnerability of the developing brain, and the idea that neuroplasticity can be adaptive or maladaptive, depending on a variety of individual factors.

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Chapter 17
Functional Brain Imaging in Stroke Patients

Chris Rorden and Hans-Otto Karnath

17.1 Introduction

Neuroimaging already plays a crucial role in the initial assessment of stroke patients. Different types of scans can reveal different properties of the brain that can be combined synergistically to guide initial treatment. In addition, these different modalities hold the potential to impact the long-term prognosis. While traditional structural scans locate the extent of the injury, other modalities such as functional imaging can help assess the extent of disruption which may be far more extensive than the core lesion visible on anatomical scans. For example, a brain region that appears structurally intact following injury may be functionally compromised because it has insufficient blood flow to function correctly (misery perfusion), has been disconnected from other regions, or relies on information from a distant region that has been injured. In all these cases, functional imaging can provide information not available from structural scans.

Indeed, functional imaging acquired in healthy individuals has already transformed our understanding of the human brain. Therefore, one might expect that functional imaging will have the same transformative impact in our understanding of stroke. Here, we temper this enthusiasm, noting some of the challenges and limitations associated with functional imaging of stroke. The aim is to provide a balanced and informed foundation for understanding the potential for this method. While we clearly recognize the potential for this modality in stroke patients, the method must be used carefully, and the findings must be interpreted in context of the inherent limitations of this technique.

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_17

Brain imaging has had a profound impact on acute stroke management. Both computerized tomography (CT) and magnetic resonance imaging (MRI) can help differentiate ischemic and hemorrhagic injury, and both from other neurological events that may have similar behavioral presentation to a stroke. Further, acute stroke management already leverages the fact that different imaging modalities provide complementary information regarding injury. A concrete example of this synergy comes from the combination of diffusion and perfusion measures in hyper-acute stroke management. Diffusion images acquired at the patient's admission can reveal lost tissue. On the other hand, perfusion images that measure blood flow can identify tissue at risk. Taken together, these two modalities can suggest tissue that might be salvaged by intervention as well as helping to more accurately predict eventual lesion size. For this reason, the diffusion-perfusion mismatch has helped refine standard of care, leading to, e.g., the rationale for thrombectomy for large vessel occlusion.

Beyond these well-established benefits for acute care, brain imaging in stroke holds great promise for both theoretical and clinical questions. Analyzing the territory of brain lesions can provide intrinsic knowledge into the function of the human brain. Since Broca's time many of our insights regarding cognitive function have come from observing the consequences of brain injury. Textbook descriptions of human language, memory, emotion, motor control, and perception have all had their foundation in neuropsychology. A skeptic could argue that brain injury had an impact in Broca's era simply because it was the only method available. Today, we have numerous methods that allow us to observe the healthy human brain directly and non-invasively. Thus, it seems that modern neuroscientists should focus on healthy humans to make inferences about brain function. However, even in modern times analyses of brain lesions still provide an indispensable method (Rorden & Karnath, 2004). Brain injury can provide a perspective of normal brain function that is not possible merely from observing healthy brain function. First, brain injury helps identify regions that are required rather than merely associated with cognitive functions (Rorden & Karnath, 2004). In contrast, brain activation techniques—such as functional MRI—in healthy humans are unable to distinguish between regions that are correlated versus those that are necessary for a given function. As an analogy, observing the brain is like listening to a highly trained orchestra, where it can be hard to distinguish the contribution of a single musician because the whole network of the symphony is working together in concert. In contrast, if one section (say, violins) stops playing we can become aware of their contribution to the network. Observing how a network is disrupted can prove a powerful tool for understanding the interactions of the network. While there are some non-invasive methods that can transiently disrupt normal brain function (e.g., Transcranial Magnetic Stimulation [TMS] and Transcranial Direct Current Stimulation [tDCS]), these methods can only target certain regions and have a relatively subtle and brief effect (for review, e.g., Beaulieu, Flamand, Massé-Alarie, & Schneider, 2017; Horvath, Forte, & Carter, 2015; Lage, Wiles, Shergill, & Tracy, 2016; Shin et al., 2012; Woods et al., 2016). While we do not claim that stroke provides a superior method to understand the healthy brain, we do think it provides a complementary tool.

Contemporary cognitive neuroscience relies on numerous tools, each with a unique set of strengths and limitations. In this context, understanding the consequences of brain injury can fill an important niche.

Beyond these clear theoretical insights, neuroimaging can impact clinical care. First of all, one of the most salient questions of patients, their family, and their doctors is the amount of recovery expected. Brain imaging can improve the quality of prognosis, identifying which individuals are likely to get better spontaneously, those that will benefit from a specific treatment and those where compensation may prove more beneficial than attempts to recover lost skills (e.g., Basilakos et al., 2014; Hope et al., 2017; Karnath, Rennig, Johannsen, & Rorden, 2011; Lunven et al., 2015; Naeser et al., 1998). In the same way that contemporary genetics can help optimize cancer treatment, we envision that brain imaging will help select optimal therapy. Better prognosis can also improve clinical trials, more accurately matching patients who are receiving different treatments based on their expected level of recovery (and thereby increasing statistical power). Finally, brain imaging can help guide brain stimulation, ensuring that stimulation is applied to intact portions of eloquent cortex. Since the location of injury varies across patients, one may want to maximize the likelihood that the stimulation is being applied to a spared region that is involved with the task, rather than destroyed tissue. Alternatively, one might want to target regions that are distant from the injury but where changes in response to a behavioral task are predictive of good outcome. While functional imaging can aid all of these questions, this final implication uniquely relies on measuring the residual brain's function because this information cannot be inferred directly from other modalities.

Modern MRI can acquire a broad range of modalities that are able to reveal different properties of the human brain. Diffusion measures can not only detect acute injuries, but it can also be used to assess the integrity of the white matter connections. Structural measures like fluid-attenuated inversion recovery (FLAIR) can reveal the structural extent of a brain injury. Furthermore, FLAIR imaging can help identify if the individual has signs of other pathology such as white matter hyperintensities that can be predictive of poor stroke recovery (e.g., Bahrainwala, Hillis, Dearborn, & Gottesman, 2014). These general measures of brain health may provide biomarkers for cognitive reserve, which can aid prognosis and treatment.

The focus of this chapter will be on neuroimaging measures of brain function, which can identify brain regions where activity levels are modulated by specific task demands. For example, if we ask an individual to read a text while we acquire functional scans we can identify brain areas that respond to visual stimuli and language comprehension.

17.2 Measuring Blood Flow in the Human Brain

There are several neuroimaging modalities that can measure blood flow in the human brain. In the acute stroke, contrast enhanced perfusion methods are popular for both magnetic resonance imaging (MRI) and computerized axial tomography

(CT, CAT). In these methods, a contrast agent (e.g., gadolinium) is injected into the bloodstream. One can then trace the speed and concentration of this bolus as it enters the brain. This can show regional cerebral blood flow as well as the amount to time it takes the bolus to transit through the tissue. In addition, one can measure the latency for the bolus to reach different parts of the brain (time to peak). These methods often reveal acute pathological perfusion that can be distant from the site of the injury (diaschisis). Since these measures are directly related to the functional disruption, they supplement the information deriving from structural imaging in their attempt to identify the neural basis of behavioral disorders after stroke. Thus, contrast perfusion not only can provide reasonably accurate measures of eventual lesion extent; it also may play a pivotal role in understanding acute brain injuries.

The bolus used for these measures generates a strong signal, so one can rapidly acquire an image of perfusion, which—in a clinical context—is ideal for eligibility for thrombolysis/thrombectomy in which the interventions are time limited. Despite these benefits, these contrast-based methods essentially only provide a snapshot of blood flow and thus do not allow us to measure subtle changes that occur as the brain switches from doing one behavioral task to rest or to a different behavioral task. For this latter purpose, which typically arises from research questions in cognitive neuroscience aiming at understanding normal brain function, we need to rely on methods that allow us to continuously acquire a relatively stable measure of blood flow. Specifically, arterial spin labeling (ASL) and blood oxygenation level dependent (BOLD) MRI provide us this possibility, i.e., to infer task-related brain activity.

For arterial spin labeling (ASL), a radiofrequency pulse is used to tag blood in the extracranial carotid artery. We can compare this brain scan to an identical brain scan where the tag is not applied, and continuously acquire these pairs of labeled and unlabeled scans. The only difference between these paired scans is whether a label was applied in the carotid artery, so differences between the images reflect blood that has moved from the neck to the brain. Note that this is conceptually similar to the gadolinium bolus: we now leverage the fact that our label will influence the image signal when it arrives in the brain. One advantage of ASL, however, is that this labeling method uses the blood itself as a tracer and does not require a contrast agent, allowing continuous acquisition of these images. ASL has started to prove its value in acute stroke care, but it can also be used to observe changes in blood flow that occur following brain activity.

Another blood flow measure allowing us to infer task-related brain activity is blood oxygenation level dependent (BOLD) MRI, which is often referred to as functional MRI (fMRI). Like gadolinium, deoxyhemoglobin has a local influence on the MRI signal. Changes in metabolic demand modify the relative concentration of deoxyhemoglobin. Therefore, one can infer that changes in MRI signal reflect changes in brain activity. Unlike ASL, we do not need to create a label: we leverage the fact that the concentration spontaneously varies with metabolism. Instead of a label, we acquire a scan where the image intensity is influenced by oxygen levels (often referred to as a T2* contrast). We thus can detect increases and decreases in oxygenation levels.

If measuring task-related changes in brain activity, ASL and fMRI measure largely the same signal. The main challenge with ASL in that context is that one must carefully pace the labeled and unlabeled images: one must provide a sufficient delay for the tagged blood to get to the brain, yet not wait so long that it has already left. The ideal post-label delay varies with many factors including age. In contrast, fMRI scans can be acquired much more rapidly, which is useful for modeling dynamic changes in the brain and is the reason why BOLD fMRI remains more popular than ASL in that context. While there are different strengths and weaknesses for fMRI and ASL, we wish to emphasize that each of these techniques is measuring the same core changes for task-related activity. For brevity, and due to its current relative popularity, we tend to use "fMRI" to describe functional brain imaging in general (and "BOLD fMRI" when we are attempting to distinguish T2* fMRI from ASL).

Contrast enhanced MRI tells us how much blood is getting to parts of the brain, and how long the blood requires to get there. In contrast, fMRI is interested in how blood flow changes in response to brain activity. Note that these two can dissociate. While enhanced MRI identifies regions with abnormal blood flow, fMRI identifies areas where the region modulates flow based on task demands. A region might have normal perfusion but may not show a fMRI signal for several reasons. For example, the region may never have had any role with that task, such as primary somatosensory areas that are directly involved with touch but are not involved with low level visual perception. Therefore, one would not expect to see activation changes in somatosensory regions in an fMRI task we compare activity during rest to a visual task. In this case, the somatosensory cortex may be intact, but its activation is not modulated by the task. Furthermore, a region may not generate fMRI signal because it is destroyed. On the other hand, a region that is intact may not generate a fMRI signal if it is disconnected from its network or if it relies on information from a distant node that has been injured. Therefore, when we do observe significant regional activation changes, we can infer that these regions are not only receiving sufficient blood flow to function, but they are connected to a task-relevant network. A crucial aspect to fMRI is that we will see different patterns of activity based on the task used. So, memory, language, finger tapping, perceptual, etc. tasks will each make unique demands on the brain and elicit different networks to respond. Therefore, any inference drawn from fMRI requires examining the task(s) used to elicit responses.

Indeed, an optimal fMRI experiment is not designed to generate the maximum sustained brain signal. Rather, the goal is to generate the most predictable change in brain activity. Again, we are not attempting to determine whether a region is getting blood flow (recall that the BOLD fMRI is an inherently poor measure of overall signal). Rather, we want to measure the dynamic changes that occur in response to task demands. A nice analogy is to think of a key—one could easily pick a lock for a key that is completely flat with no grooves. However, it is unlikely that a random key will fit a lock with a complicated shape of grooves. Likewise, an efficient fMRI study is designed to generate large, predictable changes in brain activity—brain areas that show precisely this complicated pattern of fluctuations are likely to be

involved with this task. So, the next obvious question is how does blood flow change with the response to a task? From first principles, one might intuitively think that brain activity cause metabolism, and metabolic demands would cause a local decrease in blood oxygenation (e.g., neural firing depletes the oxygen in the blood). Surprisingly, this effect is not what we look for in fMRI studies. Rather, blood supply to a particular brain area increases in response to demand, so about 5 s after brain activity we find that previously activated regions become oxygen rich. While paradoxical, empirically this effect is remarkably reliable and forms the basis for our statistical predictions. Specifically, to "cut our key" we simply look at the different times when an individual was performing a task and assume that brain regions related to this task will show increased oxygen about 5 s later (the "hemodynamic response"). This relationship is often referred to as the neurovascular coupling. Our model is driven by two empirical observations: the hemodynamic response is sluggish (it peaks several seconds after brain activity) and that it is additive (more brain activity generates a bigger response). Therefore, an optimal fMRI task has the particpant perform a specific cognitively intensive task for a period of a few seconds, and contrasts this with periods where the person rests or executes a different but similarly demanding task. We can then look throughout the entire brain to identify regions that fit our predicted pattern of sluggish and additive response.

17.2.1 The Dilemma with Measuring Hemodynamic Response in Individuals with a Stroke Lesion

The discussion of the hemodynamic response outlined above has crucial implications for translating fMRI paradigms to stroke patients. First of all, the fMRI signal is inherently a very indirect measure of brain activity. Techniques like single cell recording, electroencephalogram, and magnetoencephalogram can rapidly and directly detect the firing of neurons. In sharp contrast, with fMRI we are measuring a physiological response that occurs seconds after the firing. An important question is whether the alterations in blood flow following stroke can disrupt the neurovascular coupling. Whereas we typically see more signal in healthy humans in seconds after brain activity, stroke injury often leads to chronic changes in blood flow. The interpretative dilemma that arises from this fact is that we cannot decide whether the failure to detect the hemodynamic response in these individuals is clearly attributable to the inability to perform the task. Given the indirect nature of the hemodynamic response, one needs to ask whether absence of evidence is evidence of absence. Considering our key analogy, it is possible that stroke disrupts the amplitude of the hemodynamic response, analogous to the grooves not being as distinct or deep. With more subtle effects, it will be harder to detect regions that are truly responding. Likewise, one could expect that the hemodynamic response may exhibit abnormal latency, analogous to the grooves being cut in the wrong place so our prediction (key) does not match our observed data (the lock). One could also conceive of interactions between these effects. For example, if a cognitive task requires

a few seconds to complete, the initial firing would be normal, but if the magnitude of the hemodynamic response is insufficient to meet the sustained metabolic demands over a longer period (due to misery perfusion), then function will start to degrade (with subsequent changes in demands). Therefore, while fMRI has proved remarkably reliable in healthy adults, from first principles it may prove problematic in stroke patients. In the next section, we examine evidence that directly investigates this concern.

Consider commute times as an analogy for the neurovascular coupling. In most normal cities, commute times are modulated by demand, with it taking longer to get to work during periods of peak demand. However, consider a situation where several lanes of a freeway are closed, restricting traffic flow. In this case, the restriction may be the rate-limiting factor for the commute time, rather than the demand. Conversely, consider a city where most citizens are evacuated due to a storm threat. In this case, the freeways have an excess capacity, and the remaining individuals may have similar commute times regardless of time of day. These same principles may influence neurovascular coupling. In situations of misery perfusion, the chronically restricted blood flow may not be able to increase to meet demands. In the case of increased perfusion, the death of neighboring regions may mean that there is an overabundance of blood flow in the remaining intact areas, regardless of behavioral task performed. These possibilities suggest the need for empirical evidence regarding whether brain injury can attenuate the traditional fMRI signal.

17.3 fMRI in Stroke Patients

In recent years, several studies have investigated acute/subacute stroke patients with different fMRI paradigms (e.g., Baldassarre et al., 2014; Carter et al., 2010; Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Fridriksson, Baker, & Moser, 2009; Fridriksson, Richardson, Fillmore, & Cai, 2012; He et al., 2007; Saur et al., 2006; for reviews see Crosson et al., 2007; Hamilton, Chrysikou, & Coslett, 2011; Karnath, Sperber, & Rorden, 2018; Thompson & den Ouden, 2008). Some of these studies were designed to compare BOLD activity in different regions of interest between the patients' lesioned and the non-lesioned hemisphere. A common observation in such studies has been an imbalance of BOLD signals in the structurally intact tissue of the damaged relative to the non-damaged hemisphere. For example, Corbetta et al. (2005) examined 11 stroke patients with profound spatial neglect in the acute period of a right hemisphere stroke and observed reduced BOLD signal in intact attention specific regions of the damaged hemisphere relative to homologous regions of the non-damaged hemisphere. Likewise, Saur et al. (2006) examined 14 patients who recovered from acute aphasia after a left hemisphere stroke. Acute and subacute fMRI indicated an initially decreased signal in language-specific areas of the damaged hemisphere, followed by increased BOLD signal in both the damaged and the intact hemisphere. fMRI of these patients in the chronic period showed a reduction of this abnormal BOLD response pattern that was accompanied by lan-

guage improvement. On the basis of their respective findings, both studies thus concordantly concluded that the patients' disrupted behavior (i.e., the impairments in attentional orienting (Corbetta et al., 2005) or in language processing (Saur et al., 2006)) depended on more than the neuronal loss at the site of injury; they assumed that, in addition, the patients' disrupted behavior was causally linked to this abnormal BOLD signal in distally located, structurally intact tissue (via connections to the infarcted tissue). As noted above, however, a general concern for fMRI-based studies in stroke patients is that the local hemodynamics (i.e., the neurovascular coupling) might be abnormal in a damaged brain, i.e., that abnormal BOLD responses might not only reflect functional disruption. fMRI relies on a BOLD measure. The increased metabolic demands trigger a net increase in local oxygen. As we have described, this relationship between brain activity and subsequent oxygen influx may be disrupted following brain injury. First of all, consider the case of misery perfusion, where the injury leaves a very constrained blood supply. In this case, the blood flow may not be able to increase following metabolic demands. On the other hand, consider increased perfusion, where the destruction of neighboring regions may result in a blood supply that far exceeds the needs of the remaining tissue. In this case, neural activity might not require a change in blood flow, as the basal state is in excess of the demands of the tissue. In both these cases, neurovascular coupling may not function as it does in a healthy brain. As the BOLD response fundamentally relies on an increase in regional blood flow after a transient increase in neuronal activity (Ogawa et al., 1992; Ogawa, Lee, Kay, & Tank, 1990), BOLD responses have unsurprisingly been shown to be abnormal in stroke patients with impaired cerebrovascular reactivity (e.g., Amemiya, Kunimatsu, Saito, & Ohtomo, 2012; Carusone, Srinivasan, Gitelman, Mesulam, & Parrish, 2002; Krainik, Hund-Georgiadis, Zysset, & von Cramon, 2005; Murata et al., 2006; Röther et al., 2002).

A recent study analyzed the anatomical localization of these effects in relation to lesion location. de Haan, Rorden, and Karnath (2013) explored the BOLD signal in acute stroke patients while they performed a simple visual orientation judgment task. Each patient's normalized lesion shape was dilated into 12 adjacent 3 mm perilesional regions expanding 39 mm beyond the structural brain lesion's rim (Fig. 17.1). Analysis highlighting voxels that observed significant task-related changes thus resulted in 12 (perilesional) regions reflecting task responsive voxels for both the intact left and the damaged right hemisphere. For each patient, this percentage signal change was compared to the percentage signal change in the same voxels in the control subjects. The authors observed an abnormal interhemispheric balance consisting of reduced signal change in perilesional areas of the damaged hemisphere relative to homologous areas in neurologically healthy controls, unrelated to the patients' behavior. This suggests that the physiological changes and corresponding interhemispheric imbalance detected by fMRI BOLD in acute stroke observed close to the lesion border may not necessarily reflect changes in the neural function, nor necessarily influence the individuals' behavior. In other words, abnormal BOLD responses in stroke patients could not only reflect functional disruption but also a decoupling of the neurovascular response (without changes in neuronal functioning and/or in the individuals' behavior), or a combination of these two

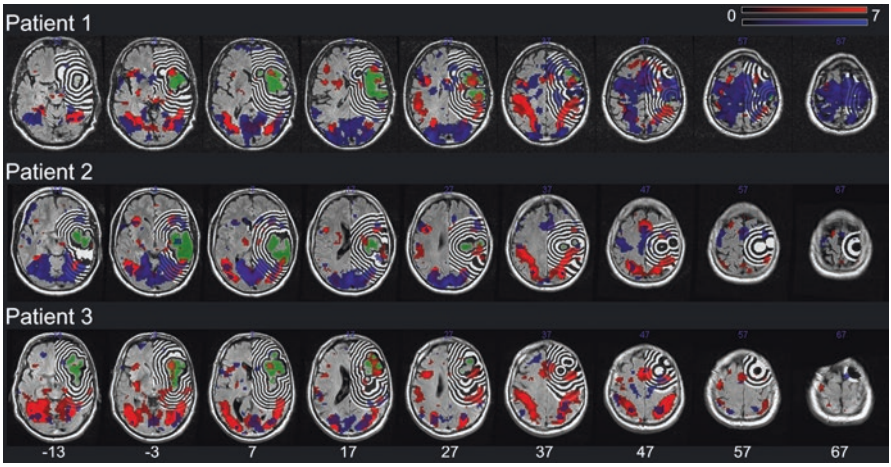

Fig. 17.1 Illustration of the fact that abnormal BOLD responses in stroke patients do not only reflect functional disruption but also a decoupling of the neurovascular response (without changes in neuronal functioning and/or in the individuals' behavior). BOLD signal in acute stroke patients while they performed a simple visual orientation judgment task. Each patient's structural brain lesion (green) was dilated into 12 adjacent 3 mm perilesional regions expanding beyond the structural brain lesion's rim. Additionally shown are the results of the statistical analysis highlighting the voxels showing significant task-related changes in the individual patient (blue) as well as the group of control subjects assigned to the respective stroke patients (red). Results revealed an abnormal interhemispheric balance consisting of reduced signal change in perilesional areas of the damaged hemisphere relative to homologous areas in neurologically healthy controls, unrelated to the patients' behavior. (From de Haan B, Rorden C, Karnath H-O. [2013]. Abnormal perilesional BOLD signal is not correlated with stroke patients' behavior. Frontiers in Human Neuroscience, 7, 669)

effects. Compounding these effects, studies in chronic patients using ASL demonstrate reduced perfusion not only in perilesional regions but also extending further into the ipsilesional hemisphere (Richardson et al., 2011). This reduced perfusion may be associated with misery perfusion, but also suggests there may be a weaker baseline signal for fMRI to detect. While we have focused on our own findings, it should be noted that other teams have also reported attenuated BOLD response in individuals with stroke (for review, see Lake, Bazzigaluppi, & Stefanovic, 2016).

17.4 Consequences of Disrupted Hemodynamic Response by Stroke

The finding of attenuated BOLD response in individuals with stroke unrelated to the patients' behavior has clear consequences that should be carefully considered. First, neuroscientists need to exercise caution when interpreting BOLD data acquired in stroke patients; fMRI protocol cannot be executed as if the data were acquired from

healthy subjects. Second, absence of BOLD activity is only meaningful in areas of the brain that are clearly distant of the structural brain lesion.

This latter concern has profound implications. Effectively, the work outlined above (de Haan et al., 2013; Richardson et al., 2011) suggests that we will often have poor perilesional sensitivity in stroke patients if using fMRI. Yet, the perilesional regions are typically the most critical to recovery. For example, an individual who enrolls in aphasia treatment has damage to portions of their language system. One could expect that recovery is often mediated by the surviving parts of the damaged module. For this reason, for transcranial brain stimulation studies, we often want to target the perilesional eloquent cortex. Unfortunately, we may have very poor ability to detect fMRI activation precisely in these regions, due to the attenuated BOLD response in these regions (see above).

A challenge in describing these shortcomings is that they must be weighed against the clear potential offered by functional brain imaging to impact stroke. Indeed, despite our concerns that fMRI has low sensitivity in perilesional regions, we have used fMRI to, e.g., guide transcranial brain stimulation (Fridriksson et al., 2018). However, it may be that relying on fMRI biased us to select more distant targets for the application of tDCS in that study. Perhaps this is not an important concern in the specific context of guiding brain stimulation in a large network, namely the language network: stimulation applied to any portion of the distributed network may propagate to other regions. In this case, identifying any nodes may be sufficient for effective treatment. According to this model, different brain regions work in concert, and it might not matter which node we stimulate, rather what is important is we stimulate some functional node somewhere even if this node is located more distant to the structural brain lesions. From this perspective, the role of neuroimaging is to ensure we do not target a destroyed area, rather than select between the residual nodes. In this case and in the specific context of guiding the locus of application in transcranial brain stimulation, the poor perilesional sensitivity of fMRI (de Haan et al., 2013; Richardson et al., 2011) is not so much of a concern, as long as we are working with a large, distributed network (as with the language system) that has other distant nodes we can identify.

So far, the issues with the influence of lesion on fMRI signal have been described in the context of studies that focus on individuals, such as choosing a personally tailored stimulation site for applying transcranial brain stimulation. However, challenges also arise when using fMRI in group studies that attempt to find general patterns of stroke patients with a deficit. Before describing some of the dangers for applying these approaches to stroke populations, we will describe the traditional approach of group fMRI analyses performed with healthy individuals. This approach would be as follows: First, we conduct statistics within each individual, identifying how likely each location is involved in a given task. Second, we warp every participant's brain to have the same size and shape as a common template brain. Third, after all individuals' images have been warped to the same space, we can compare whether the activity in each area of the brain is consistently involved with the task across our group. The first step involves the same concerns regarding the neurovas-

cular coupling that we have already addressed. The second and third steps face their own concerns with regard to stroke populations. We will discuss these steps in turn.

As noted, group analyses require us to "normalize" the size and shape of each person's brain so that they are all in alignment. Here, all of the images are co-registered into a common space, allowing us to compare the same anatomical location across our participants. This step can be disrupted by the lesion characteristics of the brain injury itself. Automated methods of normalization attempt to make a brain look like a "normal" brain. This normalization procedure is straightforward in a healthy human brain but can be disrupted by a structural defect. For example, an automated method might shrink a lesion and expand the surrounding intact perilesional regions into the lesion territory. Mathematically, this approach does indeed make the brain appear more "normal," but it artificially distorts the size and location of the brain injury. There are several modifications to the normalization step that can address this problem. First, if working in the acute setting one can leverage the fact that brain injuries do not appear on all modalities of the admission scan. Specifically, T2-weighted B0 scans are often included as part of an admission diffusion sequence, yet recent injuries will not appear on these scans (only injuries that are at least 1 or 2 days old will be observed on T2 scans). If one has these acute scans, one can simply compute how to warp the healthy appearing scan to match the normal template image. Once these transforms are computed, they can be applied to the other modalities (Mah, Jager, Kennard, Husain, & Nachev, 2014). This approach of using the healthy appearing T2 scan for warping, however, is not possible for studies of patients with a post-stroke interval of more than 2 days (the infracted brain does no longer appear "healthy" on T2 scans). There are two other approaches that can be considered. Since brain injury is typically unilateral, we can estimate what the person's healthy brain looked like if it is assumed that the brain is roughly symmetrical in humans (which it is actually not exactly). Under this assumption, healthy homologous tissue is inserted in the damaged territory of the opposite hemisphere (Nachev, Coulthard, Jäger, Kennard, & Husain, 2008) and we can use this "simulated healthy" brain for the normalization process. Again, once computed, these transforms can be applied to the real scans that show the injury. A final approach for normalization of individuals with stroke is to mask the lesion so it does not contribute to the warping estimates, ideally using a template from an aged-match population that has similar anatomical features (Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012). To summarize, while the normalization step can be disrupted by lesions, there are several available methods that can allow robust normalization.

The final step of group analyses is to identify brain locations that reliably respond to the behavioral performance in a given task across a population of individuals. While there are variations of this approach (e.g., Saxe, Brett, & Kanwisher, 2006), this base strategy remains the bread and butter of most fMRI group analyses. There are a couple of potential problems faced when adapting this approach to stroke participants. First, since each individual has a different pattern of brain injury, at some locations we will be examining locations that are intact in some of our participants and damaged in others. We need to expect that destroyed tissue will not show a fMRI BOLD response to our task. The challenge is that we are confounding the

location of the structural brain injury and its functional consequences. This makes inference difficult: Does reduced fMRI activation in a group at a given location reflect changes in structure or function? While methods have been described that attempt to identify individual variations in module location for group studies (Poldrack, 2007; Saxe et al., 2006), these methods are rarely applied in practice. At the very least, one expects low statistical power in group fMRI studies of stroke participants, so that we will need to conduct large studies and may often miss real effects. We do suggest two approaches to tackle this issue. First, one could conduct an analysis in which each voxel is restricted to include data only from those with intact tissue at that location. The structural scans can help map the lesion and look for lesion-related effects, while the masked fMRI data could provide information about brain function. To date, we know of no fMRI studies in stroke patients that have applied this approach. Another solution is specific to longitudinal studies that map changes in brain function. Here, one can compute a regression analysis to detect voxels that change their activation in response to training. For example, finding voxels where increased activity from baseline to follow-up indicates behavioral improvements. In this case, one expects that an individual with injury at a specific location will show little task-based activity at either time point and therefore statistically significant effects are driven by those who have intact cortex at the given location. This approach is described by Fridriksson (2010) but has not been widely adopted yet.

One more popular response to this conundrum is to restrict group-based fMRI analyses to the intact hemisphere. This has two potential advantages. First, one expects the hemodynamic response to be less altered, at least in the subacute/chronic phases of stroke. Once acute diaschisis has resolved, the hemodynamic response in the contralesional hemisphere should be relatively normal (though see Lake et al., 2016). Second, individual variability in lesion location does not necessarily mean that a particular area is unable to show a hemodynamic response simply due to the fact that the neural tissue at this location got infarcted. If fMRI analyses are restricted to the intact hemisphere, none of the voxels examined are destroyed. Likewise, while the location of injury will certainly influence the pattern of recovery and brain response, none of the voxels entered into the statistical test are at locations with structural injury. This is certainly a principled approach to the issue and can yield insights regarding the extent of plasticity. However, it does necessarily mean abandoning attempts to make inference about functional changes in the injured hemisphere. However, even then, findings from such studies can prove tricky because changes in fMRI signals in the undamaged hemisphere might reflect either inhibitory or excitatory mechanisms. For example, is the increased activation observed in the right hemisphere of aphasia patients maladaptive or beneficial for recovery? This is a general problem in fMRI: brain activation reveals areas involved or related to, but not necessarily required for a given task. However, it becomes amplified in situations where we are seeing stroke-related changes of fMRI activity in regions not classically associated with successful behavioral performance of the task under study. As we emphasize in the next section, the proper response is that fMRI should

be used in conjunction with other neuroscientific methods (in general, but in particular) if investigating patients with stroke lesions.

17.5 Future Directions

Task-based functional imaging relies on neurovascular coupling: we assume that brain activation evokes a delayed but large change in local blood oxygenation. There is clear evidence that this fundamental relationship can be disrupted in stroke, in particular for perilesional brain tissue. Unfortunately, this fact reduces the impact for using fMRI to understand stroke. It is difficult or can even be impossible to infer if observations of reduced signal reflect reduced activity related to the task of interest or simply are due to reduced neurovascular coupling. Despite these concerns, we feel that fMRI can still aid our understanding of stroke. For example, BOLD activity can be meaningfully interpreted if (1) only voxels are included in the analysis which correspond to structurally intact brain tissue and if (2) inferences regarding reduced signal are only meaningful for voxels, which are clearly distant from the brain lesion (e.g., are from the undamaged hemisphere). Moreover, task-based fMRI can be a reasonable approach for identifying brain stimulation targets in stroke patients. Regions where the image brightness is significantly correlated with the task of interest remain good candidates for successful treatment. In this case, we have clear fMRI evidence that these regions are involved in the task of our interest, although we cannot be certain that this region is also necessary for this task. However, as we have noted, nodes that are merely involved with a task may provide good conduits for modulating task critical nodes.

A crucial realization is that each method used in neuroscience has its own set of strengths and limitations. We espouse honestly identifying the weakness of each modality and leveraging different modalities with complementary strengths and weaknesses. For example, we can conduct multivariate analyses by using machine learning algorithms that look for unique patterns within each modality. These methods can use multiple sources of information to generate accurate prognoses. For example, information such as age at time of injury, time since injury, genes, and different imaging modalities can be combined. The classifier can implicitly learn the independent information described by each of these biomarkers. This view suggests that despite limitations, fMRI in stroke patient may provide an independent predictor for outcome. By leveraging the unique information from each biomarker, we can generate better predictive models than using each in isolation. The primary concern with this approach is that such studies are necessarily expensive and time consuming. The breadth of predictors can require a large sample size to ensure a sufficient training set for the machine learning algorithms.

Acknowledgements This work was supported by the National Institutes of Health (P50DC014664) and the Deutsche Forschungsgemeinschaft (KA 1258/23-1).

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Chapter 18
Neuropsychological Rehabilitation

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18.1 Introduction

Cognitive impairment after stroke is common and can significantly hinder recovery of function and return to functional activities and roles. With an aging population and a decline in mortality rate post-stroke, addressing cognitive impairments in stroke survivors is of critical importance. The umbrella term vascular cognitive impairment (VCI) encompasses the continuum of cognitive impairment of cerebrovascular origin, ranging from mild impairment (with no significant impact on functional abilities) to vascular dementia (see Chap. 6). Management of individuals with impairments in cognition, affect, or behavior varies depending on the severity of the

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_18

deficits and the functional consequences. Review of the evidence for rehabilitation of individuals with focal cognitive deficits post-stroke is the focus of this chapter. In this chapter, we define cognitive function broadly as interacting modular mental systems either containing and/or acting on domain-specific knowledge representations (e.g., language, spatial function, calculations).

What is cognitive rehabilitation? Most definitions converge on the idea that cognitive rehabilitation is a systematic, therapeutic process designed to remediate, alleviate, or manage cognitive deficits in order to improve daily functioning (Cicerone et al., 2000, 2011, 2019; Sohlberg & Mateer, 2001a; Wilson, 2002). Cognitive processes frequently affected by stroke include attention (e.g., focusing, shifting, dividing, or sustaining attention on a particular stimulus or task), visuo-perceptual abilities (e.g., visual search, drawing), memory (e.g., recall and recognition of verbal and visual information), language (e.g., receptive and expressive), and executive function (e.g., planning, organizing, and inhibition). In this chapter, we provide an overview of the evidence for the efficacy of procedures targeted towards rehabilitation of these cognitive deficits after stroke. While each cognitive domain is discussed in separate sections, it should be recognized that the cognitive processes involved in attention, memory, language, and executive functions interact in complex ways (Baldassarre, Ramsey, Siegel, Shulman, & Corbetta, 2016). Given the shared neural circuitry implementing these cognitive processes, stroke survivors commonly have multiple deficits that may interact with the rehabilitation process. In addition, brain damage induced by stroke also commonly affects social, behavioral, and emotional functioning and all of these domains should therefore be addressed as part of the management plan (Eskes et al., 2015). This chapter will focus on the rehabilitation of focal cognitive deficits but it is important to note that collaborative and interdisciplinary team work is increasingly recognized as fundamental to delivering effective care that will respond to the multiple and complex needs of stroke survivors (Clarke & Forster, 2015).

18.1.1 Impact of Cognitive Deficits Post-Stroke

While a comprehensive review of post-stroke cognitive deficits is outside the scope of this chapter (see Chap. 19), we first briefly summarize the impact of common deficits on stroke recovery and outcome. Post-stroke deficits in attention, executive function, language, memory, visuospatial processing, and speed of processing are common both in the acute and rehabilitation phases (Azouvi et al., 2002; Ballard et al., 2003; Demeyere et al., 2015; Hochstenbach, Mulder, van Limbeek, Donders, & Schoonwaldt, 1998; Hochstenbach, Prigatano, & Mulder, 2005; Hoffmann, 2001, Riepe, Riss, Bittner, & Huber, 2004, Stone, Halligan, & Greenwood, 1993; Tatemichi et al., 1994; reviewed in Barker-Collo & Feigin, 2006; Gillespie, Bowen, & Foster, 2006) and remain prevalent in the long term (Douiri, Rudd, & Wolfe, 2013; Ferro & Crespo, 1988; Mellon et al., 2015; Nys et al., 2005 Nys et al., 2005,

Patel, Coshall, Rudd, & Wolfe, 2003, Rasquin et al., 2004, Tham et al., 2002; Wolf & Rognstad, 2012; reviewed in Tang et al., 2018). For example, Demeyere et al. (2015) found a very high incidence of cognitive impairment (i.e., 76% of patients when using the Montreal Cognitive Assessment and 86% when using the Oxford Cognitive Screen, a recently developed stroke-specific cognitive screen) in a consecutive sample of 200 patients who were assessed within 3 weeks of stroke. The most frequent deficits were found in the domains of executive function (up to 49% of the sample) and spatial attention (up to 40% of the sample). Similarly, Park, Sohn, Jee, and Yang (2017) reported an overall rate of cognitive impairment of 83% in their sample of 104 patients who were assessed within 3 months after stroke onset. A broad range of deficits were reported with the most common being in the domains of spatial attention (63% of the sample), executive function (61%), memory (60%), and language (33%). Recent studies have also shown that these deficits persist in the chronic phase post-stroke. For example, Mellon et al. (2015) reported that over half of their sample of 256 patients of all ages were found to have cognitive impairment at 6 months post-stroke (with the weakest performance in the domains of visuospatial skills, executive function, and memory). In a systematic review and meta-analysis, Tang et al. (2018) reported an overall trend towards a significant deterioration in cognitive status in stroke survivors (i.e., cognitive functions deteriorated in eight studies, persistent but stable cognitive problems were found in three studies, and improvement in cognitive functions was found in another three studies). Finally, Douiri et al. (2013) described longitudinal data from the South London Stroke Registry including 4212 patients who were followed after first-ever stroke for up to 15 years. In this population-based study, Douiri et al. showed that the prevalence of cognitive impairment after stroke remained high over time. Among stroke survivors, the age-standardized prevalence of cognitive impairment ranged from 24% at 3 months to 22% 15 years after stroke. This study therefore showed persistently high prevalence of cognitive impairment, although these rates were lower than those described above, probably due to the screening tool used (i.e., the Mini-Mental Status Exam or MMSE) that has been shown to lack sensitivity to detect mild cognitive impairment (e.g., Pendlebury, Cuthbertson, Welch, Mehta, & Rothwell, 2010).

The impact of cognitive impairment on rehabilitation and functional outcomes has also been documented widely. The presence of cognitive impairment in general is associated with increased functional disability (Babulal, Huskey, Roe, Goette, & Connor, 2015; Claesson, Linden, Skoog, & Blomstrand, 2005; Feigin et al., 2010; Tatemichi et al., 1994; Yang et al., 2016; Zinn et al., 2004). The prevalence of disability at each year after stroke has been found to be on average twice as high for cognitively impaired patients (Douiri et al., 2013). Poor outcomes have been associated with a number of cognitive variables, including the presence of spatial neglect and related symptoms, such as anosognosia (Appelros, Karlsson, Seiger, & Nydevik, 2003; Buxbaum et al., 2004; Chen, Hreha, Kong, & Barrett, 2015; Fullerton, Mackenzie, & Stout, 1988; Gillen, Tennen, & McKee, 2005; Mark, 1993; Oh-Park, Hung, Chen, & Barrett, 2014; Paolucci, Antonucci, Grasso, & Pizzamiglio, 2001),

attention deficits (Gerafi et al., 2017; Hyndman & Ashburn, 2003; McDowd, Filion, Pohl, Richards, & Stiers, 2003; Nys, Van Zandvoort, de Kort, van der Worp, et al., 2005), deficits in working memory (Malouin, Belleville, Richards, Desrosiers, & Doyon, 2004), or verbal memory (Wade, Parker, & Hewer, 1986), and executive dysfunction (Mok et al., 2004; Park et al., 2017; Stephens et al., 2005). While the role of cognitive skills in many instrumental activities of daily living such as following a recipe, driving, or going to work seems obvious, cognitive deficits may also adversely affect physical disability via reduced response to rehabilitation (e.g., for motor skill reacquisition). For example, Cirstea, Ptito, and Levin (2006) found that arm motor skills training progress, as measured by precision and variability of performance, was correlated with memory and planning skills.

Recent longitudinal studies have confirmed that the presence of cognitive impairments in acute stroke or during the rehabilitation phase are independent predictors of short- and long-term disability. For example, Babulal et al. (2015) reported that cognitive impairment at 2 weeks post-stroke was an independent predictor of performance in complex activities required for full independence at 3 months post-stroke. Cognitive deficits post-stroke can also predict long-term functional impairments. For example, Yang et al. (2016) conducted a multi-site study involving a nation-wide sample of 893 patients and found that cognitive impairment at 3 months post-stroke was associated with disability at 5-year post-stroke. Impairment in certain cognitive domains seems to have stronger prognostic value. For example, Gerafi et al. (2017) assessed a consecutive cohort of 375 patients during the first week after admission and found that visuospatial inattention, and not language impairment, had an independent impact on long-term functional outcomes. Thus, the presence of specific cognitive impairment has wide-reaching impact and deserves early intervention.

18.1.2 Framework for Rehabilitation

Our approach to rehabilitation of cognitive disorders post-stroke is based on several principles (see Table 18.1). First, a comprehensive assessment of the cognitive profile of the individual is needed to identify strengths and weaknesses. A thorough understanding of the deficit(s), as well as identification of the preserved functions, is critical to the selection of rehabilitation techniques. This step will improve the likelihood of successful outcome and also provide important information about cause-and-effect relationships between patients, therapies, and outcomes for continued improvement of interventions. Neuropsychologists and other specialties trained in brain-behavior assessment play a key role in this first step, providing detailed assessments of affected and intact aspects of cognitive and other mental functions. Knowledge of the associations of behavioral/cognitive functions with particular brain regions is also important for determining what cognitive and neural mechanisms might be available for recruitment in a rehabilitation program. Thus, knowledge of both the neuropsychological function and neuroanatomical involvement can

Table 18.1 Factors affecting rehabilitation of cognitive function

Factors	Cognitive profile	Other psychological factors	Physical health	Environmental factors
Definition	Strengths and weaknesses that interact to produce level of functioning in a cognitive domain. Domains can include attention, memory, speech and language, visuospatial and perceptual function, executive function and limb praxis	Factors related to awareness of deficits and motivation for change (e.g., anosognosia, anxiety, and depression), disorders of conation, drive	Co-morbidities and physical issues that can impact on cognitive function, e.g., pain, fatigue, sleep disorders, delirium, sensory deficits (hearing, vision)	Physical and social contexts that can influence cognitive recovery (e.g., noise and distraction, presence of signs, cuing and feedback by spouse)

provide clinicians with the information needed to decide which rehabilitation program might be most effective.

A second principle is that the choice of intervention should be evidence-based when possible, ideally grounded on the theoretical underpinnings of the targeted cognitive system(s). Our level of understanding of the underlying mechanisms and effectiveness of rehabilitation processes has improved over the past decade due to the continuing development of imaging technology (see Cumming, Marshall, & Lazar, 2013 for a review). However, there is still a gap that remains between the development of treatments and our evolving theories of brain functions (Shigaki, Frey, & Barrett, 2014). The inclusion of theory-based interventions, well-controlled studies, and focus on relevant outcomes are highlighted as important goals for continued scientific progress in the field.

A third principle for success is that the ultimate focus of the intervention should be on patient-relevant functional goals, identified in collaboration with the stroke survivor and family. While clinical rehabilitation goals normally target daily functioning, it is important to keep in mind that outcomes have been measured at a number of levels in the rehabilitation literature. Most efficacy studies focus on changes in training performance or on different measures of the impaired domain itself (e.g., psychometric measures of cognitive abilities or neurophysiological changes such as EEG or other measures of functional brain activity). While obtaining evidence for generalization of training to other tests of the same domain is a first step, the question of whether the intervention improves daily functioning is critical for ultimate evaluation of efficacy/effectiveness. In the past decade, there has been a growing body of research exploring the use of specific cognitive rehabilitation techniques and their effect on functional outcomes, but the evidence is still limited particularly at the level of social participation and quality of life (Cicerone et al., 2019). Thus, it is often unclear if training outcomes simply represent improvements in a specific skill (e.g., due to practice) versus improved cognitive functioning per

se. Considering the generalization of learning to functional abilities is critical to our understanding of rehabilitation effects as well as improving potential clinical outcomes.

A final principle is that rehabilitation of cognitive deficits must take place in context; effective management of individuals with cognitive deficits takes into account a variety of personal and environmental factors potentially influencing cognitive function. Potential factors that can interact to influence cognitive functioning are presented in Table 18.1. While the focus of this chapter is on rehabilitation of the cognitive components, recognition and amelioration of the impact of these other factors within a multi-disciplinary setting will optimize the intervention and improve functional outcomes.

Cognitive rehabilitation processes can be grouped into one of five approaches (see Table 18.2): (1) Remediation or restoration of the damaged skill; (2) optimization of residual function; (3) compensation through substitution of remaining intact skills; (4) compensation through use of environmental supports or external aids; (5) vicariation through recruitment of functionally or structurally related brain-behavior systems. The first two approaches focus on attempting to improve the underlying impairment, with the hope of general enhancement of the damaged function. Compensatory approaches, in contrast, focus on training processes that can substitute for the damaged function—either another intact cognitive domain or by use of external devices that substitute for the function. Like compensation, vicariation engages intact cognitive processes, but unlike compensation, vicariation may engage processes irrelevant to the impaired function or task. Instead, intact cognitive processes, structurally or functionally related to the impaired brain-behavior systems, are activated so as to secondarily activate and support the impaired processes. This may occur at an implicit or procedural level, inaccessible to conventional treatment or training. A number of vicariative approaches have been proposed (e.g., intention treatment in nonfluent aphasia; Crosson et al., 2007). However, considering that more information is available on the use of remediation or compensation in clinical practice, our presentation will emphasize these approaches.

Use of remediation or compensation is not mutually exclusive and therapies may use a combination of the above approaches. While many rehabilitation techniques focus on compensation by internal or external means, there is some evidence supporting the possibility of actual restoration or optimizing of residual functions (e.g., Lillie & Mateer, 2006). A number of evidence-based reviews of cognitive rehabilitation studies in ABI are available (Cappa et al., 2003; Cicerone et al., 2000, 2005, 2011, 2019; Lincoln et al., 2002; Majid, Lincoln, & Weyman, 2000) and summaries with periodic updates are also available (Evidence-Based Review of Stroke Rehabilitation; www.ebrsr.com). Overall, more well-controlled research is needed to identify optimal cognitive rehabilitation methods. One major issue is the choice of outcome measures to evaluate generalizability, as discussed above. Other issues not yet resolved include the optimal duration and treatment intensity (Bayley et al., 2007). In addition, while we attempt to focus on evidence derived from studies of stroke survivors, more stroke-specific studies are needed. We thus included literature dealing with ABI at times, when relevant.

Table 18.2 Summary of rehabilitation approaches

Rehabilitation approach	Methods/goals	Strengths and weaknesses
Restoration of damaged function—Targets impairment	Intensive and repetitive practice and drills/ exercises to improve damaged cognitive function directly	If successful, could lead to most generalizable effects. Currently limited by atheoretical approaches, poor generalization, and lack of understanding of neurocognitive mechanisms underlying plasticity/ regeneration
Optimization of residual function—Targets impairment	Teaching of compensatory strategies to improve remaining function	Can apply to a wide range of patients and goals. Currently needs better theoretical approach and better focus on generalization; not applicable with severe deficits
Compensation through substitution of remaining intact skills—Targets functional goals	Uses alternative domain-specific processes to achieve a functional goal	Focus on functional outcome is a strength. Depends upon careful assessment of cognitive strengths and weaknesses
Compensation through use of environmental supports or external aids—Targets functional goals	Uses a range of devices and environmental supports to achieve functional goal	Wide applicability, even with severe deficits. Can require extensive training and support
Vicariation through recruitment of functionally or structurally related behavioral processes which may directly increase activation and impaired processes	Uses training techniques, exercise devices	Little direct evidence supporting this approach on distinct from compensatory approaches requires knowledge of cognitive and behavioral theory often not available to clinicians

18.2 Focal Cognitive/Perceptual Deficit Syndromes

18.2.1 Attention

18.2.1.1 Pathophysiology and Mechanisms

Attention is the faculty by which we select among various possible inputs those stimuli that will receive further processing. Posner and colleagues have developed an influential model of attention highlighting three basic functions: Vigilance (mediated by the right hemisphere and involved in achieving and maintaining an alert state); Orienting/Selection (mediated by the posterior attention network used for searching and selection of sensory information); Executive control (mediated by the anterior attention system and involved in the orchestration of complex computations, or allocation of resources in a limited capacity system; Fernandez-Duque & Posner, 2001; Posner & Petersen, 1990; updated in Petersen & Posner, 2012). Other well-known clinical models of attention also include functions related to sustaining attention over time (vigilance), selection of information, and need for control due to competing or conflicting demands (see Table 18.3) and three particular models

Table 18.3 Relationship of components of attention in three models

Posner (Posner & Petersen, 1990)	Sturm et al. (Sturm, Willmes, Orgass, & Hartje, 1997)	Sohlberg et al. (Sohlberg & Mateer, 2001a)	Behavioral symptoms
Alerting—Achieving and maintaining an alert state	Alertness (phasic): Enhancement of response readiness following a warning stimulus	Focused attention: Basic responding to specific stimuli	Reduced arousal; diminished response to input
	Vigilance: Sustained maintenance of alertness for rare events in monotonous situations	Sustained attention: The ability to maintain a consistent behavioral response during continuous or repetitive activity (includes components of vigilance and mental control)	Distractibility; difficulty in maintaining focus; attention lapses
Orienting—Selection of information from sensory input	Selective attention: Ability to focus on certain features of a task and at the same time to suppress voluntarily responses to irrelevant features	Selective attention: The ability to maintain a cognitive set in the face of distracting or competing stimuli	Spatial neglect; problems with visual search; distractibility
Executive control—Resolving conflict among responses	Divided attention: Dividing attention between two or several sources of information	Alternating attention: The capacity for mental flexibility which allows for moving between tasks having different cognitive requirements	Difficulty with interference, allocation of resources, inhibition
		Divided attention: The ability to simultaneously respond to multiple tasks or demands	

(Bundesen, 1990; Sohlberg & Mateer, 1989; Sturm et al., 1997) have formed the basis for the development and/or testing of theoretically driven rehabilitation protocols for impaired attention.

Disorders of attention are common in stroke, and impaired attention may be an important independent factor for stroke recovery (Barker-Collo, Feigin, Lawes, Parag, & Senior, 2010; Cumming, Brodtmann, Darby, & Bernhardt, 2014; McDowd et al., 2003; Robertson, Ridgeway, Greenfield, & Parr, 1997; Stapleton, Ashburn, & Stack, 2001; Tatemichi et al., 1994). Depending upon the brain region(s) affected, attentional deficits may occur in one or more components identified by Posner and colleagues (Fernandez-Duque & Posner, 2001; Posner & Petersen, 1990). Deficits in spatial attention (neglect) and non-spatial attention will be dealt with separately. There have been a number of recent reviews focused on the effectiveness of intervention for attentional impairments (Bogdanova, Yee, Ho, & Cicerone, 2016; Cha & Kim, 2013; Cicerone et al., 2019; Hoffmann, Bennett, Koh, & McKenna, 2010; Loetscher & Lincoln, 2013).

18.2.1.2 Current Research

Direct Remediation of Non-spatial Attention

There is growing evidence for a modest effect of direct computerized remediation of non-spatial attention deficits in stroke and/or mixed ABI groups, at least in the short term on untrained tests of attention, although transfer to functional improvements is still unknown. Most computerized approaches have examined daily 30–60 min sessions for up to 5 weeks, using adaptive algorithms that maintain difficulty with improved performance. Early studies by Sturm and colleagues used an attention training program (AIXTENT) that targeted four domains based on their model of attention (Table 18.3) (Sturm, Hartje, Orgass, & Willmes, 1993). In several studies of stroke survivors at 3 months—13 years post event, they reported that attention improves most from deficit-specific training (e.g., vigilance training for vigilance deficits, selective attention training for selective attention deficits), while non-specific training may even adversely affect attention functions (Sturm et al., 1997, 2002; Sturm & Willmes, 1991). Similar findings that indicate specific attention deficits benefit more from targeted training were also reported by Peers et al. (2018), in chronic stroke groups, in which selective attention training (SAT, provided by in-house training software based on the Theory of Visual Attention, TVA) or working memory training (WMT, Cogmed™) groups were compared to a wait-list control group. Thus, SAT produced significant improvement in spatial and non-spatial attention reaction time performance on a letter detection task, while working memory training (Cogmed™) was associated with improvements on at least one untrained working memory task from the Automated Working Memory Assessment (AWMA) compared to the wait-list or SAT groups. Of note, both training groups (but not the wait-list group) reported improved daily cognitive function on a self-reported everyday function measure (European Brain Injury Questionnaire, EBIQ), suggesting some functional benefit.

Attention Process Training (APT, Table 18.3) is also derived from a conceptual model of attentional functions (Sohlberg & Mateer, 1989). The APT program consists of hierarchically organized tasks that exercise different components of attention at increasing levels of complexity and task demands. Examples of these tasks include listening for number sequences, alphabetizing words heard in a sentence, detecting targets in the presence of distractor noise, or switching between complex semantic categorization tasks (Sohlberg, McLaughlin, Pavese, Heidrich, & Posner, 2000). Early APT research focused on individuals with traumatic brain injury, and Sohlberg and colleagues (Sohlberg et al., 2000; Sohlberg & Mateer, 1987) reported that APT training with brain injured individuals in the chronic recovery phases (1 year or more) experienced greater improvements in psychometric tests of attention (Paced Auditory Serial Addition Test or PASAT, Stroop, Trailmaking, Location memory) compared to a control baseline or control group receiving brain injury education. While the specific effects of the different attention training components

in the APT were not examined, the primary effects of APT overall were obtained on executive control and working memory tasks, while no training effects were seen on vigilance or orienting (Sohlberg et al., 2000). APT training in the home environment was evaluated in a study of chronic ABI (70% stroke) recovery (at least 9 months post onset; Boman, Lindstedt, Hemmingsson, & Bartfai, 2004). While performance improved on training tasks, no effects were seen on attention tasks or functional activities or self-rated quality of life. In contrast, individuals in the acute stroke phase with attention deficits were given APT training for 4 weeks and showed improved performance on an auditory-visual continuous performance task (IVA-CPT) compared to controls (Barker-Collo et al., 2009). Thus, whether the APT intervention targets specific skills or a generalized cognitive function is still unresolved (for a discussion and meta-analysis, see Park & Ingles, 2001).

A number of other computerized attention training methods have been tested in stroke, with generally positive, although limited results. Not all studies include control groups, unfortunately, and even when control groups are included in some studies, statistical comparisons between groups are lacking. With these limitations in mind, however, it appears that attentional abilities can benefit from computerized training starting at a range of time periods, from subacute (<1 month post-stroke: Kim, Chun, Kim, & Park, 2011; Prokopenko et al., 2013), early recovery (1–6 months post-stroke; Akinwuntan et al., 2010; Cho, Kim, & Jung, 2015; De Luca et al., 2014, 2018; Park, Koh, Choi, & Ko, 2013; Unibaso-Markaida, Iraurgi, Marqués, & Amayra, 2019; Zucchella et al., 2014), and chronic (Fernandez et al., 2012; Peers et al., 2018; Wentink et al., 2016; Yoo, Yong, Chung, & Yang, 2015). Improvement is usually only seen on a limited range of outcomes in any one study, however, such as digit span, visual or block span, attentive matrices, and CPT, and evidence for generalization to daily function is very limited. Thus, more and better-designed research is warranted.

In terms of other approaches, Gamito et al. (2015) used virtual reality to expose inpatients post-stroke to programmed daily life activities requiring visual search, working memory, mapping, as well as other cognitive functions and found improvements on sustained and selective attention compared to a standard care group. Other groups have examined whether transcranial direct current stimulation (tDCS) of prefrontal areas can enhance attention training (Park et al., 2013), finding more improvement on auditory and visual continuous performance tasks compared to computerized cognitive training alone.

In line with the above reports, a recent systematic review of computerized cognitive rehabilitation of attention in ABI concluded that overall, most studies support computerized cognitive rehabilitation for attention and executive function but noted a number of methodological issues that need to be addressed in future research (Bogdanova et al., 2016). A Cochrane review of rehabilitation of attention deficit post-stroke by Loetscher and Lincoln (2013) reported significant effects were limited to measures of divided attention in the short term, with lack of effects on other

attention domains or functional outcomes. Finally, a meta-analysis by Cha and Kim (2013) on the effect of computerized cognitive treatments found an overall significant medium effect size of 0.54 for both acute and chronic stroke studies, with the majority of studies including attention outcomes.

Compensatory Strategies for Non-spatial Attention Deficits

Sohlberg and Mateer (2001b) note that compensatory strategies can include environmental modifications (e.g., to reduce distraction), external aids (e.g., use of organizers), or self-regulatory strategies (e.g., orienting, pacing, key ideas log). Unfortunately, no studies have directly examined the use of compensatory strategies in subjects after stroke, although a number of studies included strategy training with direct attention remediation and reported positive results (Boman et al., 2004; Cicerone, 2002; Niemann, Ruff, & Baser, 1990; Park, Proulx, & Towers, 1999; Sohlberg & Mateer, 1987). Fasotti et al. examined the effects of teaching-specific time pressure management (TPM) strategies versus concentration training in a group of subjects in chronic recovery stages after a severe brain injury (Fasotti, Kovacs, Eling, & Brouwer, 2000). Both groups improved on tasks of speeded information processing, although the TPM group improved more and also showed more generalized benefit on psychometric tests of attention and memory. Since a non-intervention group was not included in this study, however, the benefits of strategy training per se cannot be evaluated, and specific effects of compensatory attentional strategy training warrant further study.

18.2.1.3 Clinical Applications and Future Directions

As discussed above, consistent with recommendations of previous cognitive rehabilitation reviews for treatment of stroke and ABI (Cappa et al., 2003, 2005; Cicerone et al., 2000, 2005; Lincoln, Majid, & Weyman, 2000; Teasell et al., 2006), computer-based remediation of attention deficits may be considered as an adjunct to therapist involvement (Cicerone et al., 2019). Computerized treatment or APT of domain-specific attention shows particular benefit to targeted attentional domains, although generalization to everyday functioning needs further investigation. Effective training includes a theory-based approach, with gradual increases in levels of difficulty and complexity, accompanied by feedback and reinforcement. Attention strategy training (e.g., TPM) also appears to be helpful and could be included.

18.2.2 Spatial Neglect

18.2.2.1 Pathophysiology and Mechanisms

Spatial neglect is defined as a failure to report, respond, orient, or act upon stimuli in contralesional space after brain injury, associated with functional disability (Barrett & Burkholder, 2006; Heilman, 1979). Symptoms of spatial neglect are present in up to 82% of patients acutely after stroke, and 48% during early rehabilitation (Bowen, McKenna, & Tallis, 1999; Buxbaum et al., 2004; Chen, Chen, Hreha, Goedert, & Barrett, 2015; Stone, Halligan, Marshall, & Greenwood, 1998). It is more common after right hemisphere stroke (Chen, Chen, et al., 2015; Ringman, Saver, Woolson, Clarke, & Adams, 2004) and associated with a range of failures in attending to and processing contralesional events and objects, as well as failures generating contralesional actions. The functional disability caused by spatial neglect includes errors in everyday life tasks such as dressing, bathing, eating, and mobility, associated with poor outcomes (Appelros et al., 2003; Chen, Hreha, et al., 2015; Cherney, Halper, Kwasnica, Harvey, & Zhang, 2001; Fullerton et al., 1988; Gillen et al., 2005; Katz, Hartman-Maeir, Ring, & Soroker, 1999; Paolucci et al., 2001). Despite its high prevalence after stroke, spatial neglect is undetected in more than 60% of patients during routine clinical care (Edwards et al., 2006). Without diagnosis, patients are obviously less likely to receive treatment, and they and their families also are less likely to receive appropriate management or counseling. To address this treatment gap, four recent articles from professional organizations all specified visuospatial assessment as part of a stroke practice standard (the American Heart Association: Winstein et al., 2016; the UK Intercollegiate Stroke Working Party, 2016; the American Occupational Therapy Association: Wolf & Nilsen, 2015; and the Veterans Administration/ Department of Defense, 2010). Routine mental status screening with a generic cognitive screening instrument is not sufficient to detect spatial neglect (Daffner et al., 2015).

When we identify patients with spatial neglect using a validated measure, we are likely identifying abnormalities in two distinct, closely interactive, brain networks (Goedert et al., 2012). Motor-exploratory spatial "Aiming" neglect is a *class common* disorder, demonstrated in animals across the mammalian class, from rats to primates (see Payne & Rushmore, 2004 for a review). In this syndrome, animals without hemiparesis show a spatial movement preference, spontaneously rotating or turning in one direction (Pycock, 1980; Schwarting & Huston, 1996). The behavioral-physiologic processes contributing to this symptom may be feed-forward, ballistic systems tuning spatial movement (Heilman, 2004; Riestra & Barrett, 2013). Deficits adversely affect this spatial "Aiming" motor-intentional function, altering initiation and direction of motor responses to training. This deficit is distinct from the traditionally considered perceptual-attentional "Where" spatial deficits in spatial neglect, which allow the organism to receive input from the 3-D environment. We (Riestra & Barrett, 2013) suggested that spatial "Aiming" neglect includes (1) failure to move a contralesional limb spontaneously despite intact abil-

ity to move the limb to confrontation (previously referred to as "motor neglect" or "limb akinesia"; Laplane & Degos, 1983; Heilman, 2004; Punt & Riddoch, 2006), and also 2) failure to move any body part effectively in a contralesional direction, while at the same time ipsilesional movement appears normal (directional akinesia; Barrett, Crucian, Schwartz, & Heilman, 1999; Heilman, Bowers, Coslett, Whelan, & Watson, 1985; Kim et al., 2013). Bisiach, Geminiani, Berti, and Rusconi (1990) summarized, in a classic article: "a mechanism subserving spatial aspects of motor ideation and preparation [may be] relatively independent of the sensory-based representation of the organism's environment."

Consistent with Bisiach's statement, there is strong evidence that spatial "Aiming" neglect can co-occur with relatively normal spatial perception, attention, and visual representation. In humans, we and our colleagues (Barrett & Burkholder, 2006; Barrett, Crucian, Beversdorf, & Heilman, 2001; Fortis, Chen, Goedert, & Barrett, 2011; Goedert, Chen, Boston, Foundas, & Barrett, 2014; Sacchetti, Goedert, Foundas, & Barrett, 2015) as well as numerous others (Bisiach et al., 1990; Coslett, Bowers, Fitzpatrick, Haws, & Heilman, 1990; Làdavas, 1994; Loetscher, Nicholls, Brodtmann, Thomas, & Brugger, 2012; Na et al., 1998; Nico, 1996; Tegnér & Levander, 1991) fractionated feed-forward, spatial "Aiming" errors from the more conventionally identified, spatial "Where," perceptual-attentional errors, which were feedback-dependent. Spatial "Where" neglect measured by this method was also associated with failures of stimulus detection such as extinction of contralesional sensory stimuli in the presence of matched ipsilesional stimulation (Goedert et al., 2012). Fractionable "Where" and "Aiming" spatial bias is also demonstrated as a general property of spatial performance in healthy controls (Chen et al., 2011; Chen, Erdahl, & Barrett, 2009; Fortis, Goedert, & Barrett, 2011; Galletta, Lequerica, Pekrul, Eslinger, & Barrett, 2012; Garza, Eslinger, & Barrett, 2008; Schwartz, Adair, Na, Williamson, & Heilman, 1997; Shah, Gonzalez, & Barrett, 2012) and spatial cognitive studies in patients with other neurological conditions, who did not have spatial neglect (Wagner, Eslinger, & Barrett, 2016).

Animal studies link spatial "Aiming" neglect recovery to subcortical dopaminergic activation (Andén, Dahlström, Fuxe, & Larsson, 1966; Eslamboli, Baker, Ridley, & Annett, 2003; Marshall, 1979; Milton, Marshall, Cummings, Baker, & Ridley, 2004; Schneider, McLaughlin, & Roeltgen, 1992; Ungerstedt, 1976). In these studies, unilaterally depleting dopaminergic activity induced symptoms characteristic of the spatial neglect syndrome (e.g., via unilateral lesions of ascending dopaminergic pathways, even in animals without cortical lesions). Profound ipsilesional movement and orienting bias could be pharmacologically manipulated, restoring contralesional spatial response in these animals (see Schwarting & Huston, 1996).

Other components of spatial neglect that may affect recovery and/or response to rehabilitation might be considered "orthogonal" to the input/output information flow facilitated by "Where" versus "Aiming" spatial neglect symptoms (Bisiach et al., 1990). These include differences in spatial neglect behaviors based on the reference space in which performance is tested (e.g., in body space vs near peripersonal space vs far extrapersonal space, Berti & Frassinetti, 2000; Butler, Eskes, & Vandorpe, 2004; Cowey, Small, & Ellis, 1999; Halligan & Marshall, 1991;

Vuilleumier, Valenza, Mayer, Reverdin, & Landis, 1998), or for object judgments vs pure spatial computations (allocentric versus egocentric spatial neglect; Bisiach, 1993; Coslett, 1997; Hillis et al., 2005). The reliability and validity of these other spatial neglect classifications, and standard measurement tools for classification have not yet been identified. For example, future research should evaluate what deficits occur affecting daily life activities in a pure allocentric spatial neglect syndrome: except for the adverse effect of allocentric neglect on reading, specific functional deficits in ADLs or IADLs are not yet reported (Buxbaum, 2006; Buxbaum et al., 2004; Marsh & Hillis, 2008).

18.2.2.2 Current Research

Direct Remediation of Spatial Neglect

Treatment candidacy. Professional organizations (Intercollegiate Stroke Working Party, 2016; Veterans Administration/Department of Defense, 2010; Winstein et al., 2016; Wolf & Nilsen, 2015) provide helpful, research-based recommendations for care of spatial neglect (see Table 18.4). As noted in the introduction, these articles recommend structured assessment of spatial neglect, because the first step in treatment is to identify the presence of the disorder in affected patients. Many tools for spatial neglect assessment have published validity; however, it is critical to use a tool that predicts functional disability. We thus pass over tools that have only predictive validity to identify brain lesion volume, or tools with only convergent validity (correspond well with other laboratory-based impairment assessment, however not yet demonstrated to predict patient activities in the real world). One study (Goedert et al., 2012) indicated that both the behavioral inattention test-conventional subtest (Wilson, Cockburn, & Halligan, 1987) and the Catherine Bergego Scale (CBS; Azouvi et al., 2006) account for a large proportion of variability in reported functional activity performance. In this study, motor-exploratory items on the CBS performed better in predicting daily life function. Chen and colleagues developed a set of manualized instructions so that therapists can administer the CBS (the Kessler Foundation Neglect Assessment Process, or KF-NAP; Chen, Hreha, Fortis, Goedert, & Barrett, 2012), potentially improving reliability and usability of the CBS. This version of the instrument may be more operable for clinical settings, especially for inpatient rehabilitation care.

Remediative treatment of spatial neglect. We previously suggested (Barrett, Goedert, & Basso, 2012; Eskes & Barrett, 2009; Goedert et al., 2014; Goedert et al., 2018) that spatial "Aiming" versus "Where" neglect symptoms respond differently to targeted interventions. Thus, spatial neglect rehabilitation trials that define the proportion of patients with spatial "Aiming" and "Where" neglect can increase the power to detect treatment effects and assess whether patient characteristics explain differences in spatial neglect treatment results. The stratification concept was supported by reports that patients with spatial "Aiming" neglect and frontal lobe lesions respond more robustly to prism adaptation treatment (Chen et al., 2014; Goedert

Table 18.4 Treatments for spatial neglect included in more than one professional guideline

Guideline articles reporting efficacy	Treatment	Mechanism of effect, other information for targeting treatments
American Heart Association (Winstein et al., 2016) American Occupational Therapy Association (Wolf & Nilsen, 2015: though noting mixed evidence of benefit) Intercollegiate Stroke Working Party (2016)	Prism adaptation training (Chen, Goedert, Shah, Foundas, & Barrett, 2014; Frassinetti, Angeli, Meneghello, Avanzi, & Ladavas, 2002)	"Aiming," spatial motor-intentional neglect (based on group studies of prism adaptation treatment response; Fortis, Chen, et al., 2011; Goedert et al., 2014) Frontal lobe lesions associated with better response (two systematic studies; Chen et al., 2014; Goedert, Chen, Foundas, & Barrett, 2018)
Winstein et al. (2016) Veterans Administration/ Department of Defense (2010) American Occupational Therapy Association (Wolf & Nilsen, 2015) Intercollegiate Stroke Working Party (2016)	Visual scanning training (Katz et al., 2005; Polanowska, Seniow, Paprot, Lesniak, & Czlonkowska, 2009)	Unknown "Where," perceptual-attentional (hypothesis)
Veterans Administration/ Department of Defense (2010) Intercollegiate Stroke Working Party (2016)	Compensatory self-mediated cuing strategies (Niemeier, Cifu, & Kishore, 2001; Walker et al., 2012)	Not a remediative intervention. Unlikely to affect spatial cognitive processing
Winstein et al. (2016) Intercollegiate Stroke Working Party (2016)	Limb activation (Eskes & Butler, 2006; Làdavas, Berti, Ruozzi, & Barboni, 1997; Robertson, Halligan, & Marshall, 1993)	"Aiming," spatial motor-intentional neglect (hypothesis)
Winstein et al. (2016) Veterans Administration/ Department of Defense (2010)	Cholinergic medication (Gorelick et al., 2013)	Recommended for post-stroke and vascular cognitive impairment For spatial neglect, may influence "Where" perceptual-attentional systems (hypothesis, based upon effect on signal detection in aphasia; see review in Cahana-Amitay & Albert, 2015)

et al., 2014, 2018). Future spatial neglect rehabilitation studies should assess spatial "Aiming" versus "Where" bias in participants, to assist with evaluating subgroups that may account for variability in response and differences in study results.

Pharmacological treatment. Pharmacological intervention has been attempted via dopaminergic, noradrenergic, and cholinergic strategies (see van der Kemp, Dorresteijn, Ten Brink, Nijboer, & Visser-Meily, 2017 for a systematic review). However, pharmacologic agents may selectively influence certain symptoms (Barrett et al., 1999; Geminiani, Bottini, & Sterzi, 1998; Gorgoraptis et al., 2012; Luaute et al., 2018), or may accelerate recovery, without improving overall func-

tional gains (Paolucci, Bureca, Multari, Nocentini, & Matano, 2010). Paradoxical worsening of spatial bias may also occur with dopamine agonist therapy (Barrett et al., 1999; Grujic et al., 1998). Cholinesterase inhibitors for spatial neglect are appealing, since stroke care standards recommend these agents for other forms of post-stroke cognitive impairment (Veterans Administration/Department of Defense, 2010; Winstein et al., 2016). However, better quality, controlled research on pharmacological interventions for spatial neglect will clarify the role of these interventions (Luvizutto et al., 2015).

Behavioral treatment. Four recent reviews endorsed by professional organizations included treatment recommendations (see Table 18.4: Intercollegiate Stroke Working Party, 2016; Veterans Administration/Department of Defense, 2010; Winstein et al., 2016; Wolf & Nilsen, 2015). When more than one treatment choice is available, comparative effectiveness studies are not yet available to help clinicians prescribe behavioral therapy, and many rely upon their personal experience or other "expert wisdom" resources (Chen, Pitteri, Gillen, & Ayyala, 2018).

Of the available choices, we (Barrett et al., 2012) and others (Luaute, Halligan, Rode, Rossetti, & Boisson, 2006; Nys, de Haan, Kunneman, de Kort, & Dijkerman, 2008) strongly endorsed the use of prism adaptation treatment to remediate spatial neglect. It is associated with a large treatment effect based on multiple studies (Yang, Zhou, Chung, Li-Tsang, & Fong, 2013) and reported in many studies to improve daily life activities (Champod, Frank, Taylor, & Eskes, 2018); however, our emphasis was on usability and applicability. The treatment is inexpensive (estimated at about $350/patient in a British study; National Institute for Health and Care Excellence, 2013), is compatible with existing structure for scheduling stroke rehabilitation and co-treating other deficits, and utilizes a defined training procedure, which is replicable across therapists and settings. Prism adaptation treatment does not require the stroke survivor to use any conscious strategies or "top-down" self-management, rather it only requires the stroke survivor to execute visually guided movements.

In the prism adaptation training procedure (Fortis, Chen, et al., 2011; Frassinetti et al., 2002), patients wear left-based, yoked optical prisms, which shift what they see rightward, while making multiple goal-directed hand movements. Although some parameters of the treatment varied across studies, in one standard regimen (Chen et al., 2014; Goedert et al., 2014, 2018) patients wore 20 diopter wedge prisms and completed ten sessions over 14 days, each comprising about 20 min of visual-motor hand movement training. Patients wear prisms only during treatment sessions; at other times, they may engage as usual in other rehabilitation. In a recent preliminary report of the results of clinical practice using this regimen, as part of rehabilitation in a network of inpatient rehabilitation facilities, the degree of improvement in functional independence in spatial neglect patients receiving the 10-session regimen was comparable to functional improvement reported in previous randomized trials, and exceeded the minimal clinically important difference on the Functional Independence Measure (FIM) (Barrett et al., 2019; Beninato et al., 2006). As we described in a recent treatment review (Barrett & Houston, 2019), prisms used in prior trials often either 10°, yoked wedge prisms (i.e., 17.6 diopters;

Optique Peter), or 11.4° yoked wedge prisms (i.e., 20 diopters; Bernell Vision Therapy, Mishawaka, IN).

In addition to prism adaptation treatment, a widely used alternative, the treatment most strongly endorsed by Cicerone et al. (2019) is visual scanning training. This treatment approach was demonstrated effective in the 1970s, when after 20 h of training with graded visual material to promote left-sided scanning, stroke patients with spatial neglect showed improvement of scanning impairment, and also improved reading and writing (Weinberg et al., 1979). A problem with this approach is that it requires top-down self-mediation, and is labor-intensive on the part of the therapist, who must be trained to offer frequent cues. How it should be integrated into other forms of functional training (i.e., grooming) has not been studied.

We list prism adaptation, visual scanning training, and two other remediative interventions in Table 18.4 that were included in at least two of the four recent available professional reviews. Unfortunately, only two treatments have been investigated to determine what spatial cognitive mechanisms they may target (one treatment with demonstrated effectiveness—prism adaptation treatment, and one not associated with satisfactory benefit—monocular occlusion). Reviews that do not consider targeted treatment leave open the question that if a treatment did not reach criteria for efficacy, it may have been potentially effective but targeted inappropriately, to patients whose symptoms may not have been likely to benefit. For example, a treatment that theoretically may improve Where perceptual-attention, such as cholinergic medication, may lack effect if most of the subjects recruited in a particular trial had primarily spatial "Aiming," motor-intentional neglect.

Compensatory Strategies for Spatial Neglect

In Table 18.4, we also list compensatory, self-mediated cuing strategies, recommended by both the American Occupational Therapy Association and Veterans Affairs/Department of Defense. Management and compensation for spatial neglect are only supported by small-scale prospective studies (Niemeier et al., 2001), so protocols for best practice are not yet defined.

Family members of stroke survivors with spatial neglect experience significant caregiver stress and burden (Chen, Fyffe, & Hreha, 2017), and family counseling is standard. The stroke survivor's abnormal spatial behaviors, and associated anosognosia or anosodiaphoria (lack of awareness or lack of concern about spatial neglect) may alarm and frustrate the survivor's caregivers and family. Without concepts for the specific functions of the damaged right hemisphere, family members may attribute errors to psychological or personality factors—concluding that the person is "lazy," "in denial," or "hallucinating." Research is needed to identify best practices to intervene and assist families. We feel that providing information about the spatial neglect syndrome, and specifically including family members in therapeutic assessment and treatment, can be helpful. Functional performance assessment such as the CBS can be preferable to more abstract, paper-and-pencil testing for the purpose of review and discussion with family members: family members can observe assess-

ment, and CBS items testing spatial deficits are described in concrete terms that they may find easier to understand.

Environmental manipulations, such as placing the stroke survivor's bed on the good side of the room so that she or he will "need to look" contralesionally, or standing on the stroke survivor's bad side so as to "draw attention" to that space, were examined only in an inpatient study of bed placement, and had no beneficial effect (Kelly & Ostreicher, 1985). Environmental manipulation may either exert only a small effect, or, alternately, subgroups of patients with spatial neglect may respond differently to the same environmental change. For example, we have observed that a patient with primary motor-intentional Aiming neglect may perform better when most of the room is on their contralesional side; however, a patient with a primary spatial Where neglect may become disoriented in that situation due to sensory deprivation.

18.2.2.3 Clinical Applications and Future Directions

We envision translational treatment of spatial neglect as ideally composed of three steps. First, the clinician categorizes observed spatial neglect behaviors, noting the specific components likely underlying neglect symptoms (e.g., primary spatial Where perceptual-attentional, or spatial Aiming, motor-intentional failure). Then, the clinician ranks the priority of the symptoms for treatment based upon their potential impact on the client's recovery goals. At the third step, the clinician selects a treatment tailored to the deficit underlying the highest priority impaired behavior. Thus, if postural imbalance due to directional akinesia is given priority because of its effect on sit to stand transfers, the therapist may select prism adaptation treatment, given its effect in spatial Aiming neglect. Initial assessment (e.g., the CBS to confirm motor-exploratory deficits) and systematic reassessment (e.g., repeating the CBS after treatment to confirm treatment response) are important.

Two, more difficult, questions arise. If the patient still has spatial neglect on reassessment after the initial treatment has been delivered, what is the next step? Also, some practitioners object to offering first-line, or later, treatment based on proposed or theoretically stipulated mechanisms, as in some cases it may lead to choosing relatively under-investigated treatments over treatments with demonstrated benefit in randomized controlled trials. These issues have been debated in other areas of medical care (for an excellent discussion, see Caplan, 2001). We feel that the clinical rehabilitation standard is individualized therapy, and so favor the targeted approach. Four studies of spatial neglect treatments are available that stratified patients by potentially affected brain-behavior networks (Chen et al., 2014; Goedert et al., 2014, 2018; Gorgoraptis et al., 2012), and others are calling for this research (Luaute et al., 2018). Thus, skilled practitioners trained to analyze symptoms of spatial neglect will have a growing evidence basis for their practice.

It is true, however, that in some settings skilled practitioners with the ability to identify specific spatial neglect impairments are not available. In these situations,

broad use of a single treatment of demonstrated benefit unlikely to cause worsening (e.g., prism adaptation treatment, intensive visual scanning training) may be appropriate.

18.2.3 Memory

18.2.3.1 Pathophysiology and Mechanisms

Memory (the ability to process, store, and retrieve experiences) is not a unitary function, but consists of a number of different interacting components and underlying neurocognitive mechanisms. Studies of healthy subjects and individuals after brain damage suggest a distinction between explicit, also called episodic memory (memory for remote, recent or future daily events that is accessed consciously and deliberately retrieved; tested by direct methods such as recognition and free recall paradigms) and implicit or procedural memory (memory for events that results in behavioral or performance changes without awareness; tested by indirect methods such as priming or motor learning paradigms) (Gabrieli, 1998; Squire, 1986; Tulving & Schacter, 1990). Stroke and/or brain injury frequently results in memory disturbance, with the most obvious deficits and complaints related to difficulties with deliberate information retrieval or explicit memory (Lim & Alexander, 2009; Snaphaan & deLeeuw, 2007). The severity and impaired process(es) in explicit memory depend upon the location and extent of stroke (Blum et al., 2012; Gillespie et al., 2006; Ott & Saver, 1993; Stewart, Sunderland, & Sluman, 1996). Because known memory processes involve encoding (acquisition), storage (consolidation), and retrieval (recall or recognition), memory rehabilitation techniques frequently focus on optimizing processes and/or compensatory strategies to improve encoding or retrieval steps. These strategies include teaching mechanisms to optimize remaining memory abilities such as teaching effective encoding and rehearsal strategies, or mnemonics (e.g., imagery), semantic processing, and spaced retrieval. External aids and environmental supports such as alarm watches, memory notebooks, pagers, computers, and smartphones have also been used with benefit in individuals with a broad range of memory deficit severity (e.g., Charters, Gillett, & Simpson, 2015). In cases of severe amnesia, efforts have been focused on teaching direct functional skills through the use of the normally preserved procedural implicit system. It is also important to remember that stroke effects on memory could be mediated indirectly, at least in part, by deficits in other cognitive domains important for efficient memory (e.g., changes in verbal or spatial abilities, or executive dysfunction due to focal stroke lesions or underlying vascular pathology) and thus, interventions enhancing these cognitive deficits may be helpful for memory. For example, Chen, Hartman, Galarza, and DeLuca (2012) found improved visual memory of complex figures after providing training in global spatial processing to individuals with right hemisphere stroke and spatial deficits. Reviews of the efficacy of rehabilitation for memory deficits after stroke are available (Elliott & Parente, 2014; Majid et al., 2000; Teasell et al., 2006).

18.2.3.2 Current Research

Direct Remediation of Memory Function

Repetitive, intensive exercises and practice drills with learning digits, words, or locations are unlikely to restore explicit memory function or repair underlying damaged memory processes and thus generalize to everyday memory function. While individual subjects improve on test performance with the practiced material (albeit sometimes only with extensive practice), improvements rarely generalize to new material or other contexts (Berg, Koning-Haanstra, & Deelman, 1991; Doornhein & De Haan, 1998; Glisky, Schacter, & Tulving, 1986; Godfrey & Knight, 1985; Towle, Edmans, & Lincoln, 1988; Wilson, 1997). The lack of a theoretical model has also limited this approach (Wilson, 1997).

Restitution and Compensatory Approaches for Improving Memory Function

There are a number of studies examining other restitutive strategies to optimize residual memory function in stroke survivors. These techniques can include teaching strategies which may support internal memory representations, including semantic processing (e.g., relating material to information already known), imagery (forming and linking unique visual images to information to be remembered), or association (linking new material to already known information; das Nair & Lincoln, 2012). For example, teaching imagery use has been helpful in the re-learning of daily tasks compared to standard task practice. Liu, Chan, TMC, and Hui-Chan (2004) provided systematic imagery training in 15 one-hour sessions over 3 weeks in patients 12–15 days post-stroke and found better performance on trained and untrained functional tasks up to 1 month post training (Liu et al., 2004). Kaschel et al. (2002) also taught imagery techniques to enhance memory in 30 sessions over 10 weeks and was successful in improving performance on both untrained memory tests and in daily activities as measured by significant others' reports, even at 3 months post training (Kaschel et al., 2002). Other approaches that may improve encoding or retrieval include distributed practice (using several short periods over time for practice) and spaced retrieval (retrieving and rehearsing material over gradually increasing time intervals; Schacter, Rich, & Stampp, 1985). These studies, in general, have indicated that teaching of internal strategies to enhance encoding and/or retrieval can improve performance on objective memory tests or functional tasks relative to control procedures in individuals with mild to moderate memory deficits due to stroke (Gasparrini & Satz, 1979; Gianutsos & Gianutsos, 1979). The effectiveness of internal strategy training may depend upon integrity of remaining cognitive functions (e.g., language, executive function) important for strategy use. Because learning a strategy approach assumes some residual memory function, individuals with mild to moderate memory deficits will most likely benefit from this training. Even some control procedures (e.g., psychoeducation about memory strategies, memory drills and practice) can lead to benefits on both objective and subjec-

tive measures (Doornhein & De Haan, 1998; Hildebrandt, Bussmann-Mork, & Schwendemann, 2006) and the intensity of training and practice may also be a relevant variable. Hildebrandt et al. (2006) found that 20 total hours of practice and teaching of strategies (including massed practice, semantic processing, spaced retrieval learning and coping with interference) benefited individuals with mild-moderate learning difficulties (mostly stroke survivors) compared to only 7 h of training or a psychoeducational intervention. Generalization to untrained materials and/or everyday functioning is reported in some (Hildebrandt et al., 2006; Kaschel et al., 2002; Liu et al., 2004), but not all studies (Doornhein & De Haan, 1998; Gasparrini & Satz, 1979; Gianutsos & Gianutsos, 1979). Strategy use also may be more successful when directed at specific problems in everyday functioning identified by the individual.

Use of external devices to compensate for memory deficits, such as memory notebooks and electronic reminders, has been investigated mostly in individuals with acquired head injury (Cicerone et al., 2000, 2005, 2011, 2019). Findings suggest these devices may be applicable to individuals with a wide range of memory deficits. The choice of a device will depend upon matching the required level of involvement with the device to the cognitive abilities of the individual. Some devices require minimal training (e.g., electronic pagers), while others require considerable client involvement (e.g., memory notebooks, electronic calendars/alarms). Wilson, Emslie, Quirk, and Evans (2001) reported on the use of a portable paging system (NeuroPage) in a group of 143 diverse individuals with ABI (~25% due to stroke) who were randomized to a controlled crossover design with pager and wait-list conditions. The number of memory successes on individually relevant functional tasks (e.g., taking medications) was significantly increased during the pager conditions compared to baseline and in total, 85% of participants were more successful with the pager compared to the baseline condition. Those noted most likely to benefit included individuals with some insight into memory difficulties, sufficient vision to read the screen, and a lifestyle that needed independence in tasks (Wilson et al., 2001). Of relevance to the current review, no difference was noted due to etiology of memory deficit, although a later study with a stroke group noted that maintenance of benefits was poorer compared to a TBI group, and associated with reduced executive function (Fish, Manly, Emslie, Evans, & Wilson, 2008). Other electronic memory aids such as smartphones and Google calendar provide more active reminders and may be more effective, at least for completion of daily tasks (McDonald et al., 2011). A relatively recent systematic review and meta-analysis reported a large effect size ($d = 1.27$) for the efficacy of technology vs. control in seven group students and an effect size of 0.85 in single-case experimental design studies for adults with impaired memory due to acquired brain injury or degenerative disease (Jamieson, Cullen, McGee-Lennon, Brewster, & Evans, 2014). While smartphone use has been emerging as a potential technology, caution is needed as limitations still exist in terms of older populations with disabilities needing additional assistance (Wong, Wang, Stolwyk, & Ponsford, 2017).

Memory notebooks appear a frequently used device by individuals with ABI (e.g., Evans, Wilson, Needham, & Brentnall, 2003), but research on the effective-

ness of this approach in the stroke population is limited. Group notebook training (16 h over 8 weeks) in individuals (n = 8) with mild memory deficits (Schmitter-Edgecombe, Fahy, Whelan, & Long, 1995) resulted in significantly fewer reports of everyday memory failures post-intervention compared to supportive therapy, although the group difference was not significant at 6 months follow-up. Effective use of a memory notebook may require extensive training and role playing in a variety of situations, depending upon the individual's cognitive profile and previous use of an aid (Sohlberg & Mateer, 2001a). Several case studies also have indicated that memory notebooks can be effective with extensive training in individuals with severe memory impairment due to TBI or stroke (Burke, Danick, Bemis, & Durgin, 1994; Sohlberg & Mateer, 1989; Squires, Hunkin, & Parkin, 1996).

Errorless learning and vanishing cue techniques may be central to training specific tasks such as a memory notebook, or teaching domain-specific information (e.g., caregiver names, computer operations) in individuals with severe amnesia (Kessels & deHaan, 2003). This approach draws upon a preserved implicit memory system (Baddeley & Wilson, 1994; Glisky, Schacter, & Tulving, 1985). The errorless learning method was used successfully to teach a memory notebook strategy to an individual at 8 months post-stroke (Squires et al., 1996) and functional tasks with 3 months post-stroke, although trial and error learning may more be effective in those with better memory (Miller & Radford, 2014). Since there may be no transfer to other untrained tasks, use of these techniques requires considerable time investment, and the identification of specific functional goals.

18.2.3.3 Clinical Application and Future Research

Specific drills and practice to restore memory function have not yet shown clinical benefit. For individuals with mild to moderate memory deficit, restitutive or compensatory strategies including mnemonics (e.g., semantic elaboration, imagery, spaced retrieval) or external devices (e.g., diaries, electronic pagers, handheld calendars/alarms) can be of value. Although the evidence is still limited in stroke, Cicerone et al. (2019) judged the evidence extensive enough to rate the use of both memory strategy training and external devices as a practice standard for those with mild memory impairment. In addition, those devices requiring less extensive training can be applied to functional goals with individuals with moderate to severe memory deficits, using specialized training techniques to bypass a damaged explicit memory system (recommended as a practice guideline; Cicerone et al., 2019). Similar recommendation for the use of compensatory strategies with memory impairment post-stroke was made by Teasell, Salter, Faltynek, Cotoi, and Eskes (2018) in the Evidence-Based Review of Stroke Rehabilitation (http://www.ebrsr.com/). Specific evidence for individuals post-stroke is very limited, however, and more research is required to understand the impact of interventions in this group, as well as relevant factors for stratification for treatment selection (presence of other cognitive deficits, age, gender, or stage of recovery; e.g., Cappa et al., 2005; Gillespie et al., 2015).

18.2.4 Language and Communication Disorders

18.2.4.1 Pathophysiology and Mechanisms

Language can be broadly defined as the set of visual or spoken symbols and rules by which we think and communicate about our internal and external world. Language function is localized to the left hemisphere in most individuals, and strokes involving the left hemisphere vascular territories identified a number of component abilities as defined by aphasia subtypes. In terms of spoken and written communication, aphasia syndromes can be divided into two broad categories: nonfluent and fluent disorders (Goodglass & Kaplan, 1972; for recent review, see Patterson, 2018). In nonfluent aphasia, stroke survivors have difficulty producing the correct motor speech patterns in the correct order. Lesions in the anterior left hemisphere (e.g., Broca's area, Brodmann areas 44, 45) and underlying white matter (Yourganov, Smith, Fridriksson, & Rorden, 2015) are predictive of this syndrome, and some or all of the following symptoms: disrupted articulation or programming of motor speech, impaired rhythm and/or agrammatic sentence production, anomia, and reduced phrase length. Single word comprehension and understanding of simple phrases in natural conversation may be relatively preserved. In contrast, damage to more posterior left brain areas, e.g., Wernicke's area (Brodmann area 22) and associated posterior white matter pathways (Yourganov et al., 2015), produces a fluent aphasia, characterized by relatively preserved and melodic spontaneous speech, but with neologisms (jargon) and reduced content, and associated with poor comprehension of written and spoken language, including reduced awareness of one's own errors (anosognosia). The words "expressive" and "receptive" have sometimes been used to substitute for nonfluent and fluent aphasia categories; we prefer to avoid these terms, because difficulty generating and articulating words is not the only expressive problem that people with aphasia have. Frequently, other symptoms of aphasia (for example, multiple, success approximations in naming observed in conduction aphasia) are labeled "expressive," and this term can lose its meaning. Indeed, we casually observed on many occasions that errors in patients with fluent aphasia were labeled "expressive."

There are eight classical peri- and extra-sylvian aphasia syndromes (Broca's aphasia, Transcortical Motor Aphasia, Global Aphasia, and Mixed Transcortical Aphasia are the nonfluent aphasias; Wernicke's aphasia, Transcortical Sensory Aphasia, Anomic Aphasia, and Conduction Aphasia are the fluent aphasias; Albert, Goodglass, Helm, Rubens, & Alexander, 1981; Alexander, 2003). Other aphasia subtypes are also proposed as variants of these patterns (Bookheimer, 2007; Hillis, 2007). In practice, it can be difficult to confidently classify patients as fluent versus nonfluent, or other characteristics of their speech or language may be inconsistent with the fluent versus nonfluent category (e.g., an unexpected dissociation such as difficulty in naming verbs versus nouns in a patient with fluent aphasia, which would ordinarily be expected to characterize nonfluent aphasia; Caplan, 2012). Therefore, the classical aphasia syndromes may be primarily useful as helpful short-

hand for clinical communication, or to stimulate reasoning about neuroanatomic associations for the purpose of care planning (Alexander, 2003). In addition, we are still learning about how to classify language disorders that result from damage to subcortical and cerebellar structures (Fiez, 2016).

A variety of aphasia treatment approaches have been used over the last 130 years, ranging from generic mental stimulation to theoretically driven treatment of specific cognitive-linguistic deficits in a case study approach. Evidence-based reviews (Brady, Kelly, Godwin, & Enderby, 2012; Brady, Kelly, Godwin, Enderby, & Campbell, 2016; Cicerone et al., 2019; Robey, 1998) mainly conclude that treatment is effective, with the Brady et al. (Brady et al., 2012; Brady et al., 2016) studies reporting a small-to-medium effect size of $d = 0.3$ and $d = 0.28$, respectively. Raymer and Gonzalez Rothi's (2018) review efforts to synthesize aphasia rehabilitation research and present it based on a common quality standard. As of this writing, such efforts have not yet clarified whether a single treatment, or even a group of treatments, stand out over other treatments for initial or broad application. The American Speech Language Hearing Association (www.asha.org) and the American Society for Neurologic Communication Disorders (www.ancds.org) sponsor efforts to create aphasia treatment practice guidelines, however have not yet at the time of this writing made an omnibus set of evidence-based guidelines for aphasia treatment publicly available.

18.2.4.2 Current Research

Remediative Approaches

Cicerone et al. (2000, 2005, 2011, 2019), in their systematic review and practice recommendations for cognitive disorders, summarized the evidence supporting cognitive-linguistic therapies as a practice standard during acute and post-acute rehabilitation for left hemisphere stroke survivors with aphasia. A current Cochrane review (Brady et al., 2016), a practice guideline publication from the American Heart Association (Winstein et al., 2016), and a stroke clinical practice guideline from Australia (The Stroke Foundation, 2017) also recommend cognitive-linguistic therapies for post-stroke aphasia. Thus, there is strong international consensus supporting provision of therapy services to enhance function in post-stroke aphasia. Although a number of treatments were effective in controlled studies, as noted above, we do not yet have information that clearly points to one method as broadly more effective than others, nor do we have a recommended process to select a specific approach for aphasia rehabilitation, from these or other professional sources. In the Brady et al. (2016) Cochrane systematic review of 57 studies of aphasia rehabilitation, speech-language therapy approaches were judged to result in functional improvement, compared with no intervention. The methods used in speech-language therapy were diverse, including such approaches as computer-mediated word-finding therapy (Palmer et al., 2012), intentional gesture therapy (Altmann et al., 2014), and constraint-induced language therapy (Meinzer, Streiftau, &

Rockstroh, 2007). However, again this Cochrane review neither presented a specific recommendation to support use of one speech-language therapy approach over others, nor use of biomarkers or behavioral indices to decide upon a preferred approach.

Intensity of treatment appears to be a critical variable and may explain some of the discrepancy in findings in the above reviews. Raymer and Gonzalez Rothi (2018) discussed the importance of defining intensity of aphasia treatment and recommended that workers consider the density of dosage within training sessions, consistent with Kleim and Jones (2008). They pointed out that the number of items trained and the number of opportunities to practice within a session are important aspects of language therapy intensity. The importance of intensity was also supported in a recent review of efficacy of constraint-induced language therapy (Zhang et al., 2017). Constraint-induced therapy, which involves the massing or concentration of practice and constraint of undesirable behaviors or responses, was used successfully in the motor rehabilitation of post-stroke hemiparesis (Taub, Uswatte, & Pidigiti, 1999), and was first modified for aphasia more than 15 years ago (Pulvermuller et al., 2001). Based on eight studies included in the Zhang et al.'s systematic review, three of which compared constraint-induced therapy to conventional speech-language therapy, constraint-induced language therapy was presented as useful in the treatment of chronic aphasia, although needing further investigation. The authors suggested that massed practice (high intensity dose frequency) is likely to contribute to its effect. This is contrasted with distributed practice, which is of lower intensity (Raymer & Gonzalez Rothi, 2018). Further supporting treatment intensity, Breitenstein et al. (2017) reported that a large group of patients with aphasia who received 3 weeks of >10 h of language therapy weekly, based on a therapy manual of best practices and individualized to specific patient deficits, made significant gains on impairment measures and also communication effectiveness ratings by partners or friends, as well as communication-specific quality of life ratings, when compared to a control group that received an average of 1.5 h weekly. Godecke, Hird, Lalor, Rai, and Phillips (2012) administered 20 sessions of aphasia therapy of 45–60 min 5 days/week starting 3 days after stroke recovery. The benefit observed in this study of the experimental intervention in moderate to severe aphasia could have been related to both intensity and early timing.

Pharmaceuticals used for aphasia remediation include piracetam, donepezil, galantamine, and memantine in chronic stroke (Faltynek et al., 2018). Zhang et al. (2017) reviewed 15 studies on pharmacological treatment of aphasia and concluded that donepezil and memantine both improve language impairment. However, at this point, neither the American Heart Association (Winstein et al., 2016) nor the Canadian Stroke Network (Faltynek et al., 2018) recommend pharmacologic therapy for aphasia, because consistent benefit over speech-language therapy has not yet been demonstrated, and dose and timing of drug administration need to be investigated.

Reading and writing remediation was generally included as part of aphasia rehabilitation in reviews; however, Purdy et al. (2018) also systematically reviewed 15 studies of reading comprehension treatment. In these 15 studies, there was overall evidence that reading comprehension intervention improved performance. However,

both the benefit to individuals participating in studies and the approaches themselves were quite variable. The authors concluded that an independent effect of intensity on treatment results could not be evaluated.

Group therapy or community therapy are reported to be beneficial when involving trained laypersons. In one study, group therapy was found to improve both linguistic and communicative skills in individuals with chronic stroke in comparison to a deferred treatment group and progress was maintained at 4–6 weeks follow-up (Elman & Bernstein-Ellis, 1999). Group-based therapy might give greater access to improve not only impairment measures, but functional communication skills (Marshall, 2005), and clients may find lay-administered therapies appealing, as feelings of self-efficacy or empowerment may be enhanced when stroke survivors practice language skills with perceived social equal. The involvement of trained laypersons in the community (Faltynek et al., 2018) and telerehabilitation (American Speech-Language Hearing Association position statement, 2005) are both potentially valuable to enhance professional delivery of services.

While group studies usually lack a comprehensive description of the aphasia therapy approach with individual subjects, the effects of specific cognitive-linguistic remediation techniques for specified linguistic deficits (e.g., anomia, alexia) have been evaluated in a wide variety of studies. As reviewed by Cicerone et al. (2000, 2005, 2011, 2019), the evidence suggests that cognitive-linguistic techniques directed at specific deficits in individuals with chronic aphasia can be beneficial, although the issue of generalization and effectiveness of such approaches needs more evaluation.

Many stroke survivors and their families are interested in computer-administered therapies, whether used in self-administered, or face-to-face therapy sessions. Both computers and smart tablets were used for therapy in 23 studies reviewed by Lavoie, Macoir, and Bier (2017), who found evidence of benefit, for computer-administered techniques, with possible superiority of intensive treatment. These authors found no evidence that a specific approach, or self- versus therapist-administered approach, was more effective. There is not yet much evidence for mobile or home-based technology for aphasia intervention; however, available reviews suggest benefit (Cogollor et al., 2018; Zhou, Du, & Zhou, 2018) and more research is needed to standardize the approaches, doses, and patient eligibility.

Compensatory Approaches

Simmons-Mackie, Raymer, and Cherney (2016) published a systematic review of communication partner training to improve activity and participation in aphasia. They concluded that the evidence supports this intervention to improve function in chronic aphasia, with evidence insufficient in acute aphasia. This intervention is recommended in the American Heart Association Stroke Rehabilitation Guidelines (Winstein et al., 2016).

Technological compensation via augmentative and alternative communication (AAC) systems may enhance communication and participation, according to a systematic review of 30 studies (Russo et al., 2017). Unfortunately, clinicians who can evaluate for and prescribe these specialized services are not available in every medical setting or, even, every US state; interested stroke survivors may need to obtain a referral through the American Speech-Language and Hearing Association or other national organization resources.

18.2.4.3 Clinical Application and Future Research

There is consensus that aphasia therapy is efficacious for individuals after stroke, and it is recommended as a practice standard (Brady et al., 2016; Cappa et al., 2003, 2005; Cicerone et al., 2000, 2005, 2011, 2019; The Stroke Foundation, 2017; Winstein et al., 2016). Speech and language interventions appear effective; however, research is needed to understand the specific techniques and parameters that relate to effectiveness. As Campbell, Skidmore, Whyte, and Matthews (2015) emphasized, research in aphasia is a challenge, because research participation processes, including informed consent, are biased to exclude people with communication deficits. Specific planning to include people with aphasia in research is appropriate. Specific cognitive-linguistic techniques, intensity of therapy, and compensatory techniques are important to optimal functional outcomes with aphasia rehabilitation. More research is also needed to understand the co-effects of exercise and health interventions on aphasia (Harnish et al., 2018). We look forward to research on results of combinations of aphasia interventions, attention to functional outcomes, and long-term follow-up.

18.2.5 Executive Function

18.2.5.1 Pathophysiology and Mechanisms

Executive function encompasses a range of processes that are needed to integrate information from sensory and memory systems and to organize goal-directed behaviors. A variety of models of executive function have been proposed emphasizing different control processes with distinct neural substrates. One model describes four frontal regions with specific anatomical/functional relationships that work in concert to subserve cognitive control (Stuss, 2011). These four categories of functions include: (1) energization; (2) executive functions (e.g., monitoring and task setting); (3) behavioral/emotional self-regulation; and (4) metacognition/integration. These domains relate to different anatomical regions and systems that can be differentially affected by brain injury, although more than one domain is typically involved. An understanding of these different functions is thus relevant to the development of theory-driven rehabilitation programs.

Energization refers to the process of initiating and sustaining a response. Pathology of the superior medial frontal areas has been shown to lead to apathy or abulia (i.e., a deficiency of motivated behavior). Executive functions involve the control and orchestration (e.g., planning and monitoring) of basic cognitive functions, such as memory. Damage to the dorsolateral prefrontal cortex has been shown to lead to difficulties controlling cognitive operations despite intact basic skills which can cause issues with working memory, problem-solving, and decision-making. Behavioral/emotional self-regulation includes reward and emotional processing during adaptive responding. Damage to the ventral frontal region can result in difficulties with inappropriate emotional responding and regulation. Finally, metacognitive processes refer to the orchestration of all higher-order executive capacities that are necessary to complete complex and novel tasks. Pathology of the frontal polar region has been shown to cause a lack of insight into deficits and a loss of awareness of social contexts. Different patterns of deficits therefore result from damage to different parts of the frontal lobe and, because these executive processes are subserved in concert with posterior regions (Petrides & Pandya, 1994), executive impairments have also been observed when there is little evidence of frontal lobe damage (e.g., Alvarez & Emory, 2006). For example, most of the cerebellum has been shown to be linked to executive networks (Klein, Ulmer, Quinet, Mathews, & Mark, 2016; Noroozian, 2014; Schmahmann, 2001). As a result, isolated cerebellar strokes have been shown to impair performance on a variety of cognitive tasks assessing executive functions, memory, and language (Stoodley, MacMore, Makris, Sherman, & Schmahmann, 2016).

The complexity and interaction among these domains are difficult to objectively characterize and neuropsychological assessments are critical to identify both affected and preserved domains in order to plan and guide treatment. The very nature of executive function impairments may make it difficult for a stroke survivor to learn and assume responsibility for using a compensatory strategy in learned or novel situations. Impaired insight can also be a mediating issue (Cicerone, Levin, Malec, Stuss, & Whyte, 2006). The complexity of these issues and potentially affected domains has led to a wide range of proposed interventions including computerized drill-based exercises and specific skill training with behavioral methods used in a functional context (restorative interventions). External compensatory interventions have also been developed involving the use of devices to cue and support learned strategies. Research on most interventions targets more than one domain and thus makes it difficult to identify the specific, effective processes that lead to any treatment effect. We will emphasize the results from studies including stroke survivors but many studies have used mixed samples including patients with other types of ABI.

18.2.5.2 Current Research

Computerized Drill-Based Exercises

Most computerized training protocols used in past research have been non-standardized (i.e., unique to each study or modified versions of standardized protocols). One computerized program targeting executive function that has been used in several studies with stroke patients is Cogmed QM (Åkerlund, Esbjörnsson, Sunnerhagen, & Björkdahl, 2013; Björkdahl, Åkerlund, Svensson, & Esbjörnsson, 2013; Nyberg et al., 2018; Westerberg et al., 2007). Cogmed QM (Cogmed Systems AB, Stockholm, Sweden) consists of a series of adaptive verbal and visuospatial working memory exercises typically administered over a period of 5 weeks (5 days per week for about 30–45 min per session). Others have used a broader range of therapist-guided computer exercises to restore executive function as well as other cognitive domains after stroke (e.g., Zucchella et al., 2014).

Bogdanova et al. (2016) and van de Ven, Murre, Veltman, and Schmand (2016) have reviewed the evidence (from 28 and 20 studies, respectively) for the efficacy of computer-based cognitive training for executive function after stroke and other types of ABI. After reviewing studies that have used a variety of computerized training protocols targeting executive function (including Cogmed QM), they cautiously concluded that the preliminary results warrant continuation of research in the field as some objective and subjective improvements were observed on non-trained working memory and related tasks (e.g., digit span and PASAT tasks; Åkerlund et al., 2013; Björkdahl et al., 2013; Fernandez et al., 2012; Lin et al., 2014; Lundqvist, Grundström, Samuelsson, & Rönnberg, 2010; Westerberg et al., 2007). However, it should be noted that important methodological issues were identified in most studies (e.g., lack of appropriate control groups, no adjustment for multiple testing and comparisons, small samples) and it is critical to address these limitations in future research.

Direct Skill Training

Various training protocols have been developed to help patients with executive function deficits learn and apply strategies to solve everyday problems (e.g., Goal Management Training or GMT, Problem-Solving Training or PST). In GMT, instructional material, interactive tasks, and homework assignments are used to improve the planning, adjustment, and achievement of goals (Robertson, 1996). When compared to an active control group assigned to a brain health workshop condition, GMT was found to improve performance on various tasks assessing executive function (e.g., Tower Test, visuospatial problem-solving task) in a small sample of patients (n = 20) with ABI (predominantly stroke in the chronic phase of recovery; Levine et al., 2011). Improvement in performance on tasks measuring planning and organization translating into improvement in real-life function was

also observed following GMT in a stroke patient with persistent executive function deficit (Schweizer et al., 2008).

Virtual reality (VR) based technologies also started being studied for direct skill training in the stroke population. For example, Rand, Weiss, and Katz (2009) explored the use of a Virtual Supermarket as an intervention in four patients with multitasking deficits at 5–27 months post-stroke. The intervention that is based on GMT consisted of ten 60-min sessions administered over 3 weeks during which participants were engaged in a virtual shopping task requiring planning, multitasking, and problem-solving. The participants made fewer mistakes on several measures after the intervention including one measure of executive functioning administered in a real shopping mall. However, due to the lack of a control group, practice and placebo effects could not be ruled out. Additionally, the observed improvements did not transfer to other instrumental activities of daily living.

More recently, Faria, Andrade, Soares, and Badia (2016) examined the use of a VR-based intervention (Reh@City) which consists of three-dimensional environments in which patients simulate the performance of different activities of daily living. The protocol targets a broad range of cognitive domains including executive functions by defining objectives that should be accomplished by the patient using planning, problem resolution, and reasoning skills. A small sample of patients ($n = 18$, 3–49 months post-stroke) was randomly assigned to a Reh@City or control (conventional rehabilitation) condition. Both groups underwent a 12-session intervention over 4–6 weeks. The experimental group, and not the control group, improved on a measure assessing planning skills (Picture Arrangement test from the Wechsler Adult Intelligence Scale III) from pre- to post-intervention. A trend was observed when comparing performance of both groups on the same task after the intervention ($p = 0.06$).

Spikman, Boelen, Lamberts, Brouwer, and Fasotti (2010) also assessed the effectiveness of a variant of GMT embedded in a multifaceted treatment protocol administered over up to 24 sessions and divided in three stages: (1) psycho-educative sessions aimed at improving awareness of executive deficits, (2) sessions focused on goal setting and planning, and (3) sessions focused on monitoring the execution of the plan. Seventy-five patients (3–468 months post-stroke) were randomly assigned to this comprehensive treatment condition or to a control general computerized cognitive training condition with no clues provided about strategic approaches to the tasks. The experimental group improved more than the control group on measures of social participation, level of attainment of goals, and on an ecological executive task (i.e., Executive Secretarial Task). In contrast, several conventional memory and executive tests showed only time effects or no effects at all (e.g., Stroop Test, Trail Making Test). The use of this treatment protocol therefore yielded promising results for the improvement of executive functions in daily life but future research should clarify the relationship between these changes in daily executive functioning and conventional neuropsychological tests.

Problem-solving training (PST) is another variant of a rehabilitation protocol focused on strategy training (von Cramon, Mathes-von Cramon, & Mai, 1991). This protocol involves training with a range of everyday tasks in either group or indi-

vidual sessions emphasizing various aspects of problem-solving. von Cramon et al. (1991) assigned 37 patients with mixed ABI (including 13 stroke survivors at 6 months post-injury) experiencing problem-solving deficits to a PST training procedure, or a memory training (MT) control procedure each given for an average of 25 sessions for 6 weeks. The PST group improved on a variety of tests, including tests of conceptual reasoning and planning, while the MT group improved more on tests of learning and memory. Improvement in problem-solving in the PST group was confirmed in behavioral ratings by the clinical team, suggesting some generalization to everyday activities.

Other promising findings come from the use of an occupation-based strategy training approach (CO-OP) consisting of a protocol that combines elements of direct skill training including goal setting, global solving strategy, and guided discovery. In a partially randomized controlled study, Poulin, Korner-Bitensky, Bherer, Lussier, and Dawson (2017) assigned a small sample of participants (n = 11; 2–8 months post-stroke) to a CO-OP or computer-assisted training condition. Both conditions consisted of 16 one-hour sessions over 8 weeks. Both groups experienced significant improvements in performance and satisfaction with performance in participant-chosen goals. The computer-assisted group showed large improvements in some areas of executive functioning targeted by the training tasks and the CO-OP group improved significantly on a measure of self-efficacy for performing daily activities. This study therefore provided preliminary evidence for the effectiveness of these two approaches with patients with executive dysfunction post-stroke. The effect of the CO-OP training program was also more recently compared to the effect of usual occupational therapy care in a single-blind randomized feasibility study involving a sample of 35 patients with acute stroke (Wolf et al., 2016). Cognitive flexibility was assessed using a trail making subtest (from the Delis–Kaplan Executive Function System). A medium effect size was found for the CO-OP treatment over usual care on the trail making subtest immediately post-intervention and this effect was maintained at 3 months after completion.

In a randomized clinical trial using another problem-solving intervention (i.e., an analogy problem-solving skill training protocol), Man, Soong, Tam, and Hui-Chan (2006) assessed various modes of delivery (i.e., computer-assisted, face-to-face therapist-led training, online training using video conferencing) of a 20-session program that was designed to teach patients to draw analogies to solve new problems they face in their daily life. This program that used problem-solving strategy demonstrations, principles of errorless learning, and positive feedback improved problem-solving skills (measured by a category test) regardless of the mode of delivery when compared to a no-treatment control group in a sample of 109 patients with ABI (about 50% of the sample was composed of stroke survivors). In an uncontrolled study, three post-acute aneurysm rupture survivors also improved their performance on a test of executive function (i.e., the Tinker-Toy test; Lezak, 1982) and in activities of daily living following a 6-week problem-solving training procedure using the Raven's Standard Progressive Matrices (Honda, 1999; Raven, Raven, & Court, 1998).

Most studies examining problem-solving training procedures in the stroke population have included patients in the post-acute to chronic phase of recovery. However, in a single-blind randomized pilot study comparing the effects of strategy training and reflective listening (control condition), Skidmore et al. (2015) showed greater improvement associated with strategy training on measures of cognitive flexibility (i.e., using the color word interference test) and functional independence (i.e., functional independence measure) in 30 participants with acute stroke. However, the group differences were not significant on a measure of inhibition. Overall, these results suggest that strategy training show promise for addressing disability and improving executive functions in acute stroke, although replication of these results in larger samples is warranted and the generalizability of these improvements should be investigated further.

External Compensatory Strategies to Treat Executive Function Impairments

External aids or environmental support also may be useful for rehabilitation of executive problems. Evans, Emslie, and Wilson (1998) successfully used a radio paging system (Neuropage®) and a paper-and-pencil checklist to prompt everyday actions (e.g., taking medication) in a case study design with a patient after stroke. The effect of the Neuropage® system was also assessed more recently in a study involving 36 patients after stroke (Fish et al., 2008). Of the 36 patients, 24 were provided with the radio paging system only in phase 2 of the study (Group A) and 12 only in phase 3 (Group B). The two groups did not differ in their performance before the intervention when considering the level of achievement of goals related to memory and planning (e.g., meal preparation). Group A performed better than the pager-less Group B during the second phase of the study and Group B performed better than the pager-less Group A during the third phase of the study. These findings suggested that the continuous use of the paging system may help patients with executive function deficits after stroke. Another study examined the effects of periodic auditory alerts to improve performance on an executive function task that required self-monitoring, switching, and maintenance of intention (Manly, Hawkins, Evans, Woldt, & Robertson, 2002). Alerts improved the performance of a group of ten ABI patients (including one with stroke) compared to no alerts, to a level comparable to matched controls. In terms of more recent technologies, there is very limited research on the potential benefits of mobile health apps on executive function despite their increasing availability. Preliminary findings from engagement and feasibility studies are promising but more research is needed on their effectiveness (e.g., Cuberos-Urbano et al., 2018; Kettlewell, Phillips, Radford, & das Nair, 2018).

18.2.5.3 Clinical Application and Future Research

When reviewing the level of evidence for each executive function intervention after stroke using the Physiotherapy Evidence Database (PEDro) Scale, Poulin, Korner-Bitensky, Dawson, and Bherer (2012) concluded that both remedial and compensatory approaches may improve various aspects of executive functioning such as working memory, problem-solving, goal management, multitasking, and planning skills in the chronic stage after stroke although the evidence is still limited. Further research was determined to be needed in acute and subacute stroke as very few studies have been undertaken in these populations. In a Cochrane Review including only randomized trials, Chung, Pollock, Campbell, Durward, and Hagen (2013) concluded that insufficient high-quality evidence was available to reach generalized conclusions on the effect of executive function interventions in patients with stroke and other non-progressive ABI. When considering studies of all quality published before 2014, Cicerone et al. (2019) concluded that problem-solving and strategy training should be recommended for people with deficits in executive function after traumatic brain injuries (including stroke). Poulin et al. (2012), Chung et al. (2013), and Cicerone et al. (2011) all discussed serious methodological flaws (including very small sample size and the use of uncontrolled designs) that have to be addressed in future research before specific clinical guidelines can be established.

18.3 Conclusions

The field of cognitive neuroscience has been progressing at a rapid pace in the last decade which has led to a wealth of knowledge on the neural mechanisms underlying normal and impaired cognitive functioning. There is still a knowledge gap between basic research in cognitive neuroscience and the field of stroke rehabilitation and progress has therefore been slower in the field of rehabilitation of cognitive deficits post-stroke. This knowledge gap is related to the challenges associated with conducting large and well-controlled randomized studies in rehabilitation settings as well as with the individual differences in the manifestation of cognitive deficits post-stroke. There is growing evidence supporting cognitive rehabilitation of attention, memory, language, and executive functions in stroke but the results are often mixed and the inclusion of theory-based interventions, well-controlled studies, and focus on relevant outcomes are highlighted as important goals for continued scientific progress in the field. The heterogeneity of behavioral, cognitive, and physical symptoms after stroke presents a challenging opportunity to clinicians and researchers and requires innovative approaches that take into account individual differences due to the variety of lesion sizes and sites and the complex constellations of symptoms. The use of single-case studies and clinical series, innovative treatments targeted to specific and well-defined deficits, with a focus on long-term functional outcomes is needed for advances at this stage of the field in most areas of cognitive treatment. Considering the increasing rates of stroke and the aging population it is

critical that we continue to foster innovation in stroke rehabilitation and it is hoped that this chapter has provided useful information for both clinicians and researchers dealing with the complex issues related to treatment of cognitive impairment after stroke.

Acknowledgements Dr. Champod was supported by the Nova Scotia Health Research Foundation, the Heart and Stroke Foundation, the Harrison McCain Foundation, Springboard Atlantic, and Acadia University. Dr. Eskes was supported by the Heart and Stroke Foundation, the Canadian Institutes of Health Research, the Canadian Partnerships for Stroke Recovery, the Centre for Aging and Brain Health Innovation, the Nova Scotia Health Research Foundation, Innovacorp, Dalhousie University, and Nova Scotia Health Authority. Dr. Barrett was supported by the Kessler Foundation, the National Institutes of Health, the Wallerstein Foundation for Geriatric Improvement, and the American Heart Association.

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Chapter 19
Pharmacological Treatment of Post-stroke Cognitive Deficits

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19.1 Introduction

Stroke is defined as a dysfunction of the brain due to an interruption of the cerebral blood flow. According to the World Health Organization 15 million people suffer stroke worldwide each year, and of these, 5 million die. The financial repercussion associated with stroke and the subsequent disability is substantial, summing over 30 billion dollars annually (Roger et al., 2012). Nevertheless, since the mortality rate of stroke victims is falling steadily (Towfighi & Saver, 2011), the focus of scientific and medical attention has shifted to the long-lasting disabilities that survivors suffer after stroke. It is estimated that around 30% of all stroke survivors are left with residual disabilities affecting physical, cognitive, behavioral functions, and quality of life. Therefore, in addition to medical management after acute stroke to prevent further cerebral damage, therapeutic interventions (rehabilitation, pharmacological

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_19

treatment) are initiated with the ultimate goal of achieving better recovery in terms of disability and affliction during the years that follow (Hachinski, Donnan, Gorelick, et al., 2010). Rehabilitation of physical motor impairment is extensively investigated, with studies indicating significant advances on recovery following medical treatments, physiotherapeutic therapy, and non-invasive brain stimulation (NIBS) (Chollet et al., 2014; Liepert, 2016; Van Peppen et al., 2004). However, strategies for restoration of cognitive functions in post-stroke cognitive deficits (PSCD) have received less attention with cognitive rehabilitation arguably considered to be the "lost dimension" of stroke rehabilitation (Cumming, Marshall, & Lazar, 2013; Mellon et al., 2015).

Post-stroke motor, cognitive, and behavioral impairments are evident in the immediate aftermath of stroke, with many deficits resolving spontaneously in the ensuing months (Cassidy & Cramer, 2017). Estimating the persistence of PSCD in the chronic period is challenging, given the myriad of possible sequelae. Hence, reported longitudinal estimations have varied from 30% to 50% (Mellon et al., 2015; Pendlebury & Rothwell, 2009; Rist, Chalmers, Arima, et al., 2013), showing the heterogeneity on the prevalence of PSCD. Therefore, heterogeneity of impairment at the individual level seems to be the rule, determined by the abovementioned factors and others such as previous medical conditions, age of onset, educational level, severity of stroke, lesion size and location, and genetic polymorphisms (Chang, Chang, Cragg, & Cramer, 2013). Importantly, patients with moderate PSCD are six times more likely to transition to incident dementia, compared with those without cognitive impairment, with up to a quarter of patients with cognitive impairment diagnosed with dementia in the 3 years following stroke (Merriman, Sexton, Donnelly, et al., 2018). Given this high prevalence of PSCD and their potential to evolve into dementia, expanding research on rehabilitation is crucial.

19.1.1 Principles Underlying Recovery Promoted by Cognitive Rehabilitation and Drugs

Recovery from stroke deficits is mainly supported by neuroplasticity, which can be guided and boosted through different interventions (Cramer & Riley, 2008; Cumming et al., 2013; Dobkin & Dorsch, 2013). Neuroplasticity provides to the brain an innate capacity of changing, allowing it to adjust to adverse circumstances (brain injury). Neural plasticity is sustained by neuroanatomic and neurochemical changes such as the growth of synapses and dendrites (Zhang, Zhang, & Chopp, 2008), axonal remodeling and angiogenesis (Ding et al., 2008), and increased expression of growth-related genes and proteins (Li & Carmichael, 2006). After a stroke, these brain changes take place during three different stages of evolution (Berthier et al., 2011; Cassidy & Cramer, 2017). The initial stage arises soon after the stroke wherein brain tissue and networks could be salvaged by reperfusion or

neuroprotection (Hillis & Heidler, 2002). The second stage covers from days to weeks after stroke onset and coincides with the start of brain repairing mechanisms (Hillis & Heidler, 2002). Spontaneous recovery is accentuated during this period. Finally, the third stage is confined to the chronic phase in which spontaneous recovery is no longer expected and a tendency to stabilization occurs in regard to intrinsic repair-related events. In this vein, the election and implementation of therapeutic interventions that modulate neural plasticity even several years after stroke onset take a special relevance in order to improve clinical outcomes. Improvement of PSCD relies on both the repair of dysfunctional networks and the recruitment of spared neural networks (Dobkin & Dorsch, 2013; Small, Buccino, & Solodkin, 2013) which can be stimulated through different interventions such as cognitive training, drugs, or NIBS administered alone or combined between them.

Drug treatment improves PSCD, even when given unpaired with behavioral treatments (Berthier et al., 2009; Chen et al., 2010; Hong, Shin, Lim, Lee, & Huh, 2012; López-Barroso et al., 2018). However, there is evidence that drug action is boosted when combined with behavioral interventions. Importantly, it seems that drugs combined with intensive training are associated with better outcomes than when combined with distributed therapies (Berthier, Dávila, García-Casares, & Moreno-Torres, 2014). The contribution of adding behavioral interventions to drug treatment results from harnessing *experience-dependent plasticity*, a label used to reflect wiring and rewiring changes in synapses and entire networks in response to experience (Kleim & Jones, 2008; Kolb & Gibb, 2014). Therefore, it seems that drug treatment can prime cortical and subcortical excitability, optimizing learning process promoted by cognitive rehabilitation. This would lead to obtain more pronounced and durable benefits, presumably by converting short-term benefits in long-lasting gains, which may show little decrements even after stopping drug treatment (Berthier et al., 2003; Berthier, Higueras, Fernández, Hinojosa, & Martín, 2006; Berthier, Hinojosa, Martín Mdel, & Fernández, 2003).

In this chapter, we review the pharmacological treatment of PSCD. It the past few years, there have been several tutorial reviews (Berthier, García-Casares, et al., 2011; Llano & Small, 2016) and book chapters (Flanagan & Gordon, 2009; Berthier & Dávila, 2015) on the pharmacotherapy of PSCD. Nearly all this body of work has examined the impact of pharmacological approaches in animal and human studies, focusing on the neurotransmitter systems affected by the stroke and the drugs targeting them to improve outcomes. Therefore, in this chapter besides briefly updating the state-of-the-art and the theoretical rationale for using drugs to treat PSCD, we briefly review the impact of drug treatment on key PSCD such as aphasia, neglect, and cognitive impairment. We also provide some guidelines for refining and expanding the use of efficacy measures and responder analysis methods. Finally, we dedicate a few words to the emerging strategy of combining drugs to further augment and speed up recovery and the manner in which cognition-enhancing drugs modulate neural network reorganization and activity.

19.1.2 Drug Treatment: The State-of-the-Art

Neurorehabilitation is the cornerstone treatment of PSCD, and the complementary role of pharmacotherapy is to prime the brain for enhancing the benefits provided by behavioral interventions. Nevertheless, drug trials aimed to improve cognition in Alzheimer's disease (AD) (Ferris & Farlow, 2013), Parkinson's disease (Emre et al., 2004), and vascular cognitive impairment (VCI) (Guekht et al., 2013; Leijenaar et al., 2018; Perng, Chang, & Tzang, 2018) have been straightforwardly designed, overlooking the key role of neurorehabilitation in augmenting the benefits. The "drug alone" strategy has been conceived in the requirement of proving or disproving the beneficial action of the sole drug, but it disregards the potential action of combined interventions in clinical practice. Even more, the reluctance of evaluating the effects of drugs combined with neurorehabilitation jeopardizes the possibility of revealing a synergistic effect, perhaps not fully observed with the drug-only strategy. Several trials of cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and memantine unpaired with neurorehabilitation have been performed in heterogeneous groups of patients with vascular dementia (VaD) and VCI with mixed results. Small benefits in cognition were achieved, but there was a variable success in behavior and activities of daily living (Birks & Craig, 2006; Birks, McGuinness, & Craig, 2013; Erkinjuntti, Román, & Gauthier, 2004; Farooq, Min, Goshgarian, & Gorelick, 2017; Levine & Langa, 2011), thus restricting their use in clinical practice. By contrast, preliminary evidence from stroke patients with aphasia or neglect indicates that when drug treatment is paired with behavioral interventions, there are benefits in cognitive, behavioral, and quality of life domains (Berthier, 2012; Paolucci, Bureca, Multari, Nocentini, & Matano, 2010; Walker-Batson, Mehta, Smith, & Johnson, 2016).

The neurorehabilitation of PSCD has greatly benefited from neuroscience and neuropsychology insights (Berthier & Pulvermüller, 2011; Llano & Small, 2016), yet clinical translation of positive drug trials continues to lag behind. There are two main reasons that may account for the existent difficulty to overcome the gap between the laboratory research and the application of rehabilitation for PSCD. First, no large-scale randomized controlled trials (RCTs) into the use of pharmaceutical interventions to enhance benefits of cognitive rehabilitation have taken place and, hence, there has been no regulatory approval for any drug to treat such disorders. Second, there are no profit incentives to initiate new clinical trials to generate additional data for regulatory agencies to expand indications of already existent drugs (Berthier, 2014). In part, this is due to the expiration of marketed drug licenses in several countries.

In spite of these restrictions, drug interventions in clinical practice are being increasingly used in both acute in-hospital stroke settings (Barrett et al., 2011) and outpatient rehabilitation units in nearly 40% of cases (Barrett, Levy, & Gonzalez Rothi, 2007; Engelter et al., 2012; Engelter, Frank, Lyrer, & Conzelmann, 2010). Results from a recent prospective, explorative, multicenter study revealed that half of the patients received antidepressant medications to alleviate post-stroke mood

and anxiety disorders, whereas in one-third of the cases drugs were exclusively used with the aim of augmenting rehabilitation gains (Engelter et al., 2010, 2012). While depression is the most frequently treated psychiatric condition, aphasia and neglect are the most commonly treated cognitive disorders. Importantly, patients treated with levodopa, acetylcholinesterase inhibitors (e.g., donepezil, galantamine), and other agents such as antidepressants and stimulants achieved greater improvement in a functional independence measure than untreated patients (Engelter et al., 2010, 2012). Adverse events depend upon the agent used, but in general are temporary (Engelter et al., 2010). Although more studies are needed, the prescription of these drugs in clinical practice as "off-label" medications is supported by the results of several well-designed clinical trials. For example, there is moderate evidence (Level 1b) based on "proof-of-concept" RCTs that the use of levodopa, donepezil, galantamine, and memantine significantly improves aphasia severity, deficits in speech production (naming) and comprehension in patients with chronic stroke (see Berthier, Pulvermüller, Dávila, Casares, & Gutiérrez, 2011; Salter, Teasell, Bhogal, Zettler, & Foley, 2012; Teasell et al., 2012). Finally, an important aspect to consider before implementing drug treatment for PSCD is to avoid, whenever feasible, the prescription of compounds for the treatment of comorbid disorders (e.g., topiramate for seizures and migraine) (see Cappa, Ortelli, Garibotto, & Zamboni, 2007; Llano & Small, 2016) which can deleteriously impact on cognitive functions (Falchook, Heilman, Finney, Gonzalez-Rothi, & Nadeau, 2014; Goldstein, 1995, 1998).

19.1.3 Theoretical Justification for Using Drugs in Post-stroke Cognitive Disorders

Stroke lesions may disrupt the activity of various neurotransmitter systems at the level of selected basal forebrain, brainstem and deep grey nuclei, and cerebral cortex (Berthier & Pulvermüller, 2011; Bohnen, Müller, Kuwabara, Constantine, & Studenski, 2009; Husain & Mehta, 2011). This would imply that when damage to one neurotransmitter system is not significant, there exists the possibility of rescuing salvaged components of this system by modulating its spared receptors with drugs. Similarly, theoretical and applied research indicates that the justification for using pharmacological agents to treat PSCD is to leverage the activity of specific neurotransmitters in dysfunctional but not completely infarcted tissue. Circumscribed or diffuse brain lesions affect the activity of several neurotransmitters; thus, normalizing their availability at synapses with drugs is an useful strategy to boost cognition in brain-damaged patients (Berthier & Pulvermüller, 2011). In addition, since stroke decreases integration and information capacity in several networks (Adhikari et al., 2017), it may be desirable that the beneficial effect of drug treatment is exerted in (dysfunctional and healthy) brain tissue nearby and distant to the lesion that are part of one or more neural networks with specific functions (Wirsich et al., 2018). In the case that perilesional areas share multiple receptor fingerprints with the damaged

ones, it is tempting to speculate that drugs acting on perilesional tissue can play a key role in restoring function (Berthier et al., 2017), a mechanism termed "direct restoration" (Small et al., 2013). It is also possible that after the stroke, areas distant to the damaged region are recruited and remodeled to instantiate the original function, a mechanism known as "indirect restoration" (Small et al., 2013). If these remote areas belong to the same functional network, they may have the same transmitter receptor density (Hiraoka et al., 2009; Palomero-Gallagher & Zilles, 2017), so that drug treatment can render them more adaptable to comply with new task demands. Based on the connectivity of two distant brain areas, one neurotransmitter system (i.e., acetylcholine) can interact with others (i.e., glutamate, dopamine) (Mena-Segovia & Bolam, 2017). Therefore, pharmacological agents used with the aim of modulating the activity of a single neurotransmitter to enhance a cognitive process probably also influence the function of other neurotransmitters (Froudist-Walsh, López-Barroso, Torres-Prioris, Croxson, & Berthier, 2017; Furey, 2011; Mena-Segovia & Bolam, 2017). Altogether, these arguments suggest that future pharmacological studies aimed to enhance cognition in stroke with a drug need to consider its role in modulating more than a single transmitter system. This action can be boosted further by combining two agents, predominantly acting on different neurotransmitters (Berthier, Dávila, & Torres-Prioris, 2015; Froudist-Walsh et al., 2017). Combined therapies wherein one drug is added to an ongoing treatment with another agent (i.e., add-on therapy with memantine in patients already receiving donepezil or galantamine) are regularly used for the symptomatic treatment of severe AD (Atri et al., 2013; Peters et al., 2012; Tariot et al., 2004) and this approach is being translated to treat PSCD (Walker-Batson et al., 2016; López-Barroso et al., 2018—see Sect. 19.1.9). Although several PSCD have been treated with drugs, in the next sections we analyze the status of drug treatment in the most commonly investigated PSCD (aphasia, neglect, and cognitive impairment).

19.1.4 Aphasia

Aphasia, defined as the partial or complete loss of language function after acquired brain damage, is amenable to pharmacological treatment (Albert, Bachman, Morgan, & Helm-Estabrooks, 1988; Berthier, 2005; Llano & Small, 2016). Aphasia is the most frequent PSCD after left hemisphere lesions and it is independently associated with increased length of stay and complications during the acute stroke admission (Boehme, Martin-Schild, Marshall, & Lazar, 2016). Aphasia represents the PSCD most commonly treated with single (Chen et al., 2010; Hong et al., 2012) or combined drugs (Engelter et al., 2010, 2012) alongside language therapy (Berthier et al., 2009). Table 19.1 shows pharmacological studies carried out in aphasia (only recent data are shown in the text). Several agents have been used with variable results (see Berthier & Pulvermüller, 2011; Llano & Small, 2016), probably because until now there are no guidelines for selecting the period after the stroke when the drug provides greatest benefits (Zhang, Wei, Chen, & Luo 2016) or the "right" drug

Table 19.1 Clinical trials of pharmacotherapy of post-stroke aphasia

Agent	Mechanism of action	Study design	Number of studies/authors	Outcomes
Bromocriptine	Dopamine agonist	Single cases Case series Group studies Open label RCT(cross-over designs)	15 Albert et al. (1988) Bachman and Morgan (1988) MacLennan, Nicholas, Morley, et al. (1991) Gupta and Mlcoch (1992) Sabe, Leiguarda, and Starkstein (1992) Sabe, Salvarezza, Cuerva, Leiguarda, and Starkstein (1995) Gupta, Mlcoch, Scolaro, and Moritz (1995) Ozeren, Sarica, Mavi, and Demirkiran (1995) Berthier (1999) Bragoni et al. (2000) Gold, VanDam, and Silliman (2000) Hughes, Jacobs, and Heilman (2000) Raymer et al. (2001) Ashtary, Janghorbani, Chitsaz, Reisi, and Bahrami (2006) Galling, Goorah, Berthier, and Sage (2014)	Positive effects in single cases, cases series, and open-label trials mainly in transcortical motor aphasia, dynamic aphasia, and Broca's aphasia of mild to moderate severity. Improvement on production tasks in chronic patients. Lack of improvement in non-verbal cognitive abilities. Variable outcomes in moderate Broca's aphasia and lack of positive effects in severe cases. Three of four RCTs are negative. Only three trials combined bromocriptine with speech-language therapy. Limited response to speech-language therapy improves with the addition of bromocriptine. Improvement in apathy and depression is possible. Beneficial effects on functions dependent upon dopaminergic activity with little impact on other language and cognitive deficits
Levodopa	Dopamine agonist	RCT Group studies Open label RCT (parallel and cross-over designs)	4 Hacki, Kenklies, Hofmann, and Haferkamp (1990) Seniów, Litwin, Litwin, Leśniak, and Członkowska (2009) Leemann, Laganaro, Chetelat-Mabillard, and Schnider (2011) Breitenstein et al. (2015)	Anecdotal evidence of improvement of dysarthria and aphonia. Positive effects in chronic patients when given just before each session of speech-language therapy on naming and repetition especially in patients with frontal lobe damage. However, levodopa does not augment the positive response to high-intensity language therapy in subacute and chronic aphasia
Amantadine	Dopamine agonist, Uncompetitive NMDA receptor antagonist. Possible anti-cholinergic effects	Single case Open label	1 Barrett and Eslinger (2007)	Useful in transcortical aphasias. Improvement of verbal fluency in two transcortical motor aphasic patients with left putaminal hemorrhage and right anterior cerebral artery infarction when paired with speech-language therapy. Anti-cholinergic effects of this drug may negatively affect attention and memory functioning

(continued)

Table 19.1 (continued)

Agent	Mechanism of action	Study design	Number of studies/authors	Outcomes
Dexamphetamine	Catecholamine uptake inhibition	Single cases Case series Open label RCT (parallel and cross-over designs)	8 Benson (1970) Walker-Batson et al. (1992) McNeil et al. (1997) Walker-Batson et al. (2001), Walker-Batson et al. (2016) Whiting, Chenery, Chalk, and Copland (2007) Spiegel and Alexander (2011) Keser et al. (2017)	Positive effects on overall performance in communication in subacute stroke with variable efficacy at chronic stages. Negative effect on lexical-semantic deficits. Variable outcomes on naming performance when paired with model-based (semantic plus phonological) naming therapy in chronic stages. Combined therapy with amphetamine and donepezil improved language and communication deficits. Positive effects when paired with transcranial direct current stimulation and melodic intonation therapy in subjects with chronic nonfluent aphasia
Piracetam	Neuronal and vascular unspecific effects	RCT	7 Herrschaft (1988) Enderby, Broeckx, Hospers, Schildermans, and Deberdt (1994) Huber, Willmes, Poeck, Van Vleymen, and Deberdt (1997) Kessler, Thiel, Karbe, and Heiss (2000) Szelies, Mielke, Kessler, and Heiss (2011) Güngör, Terzi, and Onar (2011) Hamzei-Moghaddam, Shafa, Nazari, and Akbari (2014)	Short-lived positive effects in the acute aphasia on overall language measures, spontaneous speech, and written language. It only benefits written language at the end of the trials (see Zhang et al., 2016). Language deficit improvement correlates with both an increase in blood flow in the left peri-Sylvian cortex and shift in alpha-rhythm from frontal to occipital regions. Lack of long-term benefits in cases with large infarcts
Physostigmine	IAChE	Open label	1 Jacobs et al. (1996)	Positive effects in combination with lecithin on chronic anomia, but not on other cognitive and mood variables. Not used in clinical practice

Bifemelane	IAChE	RCT	2 Kabasawa et al. (1994) Tanaka, Miyazaki, & Albert (1997)	Positive effects on naming, comprehension, and repetition, but not in fluency. Language improvements correlate with an increase in blood flow in the left peri-Sylvian cortex
Donepezil	IAChE	Single cases Case series Group studies Open label RCT (parallel and cross-over designs)	9 Hughes et al. (2000) Tsz-Ming and Kaufer (2001) Berthier, Hinojosa, et al. (2003), Berthier, Pujol, et al. (2003) Berthier et al. (2006) Chen et al. (2010) Berthier et al. (2014) Yoon, Kim, An, and Kim (2015) Berthier et al. (2017) Woodhead et al. (2017)	Positive effects on aphasia severity and everyday functional communication. Significant benefits on spontaneous speech, comprehension, and naming in chronic aphasia. Efficacy maintained at long-term follow-up. Beneficial effects on acute aphasia. Beneficial effect when combined with intensive sentence-repetition and audiovisual repetition-imitation training and in Wernicke aphasia associated with bitemporal lesions. Negative outcome in subjects with chronic receptive phonological impairments associated with Wernicke and global aphasias, but positive response with behavioral training
Galantamine	Competitive IAChE with dual action (allosteric modulation of the α4β42 and α-7nAChR)	Open-label case-control study	1 Hong et al. (2012)	Positive effects on aphasia severity. Significant benefits on spontaneous speech, comprehension, and naming in chronic aphasia. Good responsiveness to drug in patients with possible cholinergic involvement at subcortical sites
Memantine	Moderate affinity, uncompetitive NMDA receptor antagonist with strong voltage-dependency and fast kinetics	RCT Group study	1 Berthier et al. (2009)	Positive effects on aphasia severity and everyday functional communication. Significant benefits on spontaneous speech, comprehension, and naming. Better results pairing memantine with intensive speech-language therapy. Efficacy maintained at long-term follow-up (6 months)
Fluvoxamine	SSRI	RCT	1 Tanaka and Bachman (2007)	Positive effects on anomia

(continued)

Table 19.1 (continued)

Agent	Mechanism of action	Study design	Number of studies/authors	Outcomes
Moclobemide	IMAO-A	RCT	1 Laska et al. (2005)	Negative effect
Zolpidem	GABA agonist interacting with Ω_1 receptor	Single case	1 Cohen et al. (2003)	Positive reversible effect on verbal fluency in Broca's aphasia
Propranolol	β-blocking agent	RCT	1 Beversdorf et al. (2007)	Positive effect on naming in chronic Broca's aphasia
Vasopressin	Neurotrophic effect mediated by the V1 receptor	RCT	1 Belokoskova, Tsikunov, and Klement'ev (2002)	Positive effect on expressive and receptive language functions
Cerebrolysin	Mimics endogenous neurotrophic factors	RCT	1 Jianu et al. (2010)	Positive effect on spontaneous speech, repetition, and naming in acute Broca's aphasia

Note: Only clinical trials providing a neuroscientifically motivated rationale for the selected treatment of post-stroke aphasia are included. Other agents (haloperidol, thiazide, chlordiazepoxide) lacking a theoretical rationale were excluded. *IAChE* acetylcholinesterase inhibitor; NMDA: *N*-methyl-D-aspartate; SSRI: selective serotonin reuptake inhibitor; IMAO-A: inhibitor monoaminoxidase A; GABA: γ-aminobutyric acid; RCT: randomized controlled trial; SLT: speech-language therapy.

to improve speech production, comprehension, or both (Berthier et al., 2015). For example, the effects of piracetam on language deficits are short-lived with no long-term benefits (Güngör et al., 2011) and the outcomes of dopamine agonists (bromocriptine, levodopa) are mixed (Berthier, 2005; Gill & Leff, 2014). Regarding dopamine agonists, negative outcomes in group studies are likely to have resulted from an inadequate inclusion of candidates (global aphasias, large lesions) (Ashtary et al., 2006; Gupta et al., 1995; Sabe et al., 1995). The wrong selection of some candidates may have masked positive effects to dopaminergic manipulation in patients with a suitable profile. At present, the best candidates for dopaminergic stimulation seem to be patients with reduced drive to generate spontaneous speech (e.g., nonfluent transcortical aphasias) secondary to frontal and/or basal ganglia lesions (Cahana-Amitay, Albert, & Oveis, 2014; Gill & Leff, 2014; Raymer, 2003). The beneficial action of dopaminergic stimulation in such cases is the improvement of speech initiation, pauses in conversation, paraphasias, and naming (Albert et al., 1988; Galling et al., 2014). The action of dopaminergic stimulation to improve aphasia is through modulation of motor control, incentive reward, memory, attention, problem-solving, and learning via restoring dopaminergic activity in frontal-basal ganglia circuits (Berthier, García-Casares, et al., 2011; Berthier, Pulvermüller, et al., 2011; Cahana-Amitay et al., 2014; Gill & Leff, 2014; Seniów et al., 2009). Adding speech-language therapy to dopaminergic stimulation seems to be effective for bromocriptine (Bragoni et al., 2000; Galling et al., 2014), but it is controversial for levodopa, with one study reporting beneficial effects when levodopa was given soon before starting each daily session of aphasia therapy (Seniów et al., 2009), whereas others found that levodopa did not augment the benefit provided by intensive language therapy (Breitenstein et al., 2015; Leemann et al., 2011).

In recent years, the pharmacologic armamentarium to treat post-stroke aphasia has been expanded to incorporate anti-dementia drugs with action on the cholinergic and glutamatergic neurotransmitter systems (Berthier, García-Casares, et al., 2011; Berthier, Pulvermüller, et al., 2011) (Table 19.1). The cholinesterase inhibitor donepezil is safe and well tolerated for the treatment of acute stroke (Barrett et al., 2011), and single cases, open-label trials, and RCTs of this agent in patients with acute and chronic post-stroke aphasia showed improvements in aphasia severity, picture naming, comprehension, and everyday communication (Berthier et al., 2006; Berthier, Hinojosa, et al., 2003; Berthier, Pujol, et al., 2003; Chen et al., 2010; Yoon et al., 2015). Recent data raise the possibility that donepezil is more effective to treat production than comprehension deficits (Woodhead et al., 2017). Some support for this hypothesis comes from the study of patients with conduction aphasia and deficits in speech production (Berthier et al., 2014, 2017) and from patients with comprehension deficits associated with Wernicke's or global aphasias (Woodhead et al., 2017; Yoon et al., 2015). On one hand, donepezil significantly improved speech production in patients with chronic conduction aphasia and its action was better when it was combined with massed sentence-repetition training (40 h in 8 weeks) than with a more distributed therapy (40 h in 16 weeks) (Berthier et al., 2014). In addition, the combination of donepezil with intensive audiovisual,

repetition-imitation training improved speech production and everyday communication deficits in a patient with chronic, crossed, conduction aphasia by inducing structural plasticity in right hemisphere white matter tracts partially affected or spared by the lesion (Berthier et al., 2017). On the other hand, the extant data on the role of donepezil in aphasic patients with receptive deficits is divergent. Donepezil treatment improved auditory comprehension and other language deficits in a patient with extensive damage to the left temporal and parietal lobes sustained 8 years before and who incurred a new right temporal infarction causing severe Wernicke's aphasia (Yoon et al., 2015). Comprehension improvements with donepezil after the new stroke were associated with increased metabolic activity in bilateral perilesional areas and left cerebellum (Yoon et al., 2015). Nevertheless, donepezil led only to short-lived improvements in a patient with severe chronic Wernicke's aphasia (case 11 in Berthier, 2005). In the same vein, a recent RCT of donepezil in patients with chronic moderate-to-severe Wernicke's and global aphasias was negative in improving speech comprehension abilities (Woodhead et al., 2017). It remains to be determined whether large lesions such as those occurring in global and Wernicke's aphasia markedly deplete cortical cholinergic receptors, making these cases less responsive to cholinergic modulation. Note that in the only RCT of galantamine performed in chronic stroke aphasic patients, improvements in language performance were found mainly in cases with left subcortical involvement affecting the trajectory of the lateral cholinergic pathway (Hong et al., 2012). The potential role of rivastigmine in post-stroke aphasia has not yet been explored.

The NMDA receptors antagonist memantine given in the absence of speech-language therapy improved aphasia severity and communication deficits, and synergistic effects were obtained when intensive aphasia therapy was added (Berthier et al., 2009). The beneficial effects of the drug administered alone and in combination with behavioral training were associated with bilateral neural reorganization and the obtained gains persisted on long-term follow-up. (Barbancho et al., 2015; Berthier et al., 2009). The potential role of other pharmacological agents is included in Table 19.1**.**

19.1.5 Neglect

Post-stroke neglect is a condition characterized by a difficulty to attend, orient, or respond to stimuli presented in the hemispace contralateral to the brain lesion, usually the left side (Heilman, Bowers, Valenstein, & Watson, 1987). It is a complex syndrome with multiple underlying mechanisms and profiles, and a reported incidence ranging from 48% (Buxbaum et al., 2004) to 82% (Stone, Halligan, & Greenwood, 1993) of patients with right hemisphere strokes. Patients with different profiles of neglect often show concomitant motor deficits (hemiparesis/hemiplegia) and behavioral disorders (e.g., anosognosia for motor and cognitive deficits, somatoparaphrenia) (Orfei et al., 2007; Vallar & Ronchi, 2009). Importantly, reduced insight for neglect, expressed as either anosognosia, overestimation of spatial abili-

ties or confabulation, may impact on rehabilitation (Chen & Toglia, 2018; Starkstein, este Jorge se ha colado aqui & Robinson, 2010) and daily life functioning (Kortte & Hillis, 2011). The abnormal cognitive processes underpinning visuospatial neglect involve attention and/or sensory processing. Behavioral therapies such as prism adaptation (Rossetti, Rode, Pisella, et al., 1998) and visual scanning training are the most frequent behavioral interventions. Other promising techniques in the rehabilitation of neglect have emerged in the last decades such as virtual reality training and NIBS (Fasotti & van Kessel, 2013; Kortte & Hillis, 2011), but recovery is not always complete and mild symptoms persist (~1 year) in a large percentage (40–75%) of patients (Buxbaum, Ferraro, Whyte, et al., 2007; Nijboer, Kollen, & Kwakkel, 2013). Therefore, the use of other interventions to augment gains provided by neurorehabilitation such as pharmacotherapy is advisable.

Experimental treatments of neglect in animals with brain lesions have generally focused on dopaminergic agonists and progesterone, proving positive effects in neglect symptomatology (e.g., somatosensory neglect) (Corwin et al., 1986; Goss, Hoffman, & Stein, 2003; Wali, Ishrat, Won, Stein, & Sayeed, 2014; Yousuf, Atif, Sayeed, Tang, & Stein, 2014). In humans, pharmacological approaches have been implemented as adjuvant therapy for visuospatial neglect but the role of drug treatment for co-occurring awareness syndromes (e.g., anosognosia, confabulation) has not been examined so far. Even though neglect is the common signature of large right hemisphere strokes, there is limited research on its pharmacological treatment (ten studies) when compared with the number of drug studies carried out in aphasia (55 studies) after left hemisphere stroke (Tables 19.1 and 19.2).

Three classes of drugs have been tested for neglect: dopaminergic, noradrenergic and cholinergic (see Table 19.2). Several compounds, including bromocriptine, guanfacine, apomorphine, rotigotine, levodopa, nicotine, and rivastigmine, have been investigated with variable outcomes. Dopaminergic drugs are the agents most investigated for the treatment of neglect. The first human investigation used bromocriptine in an open-label study in two patients with visuospatial neglect secondary to large ischemic strokes in the right frontal-temporal-parietal area (Fleet et al., 1987). Daily administration of bromocriptine (3–4 weeks) improved performance in both basic reaction time tests and classical paper-and-pencil neglect tests, although there were some individual differences in response to treatment and long-term maintenance of gains. Nevertheless, a single low dose (2.5 mg) of bromocriptine given to seven patients with right hemisphere strokes worsened latent visuospatial neglect, as manifested by a decrement of the time dedicated to exploration of the left hemispace (Grujic et al., 1998). The use of a single low dose of bromocriptine in such study limits reaching conclusions for clinical practice.

The use of traditional dopaminergic drugs (levodopa and bromocriptine) is flawed by several contraindications and adverse events, thus jeopardizing treatment continuity. Therefore, there is an implicit expectation that modern dopaminergic drugs, like rotigotine and ropirinole, with better efficacy and tolerance profiles than levodopa and bromocriptine may enhance the benefits and adherence to treatment in patients with PSCD (Galling et al., 2014; Gill & Leff, 2014). Recently, a pharmacological intervention in post-stroke neglect and unilateral motor deficit was

Table 19.2 Clinical trials of pharmacotherapy of post-stroke neglect

Agent	Mechanism of action	Study design	Number of studies	Outcomes
Bromocritptine	Dopamine agonist acting in D2 postsynaptic dopamine receptors	Single case Case series Open label	4 Fleet, Valenstein, Watson, et al. (1987) Grujic et al. (1998) Hurford, Stringer, and Jann (1998) Barrett, Crucian, Schwartz, and Heilman (1999)	Positive and negative effects have been reported in acute and chronic post-stroke patients. Studies revealing worsening of neglect have reported increase in the amount of time dedicated to explore the left side of the space, decrease in measures of spatial bias (e.g., line bisection), and slight increase in left side auditory extinction. Positive effects include improvement in basic reaction time tests and pen-and-paper neglect tests (line and shape cancellation, and line bisection), as well as in social interaction and kinesis measures. Right putamen damage might be related with detrimental effect of the drug
Methylfenidate	Dopamine agonist	Single case Open label	1 Hurford et al. (1998)	Clinical improvement of neglect symptoms in perceptual (visual and auditory) and perceptual-motor tasks. However, administration of bromocriptine in the same patient induced better outcomes
Rotigotine	Dopamine agonist	Group study RCT	1 Gorgoraptis et al. (2012)	Significant improvement in the number of targets identified on the left side revealed by different objective tests in acute and chronic right hemisphere stroke patients with neglect. Positive effects were not related to prefrontal cortex preservation. No motor improvement was found
Levodopa	Dopamine agonist	Single case Open label	1 Mukand et al. (2001)	Beneficial effects in 3 out of 4 patients after 1 week of carbidopa L-dopa. Significantly improvement on the performance of standardized test of neglect and in functional status

(continued)

Table 19.2 (continued)

Agent	Mechanism of action	Study design	Number of studies	Outcomes
Apomorphine	Dopamine agonist acting on dopamine D1 and D2 receptors	Case series Open label	1 Geminiani, Bottini, and Sterzi (1998)	Significant improvement in three patients in two modalities of a search task, targeting perceptual and perceptual-motor components of neglect. Greater improvement in the perceptual-motor condition
Guanfacine	Noradrenergic agonist acting on noradrenergic alpha-2A agonist	RCT Group study	2 Malhotra, Parton, Greenwood, and Husain (2006) Dalmaijer et al. (2018)	Single dose of the drug induces significant improvement in leftward space exploration with increment in target detection. No effect on performance in sustained attention or spatial working memory tasks. Drug seems to act on dorsolateral prefrontal areas. Patients showing benefits had a spared dorsolateral prefrontal cortex
Rivastigmine	Dual inhibitor of acetylcholines-terase and butyrylcholi-nesterase	Group study Open label	1 Paolucci et al. (2010)	Drug alone has positive effect on neglect symptoms. However, significantly better results were seen when applied together with a therapy (physical therapy, swallowing, occupational therapy, and specific neglect therapy) (5–6 days/week)
Nicotine	Cholinergic agonist acting on nicotine receptors	Case series RCT	2 Vossel, Kukolja, Thimm, Thiel, and Fink (2010) Lucas et al. (2013)	Single dose of nicotine treatment facilitates attentional reorienting, improving target detection and progressive exploration of the contralesional space. A reduced reaction time in attentional paradigms (location-cueing paradigm) was found although no changes were seen in other tasks (e.g., line bisection). Improvements seem to be mediated by increased general attentional capacity, without effect in other mechanisms impaired in neglect (e.g., perceptual). The beneficial effects may be associated with intact right parietal cortex, basal forebrain, and medial temporal lobe

RCT randomized controlled trial, *IAChE* inhibitor of acetylcholinesterase

performed using rotigotine in a RCT with three phases (A_1: pretreatment; B: transdermal patches of rotigotine, 9 mg; A_2: drug withdrawal) in 16 patients. Treatment with rotigotine, administered for 7–11 days, significantly increased the number of targets identified on the left and decreased the rightward spatial bias on a shape cancellation task.

Noradrenergic modulators may also ameliorate neglect. Studies in monkeys demonstrated that the administration of guanfacine, a noradrenergic alpha-2A agonist, improves performance on spatial delayed-response tasks by modulating the activity of the dorsolateral prefrontal cortex (Arnstein, 1998). A large two-month placebo-controlled RCT of guanfacine extended release in children and adolescents with attention deficit hyperactivity disorder, showed beneficial effects in attention and behavior (Biederman et al., 2008). In 2010, guanfacine was licensed for the treatment of attention deficit hyperactivity disorder for people 6–17 years old but not for adults. Two studies with guanfacine in post-stroke neglect used a single dose (Dalmaijer et al., 2018; Malhotra et al., 2006). A small RCT showed benefits in two out of three patients with visuospatial neglect improving in the detection of targets on the left side of space on standard tests of neglect and in a computerized search task, probably by enhancing attentional abilities through stimulation of the dorsolateral prefrontal cortex (Malhotra et al., 2006). In fact, lesions in the two "responder" patients spared the right dorsolateral prefrontal cortex, whereas extensive damage to this region was found in the "non-responder" patient (Malhotra et al., 2006). These results have been replicated in a larger trial (Dalmaijer et al., 2018). Long-term treatment with this compound is warranted.

The activity of acetylcholine was also modulated in post-stroke neglect with two compounds, nicotine and rivastigmine. Nicotine acts in the central nervous system as an agonist of nicotinic acetylcholine receptors, thus increasing acetylcholine action. Two studies using single dose of nicotine in patients with visuospatial neglect have reported faster reaction times (Vossel et al., 2010) on different tasks of visuospatial exploration and orienting, improvement of target detection and exploration in both sides of space with greater improvement in the contralesional side and increased duration of search times (Lucas et al., 2013). The effectiveness of nicotine seems to depend on the location of the right hemisphere damage. For instance, a lesion-symptom mapping study reported that the effects of a single dose of nicotine in reorienting attention to contralesional space are better when the right parietal and temporal areas are spared (Vossel et al., 2010). Despite evidence showing that cognitive rehabilitation alone improves the performance on some neglect test, nowadays the more promising cognitive rehabilitation approaches come from the use of combined therapies. In this line, Paolucci et al. (2010) studied the beneficial effect derived from the administration of rivastigmine combined with behavioral therapy for neglect rehabilitation. They compared two groups (ten patients in each group) of subacute (>1 month post-stroke) neglect patients. One group received low therapeutic doses of rivastigmine (6 mg/day) for 8 weeks plus cognitive rehabilitation therapy for visuospatial neglect and the other group received only cognitive rehabilitation. The group that received a combined treatment significantly improved performance on the letter cancellation and Wundt–Jastrow illusion tests, and there was better

response on both tasks than that observed in patients receiving rehabilitation only. Thus, it seems that rivastigmine improves and accelerates recovery.

19.1.6 Vascular Cognitive Impairment

Several clinical subtypes of cognitive impairment due to vascular lesions exist, ranging in severity from mild cognitive impairment to dementia. The clinical profile of cognitive deficits in VCI (psychomotor slowing, dysexecutive deficits) is predominantly subcortical, which results in part from disruption of cholinergic pathways (Bohnen, Bogan, & Müller, 2009; Bohnen, Müller, et al., 2009; Grantham & Geerts, 2002; Mesulam, Siddiqe, & Cohen, 2003; Román & Kalaria, 2006). In support, magnetic resonance imaging of elderly non-demented patients usually shows periventricular frontal white matter vascular lesions interrupting the lateral cholinergic pathway. These lesions are associated with slow information processing (psychomotor retardation) linked to PET evidence of cholinergic denervation in posterior cortical sites (Bohnen, Bogan, & Müller, 2009, Bohnen, Müller, et al., 2009). Medications approved for the treatment of AD have also been investigated for the treatment of PSCD. Acetylcholinesterase inhibitors improve cognition in patients with PSCD presumably by increasing the availability of acetylcholine in the synaptic space. There is also some evidence that these medications increase cerebral blood flow (Grantham & Geerts, 2002; Mesulam et al., 2003; Román & Kalaria, 2006). Therefore, various clinical trials have assessed the efficacy of three available acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) in VCI and dementia of vascular origin (Table 19.3). Other compounds, supplements and herbal medicines (actovegin, citicoline, huperzine A, and vinpocetine) have also been investigated in the VaD population, but since their therapeutic effects are inconclusive they are not further analyzed here (see Farooq et al., 2017; Jian, Shi, Tian, & Ni, 2015) (see Table 19.3).

Donepezil demonstrated significant cognitive improvements on patients with mild to moderate VaD (Black et al., 2003; Chen, Zhang, Wang, Yuan, & Hu, 2016; Román et al., 2010; Wilkinson et al., 2003), although some cognitive deficits were not responsive to drug administration (Black et al., 2003). Intriguingly, significant improvement in global function was observed in patients receiving low doses (5 mg/day) (Black et al., 2003; Wilkinson et al., 2003). Donepezil has also been tried in patients with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) (Dichgans et al., 2008). Donepezil treatment resulted in no improvement in the primary outcome measure (V-ADAS-cog, a vascular disease version of Alzheimer's Disease Assessment Scale cognitive subscale-ADAS-Cog), but improvements were noted on other measures of executive function in a secondary analysis (Dichgans et al., 2008). Overall, the results of these trials indicate that donepezil may have a greater impact on cognitive than global function and activities of daily living in patients with VaD. Donepezil was well tolerated, and

Table 19.3 Clinical trials of pharmacotherapy of vascular cognitive impairment

Agent	Mechanism of action	Study design	Number of studies	Outcomes
Memantine	Moderate affinity, uncompetitive NMDA receptor antagonist with strong voltage-dependency and fast kinetics	RCTs	2 Orgogozo et al. (2002) Wilcock et al. (2002)	Positive effects on cognition in patients with mild to moderate VaD, but there was no significant improvement in global functioning. Overall, memantine was well tolerated
Donepezil	IAChE	RCTs	4 Wilkinson et al. (2003) Black et al. (2003) Dichgans et al. (2008) Román et al. (2010)	Positive effects on cognition in patients with mild to moderate VaD, although some items on the cognitive battery did not improve. Significant improvement in global function was observed in patients receiving 5 mg/day. In CADASIL, patients' measures of executive function were improved. Donepezil was well tolerated
Rivastigmine	Dual inhibitor of acetylcholinesterase and butyrylcholinesterase	RCT Open-label controlled study	3 Moretti et al. (2002) Ballard et al. (2008) Narasimhalu et al. (2010)	Positive effects on cognitive performance in patients with VaD or probable VaD. Improvement on verbal fluency in VCI patients, and executive functions in subcortical VaD patients. No differences on global assessment, activities of daily living, or behavioral measures in VaD patients. Overall, rivastigmine was well tolerated
Galantamine	Dual action: reversible and competitive IAChE and allosteric modulator of nicotine receptors	RCT	2 Erkinjuntti et al. (2002) Auchus et al. (2007)	Positive effects on language and memory, and executive function (Auchus et al., 2007's trial) in VaD patients. Mixed results on activities of daily living and global functioning. Benefits on behavioral symptoms
Citicoline	Enhances brain phosphatidylcholine and acetylcholine synthesis, both important for cell membranes reparation	RCT	1 Cohen et al. (2003)	Lack of effect. Overall, the administration of citicoline in patient with VaD did not show beneficial effects on cognition in comparison to the placebo control group. Significant decline in cognitive performance was observed in both groups at 12 months of follow-up

Huperzine A	IAChE and NMDA receptor antagonist	RCT	1 Xu et al. 2012 Zhou & Sheng (2013)	Positive effects on cognition in VaD patients compared to the vitamin C control group with significant improvements on general cognition, activities of daily living, and in dementia rating scores. Huperzine A was well tolerated
Ginkgo biloba extract (EGb761®)	Antioxidant and anti-inflammatory effects. Increases cerebral blood flow and antiplatelet effects	RCTs	2 Demarin et al. (2017) Napreyeyenko et al. (2007)	Overall small positive effects on changes in cognition were present by slowing down decline in patients with VaD, but not in the placebo group. No changes in global functioning compared to control group. Beneficial changes in neuropsychiatric symptoms and activities of daily living in one trial (Napreyeyenko et al., 2007). Small adverse reactions were reported
Folic acid (vitamin B^9)	Reduces elevated plasma levels of homocysteine	RCT	1 Jian et al. (2013)	Positive effects on cognition after 24 weeks as measured by a multimodal cognitive assessment scale. Folic acid supplementation for 3 years seems to improve cognitive domains that usually tend to decline with age
Nimodipine	Calcium antagonist	RCT	3 Besson et al. (1988) Pantoni et al. (2000) Pantoni at al. (2005)	Small positive effects on cognition in patients with small vessel VaD but not for multi-infarct dementia. Patients scored higher in lexical production and less frequently showed cognitive or global deterioration compared to placebo patients. Data on longer-term outcomes are lacking. Nimodipine was well tolerated with few side effects
Nicardipine	Calcium antagonist	RCT Open-label	2 Spanish Group of Nicardipine Study in Vascular Dementia (1999) González-González (2000)	Positive effect on cognitive decline of vascular origin. Six months administration of the drug slows the rate of cognitive decline, especially in females

RCT randomized controlled trial, *VaD* vascular dementia, *IAChE* acetylcholinesterase inhibitor

withdrawals due to side effects were relatively low (Black et al., 2003; Román et al., 2010; Wilkinson et al., 2003).

Rivastigmine has also improved cognitive performance in patients with VaD (Ballard et al., 2008), semantic verbal fluency on VCI patients (Narasimhalu et al., 2010), and executive functions in subcortical VaD patients (Moretti et al., 2002). However, no differences were observed on global assessment, activities of daily living or behavioral measures in VaD patients. Exploratory analyses showed that improvement in cognition was more pronounced in older subjects, which likely points to the well-known drug effect on concomitant AD in this age group (Ballard et al., 2008). Overall, rivastigmine was well tolerated. Finally, galantamine seems to improve cognition in VaD patients, particularly executive functions, but it does not have a documented global clinical benefit (Chen et al., 2016).

Like acetylcholinesterase inhibitors, memantine has been demonstrated to be safe and effective in the symptomatic treatment of AD. This drug is a NMDA receptor antagonist with strong voltage-dependency and fast kinetics. These properties allow memantine to block the excessive activity of glutamate without interfering with physiological glutamatergic neurotransmission (Parsons, Stöffler, & Danysz, 2007) eventually contributing to improvement (Rogawski & Wenk, 2003). Otherwise, cortical neuronal loss in patients with ischemia may be related to glutamate toxicity through excessive NMDA stimulation, and memantine blocking pathological stimulation of NMDA receptors may be helpful to protect against further damage in VaD. Thus, memantine could theoretically protect against weak excitotoxicity, while sparing synaptic responses required for normal behavioral functioning, cognition, and memory. Findings suggest that memantine could have a positive effect on cognition in patients with mild to moderate VaD, but there was no significant improvement in global functioning. In any case, beneficial effects on cognition were maintained at the 28 weeks of follow-up (Orgogozo et al., 2002; Wilcock et al., 2002). Also, there was a small reduction in a behavioral disturbance scale in subjects with mild to moderately advanced VaD (Orgogozo et al., 2002).

In summary, acetylcholinesterase inhibitors and memantine may have modest beneficial effects on cognitive symptoms of VaD, although without a concomitant global or clinical benefit in most cases. This would explain why no drug has been licensed for VaD. Moreover, some studies did not entirely rule out the possibility that a proportion of enrolled patients had concomitant AD with vascular disease, and that the beneficial effect of the drug was due to its activity directed at AD-related neuropathology rather than at pathological changes underlying VaD. Future studies need to take into consideration the specific location of vascular lesions in VCI (Grysiewicz & Gorelick, 2012). Although this key issue has not been explored in pivotal drug trials of VCI and VaD, donepezil was effective in improving cognitive failure (executive functions and goal-directed behaviors) in a case with a single strategic left-thalamic infarct (Riveros, Chabriat, Flores, Alvarez, & Slachevsky, 2011). Moreover, amnesia after basal forebrain lesions secondary to surgical repair of anterior communicating artery aneurysms (Benke, Köylü, Delazer, Trinka, & Kemmler, 2005) and general cognitive function after right hemisphere stroke (Chang et al., 2011) also improved with donepezil treatment.

In the next sections, we address some issues that require attention in future studies of pharmacotherapy of PSCD.

19.1.7 Refining and Expanding the Use of Efficacy Measures

A clinical intervention trial should be able not only to show a statistically significant improvement in primary efficacy endpoint(s), but also to reveal that the magnitude of the effect is clinically meaningful. Considering, for instance, post-stroke aphasia, note that commonly selected outcome measures (e.g., Western Aphasia Battery-Kertesz, 1982) to rate the impact of drug treatment in the type and severity of aphasia, are coarse-grained. Such assessment tools provide no fruitful information on the evolution of language processing deficits relevant for unveiling the restorative cognitive mechanisms guiding recovery promoted by drug treatment (Cahana-Amitay et al., 2014; Gill & Leff, 2014). In general, most trials on the pharmacotherapy of PSCD use a single primary outcome measure that, in some cases, is assessed after drug withdrawal to ensure that benefits are not short-lived (for discussion, see Small & Llano, 2009; Berthier, García-Casares, et al., 2011, Berthier, Pulvermüller, et al., 2011; Cahana-Amitay et al., 2014). This is correct, but insufficient. Patients with PSCD (e.g., aphasia, neglect) usually display multiple-domain cognitive impairments associated with motor/sensory deficits and psychiatric comorbidities (depression, apathy, anxiety), which reduce adaptability and quality of life (Berthier et al., 2015). In fact, patients with post-stroke aphasia and left hemisphere stroke lesions have one or more non-language cognitive deficits affecting abstract reasoning, visual memory, visual perception and construction, and executive functioning (El Hachioui et al., 2014). In the same vein, patients with neglect and right hemisphere stroke lesions also display other deficits, including impaired spatial working memory, impaired ability to recognize facial emotions and emotional prosody, as well as anosognosia (Starkstein, Fedoroff, Price, Leiguarda, & Robinson, 1992; Toba et al., 2018). Such accompanying signs indicate that analysis of treatment outcomes should ideally be multidimensional, incorporating a variety of different measures to obtain a far-reaching understanding of the putative treatment role (Cahana-Amitay et al., 2014; Gill & Leff, 2014). Nevertheless, it remains to be explored whether increasing the number of primary outcome measures can illuminate the full impact of drug treatment and whether the selected compound has an effect on target symptoms with generalization of benefits to other cognitive, behavioral, and functional domains.

19.1.8 Responder Analysis

Drug trials typically report treatment effects for efficacy measures by comparing mean change scores between active drug and placebo groups and between baseline and endpoints. Nevertheless, since the results of drug trials are influenced by

participants' variability in the therapeutic response, this information is not fully informative for clinicians. Therefore, to assist clinicians in evaluating the impact of drug treatment in an individual patient, one proposed approach is performing a responder analysis, in which changes from baseline to endpoint in the efficacy measures are individually dichotomized into "responders" and "non-responders." For example, Van Der Meulen, Van De Sandt-Koenderman, Heijenbrok, Visch-Brink, and Ribbers (2016) used six outcome measures to evaluate changes in aphasic patients after melodic intonation therapy (Albert, Sparks, & Helm, 1973) with the aim of distinguishing between improvement on trained items, improvement on non-trained items, and generalization to functional language use. Group analysis showed improvements only in one out of the six outcome measures (repetition of both trained and untrained utterances), thus indicating that the study was negative. However, responder analysis revealed individual variation with some patients responding well to treatment. This raises the question of how many outcome measures should improve with a drug treatment in PSCD to consider that the results are positive and this study also raises the importance of determining predictors of positive versus negative response to treatment. Another relevant issue is whether a drug trial could be considered positive when only cognition, and not multiple outcome measures (behavior, functionality, quality of life), is improved.

A related key point that deserves consideration is to reach consensus on what range of improvement in a given testing scale should be adopted to classify a patient with PSCD as a responder (see Malouf & Birks, 2004). Considering, for instance, the Aphasia Quotient (AQ) of the Western Aphasia Battery (WAB) (Kertesz, 1982), a measure of aphasia severity sensitive to changes after drug treatment, there is no consensus about the criteria for a positive response. At present, the more conservative definitions of a clinically relevant improvement consider a patient as a responder with an improvement $\geq$5 points in the WAB-AQ (Berthier et al., 2009; Katz & Wertz, 1997), another study required an improvement $\geq$10 points (Walker-Batson et al., 2016) and still another $\geq$20 points (Hong et al., 2012). Consensus is needed on these matters. Finally, the identification of responders to drug therapy needs to be enhanced by the identification of non-clinical variables, which might contribute to obtain a better response to drug treatment. The analysis of surrogate markers (genetic polymorphisms, lesion location, premorbid architecture of neural organization, and so forth) can aid to understand different responses to drug treatment.

19.1.9 Combined Therapies

Drugs administered to modulate the activity of a single neurotransmitter to improve cognitive deficits, such as aphasia and neglect, probably influence the activity of other neurotransmitters (Froudist-Walsh et al., 2017; Furey, 2011). This knowledge stimulated the combined use of two pharmacological agents targeting different neurotransmitter systems to alleviate cognitive deficits (Tariot et al., 2004). Two cognitive enhancing drugs (i.e., memantine and donepezil), commonly used to treat AD,

have different yet complementary mechanisms of action and may potentially provide additional benefits. The theoretical rationale for combining two drugs to treat PSCD comes for several sources of evidence. First, stroke can modify the activity of various neurotransmitters simultaneously causing, for example, depletion of cholinergic transmission and release of glutamate, which in turn produces high cell toxicity (Berthier, García-Casares, et al., 2011; Tocco et al., 2014). Second, stimulation of the cholinergic system with donepezil may facilitate the decrease of excitotoxicity mediated by glutamate and dopamine, and the addition of memantine leverages pathological-released glutamate to more physiological levels. Chronic treatment with memantine in mice with experimental stroke reduces excitotoxicity, increased vascular density, and release of brain-derived neurotrophic factor in perilesional areas (López-Valdés et al., 2014). Third, drug trials in AD in which memantine was added to treatment in patients already receiving donepezil provided additional benefits in language and communication (Atri et al., 2013; Riepe et al., 2007; Tariot et al., 2004; Tocco et al., 2014). In support, the addition of memantine reduced deficits not mitigated by the modulation of the cholinergic system with donepezil alone in a patient with chronic post-stroke nonfluent aphasia (López-Barroso et al., 2018). A pilot study in post-stroke aphasia explored a stable treatment with donepezil plus an adjunctive low dose of dextro-amphetamine administered 30 minutes prior to aphasia therapy to facilitate recovery (Walker-Batson et al., 2016). This treatment regime significantly improved aphasia severity and communication deficit causing no adverse effects (Walker-Batson et al., 2016). Although combined drug therapies seem a promising strategy, it remains to be determined whether they can lead to better outcomes than either drug alone.

19.1.10 Neural Network Modulation and Cognition-Enhancing Drugs

There are two general approaches for neurorehabilitation. Based on the altered relationship between different networks in both cerebral hemispheres, one can posit that a broad approach to neurorehabilitation may be adopted (Geranmayeh, Chau, Wise, Leech, & Hampshire, 2017). The other approach is more focused because it targets the treatment to specific anatomical sites (e.g., arcuate fasciculus, frontal aslant tract), which may have a key role in very selective cognitive domains (verbal repetition, speech fluency) (Berthier et al., 2017; Schlaug, Marchina, & Norton, 2009). These two potential treatment strategies are based on the segregated organization of neural networks into domain-specific and domain-general (Blank & Fedorenko, 2017; Brownsett et al., 2014). Although the premises underlying these two neural networks are different, they do have complex interactions among widely distributed brain regions, but not all networks are interdependent (Blank & Fedorenko, 2017).

One important question is whether some pharmacological agents may selectively modulate the activity of domain-specific networks while other compounds with more general, widespread actions may preferentially modulate domain-general networks. Some preliminary data from drug treatments of PSCD performed in sin-

gle case studies, case series, open-label and randomized clinical trials suggest that different agents might preferentially act on different networks. Since the anatomy of white matter tracts and the cortical distribution of neurotransmitter fingerprints are increasingly being identified (Amunts & Zilles, 2012; Palomero-Gallagher & Zilles, 2017; Selden, Gitelman, Salamon-Murayama, Parrish, & Mesulam, 1998), this can provide fruitful information about the selection of a given pharmacological agent to target cognitive impairments that might reflect vascular damage to specific neurotransmitter systems. For example, since the neuroanatomy of mesocortical and mesolimbic dopaminergic pathways is well known, one can assume that patients with cognitive deficits (decreased drive to generate speech, impaired goal-directed behavior) resulting from incomplete damage to such pathways could be treated with dopamine agonists (Cahana-Amitay et al., 2014; Galling et al., 2014; Gill & Leff, 2014).

The same notion may apply for the cholinergic system. Early anatomical studies on the distribution of major cholinergic pathways (e.g., Selden et al., 1998) and recent in vivo mapping of their trajectory using diffusion tensor imaging (tractography) (Hong & Jang, 2010; Liu et al., 2017) allow the identification of cholinergic involvement after stroke lesions (Behl et al., 2007). The areas of selective binding of donepezil to acetylcholinesterase can be identified with positron emission tomography and [5-11C-methoxy] donepezil (Hiraoka et al., 2009), and changes in the pattern of connectivity under pharmacological manipulation with this drug have been identified (Wirsich et al., 2018). Preliminary data using these methodologies have shown that patients with disrupted trajectory of cholinergic pathways in the white matter can benefit with cholinesterase inhibitors (galantamine, donepezil) (Berthier et al., 2017; Hong et al., 2012). In addition, the modulation of a widely distributed neurotransmitter (glutamate) with the drug memantine showed that benefits in post-stroke aphasia are related to bilateral brain reorganization (Barbancho et al., 2015), although connectivity analysis in healthy subjects under memantine treatment failed to show changes in resting state networks (Wirsich et al., 2018).

Altogether, these findings illuminate the cortical hubs and white matter tracts participating in the recovery process from stroke deficits (Berthier et al., 2017; McKinnon et al., 2017; Piai, Meyer, Dronkers, & Knight, 2017; Wan, Zheng, Marchina, Norton, & Schlaug, 2014). Therefore, there are now clues to stimulate compensatory activity of healthy brain tissue with intensive rehabilitation and biological interventions (e.g., drugs, NIBS). In particular, the modulation of these structures with biological treatments is emerging as a promising treatment option. An exciting approach might be directing drugs to anatomic target sites or specific tissue where the concentration of specific neurotransmitters is more abundant. Up to now, attempts to modulate specific cortical regions (left superior temporal lobe) rich in cholinergic receptors (Zilles & Amunts, 2009) and presumably participating in recovery have been made using the acetylcholinesterase inhibitor donepezil (Woodhead et al., 2017). Similarly, cholinergic potentiation with donepezil alone and paired with intensive rehabilitation improved speech production and communication, and induced structural plasticity in white matter tracts important for such functions (Berthier et al., 2014, 2017).

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Chapter 20
Non-invasive Brain Stimulation in Human Stroke Survivors

Susan Wortman-Jutt, Onno van der Groen, and Dylan Edwards

20.1 State of the Field in Human Non-invasive Brain Stimulation

The use of electromagnetic currents toward understanding and curing human disease has long been of interest. In the 1980s, a dramatic increase in our understanding of brain function, along with parallel improvements in non-invasive brain stimulation (NIBS) technologies, subsequently caused rapid expansion of the field. Intraoperative monitoring techniques that incorporated single pulse stimulation were developed concurrently for the purpose of measuring corticospinal integrity (Merton & Morton, 1980a, 1980b); however, with the introduction of transcranial magnetic stimulation (TMS), the use of NIBS decisively exploded, opening a new window into the exploration and modulation of the brain (Barker & Jalinous, 1985). Single pulse TMS, used initially to study inter-cortical physiology of the intact corticospinal tract, was thereafter investigated toward the rehabilitation of neurological and psychiatric conditions.

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R. M. Lazar et al. (eds.), *Neurovascular Neuropsychology*,
https://doi.org/10.1007/978-3-030-49586-2_20

Conditioning paradigms, in which a test pulse was preceded by a single pulse in the same location (*paired-pulse*), enabled the study of intracortical physiology (Kujirai et al., 1993b). Although the after-effects of a single pulse of TMS are thought to be resolved at <1 s, trains of pulses at regular intervals were shown to have a more durable effect that could result in excitation or inhibition, depending upon stimulation frequency. These effects could last several tens of minutes before returning to baseline. The notion of non-invasive *neuromodulation* as a method to understand brain function and as a possible clinical treatment was therefore appealing, and a variety of experimental applications began. As an extension of this, neuromodulation for the purpose of augmenting brain function, as well as for the adaptation and enhancement of behavioral skills, has been sought. This is especially the case for *transcranial direct current stimulation* (tDCS), where applications extended beyond the laboratory to uncontrolled use within the community, such as for putative augmentation in sport, gaming, academics, and employment (Edwards et al., 2017).

Today, according to the National Institutes of Health U.S. Library of Medicine (see clinicaltrials.gov), we have about 35 registered trials using NIBS in stroke in the United States, ranging from completed through emerging. Of note, a Cochrane Database review conducted by Klomjai, Katz, and Lackmy-Vallee (2015) counted 141 publications investigating rTMS and stroke and 132 separate publications examining tDCS and stroke between 1988 and 2012 alone (Klomjai et al., 2015). Finally, a PubMed search using the terms "non-invasive brain stimulation" and "stroke" yielded 248 publications within the past 5 years, up to and including 2018.

Interest in the various forms and applications of neuromodulation has never been higher than in recent years. Caution regarding "hype cycle" publication bias (Heroux, Loo, Taylor, & Gandevia, 2017) and funding pressures that reward innovation and clinical impact (potentially rushing papers to publication at the risk of reduced academic precision and validity) are reminders that a full understanding of neuromodulation benefits and applications remains unclear. In addition to investigator- and industry-initiated trials that will slowly provide insight into effects of NIBS, regulatory and funding bodies have formally identified the need for further controlled and careful exploration. In the United States, The Institute of Medicine of the National Academies convened a workshop titled *Non-invasive Neuromodulation of the Central Nervous System: Opportunities and Challenges*, to raise and discuss a host of issues surrounding this topic (the published outcome can be found here: National Academies of Sciences & Medicine, 2015). The National Institutes of Health (NIH) has dedicated funding toward further exploration of this topic as well. The Food and Drug Administration (FDA) has approved psychiatric application of repetitive TMS (rTMS) in medication-refractory depression, and at the time of this writing, applications are under consideration for Alzheimer's disease and stroke rehabilitation. On the strength of reimbursement for the clinical application of rTMS, the rTMS industry is sponsoring trials and demonstrating unprecedented efforts to refine devices and coils. This includes the development of ancillary equipment, such as robotic neuro-navigation-based positioning devices, in an environment where an increasing number of companies are edging for market share. Debate

is ongoing concerning the balance of scientific exploration versus ethical obligations in which only scarce evidence of efficacy exists. The safety profile of NIBS is nonetheless strong, particularly given that it targets populations in need with few other options. Caution must be taken however, that this is not used as an argument in favor of accelerated clinical applications with incompletely understood protocols; rather, incremental and methodical assessment of the effects and mechanisms of the various combinations and permutations of stimulation protocols should be carefully undertaken.

20.2 NIBS in Stroke

The two most common methods of NIBS relevant to this discussion on stroke applications are TMS and transcranial electrical stimulation (TES). Evidence that electrical fields can reach and affect human cortical neurons using TMS and TES is categorical. The most striking proof of this is the evoked muscle twitch of the contralateral hand with stimulation over the primary motor cortex (M1) (Rothwell et al., 1999). The effects in other cortical areas are less obvious; yet, corroborating evidence from diverse studies indicates that neurons in other cortical areas, accessible from scalp sites, can be similarly affected (Kuo & Nitsche, 2012; Pascualleone, Gates, & Dhuna, 1991; Stewart, Walsh, & Rothwell, 2001).

Figure 20.1 provides an overview of how these two methods can be distinguished in terms of common applications in stroke.

We start by illustrating device differences, which have been discussed elsewhere at length (Hallett, 2007; Peterchev et al., 2012; Wagner, Valero-Cabre, & Pascual-Leone, 2007b). TMS uses a short-duration high-intensity current inside a magnetic coil that induces a parallel electric field in the underlying conductive tissues (e.g., cerebrospinal fluid, or CSF, and brain parenchyma). The waveform for the TMS pulse can be biphasic or monophasic (i.e., current flows in one direction or both directions in the brain). TMS can be delivered as a single pulse, as a combination of two pulses (paired-pulse), repetitively at a specific frequency (rTMS) or patterned (theta-burst, burst of 3 pulses at 50 Hz, repeated at intervals of 200 ms). TES is delivered via electrodes attached to the scalp using a conductive medium. The current flows through the scalp, the (higher impedance) skull, and into the brain, and its direction is orthogonal to that of TMS, or "normal" (inwards) to the scalp. Like TMS, TES can also be delivered in short pulses at high intensity (for example, during intraoperative monitoring of corticospinal function), but is more commonly applied at low intensities, and held for some duration after a ramp up (with the intent of *neuromodulation*, or after-effects). The waveform for TES is often direct current (DC, the unidirectional flow of electrical charge), although more recently alternating current (AC) and random currents (e.g., random noise stimulation, tRNS) have been applied. For TES at low intensities, which is the most common application, there is typically no visible sign that stimulation is applied, since it is below *motor threshold*.

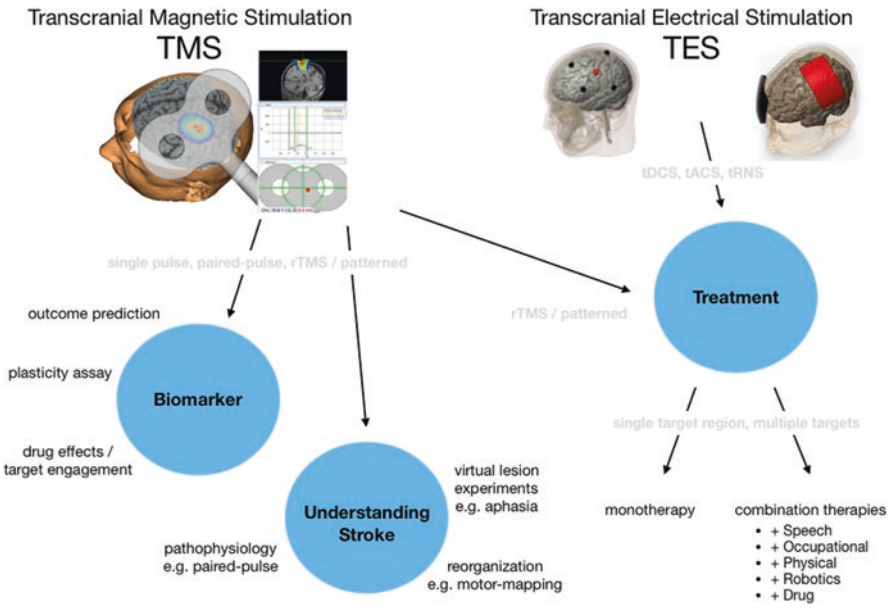

Fig. 20.1 Schematic of NIBS applications in stroke. In this chapter, we focus on the two most common forms of electromagnetic stimulation used in stroke applications: TMS and TES. While both methods have been extensively studied in post-stroke recovery as a treatment in isolation (monotherapy) or as a supplement to other therapies (combination therapy), the history of TMS, and its other applications such as understanding the pathophysiology of stroke and recovery, as well as its use as a biomarker and predictive tool, are advantages in favor of TMS. *rTMS* repetitive TMS, *tDCS* transcranial direct current stimulation, *tACS* transcranial alternating current stimulation, *tRNS* transcranial random noise stimulation. Left image from Cognitive Plasticity in Neurologic Disorders, Tracy, Hampstead, & Sathian, 2014, Tracy JI, Benjamin M. Hampstead, K. Sathian, Editors. © Oxford University Press, 2015. Reproduced with permission of Oxford Publishing Limited, through PLSclear. Middle image, reprinted from NeuroImage, 74, Edwards D, Cortes M, Datta A, Minhas P, Wasserman EM, Bikson M, Physiological and modelling evidence for focal transcranial electrical brain stimulation in humans: A basis for high-definition tDCS, 266–275, Copyright (2013), with permission from Elsevier. Right image, reprinted from Clinical Neurophysiology, 121, Bikson M, Datta A, Rahman A, Scaturro J (Bikson, Datta, Rahman, & Scaturro, 2010), Electrode montages for tDCS and weak transcranial electrical stimulation: Role of 'return' electrode's position and size, 1976–1978, Copyright (2010), with permission from Elsevier

20.3 Biomarker

20.3.1 TMS as an Outcome Predictor

The role of TMS as a predictor for spontaneous or intervention-related recovery following stroke, although explored relatively infrequently, is beginning to show promise. The outcome in upper limb motor function after stroke is varied, with between 30% and 66% of stroke survivors suffering chronic upper limb impairment

and only 5–20% demonstrating complete functional recovery (Heller et al., 1987; Kwakkel, Kollen, Van der Grond, & Prevo, 2003; Nakayama, Jørgensen, Raaschou, & Olsen, 1994; Sunderland, Tinson, Bradley, & Langton Hewer, 1989; Wade, Langton-Hewer, Wood, Skilbeck, & Ismail, 1983). The use of clinical assessments to accurately predict functional limb recovery post-stroke can be challenging (Nijland, van Wegen, Harmeling-van der Wel, & Kwakkel, 2013), often leading to difficulties in making decisions regarding treatment method and discharge planning. In order to improve outcome prediction, clinical assessment data may be combined with *biomarkers* to develop outcome prediction algorithms (Boyd et al., 2017; Stinear, 2017). A biomarker is an indicator of a disease state, used clinically to reflect underlying molecular/cellular processes that may be difficult to measure directly in humans (Bernhardt et al., 2017). Biomarkers can be used to understand recovery or treatment response (Bernhardt et al., 2017). Using biomarkers as a resource for stroke outcome prediction may improve clinical pathway planning and goal setting, benefiting patients, caregivers, clinicians, and researchers (Boyd et al., 2017). Biomarkers provide opportunities to identify patients who might benefit from a specific intervention in the acute phase of stroke. These patients could then be stratified and selected for appropriate clinical trials (Stinear, 2017).

The muscle response to a single pulse TMS over the M1 hand area, known as a *motor evoked potential* (MEP, see Fig. 20.2), relates to the integrity of the corticospinal tract and severity of hemiparesis (Berardelli, Inghilleri, Cruccu, Mercuri, & Manfredi, 1991; Binkofski et al., 1996; Dominkus, Grisold, & Jelinek, 1990; Ferbert, Vielhaber, Meincke, & Buchner, 1992).

This information has recently been shown to be useful in predicting recovery in the subacute phase (Stinear et al., 2017) and also with intensive intervention in the chronic phase. TMS measures may be particularly useful in stroke survivors who lack the capability to voluntarily move their arm, due to a damaged or inaccessible corticospinal tract (Stinear et al., 2017; Stinear, Barber, Petoe, Anwar, & Byblow, 2012). If an MEP can be collected in the latter instance, then the corticospinal tract must be intact.

The degree of upper limb recovery after stroke, however, can't be fully predicted based on a single biomarker; therefore, outcome prediction algorithms have been developed (Stinear et al., 2012, 2017). The predictive value of these algorithms is currently not high enough for individual patient prognosis; however, they can be enhanced by increasing the information content of existing biomarkers and by the addition of further biomarkers. For example, it is likely that the predicative value of TMS could be improved by using a continuous-scale variable for motor cortex excitability across hemispheres, such as the *resting motor threshold* (RMT), rather than a dichotomic variable. It has been shown in a cross-sectional study, designed to predict impairment, that interhemispheric differences in RMT may better correlate with motor impairment than ipsilesional RMT alone when an MEP is present bilaterally (Boes et al., 2017). Whether the RMT is a superior biomarker for outcome prediction requires further investigation.

Other TMS protocols may also be used as biomarkers to enhance the predictive value of these algorithms (Stinear & Byblow, 2017). These include, but are not

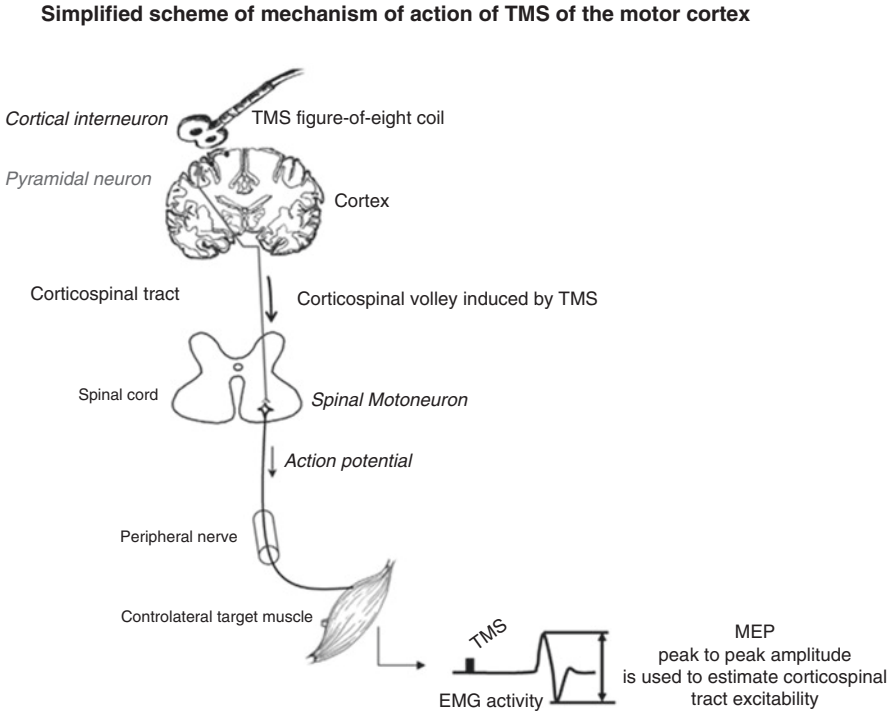

Fig. 20.2 Transcranial magnetic stimulation (TMS) applied over the motor cortex preferentially activates interneurons oriented in a plane parallel to the brain surface. This placement leads to a transsynaptic activation of pyramidal cells evoking descending volleys in the pyramidal axons projecting on spinal motoneurons, also termed the corticospinal tract. Motoneuron activation in response to corticospinal volleys induced by TMS leads to a contraction in the target muscle, evoking a motor evoked potential (MEP), recorded with electromyography (EMG) by using surface electrodes applied over the muscle belly. Its peak-to-peak amplitude is used to estimate excitability of the corticospinal tract. From Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). Klomjai W, Katz R, Lackmy-Vallee A., Ann Phys Rehabil Med. 2015. Reprinted with permission of Elsevier Publishing

limited to, *short-interval intracortical inhibition* (SICI) (Kujirai et al., 1993a) and the *cortical silent period* (CSP), both measures of cortical inhibition (Robert Chen, Lozano, & Ashby, 1999). Previous studies report that motor cortex disinhibition occurs in the affected hemisphere after acute stroke (Liepert, Storch, Fritsch, & Weiller, 2000). The degree of disinhibition may be useful information to predict stroke outcome.

Less research has been conducted regarding the predictive value of TMS in lower limb function following stroke. Mixed results have been found regarding its predictive value in the lower limbs (Chang, Do, & Chun, 2015; Dawes et al., 2008; Hendricks, 2003; Piron, Piccione, Tonin, & Dam, 2005; Smith, Barber, & Stinear, 2017). This is likely due to the presence of bilateral and alternative descending pathways (Dawes et al., 2008; Jang et al., 2013), resulting in redundancy in

neuroanatomical control of the lower extremities. Further, in addition to the return of voluntary movement in the legs, there are a number of other compounding factors, such as postural control, that may not be as readily predicted by TMS, but are nonetheless crucial to achieving independent mobility (Connell, Smith, Byblow, & Stinear, 2018; Kollen, Van De Port, Lindeman, Twisk, & Kwakkel, 2005). It is worth noting, however, that TMS used in combination with MRI may predict recovery in chronic stroke survivors (Stinear et al., 2007).

20.3.2 TMS as a Plasticity Probe

rTMS permits the induction of long-lasting changes in cortical excitability and plasticity (Wagner, Valero-Cabre, & Pascual-Leone, 2007a). Several studies have used rTMS as a plasticity probe; that is, it has been used as a test protocol to assess the response of a previously applied separate NIBS protocol (Karabanov et al., 2015). The potential for rTMS to be used to evaluate intrinsic plasticity-response in health and disease however, has yet to be realized. With evidence supporting the use of rTMS to transiently alter excitability for a period outlasting the stimulation (Chen & Seitz, 2001; Fitzgerald, Fountain, & Daskalakis, 2006), the initial enthusiasm has been to capitalize on the therapeutic potential, that is, aiming to restore putative excitability deficiencies that may relate to dysfunction (a paradigm that is not always judged to be consistently substantiated). Such studies identified that while the average response across a group can sometimes show an effect, there are vast inter-individual differences (Boroojerdi et al., 2000; Maeda, Gangitano, Thall, & Pascual-Leone, 2002). These differences can be interpreted as due to chance, or from classification of individuals into responders and non-responders prior to examining group effects (Lopez-Alonso, Cheeran, Rio-Rodriguez, & Fernandez-del-Olmo, 2014; Ridding & Ziemann, 2010). The link between rTMS effects and adaptive plasticity remains tenuous. However, at least in the motor systems, both have been shown to involve the NMDA receptor via pharmacologic experiments (Soundara Rajan et al., 2017; Tang, Thickbroom, & Rodger, 2017). Downstream effects on AMPA receptors mediated by NMDA receptor activity are well established for adaptive changes in synaptic strength in the glutamatergic system that underlies learning. The extent to which plasticity-inducing protocols versus naturally occurring adaptive plasticity share similar mechanisms remains to be further explored, including predicting the capacity for adaptive plasticity using non-invasive neuromodulation in early or chronic stages after stroke. Furthermore, other TMS protocols could also have a role in the cross-sectional evaluation of plasticity potential at an individual level. These protocols may include repeated stimulation in the same location (e.g., rTMS), paired stimulation (by coinciding the pairing of two different areas such as paired-associative stimulation (PAS)), or other associative stimulation protocols (Suppa et al., 2017).

20.3.3 TMS to Test Drug Effects/Target Engagement

Pharmacologic treatment has a potential place in stroke prevention and early management and recovery, yet human in vivo assessment of drug target engagement and physiological effects at the individual level are difficult to conduct. TMS measures have been used to evaluate the effects of various drugs (Ziemann et al., 2015); for example, the drug carbamazepine (a voltage-gated sodium channel blocker) resulted in an increase in RMT but did not alter MEP amplitude or cortico-silent period in stroke patients with partial seizures (Turazzini, Manganotti, Del Colle, Silvestri, & Fiaschi, 2004). In stroke recovery as in healthy human function, therapeutic activities in the engaged and motivated patient with sufficient intensity, feedback, and incremental overload can lead to adaptive change. One application of pharmacological interventions in this context may be to augment adaptive plasticity associated with naturalistic interventions such as behavioral training, as opposed to stand-alone drug interventions. As with other drug interventions, dosing, side effects, and non-specific targeting remain an issue, as does a solid confirmation of drug target engagement in vivo. As a proof of concept, NIBS (rTMS neuromodulation; iTMS) was shown to (a) effectively lead to short-term plasticity in neurodegenerative disease (Parkinson's disease) and (b) be modified by a clinically useful medication (levodopa) (Rodrigues, Walters, Stell, Mastaglia, & Thickbroom, 2008). Two important points are relevant here: (1) that an rTMS paradigm involving repeated pairs of stimuli delivered in the same location (primary motor cortex) at a precisely timed inter-stimulus interval (consistent with synaptic latency, 1.5 ms) can lead to upregulation of cortical excitability in the diseased brain and (2) that a drug considered to have an action on the dopaminergic system can indirectly affect glutamatergic-NMDA receptor mediated plasticity. The neurobiological basis of adaptive plasticity involving neuronal and non-neuronal elements is still being uncovered, yet the role of LTP- and LTD-like changes in synaptic strength, known to be important for learning and memory, is potentially implicated. Whether NIBS can be exploited to demonstrate drug target effects remains to be explored in stroke recovery.

To use NIBS to evaluate drug target effects, the following steps need to be taken. First, it would be important to understand the mechanism of plasticity (neuromodulation/after-effect) using the NIBS method (possibility quite different for each of the aforementioned methods). Next, the manner in which this form of plasticity relates to meaningful endogenous plasticity, such as motor learning, or speech-language therapy-related recovery must be established. Additionally, these effects must be tested to ensure they are robust within an individual (rather than noisy outcome measure, low reliability). Finally, the effect of drug dose on this outcome must be understood. Each of these items has caveats and limitations, but can plausibly be ascertained.

20.4 Understanding Stroke

20.4.1 TMS to Understand Pathophysiology

In the post-stroke brain, single and paired-pulse TMS techniques have been used to explore local (e.g., M1, intracortical) and network effects (e.g., transcallosal inhibition) resulting from the stroke lesion. Acknowledging that post-stroke changes typically cannot be expressed in relation to the pre-morbid condition, scientists evaluate physiology in regard to homologous contralesional cortex or age-matched, healthy control subjects (Bolognini, Pascual-Leone, & Fregni, 2009; Schambra et al., 2015). Still others explore physiology in relation to imaging results and symptoms (Boes et al., 2017). The reliability of TMS measures needs to be carefully considered in repeated-measures experimental designs and when tracking individuals longitudinally. When comparing the lesioned area to the contralesional cortex, one has to keep in mind the possible network effects of the affected hemisphere on the non-affected hemisphere, which we will review later. TMS measures will shed light on the neurophysiological underpinnings of symptoms and differences between the early post-stroke period and the chronic phase. In the acute stage of stroke, TMS may provide an opportunity to probe pathophysiology (e.g., spreading depression in the core infarct and penumbra) (Fabricius et al., 2006; Strong et al., 2002). This may provide clues as to suitable drug type, timing and dose, as well as the time course and intensity of behavioral intervention. Different TMS protocols can give insight into the pathophysiological changes occurring in stroke. Single pulse TMS relates to corticospinal integrity, including from cortical interneurons, down to the level of the muscle. *Central motor conduction time* (CMCT) is the duration for a signal to travel through the central nervous system (Udupa & Chen, 2013), which may be affected in stroke survivors (Heald, Bates, Cartlidge, French, & Miller, 1993; Talelli, Greenwood, & Rothwell, 2006). The cortical silent period (CSP) is a measure of the inhibitory effect of TMS, possibly due to activation of intracortical inhibitory neurons. In stroke patients, the duration of the CSP is prolonged in the acute phase (Liepert et al., 2000). Paired-pulse protocols allow for the investigation of intracortical inhibition or facilitation (SICI/ICF). In these protocols, a conditioning pulse is followed by a test pulse. For an overview of stroke-related TMS changes, see the review by Talelli et al. (2006).

20.4.2 Virtual Lesion Experiments

The extent to which acute stimulation either interrupts or augments neural function is unclear. While NIBS has increased our understanding of brain function, it may be argued that historically it is the study of brain lesions which has been most transformative (Pascual-Leone, Walsh, & Rothwell, 2000). The technical and ethical

constraints of studying brain lesions in situ are formidable, however. A method by which a targeted brain area may be deactivated, then re-activated again via TMS, toward the creation of a *virtual les*ion, has therefore been a valuable resource for neuroscientists (Pascual-Leone et al., 2000). In virtual lesions, pulses of TMS are used to temporarily hinder a specific brain function. The underlying neurophysiological mechanism is still a point of discussion. TMS might interrupt the relevant signal or it might add neural noise (Miniussi, Harris, & Ruzzoli, 2013), injecting activity that competes or interacts with resources to solve the task. Despite this discussion, TMS has been valuable in determining the function of specific brain areas.

Murakami, Ugawa, and Ziemann (2013) report, for instance, that virtual lesion studies have added to the body of knowledge regarding the *motor theory of speech perception*, a controversial theory which purports that the ability to comprehend language, particularly action words, is grounded in sensorimotor functions such as vision and movement. A study by Vesia, Niemeier, Black, and Staines (2015) used virtual lesions of the right posterior parietal cortex to demonstrate that lesions to this area caused participants to experience *visual extinctions*, the disappearance of objects from half of one's visual field. An understanding of the result of virtual lesions to this area may have clinical applications toward recovery from *visual neglect*, a post-stroke sequela in which the patient experiences a loss of attention to, or awareness of half of the patient's visual field, often accompanied by a general neglect of the hemiparetic half of his or her body. While medications have been used in the creation of virtual lesions in the past (Lomber & Galuske, 2002), TMS currently serves as the best means of safely interrupting brain activity, thereby enabling scientists to view the direct effects of a pseudo-stroke lesion, and subsequent brain recovery, in real time. Unlike other forms of brain injury, which may have diffuse effects, the virtual lesion closely mimics stroke, which tends to impact focal brain regions. It should be noted however that unlike the results of targeted TMS, focal strokes may result in diaschisis, affecting more remote brain regions, as can be observed, for example, when a lesion in Broca's area causes a reduction in the metabolism of Wernicke's area.

The study of virtual lesions may yield translational applications. As one example, the use of TMS to temporarily arrest speech has been used experimentally to map language networks. The hope is that one day TMS may be applied clinically to damaged language areas with enough precision to directly target and promote aphasia recovery (Choi, Park, & Paik, 2015). Similarly, Fossataro, Bruno, Giurgola, Bolognini, and Garbarini (2018) used virtual lesions of the motor cortex to demonstrate that downregulation of this area in healthy subjects could cause an impairment in the sense of proprioception, a deficit seen in stroke and potentially of interest to stroke researchers. Using virtual lesions, scientists may safely explore mechanisms leading to injury from stroke, ultimately leading the way toward improved recovery from stroke impairment.

20.4.3 Reorganization: Motor Mapping

Mapping the representation of limb and face musculature on the M1 during invasive procedures has been demonstrated since the time of Penfield in the mid-twentieth century (Penfield & Rasmussen, 1950). This work expanded into non-human primates, in which important discoveries were made, such as the reduction of limb muscle representation in relation to reduced voluntary control after a cortical lesion. The expansion and reorganization of these areas ensued in parallel with functional muscle recovery (Nudo, Wise, SiFuentes, & Milliken, 1996). Similar work has also been shown in human motor-stroke recovery (Byrnes, Thickbroom, Phillips, & Mastaglia, 2001). The finding of motor map expansion in neurorecovery has also been demonstrated in other conditions, such as cerebral palsy (Friel et al., 2016). The relationship of motor map changes to functional recovery are still unclear. The notion of map expansion post-stroke as the mechanistic underpinning of volitional recovery is not fully accepted (Krakauer & Carmichael, 2017). Improvements in voluntary motor control can occur in the absence of detectable motor map changes (Conner, Culberson, Packowski, Chiba, & Tuszynski, 2003). It is plausible that map changes may dynamically change according to phase of recovery, or phase of motor skill acquisition and retention. Additionally, the relationship of motor map features to elements of voluntary control post-stroke (e.g., gross muscle activation and power, dexterity) remains to be established. TMS provides a unique window into the organization of adjacent muscle representations post-stroke. Several lines of evidence support an enhancement of corticospinal excitability in muscle adjacent to denervated muscle representations (Cohen, Bandinelli, Findley, & Hallett, 1991; Edwards et al., 2013, 2013), which can be interpreted as encroaching on denervated muscles. An alternative explanation is the heightened excitability of adjacent healthy neuronal tissue that is seen as a greater spatial area in which responses can be elicited. A weak spread of current from an adjacent area may not typically manifest in a response, but in the case of heightened excitability, it will.

A further consideration when using TMS to evaluate motor maps is that an impairment in voluntary motor function does not always indicate reduced corticospinal integrity. As an important reminder, the MEP represents the excitability of the entire corticospinal pathway, intracortical interactions, pyramidal cell firing, summation of descending volleys in the spinal cord, excitability of the alpha-motor neuron pool, peripheral nerve efferent function, the neuromuscular junction, and muscle excitability.

It is considered that absence of an MEP typically relates to poor voluntary motor function (Hendricks, Hageman, & Van Limbeek, 1997; Pennisi et al., 1999); however, poor voluntary function is not always explained by dysfunctional corticospinal integrity. This has been demonstrated with traumatic injury to the corticospinal tract in spinal cord injury (Edwards, Cortes, Datta, et al., 2013, Edwards, Cortes, Thickbroom, et al., 2013) and in chronic stroke. In Fig. 20.3, we show an example of motor mapping in stroke hemiparesis in a patient with a chronic cortical and subcortical stroke in which there is an absent evoked potential response in the

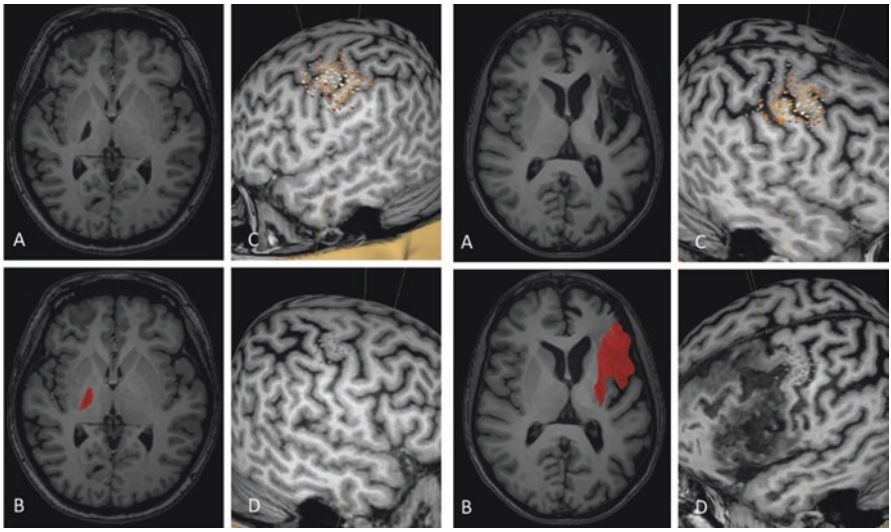

Fig. 20.3 Illustration of lesion and motor mapping data for two chronic stroke patients with residual hemiparesis. A challenge for targeted non-invasive brain stimulation as a therapeutic tool in post-stroke motor recovery is that the patients with similar symptoms can have different anatomical disruption which raises the question whether the stimulation target should be different in each case. Left panel: sample data for a patient with subcortical stroke, (**a**) axial T1 MRI with right subcortical stroke, (**b**) stroke lesion mask employed for quantitative analysis of infarct volume, (**c**) topographic maps of TMS motor evoked potentials (MEPs) in a distal arm muscle affected by the stroke in the unaffected (left) hemisphere, and (**d**) affected hemisphere (right). Response amplitude is normalized from minimum (red) to maximum (white). Grey indicates no response. Right panel: The same format as the left panel **a**–**d**, yet here the lesion extends to the cortex. Note in the left panel and right panel, image **d** shows no motor map on the affected side, despite having a preserved M1 hand area

affected hemisphere despite a relatively preserved M1. The relationship with MEPs following TMS, anatomical location of the lesion, and function, requires further investigation.

20.5 Treatment

20.5.1 Treatment Considerations

Thus far, we have discussed NIBS as a probe of brain function to understand stroke; however, it can also be used as a method of treatment, or as an adjuvant to speech, occupational, physical, robotic, or drug therapies. Electroconvulsive therapy (Abrams, 2002) and cranial electrotherapy stimulation (Limoge, Robert, & Stanley, 1999) preceded the modern rapid rise and interest in NIBS as a treatment. NIBS has

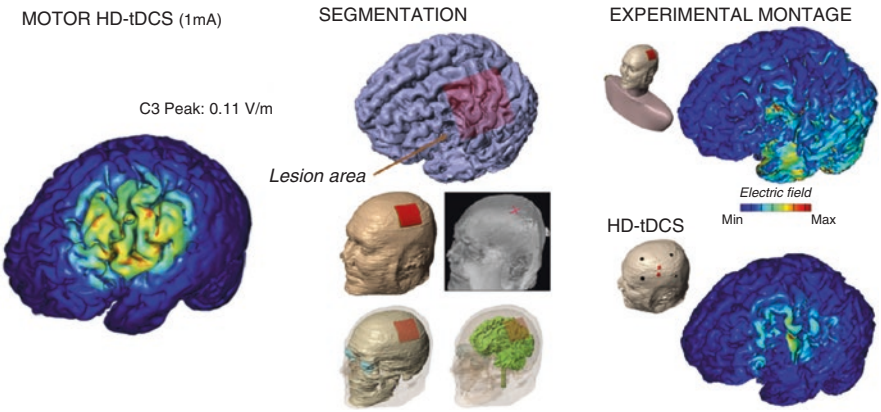

Fig. 20.4 Left Panel: A computer simulation showing the focality of high-definition tDCS (HD-tDCS) with a 4 × 1 ring configuration. The anode was centered on C3 over approximately the hand motor cortex of the left hemisphere. The four cathodal return electrodes were placed around C3 in adjacent position. The current spread was generally restricted to inside the ring. © 2016 IEEE. Reprinted, with permission, from Caparelli-Daquer et al. (2012). Right Panel: Computational modeling showing the current flow during tDCS in a stroke survivor. Brain lesions are considered to be largely cannibalized and filled with cerebral spinal fluid (CSF), which is more conductive than brain tissue, significantly altering the current flow. The top row shows the current flow with a conventional montage. The bottom row shows HD-tDCS. The HD-tCS setup results in a much more focal stimulation pattern in the patient compared to the standard setup. Reprinted/adapted by permission from Springer nature: Springer. A Role of Computational Modeling in Customization of Transcranial Direct Current Stimulation for Susceptible Populations. In: Knotkova H., Rasche D. (2016) (eds) Textbook of Neuromodulation by Truong D, Minhas P, Mokrejs A, Bikson M. © 2015

shown promise for the improvement of post-stroke deficits, including upper and lower limb hemiparesis, aphasia, and concomitant depression; however, the literature demonstrates that issues surrounding dosage, locus, and duration of stimulation persist. When NIBS is used as a treatment, it is important to consider the resulting sequelae of post-stroke brain damage since this, for example, can significantly affect current flow in TES (Fig. 20.4). The list of post-stroke disorders is expansive and includes hemiparesis and hemiplegia, aphasia, motor-speech disorders, swallowing disorders (dysphagia), cognitive and perceptual disorders such as neglect, and post-stroke depression, any number of which may be combined in one individual stroke survivor. It is common, in fact, for patients to present with multiple afflictions following stroke (Boehme, Martin-Schild, Marshall, & Lazar, 2016). Consideration must also be given to pre-existing and concomitant disease processes that may have led up to the stroke and could impact recovery. Similarly, the effects of patients' medications, as well as their educational and social histories, and their level of family support, may each have an impact on rehabilitation outcomes (Hill, Weston, & Jackson, 2014; Marshall et al., 2015; Reeves, Prager, Fang, Stamplecoski, & Kapral, 2014). As a consequence, the patient must be observed from a holistic perspective. Contemporary rehabilitation settings attempt to address all such factors in providing

post-stroke care; however, resources for providing holistically oriented therapies are, more often than not, lacking. Rather, therapeutic modalities are segregated in rehabilitation facilities, so that disorders of limbs, perception, speech, and cognition are each addressed separately, contrary to the simultaneous use of these functions in patients' daily lives (Reistetter et al., 2014). It is nonetheless important for the practitioner of NIBS to be aware that a patient presenting with hemiplegia is rarely dealing with hemiplegia in isolation, much as a patient with aphasia may have other cognitive or physical debilities following stroke. When considering the type of NIBS to be employed, the area of stimulation, and dosage of electrical current, it is therefore important to view the patient in context and to consider how stimulation over one area may possibly affect other functions.

Over the years, we have gained a large amount of knowledge regarding varied brain networks, each supporting specific functions; however, the decision regarding where to stimulate remains difficult. Consideration of whether to stimulate the perilesional area or inhibit the contralesional hemisphere should be based on an understanding of naturally occurring spontaneous recovery processes and a complete overview of the patient's deficits. One proposed method for countering maladaptive plasticity following stroke has been to provide inhibitory NIBS over the unaffected hemisphere, thereby reducing interhemispheric inhibition. If, however, a patient with aphasia demonstrates an improved ability to name objects when tapping out syllables, possibly indicating preserved function in the right-hemisphere language homologue, would it make sense to inhibit language function in the right hemisphere? It has been suggested that bilateral NIBS may reduce competition between hemispheres and promote experience-dependent plasticity in the affected hemisphere prior to, or during rehabilitative therapies (Takeuchi & Izumi, 2012). The latter may, in this scenario, be the superior choice, based not solely upon the literature, but in combination with a comprehensive view of the patient's needs and abilities. Communication with a patient's family, doctors, or therapists may further assist the clinician in determining the best location for stimulation for a particular patient, without relying exclusively on lesion location. Patients in the clinical realm are heterogeneous. Clinical considerations specific to an individual patient might therefore require further investigation. For example, what is the best location to stimulate a stroke patient who is ambidextrous? Similarly, an aphasic patient may be multilingual, or a right-hemisphere stroke patient may have unexpected word-finding difficulties. These are important issues to consider, especially given the likelihood that stimulation in one area may have repercussions in another.

20.5.2 TMS as Treatment

Of all the available TMS protocols, rTMS may be described as the "therapeutic" component of TMS, in that its effects last beyond the initial period of cortical modulation (Klomjai, Katz, & Lackmy-Vallee, 2015). As such, it has been successfully used in neuropsychiatric treatments (Janicak et al., 2010). The reasoning was that

the left dorsolateral prefrontal cortex (DLPFC) was a dysfunctional cortical node implicated in depression and that upregulation of excitability using high-frequency stimulation might ameliorate symptoms of depression. The logic for the selected rTMS protocol (10 Hz stimulation) came from earlier studies of the M1 (Pascual-Leone, Catala, & Pascual-Leone Pascual, 1996). The approval of rTMS as a treatment was initially for a specific device, with a specific protocol, within a defined patient population (medication-refractory depression). Now that the treatment application is gaining momentum, further questions are being explored, such as optimal dose, maintenance schedules, and clinical features of responders and non-responders. The application of rTMS in stroke recovery treatment is appealing because it addresses a substantial area of need and an opportunity for industry. As of this writing, no fewer than nine US government-funded trials for post-stroke deficits involving NIBS are listed by the National Institutes of Health (Clinicaltrials.gov), with new trials poised to commence for both motor-limb and speech-language post-stroke recovery. Recent clinical trials reveal opportunities for further investigation. For example, in a recently completed multicenter, randomized, double-blinded clinical trial in which 1 Hz rTMS (active or sham) was delivered to the contralesional motor cortex as an adjunct to upper limb motor therapy, Harvey et al. (2018) found no significant difference between those subjects receiving active versus sham rTMS (Harvey et al., 2018; Clinicaltrials.gov: NCT02089464). The authors noted however that among these 167 participants, those with intracerebral hemorrhage had unanticipated gains, suggesting that this population should be investigated separately in future studies. The authors further posit that rTMS delivered at a higher frequency might be of benefit and note that, while targeting the non-lesioned cortex is supported based upon reduced risk of seizure and a reduction in contralesional disinhibition, their results do not mitigate the potential benefits of targeted rTMS to the perilesional area. In fact, Kim and Yim (2018) found significant positive effects on hand function using 20 Hz rTMS for 15 min over the affected hand cortex coupled with mirror therapy among 20 subjects (Kim & Yim, 2018). Interestingly, in the first randomized, double-blind clinical trial of dual-hemisphere rTMS for subacute, post-stroke, non-fluent aphasia, Khedr et al. (2014) not only found significant language improvement in patients receiving real versus sham stimulation, but likewise noted an improvement in depression in those 30 patients studied (Khedr et al., 2014). The authors note that while an improvement in language could ostensibly improve depression in patients with aphasia, it is also possible that stimulation to the left inferior frontal gyrus (IFG) could spread to left dorsolateral prefrontal cortex (DLPFC). This is consistent with the literature on rTMS for Major Depressive Disorder (MDD), including a recent trial by Wang et al. (2017), which noted the benefits of rTMS for depression among 200 hospitalized patients (Wang et al., 2017).

An improvement in treatment effectiveness of TMS might occur by using neuronavigation. Neuronavigation with robotic coil positioning (see Fig. 20.5) provides greater targeting precision and stability. The extent to which increased stability in targeting leads to more robust neuromodulation effects remains to be confirmed, yet some evidence in experiments in which targeting biofeedback (neuronavigation) is compared to absent biofeedback (i.e., traditional hand-held approach using scalp

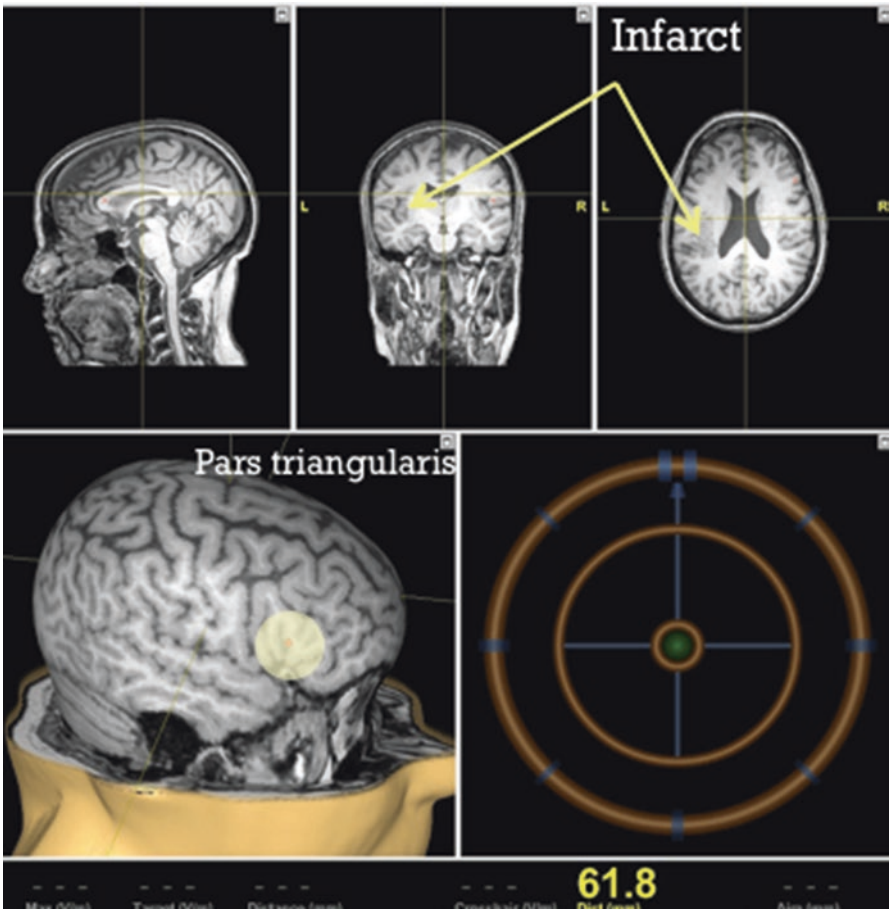

Fig. 20.5 Repetitive transcranial magnetic stimulation (rTMS) has been studied as a therapeutic adjunct to speech and language therapy in subacute stroke, by targeting the Broca's area homologue in the right hemisphere of aphasic patients prior to inpatient therapy. The top middle and right panel show the darkened area of lesion in the coronal and axial planes, respectively. The bottom left pane indicates the TMS target, which uses MRI-guided frameless stereotaxy

sites) suggests that this could be favorable (Bashir, Edwards, & Pascual-Leone, 2011; Bashir, Perez, Horvath, & Pascual-Leone, 2013).

20.5.3 TES as Treatment

The most common applied TES intervention in stroke is tDCS, which is polarity dependent. It has been shown that anodal stimulation increases excitability, while cathodal stimulation causes excitability to decrease (Nitsche & Paulus, 2000). In

stroke studies, cathodal tDCS usually targets the unaffected hemisphere (Fregni et al., 2005); in contrast, anodal tDCS directs stimulation over the affected hemisphere (Hummel et al., 2005). This approach is based on the prevailing but dated and simplistic interhemispheric mutual inhibition model, which served well as a starting point and still has traction for spurring clinical trials; however, this model requires further refinement. The interhemispheric inhibition model suggests that after stroke, ipsilesional excitability is reduced when compared to the contralateral hemisphere. This is associated with more interhemispheric inhibition on the ipsilesional motor cortex than in the contralesional hemisphere (Nowak, Grefkes, Ameli, & Fink, 2009). This imbalanced inhibition is thought to hamper neuroplasticity and limit advances in motor recovery (Boddington & Reynolds, 2017; Murase, Duque, Mazzocchio, & Cohen, 2004).

tDCS has been applied as a stand-alone treatment, but more often in combination with rehabilitative therapy. (For a topical review comparing approaches to tDCS for aphasia with tDCS for motor-limb, see Wortman-Jutt & Edwards, 2017a, 2017b.) Chang, Kim, and Park (2015) examined the effects of tDCS plus physical therapy on post-stroke lower limb function in 24 patients, using TMS to determine whether tDCS enhanced cortical excitability (Chang, Kim, & Park, 2015). The authors reported that MEPs in patients receiving tDCS were both higher and reduced in latency when compared with patients receiving sham stimulation. They also found improvements in some motor functions in the tDCS group compared to the sham group and concluded that anodal tDCS and conservative physical therapy appeared to be beneficial.

Fridriksson et al. (2018) reported similarly promising results for aphasia recovery (Fridriksson et al., 2018). In their recent double-blind prospective randomized clinical trial to assess the effects of adjunctive anodal tDCS in 74 subjects with aphasia, the authors reported a 70% increase in speech production (naming) in those subjects receiving anodal tDCS to perilesional areas. In another aphasia study, Dos Santos et al. (2017) compared the effects of a single session of anodal tDCS, TMS, and sham stimulation in 13 patients with aphasia and then probed for differences in current flow in those patients who received tDCS, but presented with varied naming scores (Santos et al., 2017). The authors found differences in current distribution in those aphasic patients receiving tDCS; however, they did not find a significant difference in naming ability between TMS, tDCS, or sham stimulation. The authors point to inter-individual variability in post-stroke lesions and rates of recovery as a factor in their outcomes and recommend more highly powered clinical trials for future comparisons between tDCS and TMS going forward. In another single session protocol, Spielmann, van de Sandt-Koenderman, Heijenbrok-Kal, and Ribbers (2018) compared two separate tDCS configurations in a randomized cross-over study of 13 patients with aphasia and found that stimulation of the inferior frontal gyrus (IFG) of the left hemisphere ("Broca's region") was optimal (Spielmann et al., 2018).

Thus far, we have discussed tDCS, which is only one of the possible TES protocols in stroke treatment. Two other TES protocols with potential for stroke treatment are transcranial alternating current stimulation (tACS) and transcranial random

noise stimulation (tRNS). tACS is a type of TES that applies an oscillatory current at a specific frequency. tACS is thought to entrain brain oscillations (Helfrich et al., 2014). In one study, 20 Hz tACS was applied in subacute stroke survivors to test whether it could promote functional recovery (Wu et al., 2016). The patients received their usual rehabilitation for 15 sessions; however, half of the participants received tACS. They found a significant decrease in NIH Stroke Scale (NIHSS) scores (with high scores representing greater impairment) in the patients who received tACS, indicating improved function. More research is required into the efficacy of tACS in stroke rehabilitation.

Transcranial random noise stimulation (tRNS) is a form of TES that uses varied frequencies, applied to the cortex, to increase excitability and influence ancillary behaviors (Terney et al., 2008; Fertonani et al., 2011; Hayward et al. 2017). Responsible neurophysiological mechanisms are thought to include long-term potentiation (LTP) and the so-called *stochastic resonance effect*(SR), a phenomenon known to enhance the detection of informational signals following the application of an appropriate level of random noise (Moss et al., 2004; Ward et al., 2002). tRNS has recently been shown to improve visual perception and decision-making in healthy subjects (van der Groen, Tang, Wenderoth, & Mattingley, 2018; van der Groen & Wenderoth, 2016). To-date, one small feasibility study in stroke patients combining tRNS with upper limb training showed promising results (Hayward et al., 2017). The authors noted that tRNS was a safe adjuvant to upper limb motor training in the small group of subjects studied and recommended further trials to study its potential applications in stroke recovery.

While the variability in results across TES and TMS studies is apparent, as is the need for suitably powered clinical trials, investigation into NIBS as a potential tool for the rehabilitation of stroke is ongoing.

20.5.4 NIBS in Combination with Drugs

Neurochemical changes occur during the acute phase of stroke, and frequently conflict with one another (Sahu, Nag, Swain, & Samaddar, 2017). Flooding of the neurotransmitter *glutamate*, for example, leads to an increase in the number of chemical signals being sent between neurons, while simultaneously, neuroprotective mechanisms such as the upregulation of *gamma-aminobutyric acid*(GABA) reduce neuronal excitability, causing the opposite effect (Kubis, 2016). Additionally, healthy brain areas that are anatomically remote in relation to the stroke lesion may experience repercussions from the stroke due to neural inter-connectivity, an effect known as *diaschisis*. As with a given patient's functional presentation and history, it is therefore important to know the medications a stroke patient may be taking, particularly in the acute phase. NIBS can interact with various medications differently, further complicating decisions about site of lesion and intensity of stimulation—or whether to stimulate at all. For example, the effects of tDCS may be reduced by NMDA-antagonists, while NMDA-agonists may enhance the positive effects of

anodal stimulation (Nitsche et al., 2004). Further, the presence of GABA is reduced during anodal tDCS, while cathodal tDCS prompts a reduction in glutamate (Schulz, Gerloff, & Hummel, 2013). In both instances however, the effects may be altered due to medications.

Patients take a range of pharmacological substances following stroke, such as medications for pain (Treister, Hatch, Cramer, & Chang, 2017) or depression (Cipriani et al., 2012), often related directly to the stroke itself. Stroke patients may additionally require medications for any number of comorbidities, from hypertension (Chen & Yang, 2013) to diabetes (Luitse, Biessels, Rutten, & Kappelle, 2012). Such medications may however inadvertently reduce patients' ability to benefit fully from behavioral rehabilitation therapies, due to side effects such as sleepiness (Chen & Marsh, 2018), depression or agitation (Sami & Faruqui, 2015). In making the decision to prescribe medications post-stroke, physicians must often weigh the potential side effects of some drugs against the benefits of improving other cognitive and motor functions, or extending the lifespan of the patient. Antihypertensive medications, as one example, are often given to reduce the risk of stroke recurrence (Boan et al., 2014); however, these can sometimes pose a danger when interacting with certain foods (Jauregui-Garrido & Jauregui-Lobera, 2012). While these and other drugs may modify the response to NIBS, the possibility should likewise be considered that NIBS can leverage changes in excitability to a therapeutic advantage, whereby more powerful symptom reduction, or lower dose of medication, could be achieved. It has been noted, for example, that tDCS may be advantageous in reducing the number of medications taken, or lowering the dosage of medications, thus preventing multiple drug interactions in patients (Brunoni et al., 2012; Wortman-Jutt & Edwards, 2017a, 2017b).

For clinicians approaching NIBS for the first time, and even for seasoned health professionals, it is important to take into account the turbulent changes already taking place within the recovering post-stroke brain, consider patients' medical and social histories, and to be cognizant of patients' medications, before inciting further neural reorganization by means of NIBS. At present, there is no universally accepted stroke recovery drug. Failure to prove beneficial effects of medications, such as d-cycloserine (Nitsche et al., 2004), may be the result of dosing, study design, or inter-individual variability; or it may be due to a true non-beneficial effect. As of this writing, there is mounting promise with the drug fluoxetine, a selective serotonin-reuptake inhibitor (Chollet et al., 2011). Trials are ongoing; nonetheless, the use of NIBS to optimize pharmacotherapy is appealing and requires further exploration.

20.5.5 The Impact of Stroke on Brain Networks

Historically, accounts of the relationship between brain structure and function have mapped specific functions to defined brain locations as noted in physiological studies (Buch, Mars, Boorman, & Rushworth, 2010; Duque et al., 2005), imaging

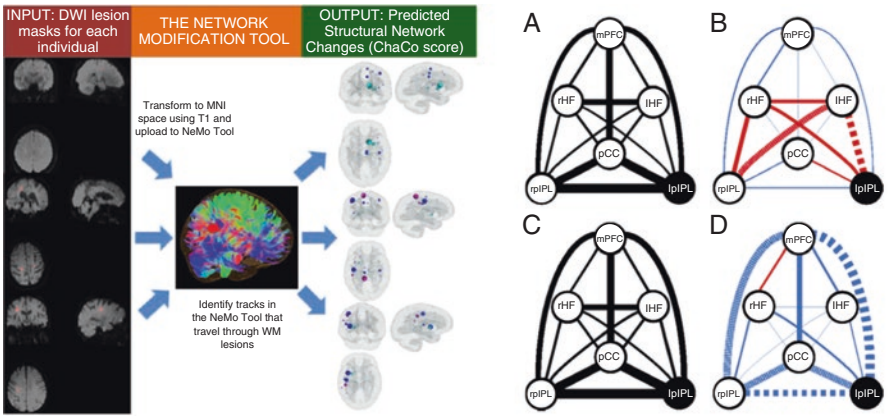

Fig. 20.6 Left panel: The impact of an isolated stroke lesion affects a broader network. The left panel illustrates the projected intra- and interhemispheric effects of an isolated lesion. (Right) The impact of targeted cortical stimulation to one brain region may affect a broader network. The right panel shows connectivity between brain regions using resting-state functional MRI, where changes in the default network interactions result from targeting a single brain region with rTMS. Schematic representation of functional connectivity changes across multiple regions within the default network. The thickness of the lines connecting default network regions is proportional to the connectivity strength between these regions. Connectivity is displayed before 1-Hz (**a**) and 20-Hz (**c**) rTMS (Left). From**:** Kuceyeski A, Kamel H, Navi BB, Raj A, Iadecola C. Predicting future brain tissue loss from white matter connectivity disruption in ischemic stroke. Stroke**.** 2015; 45(3):717–22. doi: https://doi.org/10.1161/STROKEAHA.113.003645. Adapted with permission of *Lippincott Williams & Wilkins* (LWW) an imprint of *Wolters Kluwer, publisher*. Right Panel: Changes in functional connectivity between default network regions as a result of 1-Hz (**b**) and 20-Hz (**d**) rTMS. Scaling of line thickness to changes in correlation strength is different between Right and Left. Decreases in functional connectivity are depicted with blue lines, and increases are depicted in red. Large dashed lines signify significant changes (corrected for multiple comparisons). Small dashed lines signify significant correlation changes not surviving corrections for multiple comparisons. These results suggest that coupling between regions in the default network is dynamic. From: Eldaief MC, Halko MA, Buckner RL, Pascual-Leone A. Transcranial magnetic stimulation modulates the brain's intrinsic activity in a frequency-dependent manner, Proc Natl Acad Sci USA, 2011; 108(52): 21229–21,234. Reprinted with permission of PNAS, publisher

studies (Biswal, Yetkin, Haughton, & Hyde, 1995), and lesion-symptom mapping (Le Heron, Apps, & Husain, 2017; Schwartz, Faseyitan, Kim, & Coslett, 2012). Collectively, these studies demonstrate that divergent brain areas may have anatomical and/or functional connectivity that cooperatively support specific behaviors, a term recently coined the *Connectome* (Sporns, Tononi, & Kotter, 2005). The connectome is also implicated in stroke recovery (Silasi & Murphy, 2014). Figure 20.6 illustrates examples of how the connectome might be considered in stroke recovery, as well as in NIBS applications.

Connectivity within the brain includes intracortical neuronal networks, which remains a less-well characterized impact of stroke, such as in the penumbra, or remotely connected areas. In the present discussion, we refer to the connection between cortical hubs (or cortical-subcortical) via white matter projections.

Human behaviors are not governed by single brain areas, but are due to interactions between different cortical areas (Bassett & Bullmore, 2009; Geschwind, 1965a, 1965b). This is notable given that during a stroke, cortical networks are differentially affected. For example, Kuceyeski, Kamel, Navi, Raj, and Iadecola (2014) used a "Network Modification Tool" to assess the degree of damage to cortical substrative networks following a single stroke brain lesion (Kuceyeski et al., 2014). The authors found that remote degeneration of tissue following a focal brain lesion may be predicted, based upon network connectivity using this technology. In determining the locus of stimulation for TMS, it is therefore important to consider the spread of effects caused by network disruption. Nonetheless, when Hartwigsen et al. (2010) used TMS to create a virtual lesion over parietal and frontal areas concurrently in healthy subjects, the authors found that a single virtual lesion alone was not enough to cause disruption to lexical-semantic decision-making. In order to explore inter- and intra-hemispheric activity, some recent aphasia studies have therefore applied multifocal rTMS to separate cortical areas simultaneously (Hartwigsen et al., 2010; Hartwigsen, Baumgaertner, et al., 2010). This model provides opportunities to observe language networks at work, rather than merely one specific language area in isolation. Taken together, the stroke induced disconnectivity, and virtual lesion studies support a lesion-induced network disruption that might contribute to symptoms.

20.5.6 Focality of a Single Cortical Target

Before considering the remote impact of a single pulse TMS (or focal TES), it is useful to consider the spatial extent of stimulation targeting a single cortical region.

Please note, for TES (single pulse short-duration, or longer duration *neuromodulation* such as tDCS), the electric field can have an effect (putatively, differential) under the anodal or cathodal electrode, and indeed the macroscopic and microscopic distribution, polarity, and effects are complicated (Bikson, Name, & Rahman, 2013), so one should consider the position of both electrodes, not only the electrode over the region of interest (if both electrodes are cephalic). In some cases, one of the electrodes may be extra cephalic.

With TES, the spatial extent of cortical currents is dependent on size, number, and position of electrodes (as well as other factors such as stimulation intensity and waveform). Using large electrode pads (e.g., 5 × 7 cm), such as applied with conventional tDCS, there is appreciable current spread and a broader distribution on the cortex than originally intended (originally thought to be relatively confined to the cortical region beneath the electrode pad (Nitsche & Paulus, 2000; Sadleir, Vannorsdall, Schretlen, & Gordon, 2010). By using smaller electrodes and altering the configuration on the scalp, it is possible to reduce the spatial distribution of currents on the cortex, thereby increasing focality (Edwards, Cortes, Datta, et al., 2013; Edwards, Cortes, Thickbroom, et al., 2013).

Hartwigsen (2015) notes that the focality of neuronal stimulation during TMS is dependent upon several factors, including the size of the coil, its spatial resolution, the stimulation intensity and duration, as well as the specific tissue being stimulated. When high-frequency bursts are used, for example, the author reports focality may be reduced; consequently, precision in placement of the coil is of utmost importance in TMS, without which focality cannot be ensured (Hartwigsen, 2015).

20.5.7 Network Effects of NIBS

A spatially confined stimulus using one TMS coil positioned over a single scalp location may have far-reaching effects. The neuromodulatory effects of rTMS may create distributed changes not only between network nodes, but within subsystems of a given cortical network, based upon the frequency of stimulation. In one study by Eldaief, Halko, Buckner, and Pascual-Leone (2011), 25 healthy participants received either 1 Hz or 20 Hz stimulation within the left posterior inferior parietal lobule. While 20 Hz rTMS to this area was found to reduce connectivity within the network node, it actually increased the functional correlation between the default node and the hippocampal subsystem (Eldaief et al., 2011). According to the authors, this suggests that variability in response to rTMS within subsystems of a single network may be frequency dependent.

tCS configurations can also be optimized in order to stimulate spatially different targets within brain networks. Ruffini, Fox, Ripolles, Miranda, and Pascual-Leone (2014) note that in addition to targeting either one localized area or multiple cortical areas using tCS, "pattern targeting" may be used, in which the return current is leveraged by placing it closer to the active electrode, as in high-definition tDCS (Ruffini et al., 2014). Similarly, multifocal tDCS has been applied to optimize the targeting of entire brain networks (Ruffini et al., 2014). Fischer et al. (2017) used multifocal tDCS to stimulate the left motor cortex and its correlated network areas, as determined by resting-state fMRI (Fischer et al., 2017). The authors report that the left cortical hand region was isolated first, which was then used as a "seed region" to establish a network map of correlated brain regions. The authors subsequently found that multifocal tDCS stimulation to target the entire motor network produced a greater increase in cortical excitability of the M1 bilaterally, as compared with traditional two-electrode tDCS over one isolated region of the motor cortex.

20.5.8 Multifocal Stimulation

Contemporary methods for neuromodulation attest to the benefits of stimulating multiple nodes of a cortical network simultaneously, rather than just one area, as has been traditionally done. Recent research in healthy subjects, for example, suggests that by stimulating two brain areas with TMS using small temporal intervals, it is

possible to strengthen connections (Buch, Johnen, Nelissen, O'Shea, & Rushworth, 2011), fostering alternative pathways between brain areas. This is based on *Hebb's principle*, which states that pairing pre- and postsynaptic activity strengthens synaptic connections; or, put more simply, "what fires together, wires together" (Hebb, 1949). Importantly, change in connectivity was noted only when participants were actively engaged in a motor task. This is known as *state dependent effect NIBS*, which has been frequently observed in the literature (Silvanto, Muggleton, & Walsh, 2008). When clinicians apply NIBS, it is therefore important to engage the patient in a meaningful task, as this may influence the efficacy of the intervention. State-dependency can also be obtained by combining two types of NIBS, using one type of NIBS as a form of preconditioning. For example, it has been shown that preconditioning the motor cortex with tDCS can modulate subsequent rTMS excitability (Lang et al., 2004; Siebner, 2004). It is therefore important to keep in mind that dual NIBS-effects given in succession can interact with each other.

Further research should investigate if network analysis can be useful in predicting stroke outcome, since the degree of motor and cognitive recovery following stroke is not only dependent on the primary degeneration of affected neuronal tissue, but also on remote degeneration of brain areas, so-called *Wallerian degeneration* (Puig et al., 2010, 2017). MRI and TMS can play a crucial role in the assessment of changes in these functional networks. MRI has been used to assess which regions are susceptible to remote degeneration and to predict outcomes in motor function and cognition (Kuceyeski et al., 2014; Kuceyeski et al., 2016). TMS can also be combined with electroencephalography (EEG) to induce so-called *TMS-evoked-potentials*(TEPs). TEPs measure excitability and plasticity in the stimulated region as well as in functional networks (Daskalakis, Farzan, Radhu, & Fitzgerald, 2012; Hill, Rogasch, Fitzgerald, & Hoy, 2016; Taylor, Walsh, & Eimer, 2008). This technique, still in development, is a promising biomarker for stroke outcome prediction in both motor and cognitive domains.

20.5.9 Limitations and Future Directions of NIBS in Stroke Recovery

NIBS is a remarkable modern tool for probing and modulating central nervous system function in a safe and painless manner in the awake human. While still a blunt instrument, NIBS can interact with local and network brain physiology, and build our understanding of, and perhaps promote, adaptive recovery. Currently, there are exciting new approaches being tested in laboratories worldwide. One example previously mentioned is multifocal stimulation. Another example is to combine NIBS in stroke survivors with psychosocial and behavioral therapies. For example, the combination of rTMS with psychotherapy in major depressive disorder has shown promising results (Donse, Padberg, Sack, Rush, & Arns, 2017); however, the efficacy of this approach has yet to be confirmed in stroke survivors. In addition to presently available brain stimulation methods, the continual development of

technological advancements allows for new brain stimulation approaches. Neurons in deeper brain areas, for example, may be stimulated with temporally interfering electrical fields (Grossman et al., 2017). Another promising development is so-called *closed-loop stimulation* (Buetefisch, Heger, Schicks, Seitz, & Netz, 2011; Zrenner, Belardinelli, Müller-Dahlhaus, & Ziemann, 2016) in which brain stimulation is triggered based on a specific behavior or neurophysiological signal. For example, in *brain-state dependent stimulation* (BSDS) (Gharabaghi et al., 2014), NIBS is combined with EEG and brain stimulation is triggered based on a neurophysiological marker in the EEG signal. This approach allows for the optimization of the timing of NIBS in relation to the brain state.

The approaches outlined herein are promising and exciting new avenues that may improve the efficacy of NIBS in stroke rehabilitation. The utility of NIBS as a stroke recovery treatment remains ambiguous; nonetheless, expression of interest is demonstrated by funding bodies and through the popularity of related journal articles, positive published experimental findings, and positive clinical trial results. Justifications for opposition however includes a lack of reproducibility studies and emerging failed trials (Harvey et al., 2018). The fault may lie as much in the outcome measures as the therapeutic protocol; for example, NIBS (e.g., tDCS) can be shown to alter motor learning in health and stroke, but not to change impairment (Giacobbe et al., 2013). The role of functional and impairment measures in stroke recovery is still debated (for a review see Krakauer, 2005).

Study design in clinical intervention studies has long been debated. On the one hand, if effects are strong enough across a group, inter-individual variability will not obscure an average group effect. Group-level difference as an a priori established valid and reliable metric of clinical relevance is therefore suitable. However, an alternative approach is that the vast inter-individual variance warrants a case series or similar analysis, as ultimately individual level prescription of therapies with predictable meaningful outcome is the end-goal. Caution is advised, however, in determining how failure is to be defined in each subject; and further, attention must be paid to the dilemma of how to combine findings across patients. Nonetheless, a better understanding of the inter-individual variance will likely result in better stroke outcomes, since this will allow us to tailor NIBS to individual patient's needs (Li, Uehara, & Hanakawa, 2015). In an era of evidence-based medicine, we are faced with an overwhelming failure rate of clinical trials. One feature that is often lacking in clinical studies is a strong theoretical underpinning. Time spent on developing and testing theories is an important component of rehabilitation research.

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https://doi.org/10.1007/978-3-030-49586-2