HANDBOOK OF

FRONTAL LOBE ASSESSMENT

SARAH E. MACPHERSON | SERGIO DELLA SALA

WITH SIMON R. COX | ALESSANDRA GIRARDI | MATTHEW H. IVESON

OXFORD

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To Sophie and Joseph
and
To Emma and Marta
who will eventually develop their frontal lobes!

Acknowledgments

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Sarah E. MacPherson and Sergio Della Sala
August 2014

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Advance Praise

The effects of lesions to the frontal lobes on cognition, emotion, and personality are among the most difficult to assess in all of neuropsychology. Many very different tests have been proposed, but the utility of quite a number has been questioned, and the literature on their application is complex and diffusely located. This Handbook is therefore enormously valuable in synthesizing a vast amount of material on the 30 most widely used different types of test. The Handbook will prove an essential resource for anyone involved in the assessment of the behavioural consequences of frontal lobe lesions.

Professor Tim Shallice, University College London, UK

Clear and insightful chapters detailing convergent evidence on the usefulness of the tests currently used to assess frontal lobe functional domains will enable you to become familiar with the costs and benefits of using both classic and novel, state-of-the-art, test instruments including commentary on each test's validity and reliability. If you evaluate or study patients with frontal lobe lesions or dysfunction, you must have this book in easy reach as it is a one-stop shop designed to simplify your decision making about which frontal lobe tests are right for your clinical patients or research participants. There is simply no substitute for it.

Professor Jordan Grafman, Ph.D., Rehabilitation Institute of Chicago, USA

This is an excellent, much-needed resource. If evidence were needed of the richness and variety of frontal lobe functions then readers need look no further than this text. The authors provide an accomplished account of the tools of frontal lobe assessment, their evidence-base and neural correlates that will be of immense value to clinicians and researchers alike.

Professor Julie S Snowden, Consultant Neuropsychologist,
Cerebral Function Unit, Greater Manchester Neuroscience Centre,
Salford Royal NHS Foundation Trust, UK

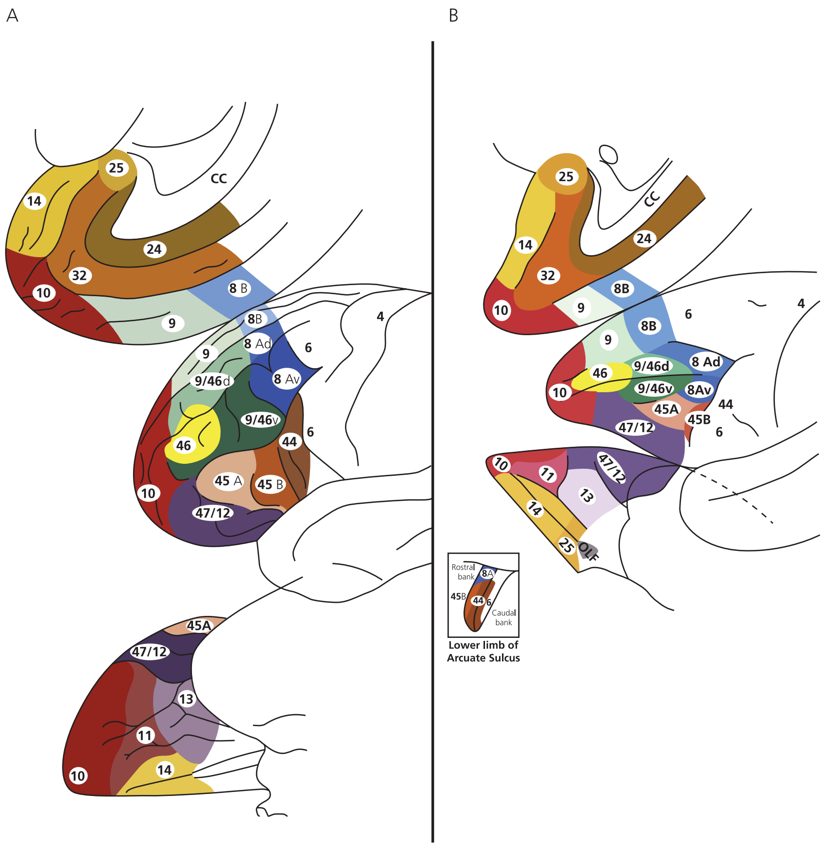
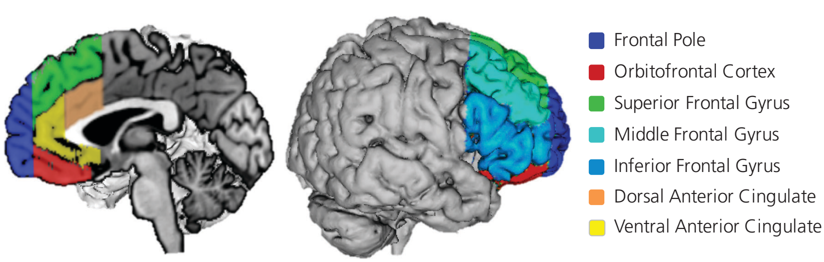


Fig. 1.6 Cytoarchitecture of (A) human and (B) monkey prefrontal cortices. Reprinted from *Cortex*, 48 (1), Michael Petrides, Francesco Tomaiuolo, Edward H. Yeterian, and Deepak N. Pandya, The prefrontal cortex: comparative architectonic organization in the human and the macaque monkey brains, pp. 46–57, Copyright (2012), with permission from Elsevier.



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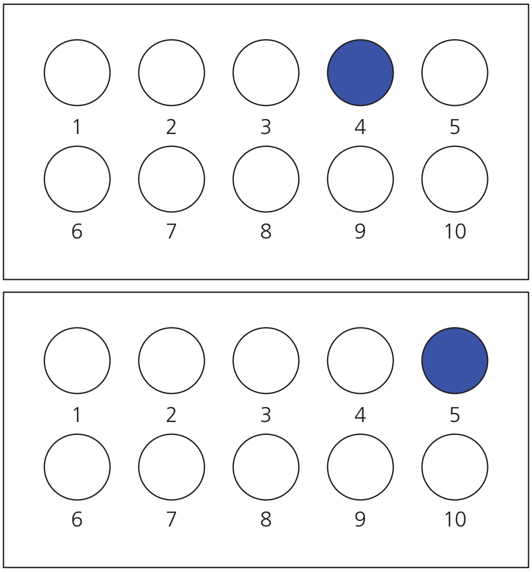

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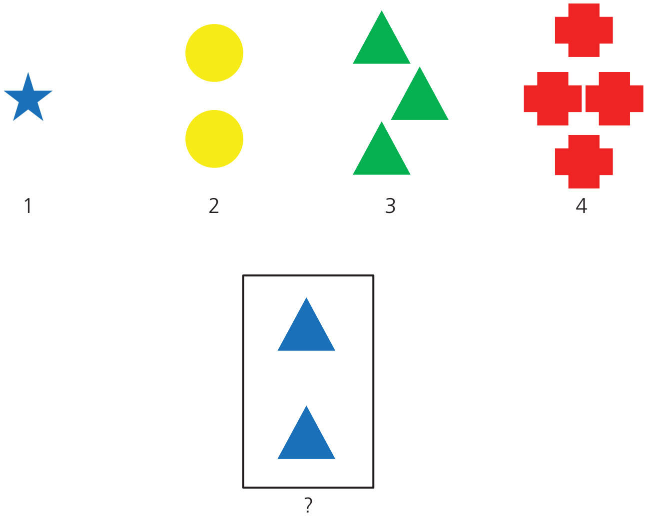

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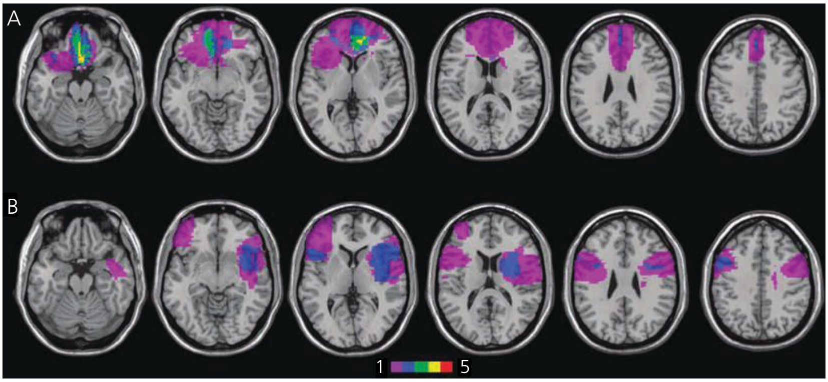

Fig. 8.2 Overlaps of lesions for (A) ventromedial prefrontal group who were impaired on emotion recognition and (B) non-ventromedial prefrontal group who were comparable to controls (Heberlein et al. 2008). Reprinted from Andrea S. Heberlein, Alisa A. Padon, Seth J. Gilihan, et al. Ventromedial frontal lobe plays a critical role in facial emotion recognition, *Journal of Cognitive Neuroscience*, 20(4), pp. 721–733, © 2008 Massachusetts Institute of Technology. Reprinted by permission of MIT Press Journals.

Fig. 9.3 Example of two trials from the Cambridge Gambling Task. Note the difference in probabilities between A (4:2) and B (5:1). Reproduced from Robert D. Rogers, Adrian M. Owen, Hugh C. Middleton, Emma J. Williams, John D. Pickard, Barbara J. Sahakian, and Trevor W. Robbins, Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex, *Journal of Neuroscience*, 20(19), pp. 9029–9038, Figure 1. © 1999, The Society of Neuroscience, with permission.

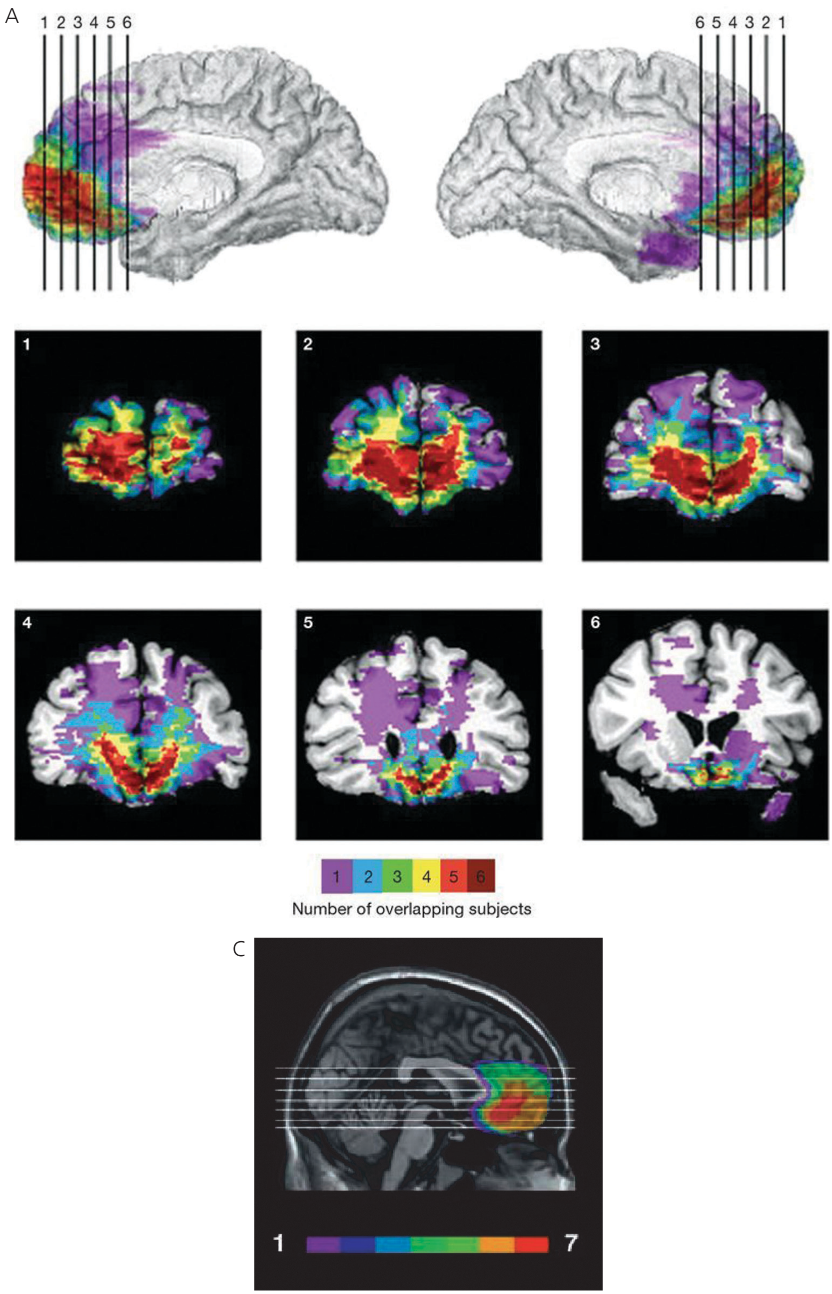

Fig. 9.6 Lesion overlaps in moral decision-making studies. (A) Reprinted by permission from Macmillan Publishers Ltd: *Nature* 446(7138), Michael Koenigs, Liane Young, Ralph Adolphs, Daniel Tranel, Fiery Cushman et al., Damage to the prefrontal cortex increases utilitarian moral judgements, pp. 908–911, Figure 1. Copyright, 2007, Nature Publishing Group. (C) Reproduced from Laura Moretti, Davide Dragone, and Giuseppe de Pellegrino, Reward and social valuation deficits following ventromedical prefontal damage, *Journal of Cognitive Neuroscience*, 21(1), pp. 128–140. © 2008 by the Massachusetts Institute of Technology. Reprinted by permission of MIT Press Journals.

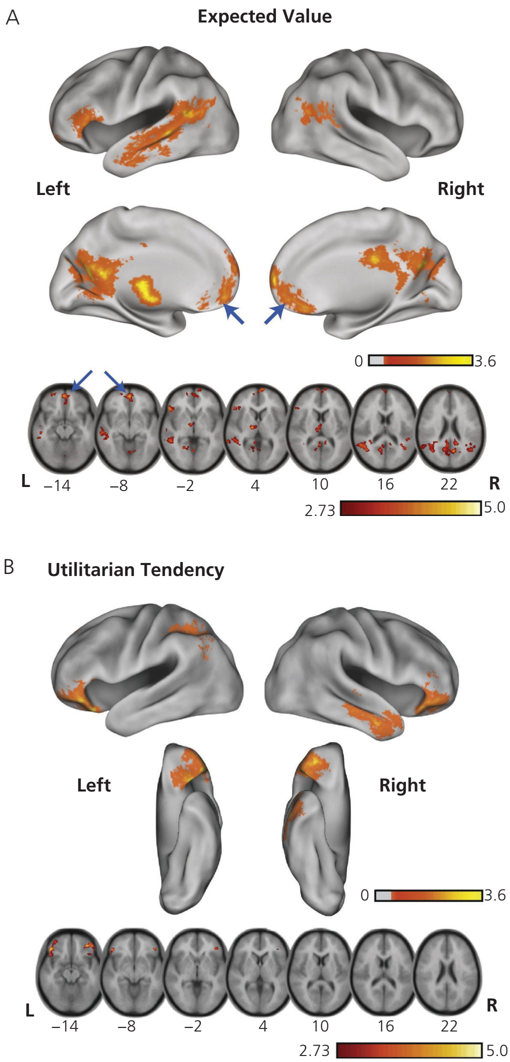

Fig. 9.7 Utilitarian responses in Moral Decision-Making studies. Top panel: network whose activation increases linearly with value of expected outcome. Ventromedial prefrontal activation (arrows) sensitive to the "expected moral value" is reported in several studies of economic decision-making. Bottom panel: regions demonstrating increased BOLD activation with increased tendency towards utilitarian responses. Reprinted from Amitai Shenhav and Joshua D. Greene, Moral Judgments Recruit Domain-General Valuation Mechanisms to Integrate Representations of Probvability and Magnitude, pp. 667–77, Figure 3. Copyright (2010), with permission from Elsevier.

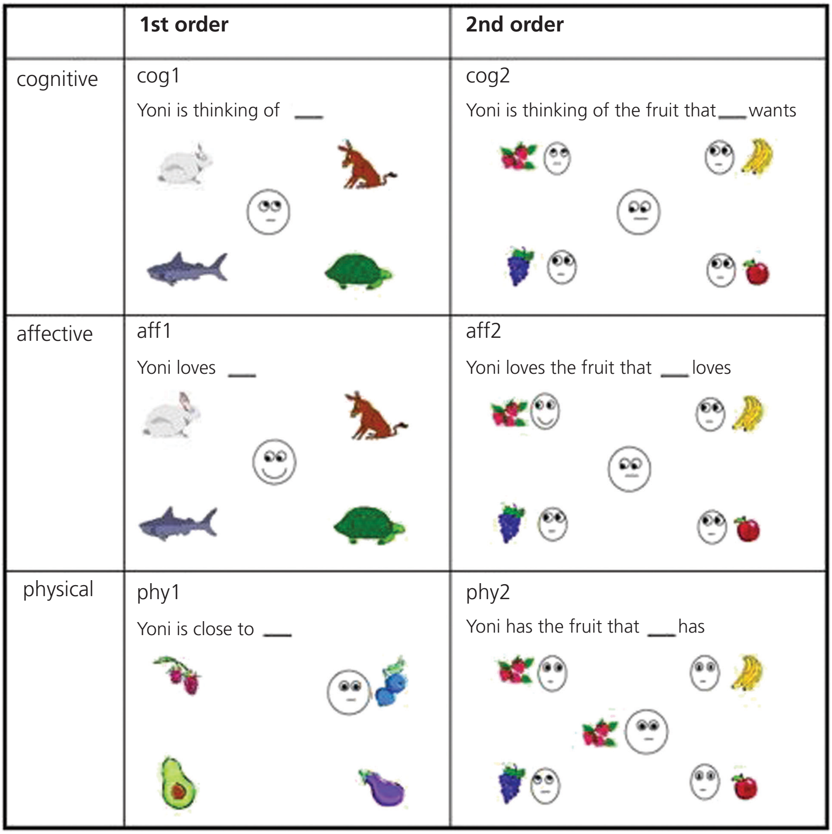

Fig. 10.3 Stimuli used in the modified Judgment of Preference Task. Reprinted from *Neuropsychologia* 45 (13), from Elke Kalbe, Marius Schlegel, Alexander T. Sack, Dennis A. Nowak, Manuel Dafotakis, Christopher Bangard, Matthias Brand, Simone Shamay-Tsoory, Oezguer A. Onur, and Josef Kessler, Dissociating cognitive from affective theory of mind: a TMS study, pp. 769–780. Copyright (2010), with permission from Elsevier.

Chapter 1

Introduction: Fractionating the frontal lobe syndrome

1.1 Frontal lesions and behavior change

When one hears the term "frontal lobe function," even the most junior psychology student might think of the classic "crowbar" case of Phineas Gage (Harlow 1848; MacMillan 2002). Nowadays, it seems surprising that the accepted wisdom was once that this region was associated with few, if any, cognitive functions (e.g., Pfeifer 1910; Feuchtwanger 1923). Gage experienced severe personality changes as a result of a tamping iron penetrating his frontal lobes, and yet many medical textbooks published around that time, including the first five editions of Dalton's physiology textbook, *A Treatise on Human Physiology* (1859–1871), stated that Gage was, "in perfect health … with the mental and bodily functions entirely unimpaired" (see Barker 1995). Paradoxically, the *American Phrenological Journal* reported in 1851 that the frontal lobes were not a monolithic entity and that a number of cognitive abilities would have been impaired by Gage's damage to the various phrenological organs (Anonymous 1851). Yet, it took John M. Harlow, Gage's physician, 20 years to report to the medical community that Phineas Gage was "no longer Gage" due to his frontal lobe damage (Harlow 1868; MacMillan 2002). Whereas accounts may vary of what happened that fateful afternoon in September 1848, this story has fuelled the interests of both scientists and laypeople alike (Kean 2014).

Delving a little deeper into the literature, a number of similar cases of behavior change had been reported in patients with frontal lobe damage. For example, one of the most prominent photographers of the nineteenth century, Eadweard J. Muybridge (Figures 1.1 and 1.2), suffered personality changes following head trauma from a stagecoach accident (see Shimamura 2002). These changes included becoming more eccentric, irritable, a riskier decision-maker, and often Muybridge was described as displaying uncontrollable outbursts. He was even acquitted of the murder of his wife Flora's lover and father of her son, after his friends testified that he was a different man post accident. Although the exact localization of his brain damage is unknown, Muybridge's symptoms were consistent with someone who had damage to the orbitofrontal cortex (Shimamura 2002).

In another example, in the early twentieth century, the Italian psychiatrist Cesare Agostini (1914) published a report describing the considerable

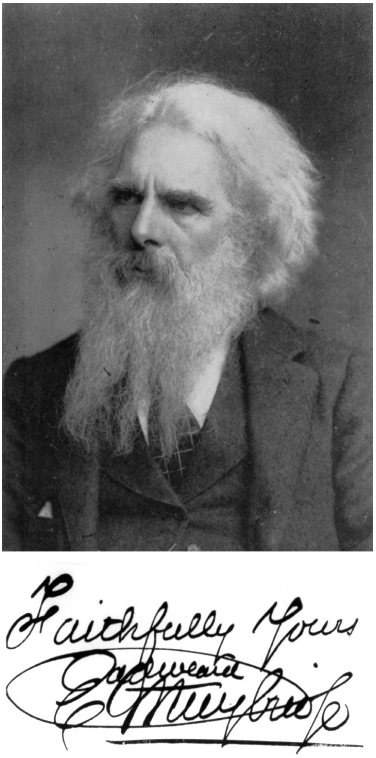

Fig. 1.1 Portrait of Eadweard J. Muybridge, Wm. Vick Studio, *c*.1881. © The Library of Congress.

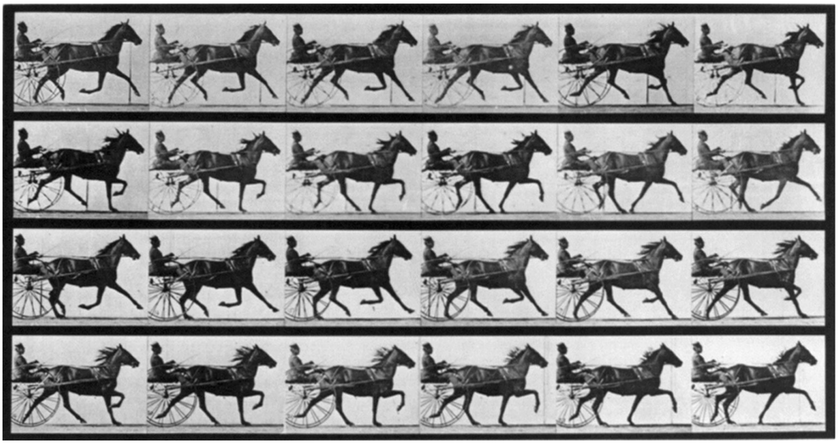

Fig. 1.2 Photograph by Eadweard J. Muybridge: Horse in Motion from Animal Locomotion, 1887. © The Library of Congress.

personality change experienced by one of his patients, P. Vincenzo, a 47-year-old laborer (Figure 1.3). The patient was described as having become irritable, quick- and bad-tempered, and had an inclination for criminal behavior. In 1907, Vincenzo stabbed a road worker to death after a minor row over a barrow. It was not until Vincenzo's death due to an epileptic seizure in 1909 that he was diagnosed as having a right orbital frontal lobe tumor. These patients, as well as other single-case examples reported in the eighteenth and early nineteenth centuries, consistently showed that orbital and medial prefrontal damage resulted in severe personality change.

It was therefore astonishing that damaging the frontal lobes would become a treatment for mental illness. Egas Moniz, the Portuguese neurologist and Nobel Prize winner in 1949, devised the infamous frontal lobotomy (Moniz 1936), later aggressively promoted in the USA by Walter Freeman (e.g., Freeman and Watts 1942), arguing that the benefits of this surgical procedure for reducing the symptoms of mental illness outweighed the acute personality changes that resulted (for scientific criticisms see Valenstein 1986; for literary criticisms read *Suddenly, Last Summer* by Tennessee Williams; for patients' stories see Raz 2013). The behavioral effects of frontal lesions are now laypeople parlance, and "frontal" has become a defining adjective. Indeed, even movies feature characters with behavioral changes due to lesions in the frontal lobes (Table 1.1 and Figure 1.4; for specific symptoms such as anarchic hand, see Della Sala 2009).

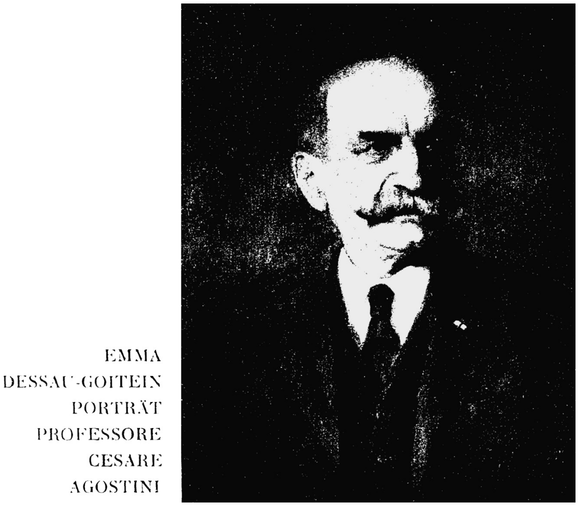

Fig. 1.3 Portrait of Professor Cesare Agostini. © JCS Universitätsbibliothek Frankfurt am Main/Digitale Sammlung Judaica. http://sammlungen.ub.uni-frankfurt.de/2926241.

Table 1.1 Behavioral effects of frontal lesions as shown in movies

Movie	Character with frontal lobe lesion	Aetiology	Behaviour	Relevant sentence
A Fine Madness (1966)	Sean Connery (poet Samson Shillitoe)	Frontal lobotomy	Aggressive behaviour, social faux pas	Samson's wife: "Hey, Samson, Mr Butler's got some great news for you!" Samson: "Mister? When did he get the operation?"
Planet of the Apes (1968)	Robert Gunner (astronaut Landon)	Frontal lobotomy	Mutacism and abulia	Taylor, Landon's friend: "You cut up his brain, you bloody baboon!… You cut out his memory. You took his identity."
Night of the Living Dead (1968)	Zombie	Thin frontal lobe	Impulsivity	Scientist: "Kill the brain, and you kill the ghoul."
One Flew Over the Cuckoo's Nest (1975)	Jack Nicholson (anarchic criminal "Mac" McMurphy)	Frontal lobotomy	Catatonia	Martini (Danny DeVito) and Scanlon (Delos V. Smith Jr), Mac's fellow interns in the mental institution seeing him after surgery: "Nothing like him," "Sure," "Just like one of those store dummies ain't that right?," "Damn right. Whole thing you know, too blank."
Zelig (1983)	Woody Allen (common man Leonard Zelig)	Not specified	Environmental Dependency Syndrome	Zelig's conned victim (Louise Deitch): "He painted my house a disgusting colour. He said he was a painter. I couldn't believe the results."
Regarding Henry (1991)	Harrison Ford (attorney Henry Turner)	Gun shot in the right frontal lobe (though curiously with paralysis in the right limbs)	Childlike behaviour	Dr Sultan (James Rebhorn): "Mrs Turner, your husband, incredibly lucky. The bullet wound to the head caused minimum damage. See (pointing to scans) it hit the right frontal lobe, which is the only part of the brain which has redundant systems. I mean if you have to be shot in the head, that's the way to do it."
The Shadow (1994)	John Lone (warlord Shiwan Khan)	Glass shard head injury	Confusion and lack of mental power	Doctor (Aaron Lustig) to Khan: "Save your life, that's what. Of course we had to remove a section of your frontal lobes, but you'll never miss it, believe me. It's a part nobody ever uses."

A Life Less Ordinary (1997)	Stanley Tucci (dentist Elliot Zweikel)	Brain injury during a "William Tell" shooting game	Disinhibition and impulsiveness	Elliot (operating an injured leg without any surgical experience): "They wanted me to take a break you know, take a break. Go get counselling, you know. Fuck off.... The principles of surgery are the same above or below the neck!"
"My Sister, My Sitter," 17th episode, Season 8, *The Simpsons* (1997)	Bart Simpson	Fall downstairs and banging head against wall	Anosodiaphoria	Lisa: "Bart, are you okay?" Bart: "Yeah, I think so. It's just a bump on my head." Lisa: "Eww! Your arm! It's got extra corners!" Bart: "Oh, cool! It must be dislocated or something."
"HOMЯ," 9th episode, Season 12, *The Simpsons* (2001)	Homer Simpson	Crayon stuck in his frontal lobe	IQ boosted after removal	Scientist: "We could perform a surgery and remove the crayon from your brain. It could vastly increase your brain power. Or it could possibly kill you." Homer: "Hmm... increase my killing power, eh?"
"The Social Contract," 17th episode, Season 5, *House* (2009)	Jay Karnes (editor Nick Greenwald)	Doege–Potter syndrome	Disinhibition	Dr Lisa Cuddy: "I was paged." Nick: "I would do her in a minute with fudge and cherries on top..." Dr Remy "Thirteen" Hadley: "He has frontal lobe disinhibition."

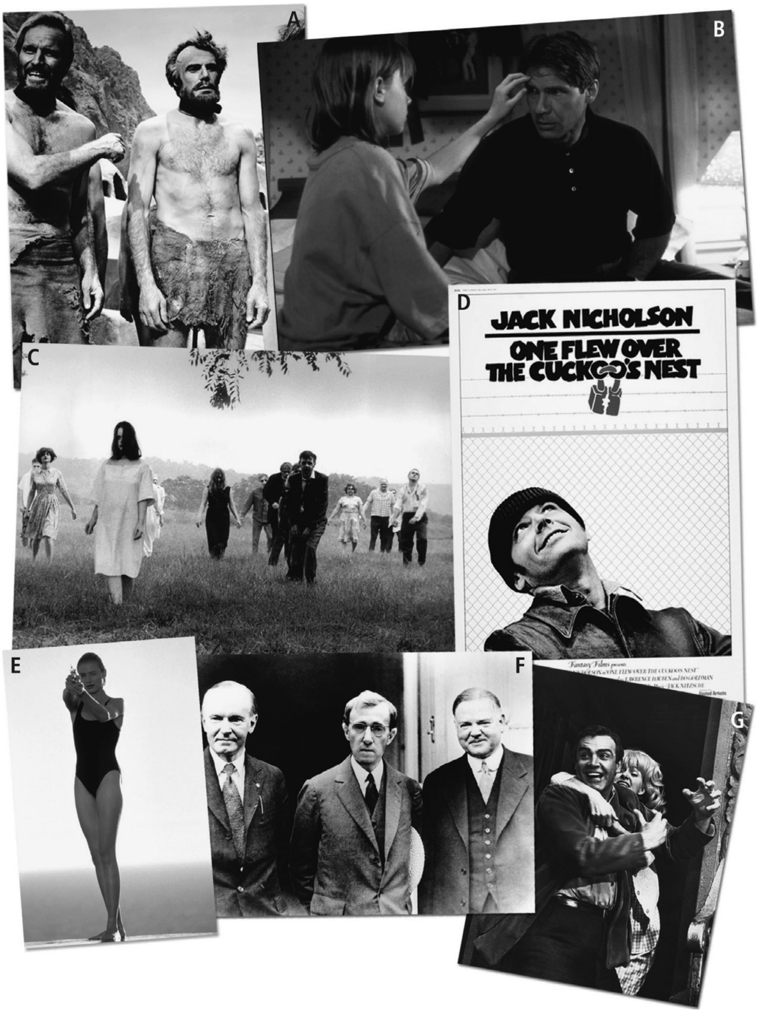

Fig. 1.4 Movies featuring characters with behavioral changes due to frontal lesions. (A) *Planet Of The Apes (1968)* (reproduced courtesy of 20th Century Fox/The Kobal Collection); (B) *Regarding Henry* (reproduced courtesy of Paramount/The Kobal Collection/Duhamel, Francois); (C) *Night Of The Living Dead (1968)* (reproduced courtesy of Image Ten/The Kobal Collection); (D) *One Flew Over The Cuckoo's Nest* (reproduced courtesy of United Artists/Fantasy Films/The Kobal Collection); (E) *A Life Less Ordinary* (reproduced courtesy of Polygram/The Kobal Collection); (F) *Zelig* (reproduced courtesy of Orion/Warner Bros/The Kobal Collection); (G) *A Fine Madness* (reproduced courtesy of Pan Arts/Warner Bros/The Kobal Collection).

1.2 **Neuroanatomy of the frontal lobes**

The writings of thirteenth-century Florentine writer and philosopher Brunetto Latini propose that different functions can be mapped on to distinct neuroanatomical regions, including functions associated with the frontal lobes. His enchanting poem *Il Tesoretto* (Little Treasure), written *c.*1261–1266, declares, "Anterior is the lodging of all intellectual properties and the stamina to learn that which one could understand" (Figure 1.5).

The French physician and anatomist Félix Vicq d'Azyr referred to three brain regions within each hemisphere; the frontal, parietal, and occipital lobes (Vicq d'Azyr and Moreau de la Sarthe 1805), labels which are still used today. However, it was not until the nineteenth century that anatomists acknowledged that different gyri and sulci within the brain formed patterns. Within the frontal lobes, three gyri on the lateral surface (Ecker 1869, 1873) as well as gyri on the orbital and medial surfaces of the frontal lobes (Leuret 1839; Valentin 1841; Foville 1844; Gratiolet 1857) were illustrated. Further advancement in the early 1900s led cortical regions to be considered in terms of their differences in cellular structure and organization (Campbell 1905; Brodmann 1909; Vogt and Vogt 1919; Von Economo and Koskinas 1925). Whereas similar nomenclatures were

Il Tesoretto

Nel capo son tre celle
E io ti diro' di quelle.
Davanti e' lo ricetto,
di tutto lo intelletto
e la forza d'aprendere
quello che puoi intendere

Little Treasure

In the head there are three rooms
And I'll speak about those.
Anterior is the lodging,
of all intellectual properties
and the stamina to learn
that which one could understand

Fig. 1.5 Portrait of Brunetto Latini (© DeAgostini Picture Library/Scala, Florence) and *Il Tesoretto*, canto VII, by Brunetto Latini (*c.*1261–1266).

devised, anatomists most usually employed Brodmann's (1909) to differentiate regions by their cytoarchitectural differences—and still do so. This classification system has led to the identification of various frontal subregions, including the dorsolateral prefrontal cortex that comprises Brodmann's Areas (BAs) 9 and 46, the anterior cingulate cortex (BAs 24, 25, 32, and 33), the inferior frontal gyrus (BAs 44, 45, and dorsal parts of 47), the orbitofrontal cortex (BAs 11–14, and ventral parts of 47) and the frontal pole (BA 10) (Devinsky et al. 1995; Rajowska and Goldman-Rakic 1995; Pandya and Yeterian 1996; Uylings et al. 2010). The frontal lobes also include the primary motor (BA 4), supplementary motor regions (BA 6), and the frontal eye fields (BA 8), but these regions are not thought to play a relevant role in complex cognitive behavior, decision-making, nor in moderating social behavior.

It might be surprising for some to read that more than one hundred years ago, Jakob, a German neurobiologist working in Argentina, first advocated the importance of also studying the anatomical connectivity of the frontal lobes in order to understand its function (see Théodoridou and Triarhou 2012 for a translation). As Jakob's writings were in Spanish and German, they were largely ignored by English-speaking scientists. Yet, his view is still held today (cf. Catani and ffytche 2005; ffytche and Catani 2005; see Catani and Stuss 2012a, 2012b) and has led to the identification of a number of different cortico-cortical connections in relation to the subdivisions of the frontal lobes (Pandya and Yeterian 1996; Rolls 1996; Barbas 2000; Zald 2007; Rolls 2014a, 2014b). In terms of frontal intra-connectivity, short-range fiber anatomy and its functional significance are relatively underexplored in humans. The lateral prefrontal cortex is connected to premotor regions via the superior and inferior frontal portions of the longitudinal fasciculus, which run parallel to the superior and inferior frontal sulci (Catani et al. 2012). The anterior cingulate cortex is densely interconnected with most parts of the frontal cortex (Barbas 1995), although it has become clear that dorsal regions of the anterior cingulate preferentially connect with dorsal frontal cortex, that posterior regions are intimately associated with motor and premotor cortex, and that anterior ventral regions are associated with the orbitofrontal cortex (Beckmann et al. 2009; Yeterian et al. 2012). Other short-range tracts have recently been investigated: the fronto-orbitopolar tract connects orbitofrontal and frontopolar regions, medial and lateral frontal pole regions interconnect via the fronto-marginal tract, and a complex series of longitudinal and lateral tracts interconnect gyri along the walls of the frontal sulci (Catani et al. 2012). Thus, direct connectivity between dorsolateral and orbital frontal regions is minimal.

In relation to the frontal subregions and their differential connections with other brain regions, the branches of the superior and inferior frontal portions of the longitudinal fasciculus extend posteriorly to form long-range connections with the parietal lobe (Thiebaut de Schotten et al. 2012). Furthermore, the arcuate fasciculus is a dorsal projection which arcs around the sylvian fissure, connecting temporal, parietal, and lateral frontal regions. The orbitofrontal cortex receives inputs from the amygdala, hippocampus, olfactory cortex, and insula, along with auditory and visual information from temporal and occipital cortices via the uncinate and inferior fronto-occipital fasciculi (Petrides and Pandya 2004; Catani and Thiebaut de Schotten 2008; Catani et al. 2012; Yeterian et al. 2012). Via U-shaped fibers from the cingulum bundle that, like the cingulate cortex, loop around the corpus callosum, the anterior cingulate cortex is also connected to parietal, occipital, and temporal lobes, including radiations into the parahippocampal gyrus (Mufson and Pandya 1984; Catani and Thiebaut de Schotten 2008). The orbitofrontal cortex, anterior cingulate cortex, and lateral prefrontal cortex can also be differentiated on the basis of their distinct connections to the mediodorsal nucleus of the thalamus (Klein et al. 2010).

1.3 Fractionation of frontal lobe functions

Despite these developments over the past 150 years or so, in terms of neuroanatomical and histological research, fractionation of the frontal lobes into specific functional domains has made remarkably slow progress (Della Sala et al. 1998b; Frith 2000). In his 1966 book *Higher Cortical Functions in Man*, Alexander Luria proposed the existence of several “frontal lobe syndromes” in which distinct frontal regions are associated with different functional domains: the premotor area with the changing aspects of motor and skilled movements; the prefrontal convex division (which includes the dorsolateral prefrontal cortex) with planning and monitoring in goal-directed behavior; and the mediobasal or orbital prefrontal region with changes in personality (Della Sala et al. 1998a).

Almost 40 years later, Stuss and Knight (2002) predicted that the first decade of this millennium would provide us with a clearer sense of whether general versus multiple hypotheses would best explain the role of the frontal lobes. Yet, in the second edition of their *Principles of Frontal Lobe Function* book (2013), they admit that their prediction did not come true. Several theories within the frontal lobe literature have highlighted the role of the frontal lobes as a supervisory system or central executive that controls and regulates other cognitive domains such as language, memory, and attention (Norman and Shallice 1980, 1986; Baddeley 1996; Stuss et al. 2002). However, there remains a debate as to whether the functions of the frontal lobes can be fractionated into separate functions (Stuss and Benson 1986; Shallice 2002) or whether they are simply functions that overlap (Duncan and Miller 2002).

With the emergence of functional neuroimaging techniques in the late twentieth century that have come to dominate the frontal literature, researchers are now able to better understand the brain regions associated with different cognitive processes (Frackowiak et al. 1997; Rugg 1997; Gazzaniga 2000). On the basis of functional neuroimaging research, Duncan and Miller (2002) proposed the Adaptive Coding Model, which claims that the neurons within the prefrontal cortex do not have set functions; instead they contribute toward many functions. Functional neuroimaging studies have demonstrated the same "multiple-demand" pattern of frontal activity involving the inferior frontal sulcus, anterior insula/frontal operculum, dorso-medial prefrontal cortex, and the intraparietal sulcus, despite tasks requiring different cognitive demands (Duncan 2006, 2010). Similarly, Fuster (2013, p. 12) has proposed the Cognit Paradigm of Cognition, which claims that, "… all higher cognitive functions, like perception, use the same system of widely distributed, interconnected and overlapping cortical networks." Cognits or units of knowledge within networks of cell assemblies (Hebb 1949) are formed and distributed throughout the cortex. Cognits within the prefrontal cortex contain units of executive memories important for future goal-direction actions.

These global frontal theories suppose that it is not possible to ascribe different functions to distinct frontal subregions, given the flexibility of frontal neurons. Yet, it is not easy to reduce frontal functions to a single frontal process. In addition to the cytoarchitectural and hodological (i.e., the study of connectional anatomy; Catani 2007) differentiation of frontal lobe regions (which are likely to constrain the type of information processing each region performs; Barbas 2000; Zald 2007), lesion studies suggest that different frontal subregions are associated with a number of cognitive processes (Shallice and Burgess 1996; Shallice 2002; Stuss et al. 2002; Koechlin et al. 2003). Researchers have stressed the importance of not relying solely on neuroimaging evidence as the only source of data and have argued for the benefits of cross-method agreement (e.g., Duncan and Owen 2000; Burgess et al. 2005; Burgess 2011; Stuss and Alexander 2009). Functional neuroimaging studies simply indicate localized magnetic inhomogeneities due to metabolism of oxygen or glucose within certain brain areas during a particular cognitive task. Thus, they may be used to infer which brain regions may be *involved* in a particular cognitive task. By contrast, lesion studies provide information about the pattern of spared and impaired abilities among individuals with brain damage when compared with a control group, allowing inferences about which regions may be *necessary* for a particular cognitive task. For example, in neuroimaging studies, certain frontal regions such as the frontal pole are activated by a wide variety of tasks, yet patients with lesions in these same regions do not necessarily show impairments on these same tasks. Burgess et al. (2005) describe the case of patient AP who suffered a head injury resulting in his frontal pole being removed. AP showed significant multitasking difficulties in everyday situations but performed within normal limits on measures of frontal executive functions (Shallice and Burgess 1991; Metzler and Parkin 2000). Nonetheless, neuroimaging studies have suggested that the frontal pole is activated while performing these traditional frontal executive measures (e.g., Ramnani and Owen 2004). Neuroimaging alone cannot demonstrate brain regions that are necessary for a particular cognitive function.

Tsujimoto et al. (2011) recommended that neurophysiological studies of non-human primates should be considered as an additional source of information when attempting to understand the functions of frontal subregions (typically these involve rhesus macaques) as there are several similarities between monkey and human brains. First, the prefrontal cortex of a monkey brain, like the human brain, consists of regions that are segregated both in terms of cellular composition and implied function (Brodmann 1909). Furthermore, the broad anatomical layout of the regions within the frontal lobes is fairly similar between the two species (Brodmann 1909; Petrides and Pandya 1994; Pandya and Yeterian 1996), with the position of major prefrontal regions such as the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, ventromedial prefrontal cortex, the frontal pole, and anterior cingulate cortex showing rough correspondence in terms of cytoarchitecture between human and monkey brains (Figure 1.6). The distribution of myelinated cells is also similar between the corresponding regions of each species (Pandya and Yeterian 1996) and some have observed that the position and connections of the frontal areas are similar across species (Ulying and Van Eden 1990). However, it should also be noted that the anatomy of the monkey cortex differs from the human cortex in terms of the number of granular and agranular layers (Petrides and Pandya 1994). Neubert et al. (2014) used both structural and functional imaging to parcellate both human and monkey prefrontal cortex. Although the authors noted similarities in the cortico-cortical and subcortical connections of prefrontal regions in both species, they noted that the frontal pole in humans showed functional connections to other prefrontal regions and the inferior parietal lobule. By contrast, the frontal pole in the monkey brain showed functional connectivity with temporal regions and the amygdala. The frontal pole is significantly larger in proportion to brain and frontal lobe size in humans when compared with apes, and in humans it has increased connectivity with higher-order association areas when compared with any other primate (Semendeferi et al. 2001). Moreover, the human anterior cingulate cortex is thought to have undergone recent neocortical specialization that allows a

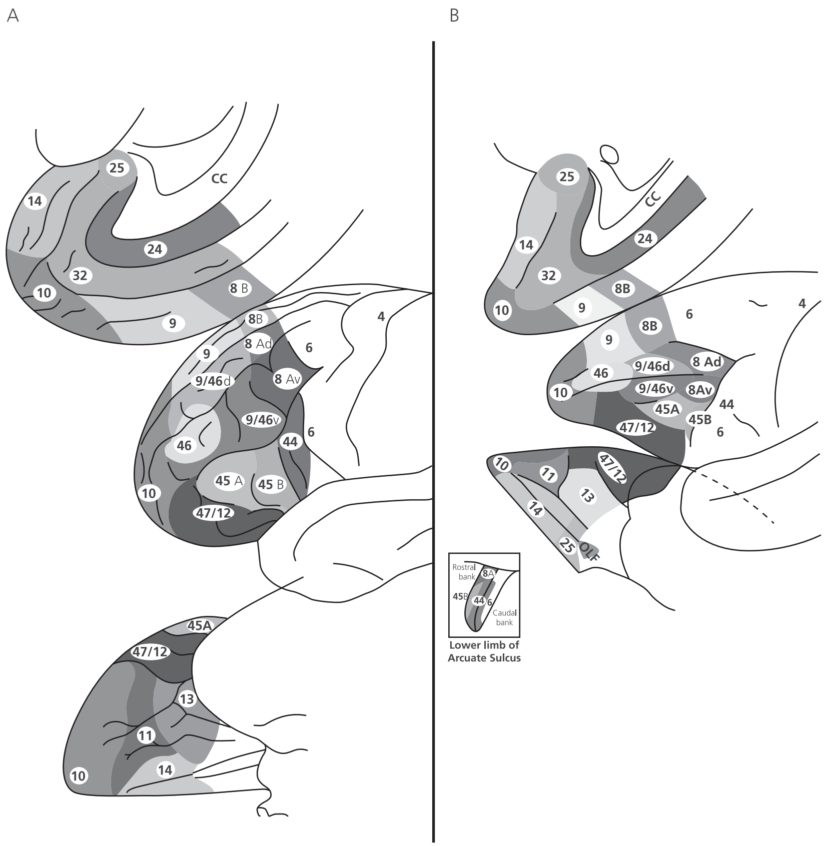

Fig. 1.6 Cytoarchitecture of (A) human and (B) monkey prefrontal cortices. Reprinted from *Cortex*, 48 (1), Michael Petrides, Francesco Tomaiuolo, Edward H. Yeterian, and Deepak N. Pandya, The prefrontal cortex: comparative architectonic organization in the human and the macaque monkey brains, pp. 46–57, Copyright (2012), with permission from Elsevier. Please see color plate section.

type of widespread connectivity with other brain regions that was present only in our most recent ancestors (Allman et al. 2005). When Goulas et al. (2014) constructed whole brain connectomes using diffusion-weighted magnetic resonance imaging (MRI) in humans and the CoCoMac neuroinformatics database (http://cocomac.g-node.org) in macaques, they found that the anterior cingulate cortex showed poor cross-species correspondence. Pandya and Yeterian (1996) have also noted some differences in the functional connectivity from, to, and between prefrontal regions in monkeys and humans. Despite these specific differences, however, the literature suggests that non-human primate models are a good approximation of human architecture.

Indeed, the work of Goldman-Rakic and colleagues with non-human primates was seminal in understanding the specialization of the frontal lobes in terms of working memory and online processing (e.g., Goldman-Rakic 1987, 1996), supporting the findings from lesion studies (e.g., Petrides and Milner 1982) and neuroimaging data (e.g., Owen 1997; D'Esposito et al. 1998; Petrides 2000a). Although Burgess (2011) states that data acquired using one research technique may question the conclusions of another, it is important that researchers and clinicians consider different strands of evidence to determine brain regions that are essential for specific functions.

Fractionation models of frontal lobe functions state that there are distinct frontal processes localized in different subregions within the frontal lobes (Stuss and Benson 1986; Stuss and Alexander 2000; Shallice 2002). Stuss et al. (1995, p. 206) proposed that, "… the frontal lobes (in anatomical terms) or the supervisory system (in cognitive terms) do not function as a simple (inexplicable) homunculus…. The different regions of the frontal lobes provide multiple interacting processes." Norman and Shallice (1980, 1986) propose the Supervisory Attentional System Model, which is a monitoring system that oversees and controls action and deals with novelty in conditions where the routine range of actions is inadequate. In relation to the Supervisory Attentional System Model (Norman and Shallice 1980, 1986), Shallice and Burgess (1996) proposed that there is a variety of subsystems located in the prefrontal cortex which put into operation different processes in these non-routine situations (see also Stuss and Alexander 2007; Shallice and Cooper 2011). Patients with prefrontal lesions might perform poorly due to difficulties in "energization" where they fail to initiate a non-routine task, "task-set" where patients have difficulty switching from a novel to a routine state, "monitoring" where patients are poor at monitoring their task performance and adjusting their behavior if necessary, and, more recently, "attentiveness" where patients care less about performing well on a highly demanding task (Shallice et al. 2008). Authors have argued for the fractionation of these executive processes into multiple components (Shallice and Burgess 1993, 1996; Burgess and Shallice 1994; Baddeley 1996; Burgess 1997; Collette et al. 2006) and more recently for the localization of these different processes in different frontal subregions (Shallice et al. 2008).

Only recently have lesion studies begun to differentiate patients with frontal lesions into separate groups (e.g., Stuss et al. 1995; Shallice and Burgess 1996; Stuss and Alexander 2005) rather than categorizing different frontal impairments under the umbrella of a "frontal lobe syndrome." Nearly 30 years ago, Marcel Mesulam (1986, pp. 321–322) wrote in an editorial,

> These quantifiable deficits in standard tests are not always impressive. In fact, some patients with sizable frontal lobe lesions may have routine neurological and

> neuropsychological examinations that are quite unremarkable. This creates a problem in the assessment of these patients, especially since the behavioral derangements—which sometimes constitute the only salient features—are also too complex to test in the office.... It is not uncommon to find patients with a history of major behavioral difficulties who behave impeccably in the office.... The clinical adage that judgment and complex comportment cannot be tested in the office is particularly pertinent to the evaluation of patients with frontal lobe damage.

At that time, it was difficult to quantify frontal lobe deficits because suitable instruments to identify and quantify the various cognitive impairments associated with frontal lobe damage were not available. Since then, better instruments have been developed.

In 1995, Donald Stuss and colleagues argued that one reason why frontal tests do not typically correlate strongly with one another is because "... they evaluate anatomically and functionally separate systems within the frontal lobes" (Stuss et al. 1995, p. 192). Frontal patients with damage to one of these systems will perform poorly on tasks tapping that system but may perform well on tasks tapping the unaffected systems within the frontal lobes. Indeed, lesions in the dorsolateral prefrontal cortex have been shown to impair tests thought to tap executive processes including mental flexibility, initiation, inhibition, and problem-solving (Milner 1963; Petrides and Milner 1982; Stuss and Benson 1986; Goldman-Rakic 1987), with patients performing poorly on traditional tests assessing executive processes such as the Delayed Response task (Vérin et al. 1993), Recency Judgment (Milner et al. 1991), the Self-Ordered Pointing task (Petrides and Milner 1982), the Stroop task (Vendrell et al. 1995), and the Wisconsin Card Sorting task (Milner 1963). Damage to the orbitofrontal cortex can affect emotional processing and the regulation of social behavior whereby patients might display emotional lability, a lack of impulse and anger control, or produce inappropriate laughing, crying, and sexual behavior (Rolls 1996). Lesions in the orbitofrontal cortex of non-human primates and humans can also impair the ability to alter behavior flexibly in response to a change in stimulus–reward associations (Rudebeck et al. 2008). Patients have been reported to perform poorly on the Reversal Learning Task (Rolls et al. 1994) and the Faux Pas task (Stone et al. 1998). Finally, the anterior cingulate cortex is thought to act as a conflict-monitor when multiple possible behaviors compete for selection (Botvinick 2007) or track environmental volatility and unexpected events (Rushworth and Behrens 2008). Patients with dorsal anterior cingulate lesions have been shown to perform poorly on stimulus–response compatibility tasks such as the Stroop task (Turken and Swick 1999; Stuss et al. 2001b). In summary, recent clinical studies provide support for the existence of dissociations between the effects of damage to different frontal subregions.

1.4 Fractionation and frontal lobe assessment

There are several tests used in clinical practice and research worldwide that have been devised to assess the functions subsumed by the frontal lobes of the brain. Such tests have tended to focus on understanding and assessing higher-order control of goal-directed behavior rather than the more emotional and social aspects of frontal lobe functions. Even the "bibles" of neuropsychological assessment do not consider frontal tasks tapping more emotional and social frontal functions (e.g., Strauss et al. 2006; Lezak et al. 2012). A lack of standardized tests may explain why such tasks have not characteristically been included in neuropsychological assessments. Even now, many of these tests are still in an experimental form and do not have normative data, although experimental tasks can be useful in understanding and evaluating the impairments that patients might exhibit (Lezak et al. 2004). Practising clinicians tend to use standardized tests that are readily available and provide normative data. Even if experimental tests are used to further understand the specific cognitive impairment associated with the clinical diagnosis, clinicians would not typically report the results due to the lack of normative data, which might present difficulties in medico-legal cases.

Until recently, assessments of emotional and social frontal functions have relied upon naturalistic observations reported by family members which may point the clinician towards certain difficulties that the patient might have. These observations are particularly useful in the case of frontal patients who might perform well on structured standardized tests of frontal executive abilities in a clinical setting but who perform poorly on more open-ended tasks in a real-life setting (Newcombe 1987; Shallice and Burgess 1991; Capitani 1997). Another method of assessing whether frontal patients have undergone social and emotional changes caused by their brain damage has been self-report and family-report questionnaires. These provide a more structured method of identifying patient difficulties than naturalistic observations. However, frontal patients who lack insight into their condition may fail to recognize their impairments; as the face validity of these questionnaires is often evident, this may lead relatives to deny the presence of some behavioral disabilities in their family member, even when certain behaviors are evident during the testing session. Moreover, when self- and family-report questionnaires are completed, these can provide conflicting information and so care has to be taken when considering whether they are reliable or valid guides to an individual's ability. Hence, there has been a move for clinicians and researchers to devise experimental tasks assessing more social and emotional aspects of frontal lobe function, although few provide normative data as yet (e.g., Judgment of Preference task, Moral Decision-Making, Reading the Mind in the Eyes, Ultimatum Game).

It is important that clinicians be aware that different frontal tasks might tap processes associated with distinct regions of the frontal lobes. If a neuropsychological assessment only includes traditional frontal executive measures, as has typically been the case in the past, it might be concluded that a patient performing within normal limits on those tasks does not have frontal lobe dysfunction. Yet, a patient's relatives may still complain that the patient performs poorly on everyday tasks that involve emotional and social processing or multi-tasking (Burgess et al. 2009). There are several single case reports of patients as well as clinical groups, including frontotemporal dementia (Lough et al. 2001; Gregory et al. 2002) and amyotrophic lateral sclerosis (Girardi et al. 2011), showing a dissociation between impaired social processing and intact executive function (Eslinger and Damasio 1985; Shallice and Burgess 1991; Brazzelli et al. 1994; Rolls et al. 1994). There are also examples of patients in the literature showing the opposite dissociation of intact social and emotional processing but impaired executive abilities (e.g., Bechara et al. 1998). Diagnosis of the nature of the frontal lobe involvement in these patients can be achieved through the appropriate neuropsychological assessment, which includes a small number of tasks thought to tap the distinct frontal subregions. By doing so, the assessment will be more focused and less time-consuming, and provide a thorough account of the nature of the frontal deficit and its effect on an individual's daily living. Cubelli et al. (in press) maintain that the job of the neuropsychologist is to design and refine the clinical assessment, to interpret the findings, and to disentangle the patient's observed pattern of performance; in other words, examining a patient is a skilled and time-consuming task, which requires specific and interdisciplinary competence and expertise. Without diagnostic interpretation, tests results are void. Cubelli and Della Sala (2011) highlight that a clinical neuropsychological assessment should include four steps: (1) an interview to obtain a personal and clinical history; (2) a concise screening battery; (3) a full-scale neuropsychological examination to diagnose the gross clinical syndrome (e.g., dysexecutive syndrome, episodic amnesia, Wernicke's aphasia); and finally (4) experimental tests to determine the specific cognitive impairment associated with the clinical syndrome. Therefore, it is important for clinicians and researchers to be made aware of the functions assessed by individual frontal tests and to understand which frontal regions might be impaired in their patient groups.

Some extensive manuals of neuropsychological tests have been published, encompassing various cognitive domains (Strauss et al. 2006; Lezak et al. 2012). Such compendiums supply useful descriptions of how to administer neuropsychological tests and to which populations, including scoring instructions and copies of the procedure. However, whereas they clearly acknowledge that executive functions can be subdivided into different higher-order processes (e.g., planning, initiation, inhibition, flexibility), the manuals largely neglect the issue of localization within the frontal lobes and simply include a chapter discussing "executive function." Moreover, frontal tasks assessing more social and emotional processing are not discussed. It has become evident that the frontal lobes cannot simply be considered in terms of executive abilities but also in terms of other more social and emotional type tasks, goal neglect, and multi-tasking. In this book, the influence of focal frontal lesions on test performance on the wide array of tasks purporting to tap the frontal region and the regions of activation determined through neuroimaging will be discussed. The aim is to link each test to the best possible evidence of what subregions within the frontal lobe (and which cognitive processes) the tests really tackle. Clinicians or researchers wanting to use a given test will have the opportunity to examine what this test is thought to assess, and select the best instrument for their purposes.

Some of the tests reviewed here are published tests that can be purchased from publishers and include normative data. Others, however, are more experimental in nature and may be available only from the author directly. We appreciate that there are no behavioral measures that can exclusively tap the functioning of one region alone. However, a review of the current literature suggests that tasks do exist which may be more sensitive to the dysfunction of one frontal region than another, though how best to quantify the behavioral sequelae of region-specific insult within the frontal lobes is the subject of ongoing debate. Only those frontal tests with evidence from lesion and neuroimaging studies to support the involvement of particular frontal subregions have been considered. This means that only neuropsychological studies involving patients with focal frontal lesions (e.g., tumors, stroke) or studies examining structural brain changes in neurodegenerative diseases will be considered, as they allow us to conclude that the structure damaged by the lesion is necessary for performing that task.

One of the difficulties with reviewing the frontal lobe test literature is that different versions of the same task may exist. For example, the Tower tests refer to a group of tests including the Tower of London (Shallice 1982) and its several versions (e.g., Allamanno et al. 1987), Tower of Hanoi (Byrnes and Spitz 1977), the Stockings of Cambridge subtest from the Cambridge Neuropsychological Test Automated Battery (Robbins et al. 1994), and the Tower subtest from the Delis–Kaplin Executive Function System (Delis et al. 2001). While the overall processes involved in successfully performing the Tower tests are likely to overlap, different versions of the same test may vary in terms of the stimuli presented, rules the participants must follow, or indices of performance calculated. Even small differences in the administration and scoring of a test might result in differences in terms of the localization of the processes associated with performing those tests (Gilhooly et al. 1999, 2002; Phillips et al. 1999, 2003). Therefore, within each test summary, multiple versions of the same test will be described under the same heading, with the commonalties and differences between the versions of the test discussed.

Different test batteries are also available within the clinical psychology literature, allowing clinicians to create a profile of patients' strengths and weaknesses in terms of their frontal lobe abilities. For example, the Delis–Kaplan Executive Function System (Delis et al. 2001) was devised to allow clinicians to assess executive abilities such as mental flexibility, initiation, and problem-solving within the same battery of tests. Similarly, the Cambridge Neuropsychological Test Automated Battery (Robbins et al. 1994) is a computerized set of neuropsychological tests developed to examine aspects of cognition including executive abilities. The Behavioral Assessment of the Dysexecutive Syndrome (Wilson et al. 1996) was devised to assess executive dysfunction in patients with frontal lobe lesions in a way that might generalize on to performance in the real world, and the INECO Frontal Screening is a brief tool to assess executive abilities in neurodegenerative diseases (Torralva et al. 2009a). The Frontal Assessment Battery (Dubois et al. 2000) was devised to identify neurodegenerative diseases with frontal involvement and the Executive and Social Cognition Battery (Torralva et al. 2009b) was devised to identify deficits in executive abilities and social cognition in early behavioral variant frontotemporal dementia. More recently, the Rotman–Baycrest Battery to Investigate Attention (Stuss et al. 2005) was developed to probe levels of attention and cognitive control. Whereas we acknowledge that such test batteries exist, the aim of this book is to examine relationships between the processes underlying specific frontal tests and localization of these processes within frontal subregions. It is difficult to provide evidence of localization of an entire test battery. In such cases, individual components of the test battery will be discussed when they correspond with an overall test such as the Tower Tests from the Delis–Kaplin Executive Function System.

It may also be the case that some of the frontal tests reviewed could be categorized as assessing more than one frontal-related function. Therefore, a test could easily be considered under multiple headings. For example, the Hayling Sentence Completion test could be considered a test of initiation and inhibition *and* of mental flexibility (T. Shallice, personal communication). In this instance, a test is related to the heading associated with the cognitive ability that the authors/manual claim it was initially devised to assess. However, where appropriate, the test description will discuss related frontal processes associated with performing that task.

1.5 Classification of frontal lobe subregions

In terms of the localization of frontal processes, the frontal subregions will be described in terms of the dorsolateral prefrontal cortex (BAs 9 and 46), the orbitofrontal cortex (BAs 11, 12, 13, 14, and 47) and the anterior cingulate cortex (BAs 24, 25, 32, and 33). The term “ventromedial” prefrontal cortex is frequently used in the neuropsychology literature to refer to both orbital and medial frontal regions, although this region is often not explicitly defined in terms of Brodmann’s areas. Therefore, the term ventromedial prefrontal cortex will be used to refer to the orbitofrontal cortex and ventral portions of the anterior cingulate cortex. The dorsal/ventral demarcation within the anterior cingulate is dorsal to the genu of the corpus callosum (after Bush et al. 2000; Beckmann et al. 2009; Van Overwalle 2009). In addition, whereas the frontal pole is often categorized together with the ventromedial prefrontal cortex, it has been associated with performance on a wide variety of tasks including multi-tasking and prospective memory (for reviews see Burgess et al. 2005 and Gilbert et al. 2006). Consequently, the frontal pole will be considered separately to provide a clearer overall picture of the localization of processes within the frontal lobes. See Figure 1.7 for the frontal subregions.

1.6 Issues of frontal lobe assessment

One difficulty with investigating fractionation of frontal lobe functions is that the terms “frontal” and “executive” are used interchangeably in the literature, and yet these terms are not synonymous (Stuss 2006). Baddeley (1996) proposed that the frontal lobes are a possible substrate for the executive control of cognitive functions, although he identifies that there are problems with using cognitive accounts to support arguments about localization. Whereas the frontal lobes are likely to be where executive abilities are best represented, executive functions do not necessarily relate to anatomical structure

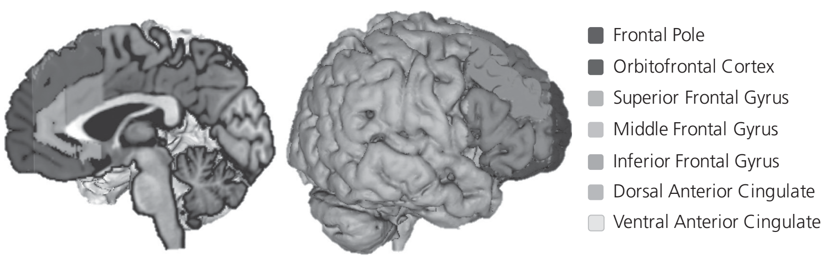

Fig. 1.7 Subdivision of the frontal lobes. Please see color plate section.