In neurology, there are many different types of “blind spots.” The simplest example is the physiological visual blind spot formed by ganglion cell axons exiting the retina. A more extreme case is an occipital lobe lesion in which the blind spot encapsulates an entire contralateral visual field. The blind spots of neurology are by no means confined to the visual system. For example, the hemineglect syndrome is a condition in which a right parietal lobe lesion results in anosognosia and asomatognosia. Each of these clinical situations involves a perceptual modality that renders the patient oblivious to a particular sensory experience.

But consider the following scenario: a brain lesion that results in an inability to perceive social cues, uncontrolled profanity, and impulsivity, ultimately letting slip “the animal propensities” normally suppressed by an intact cerebral cortex – in other words, a brain lesion that changes one’s personality. Such a presentation represents a neurological syndrome affecting the most complex mental processes such as insight, judgment, self-awareness, empathy, and social adaptation.

The most famous case resulting in compromise of these complex mental processes is that of Phineas Gage, a 25-year-old construction foreman employed by Rutland and Burlington Railroad. In September 1848, chance and human error led to the occurrence of an unfortunate but instructive scenario. Gage was in charge of delivering blasts to level the uneven rocky terrain in order to facilitate laying new rail tracks. He would drill holes into the stone, fill the space with explosive powder, cover the powder with sand, and then use a tamping iron to prepare for the blast. One day, he forgot to sandwich the sand between the tamping iron and the explosive powder. The result was the propulsion of a tamping iron, three feet seven inches long, through Phineas’s left cheekbone, into the frontal lobes and through his skull, eventually landing approximately 25–30 yards behind him. Despite the obvious trauma to the skull and underlying cortex, Gage still managed to talk and even walk away from the accident with the assistance of his fellow workers.

Dr. John Harlow, Gage’s personal physician, made the following observations [1]:

“[He is] fitful, irrevocent, indulging at times in the grossest profanity which was not previously his custom, manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires, at times pertinaciously obstinate, yet capricious and vacillating, devising many plans of future operation, which are no sooner arranged than abandoned… A child in his intellectual capacity and manifestations, he has the animal passions of a strong man.”

Gage’s subsequent medical recovery and preservation of intellectual functions belied a profound disintegration of personality in which “Gage was no longer Gage” [1]. As a result of these personality changes, Gage became unreliable on the job, and his employers eventually dismissed their once “most efficient and capable man” [1]. Subsequently, Gage was unable to maintain any consistent employment, and toured with circuses including Barnum and Bailey for a period of time until his death from status epilepticus.

As a consequence of his accident, Phineas Gage had acquired a “blind spot” for behavior and social interaction. His ability for insight, judgment, self-awareness, empathy, and social adaptation was compromised, forever obliterated by a turbo-charged projectile that destroyed much of his prefrontal cortex. The main conclusion derived from Gage’s case was that frontal lobe damage leads to dramatic alterations of strategic
thinking, personality, emotional integration, and conduct while leaving language, memory, and sensory-motor functions intact [2]. Dr. Harlow, Gage’s physician, eloquently depicted the functional consequences of his patient’s lesion. A term that encapsulates these compromised functions is comportment.

**Definition of comportment**

According to the Oxford English Dictionary, the word “comportment” first was used in the English language in 1599, and is defined presently as “social bearing, carriage, demeanor, deportment, behavior, outward conduct, and course of action” [3]. A more neurologically based definition of comportment is the complex mental processes that include insight, judgment, self-awareness, and social adaptation [2]. At the same time, comportment does not include cognitive functions such as memory, language, planning, set-shifting, and attention. Comportment can be better understood through analysis of its individual components: insight, judgment, self-awareness, social adaptation, and empathy.

**Insight**

Insight allows for an awareness of one’s social behavior as well as the severity of one’s disease. Patients with prefrontal lobe pathology have a profound dissociation between knowing how to behave in a particular situation and behaving in a manner that comports with that knowledge. In the clinical setting, patients with schizophrenia and frontotemporal dementia (FTD) frequently lack insight into the fact that they suffer from a disease. The most extreme case of denial of disease or anosognosia is the right inferior parietal lobe syndrome associated with a left hemineglect.

**Judgment**

Comportment also includes judgment, which is related to insight. Judgment involves making appropriate decisions under certain circumstances. Poor judgment is commonly seen in patients with prefrontal lesions who act in an inappropriately friendly manner to strangers or make inappropriate remarks. Illustrative cases include a 63-year-old woman who developed intimate relations with strangers after suffering prefrontal injury from an operation for an olfactory groove meningioma [2]. Furthermore, the ability to understand a complex situation, to have empathy, and to catch the punch line of a joke is dependent on judgment [2].

**Self-awareness**

Perhaps the most complex constituent of comportment is self-awareness. This component enables an individual to distinguish him- or herself from the environment, and allows for personal autonomy. Commonly, patients with frontal lobe damage develop imitation and/or utilization behaviors. These phenomena result from a loss of this ability to separate the self from the environment. In an experiment involving two patients with left inferior prefrontal lesions after tumor resections, Lhermitte found that the individuals exhibited a tendency to imitate the examiner’s gestures, and their behaviors were heavily influenced by external stimuli in a non-clinical environment [4]. One subject even went so far as to give the examiner an injection after a syringe was placed near her. The mechanism behind this utilization behavior is thought to result from a loss of personal autonomy, creating what is known as the environmental dependency syndrome. Intact prefrontal regions function to prevent such enslavement to the surrounding environment.

**Social adaptation**

Social adaptation refers to social learning from both positive and negative experiences. Social learning is dependent on the ability to interpret and respond to social cues. Individuals must be able to weigh decisions that may result in reward versus punishment. Furthermore, social adaptation is dependent on counterfactual thinking, in which an individual will compare the actual outcome from an action with a hypothetical outcome if the alternative decision was chosen. For example, the guest who makes a blunt observation about the host’s improperly fitting dress may elicit social awkwardness from other individuals, and this negative result will presumably deter any further mistakes by the guest. In normal subjects, the feeling of responsibility for a negative result leads to feelings of regret, an important factor in social adjustment.

The ability to adapt socially depends on recognizing mental states based on social cues (i.e., facial expression, voice pitch, and body gestures). This ability to interpret the mental states of others in order to
predict and explain behavior is described in the cognitive neuroscience literature as theory of mind [5]. Failure to perceive or infer accurately what others feel may lead to the expression of inappropriate behavior as well as a failure to modify one’s own behavior based on social cues [6]. Neurodevelopmental disorders such as autism, and traumatic brain injury to frontal regions are associated with impaired ability to recognize the mental states of others [5].

Empathy

Empathy refers to the ability to recognize mental states of others, and is critical for social adaptation. Social psychologists describe empathy as consisting of a cognitive part responsible for the intellectual/imaginative apprehension of another’s mental state, and an affective part responsible for an emotional response to others’ emotions [7]. Thus, empathy refers to the ability to understand and share the feelings of others.

Empathy derives from three main cognitive steps [8]. The first step involves the sharing of another’s emotion. The second requires recognition that an internally represented emotion is located outside of oneself. The final step depends on the intentional suppression of one’s own viewpoint to accurately infer the other’s perspective [8].

Loss of empathy is an early symptom of FTD, a focal neurodegenerative disorder involving the frontal and temporal lobes [8]. Many functional neuroimaging studies have been performed to establish a functional localization of empathy. One network involves the amygdala, cingulate, and orbitofrontal cortices involved in perception and emotion regulation [5]. Another network involves the dorsolateral and ventromedial prefrontal regions engaged in holding and manipulating this information [5].

Comportment therefore is very much a function of the gestalt of insight, judgment, self-awareness, social adaptation, and empathy. As human beings we have the capacity for comportment, but we are also prone to the occasional situation where our decisions lack judgment and insight. The band Main Ingredient captures this concept in the lyrics from their 1972 hit single, “Everybody plays the fool, sometime/There’s no exception to the rule.” Whether it is the basic faux pas at the cocktail party or the romantic relationship where a person exhibits less than the desired empathy and sensitivity, there is a wide margin of normal error regarding the functions of comportment. However, the factor that distinguishes a normal individual from a patient with a prefrontal lesion is the ability to adapt and learn from mistakes. Accordingly, the Phineas Gage of the world will always be prone to repeating the same errors despite negative experiences.

Functional neuroanatomy of comportment

The case of Phineas Gage has served as the guiding compass towards our understanding of the prefrontal cortex as a region critical for comportment. Modern neuroimaging using the skull of Gage has shown bihemispheric prefrontal lesions involving the orbitofrontal cortex, the medial frontal cortex, and the anterior cingulate gyrus (Figure 17.1) [9].

The prefrontal cortex can be subdivided both anatomically and functionally. Anatomically, the three major anatomical divisions include: (1) orbitofrontal cortex, (2) superior medial (anterior cingulate) cortex, and (3) dorsolateral cortex [10]. Functionally, the prefrontal cortex consists of two axes, one for working memory, executive function, and attention, and the other for comportment [2]. The dorsolateral prefrontal cortex is the anatomical region responsible for the first axis, whereas the medial frontal and orbitofrontal cortices are mainly involved in comportment, influencing both affect and behavior (Figure 17.2) [2].

The orbitofrontal and medial frontal cortices have multiple connections by which they influence comportment, and each serves as the origin for a frontal-subcortical circuit. Each of these pathways has subcortical projections that project to the thalamus via the basal ganglia by direct and indirect pathways [11]. The direct pathway has two consecutive inhibitory GABA-ergic connections that cause disinhibition of the thalamus, whereas the indirect pathway has an excitatory glutamatergic pathway that has an overall inhibitory affect on the thalamus [12]. Eventually, the thalamus provides a feedback loop terminating in the cortical region from which the circuit originated.

Furthermore, each circuit has both efferent and afferent connections with other cortical regions. For instance, the orbitofrontal cortex sends projections to and receives connections from the dorsolateral prefrontal region [12]. Cortico-cortical connections communicate by glutamatergic pathways. The orbitofrontal and medial frontal cortices exhibit extensive limbic connectivity [13]. This chapter will focus on these two frontal circuits.
Figure 17.1. Trajectory of the tamping rod used by Phineas Gage through his skull and brain. Reproduced from Damasio H, Grabowski T, Frank R, Galaburda AM, Damasio AR. The return of Phineas Gage: clues about the brain from the skull of a famous patient. Science. 1994;264(5162):1102–5 with permission from the American Association for the Advancement of Science.

Figure 17.2. General characteristics of prefrontal circuits. Image courtesy of Robert Baden.

Orbitofrontal circuit

The orbitofrontal circuit (OFC) consists of four main components: (1) orbitofrontal cortex; (2) ventral caudate; (3) medial globus pallidus; and (4) ventral anterior and medial dorsal thalamus (Figure 17.3). The orbitofrontal circuit begins with projections from the cortex to the subcortical region of the ventral caudate [12]. Information is eventually sent to the ventral anterior and medial dorsal thalamus via the medial globus pallidus [12]. Eventually, the information is relayed back to the orbitofrontal cortex [12]. Each of the four components of the OFC receives afferents from the amygdala. Furthermore, the orbitofrontal cortex sends inputs to the preoptic region of the lateral hypothalamus, which is critical for the hormonal modulation of emotions [6].
The circuit’s main function is the pairing of thoughts, memories, and experiences with corresponding visceral and emotional states [2]. The OFC is uniquely suited to evaluate the costs and benefits of specific behavioral responses to the environment, particularly in situations where those reinforcers must be inferred from minimal or complex input [11]. Thus, this circuit is heavily involved in the process of decision-making, weighing actions that may result in reward versus those that may result in punishment. In addition, the OFC represents both concrete primary, unlearned reinforcers, such as touch and taste, and more abstract secondary, learned reinforcers emanating from visual, auditory, olfactory, and multimodal sources. The medial orbitofrontal cortex is involved in monitoring and decoding reward whereas the lateral orbitofrontal cortex evaluates punishment, motivating behavioral change [11]. There is also an anterior-posterior gradient in which the reward value for more concrete, primary reinforcing factors such as touch and taste are encoded in the posterior OFC while the value of more complex secondary reinforcing factors such as money are encoded in the anterior OFC [8].

Since the orbitofrontal circuit includes both cortical and subcortical regions, any disruption of the pathway at the level of the orbitofrontal cortex, the basal ganglia, or the thalamus may result in compartmental dysfunction. Furthermore, most disease processes are not purely confined to the orbitofrontal regions, and thus there is no such thing as a pure orbitofrontal syndrome. The orbitofrontal region is prone to injury from closed head trauma, anterior communicating aneurysm rupture, and subfrontal meningioma [12]. Degenerative processes such as FTD may also involve the orbitofrontal cortices as well as other regions of the prefrontal cortex. Occasionally Creutzfeldt–Jakob disease and herpes encephalitis can affect the orbitofrontal cortices [12]. Neuropsychiatric disorders of the orbitofrontal regions including obsessive-compulsive disorder are associated with increased metabolism of the orbitofrontal cortex [12]. Disease processes involving the subcortical projections of the OFC include Huntington’s disease, neuroacanthocytosis, post-encephalitic Parkinson’s disease, and thalamic infarcts.

In general, patients with orbitofrontal lesions are socially disabled, and manifest interpersonal disinhibition, impulsive decision-making, lack of consideration, and impaired judgment. The ability to infer rewards and punishment from subtle environmental cues is critical for emotion recognition and social adaptation. Patients with OFC lesions show deficits in both the production and recognition of emotional expression from the face, voice, or gestures [6]. Beer and colleagues [14] found that five patients with focal bilateral OFC damage were significantly worse than normal controls at identifying self-conscious emotions (i.e., embarrassment, shame), but not other emotions (anger, disgust, fear, happiness, sadness, contempt, surprise, or amusement) [14]. Blair and Cipolotti [15] found that a patient suffering from a unilateral right orbitofrontal lesion was not only impaired in recognizing angry and disgusted facial expressions, but also had a lower autonomic response to these expressions than did controls [15]. Patients with bilateral orbitofrontal lesions have been found to have mindreading and theory of mind deficits, whereas patients with unilateral damage of the left dorsolateral prefrontal cortex performed normally on these tasks [5].

The inability to weigh actions that result in reward versus those that result in punishment also relates to the ability to feel regret. Regret is a cognitively mediated emotion triggered by our ability to reason counterfactually or compare what is with what might have been [16]. In a study comparing OFC patients with normal controls in the performance of a simple
gambling task, Camille and colleagues found that patients with orbitofrontal lesions were neither able to anticipate the negative consequences of their choices nor experience regret [16]. These patients did not modify their gambling based on feedback, and continued to make the same gambling errors in the experiment, ending up with greater net losses compared with controls [16]. Thus patients with orbitofrontal lesions are unable to learn from mistakes. The feeling of regret reinforces the decisional learning process, and without this capacity, individuals fail to make the necessary practical adjustments.

In summary, patients with OFC lesions develop a range of comportmental deficits. A triad of these deficits has been described as altered emotional experience with blunting and lability, deficient decision-making, and impaired goal-directed behavior with general disorganization [11].

Medial frontal circuit

The medial frontal circuit begins in the cortex of the anterior cingulate region and includes the nucleus accumbens, globus pallidus, substantia nigra, and the medial dorsal nucleus of the thalamus (Figure 17.4) [12]. As in the OFC, the medial dorsal nucleus of the thalamus provides feedback to the circuit’s origin from the frontal cortex. Furthermore, the anterior cingulate cortex has both efferent and afferent connections to the dorsolateral prefrontal cortex and the amygdala [12].

The cingulate cortex may be a critical area in directing vigilance toward events of emotional or motivational significance [6]. Lesions of the medial frontal cortex result in an amotivational state consisting of motor, cognitive, affective, emotional, and motivational apathy [11]. The medial prefrontal cortex also processes the affective, evaluative, and attentional aspects of pain perception [17]. Infarction in the territory of the anterior cerebral artery is among the most common causes of medial frontal injury [12]. In addition, gliomas, multiple sclerosis, encephalitides, and FTD can also impair function of the medial frontal cortex and its connections [12].

In addition to motivation and pain perception, the medial prefrontal cortex appears to play a critical role in theory of mind. A review of recent functional neuroimaging studies on the localization theory of mind concluded that the medial prefrontal cortex was activated in almost 90% of these paradigms [18]. Clinically, these findings are of little surprise, as FTD patients with degeneration of the medial prefrontal cortex have been found to exhibit a selective drop in empathetic concern as rated by spouses and long-term caregivers [19].

Functional neuroimaging studies also suggest that the cingulate cortex is part of a neural circuit responsible for the generation of emotions related to empathy. Studies have mainly focused on how the response in the cingulate cortex in a subject undergoing noxious stimuli is similar to that elicited when others undergo the same painful stimuli. In one study, participants received painful stimuli in one set of trials, and, in a second set, received a signal that their partner who was present in the same room would receive the same noxious stimuli [20]. The anterior medial cingulate cortex as well as the anterior insula and cerebellum were activated in both conditions [20]. Another investigation revealed increased activity in the anterior cingulate cortex in subjects during the application of painful pinprick stimuli as well as when these subjects observed others undergo the same stimulation [21].

Analogous functional neuroimaging studies have been performed while subjects viewed pictures of people suffering and imagined themselves in the same position. In one recent study, participants were shown pictures of people with their hands or feet in painful situations and asked to imagine themselves or another
individual in the same situation [22]. Functional magnetic resonance imaging (fMRI) revealed increased activation in the anterior medial cingulate cortex, the parietal operculum, and the anterior insula. In another study, subjects were exposed to videos of patients acting as if they were undergoing a painful auditory treatment for a neurological disease with either a positive (treatment success) or a negative outcome (treatment failure) [17]. Participants were asked to imagine the feelings of the patient and to imagine themselves in the patient’s situation. Empathic concern (as elicited by empathy scores) was stronger when patients focused on the feelings of others, whereas adopting the self-perspective led to stronger personal distress. Empathy scores (as measured by the Interpersonal Reactivity Index [23, 24]) correlated with activity in the anterior medial cingulate cortex, the insular cortices, and the fusiform gyrus [17]. During the task of perspective-taking, the anterior medial cingulate cortex was again activated, along with the middle insula, lateral premotor areas, and both parietal cortices [17].

Finally, the medial prefrontal cortex may play a role in the response to violent behavior. In a study requiring healthy individuals to imagine scenes in which they witnessed the assault of their mother in an elevator under three different conditions: (1) passively watching the assault; (2) being restrained by one of the perpetrators; and (3) violently attacking the perpetrators, positron emission tomography (PET) scans showed reduced activation of the medial prefrontal cortex in all three scenarios [25].

Prefrontal and temporal circuits

Although comportment is largely a function of the prefrontal circuits, these pathways do not exist in isolation, and are dependent on connections with areas such as the limbic system and the dorsolateral prefrontal cortex. The orbitofrontal cortex has both afferent and efferent connections with the dorsolateral prefrontal cortex, temporal pole, and amygdala [12]. The amygdala likely plays a role in social judgment similar to that of the orbitofrontal cortex. The role of the amygdala is thought to involve evaluation of a stimulus’s emotional significance and the determination of an appropriate behavioral response. For instance, patients with bilateral damage to the amygdalae typically rate people as more approachable and trustworthy [26]. A case study of patient N. M., who had bilateral amygdala damage, was found to be impaired in recognizing fear from facial expressions [27]. In addition, studies have shown elevated activation in the right amygdala during emotion recognition [28]. Diseases that commonly affect comportment such as autism and FTD frequently compromise both frontal and temporal structures. Thus the circuitry responsible for social cognition involves diffuse connections within the prefrontal cortex as well as to the temporal cortex [5].

Measuring comportment

The complex functions associated with comportment make it difficult to objectively measure this capacity. The components of comportment such as insight, judgment, self-awareness, social adaptation, and empathy are difficult to assess in isolation. Moreover, comportment can vary in normal individuals, as everyone has occasional lapses in insight and judgment. Furthermore, the hospital or clinical environment is an artificial setting where patients’ responses to tests of judgment may be inapplicable to the real world.

Informal ways of assessing comportment include observing the way an individual dresses him- or herself, or whether or not there is insight into the disease. Few bedside neuropsychological tests are geared to detecting orbitofrontal deficits, although some patients with lesions in this region may have difficulty with set shifting on the Wisconsin Card Sorting Test [12]. However, this test primarily focuses on the assessment of dorsolateral prefrontal cortical function.

Unlike memory or executive function, there are no objective tests to measure comportment. Hypothetical problems geared to assessing social judgment do not appear to have a high sensitivity for comportment and have little predictive value. For example, a commonly presented scenario requires a patient to make judgments in the event that a fire breaks out in a theater. However, the real-life relevance of responses to this situation is questionable. To illustrate, patient E.V.R., a 44-year-old accountant who developed problems with decision-making and social learning following resection of a bilateral orbitofrontal meningioma, performed well on hypothetical tasks requiring judgment [13]. He created satisfactory and logical assessments of dilemmas such as a poor father with three starving children stealing from a grocery store, and a psychiatrist refusing to treat a patient who had killed a person for food while stranded on a deserted island.
Social judgment may often seem to be intact in the artificial environment of a clinic, and these patients often appear normal when presented with challenging ethical questions in a controlled setting. However, patients such as E.V.R. would likely act in a much different manner when challenged in the real world. Thus, comportment may be one of those higher mental facilities that warrant testing outside the clinic or hospital and within the patient’s own environment. Lhermitte’s study of his two patients with prefrontal lobe injury is a perfect example of how deficits, which in this case was self-awareness, were best elicited in a non-clinical environment.

There are also no standard questionnaires that specifically address comportment. The Neuropsychiatric Inventory (NPI) [29] was developed to provide a means of objectively characterizing neuropsychiatric symptoms among persons with dementias, including Alzheimer’s disease (AD) and FTD, and has enjoyed widespread use. This inventory mainly focuses on symptoms of apathy, agitation, anxiety, irritability, dysphoria, disinhibition, delusions, hallucinations, and euphoria [29]. Patients with FTD may exhibit these symptoms more often than AD patients, but unfortunately the NPI does not provide any insight into comportment.

There are measures that do permit the assessment of comportment, although these often are limited to the individual processes that comprise it (i.e., insight, judgment, self-awareness, social adaptation, and empathy). For example, a study of persons with probable AD required subjects to self-estimate their ability to perform tasks requiring memory, attention, generative behavior, naming, visuospatial skill, limb praxis, mood, and uncorrected vision pre- and post-testing [30]. Probable AD patients tended to overestimate their memory performance compared with controls [30]. From this study, the investigators developed an anosognosia ratio for their subjects, finding that probable AD patients had falsely elevated self-assessment scores for visuospatial and memory task both pre- and post-testing. Perhaps this is one technique that might be used to measure insight, but it would still fail to distinguish between posterior cortical processes such as AD from frontal cortical processes such as FTD or traumatic brain injury (TBI). Several scales measuring insight have been used in schizophrenia, including the Insight and Treatment Attitude Questionnaire (ITAQ) – the score being dependent on a patient’s agreement to psychiatric treatment – the Scale to Assess Unawareness of Mental Disorder (SUMD), with subscores resulting from a patient’s awareness and attribution of their symptoms [31, 32], and the Self-Awareness of Deficits Interview [33], which uses an interview-rated semi-structured interview to assess such problems.

Several scales have also been developed to measure empathy. The earliest examples included the Questionnaire Measure of Emotional Empathy [34] and the Balanced Emotional Empathy Scale [35]. More comprehensive scales such as the Interpersonal Reactivity Index (IRI) [23, 24] measure perspective taking, empathic concern (the capacity to feel warm, concerned, compassionate feelings for others), fantasy items (ability to identify with fictional characters), and personal distress (occurrence of self-oriented response to others’ negative experiences) [7]. The IRI has been used to quantify empathy in studies of patients with dementia and TBI [8]. The Empathy Quotient (EQ) [7], developed for the assessment of individuals with autism, is a recent scale that is sensitive to lack of empathy.

Disease processes affecting comportment

A variety of diseases that preferentially affect the prefrontal cortex and that result in increased aggression, loss of empathy, and disinhibition have provided neuropsychiatrists with insight into the brain structures responsible for comportment. Developmental disorders such as autism and Asperger’s Syndrome (AS) may result in abnormalities in connections between the frontal circuits and the temporal lobe. Degenerative processes such as FTD cause progressive dysfunction of all three prefrontal circuits. Physical injury to the prefrontal cortex either from trauma or tumor resection offer further clues to the cortical areas and pathways necessary for maintaining social cognition and behavior. Finally, schizophrenia results in functional impairment of social cognition. The pathogenesis of these four processes as well as relevant functional neuroimaging studies will be discussed in this section.

Frontotemporal dementia

In his paper, “On the Relationship Between Senile Cerebral Atrophy and Aphasia” [36], Arnold Pick described a 41-year-old woman who “became careless, clumsy…did not change her clothes or the
bedding, and stopped combing her hair...did not initiate conversation, repeated questions, tended to give stereotypical answers, and often perseverated...she had unusual fits of anger, verbally abuse and hit her children or whatever was nearby, including cattle.” This was the index report of a tau-positive dementia illness, which came to be named Pick’s Disease, and is now known as FTD.

Pick’s clinical observations are still relevant today for considering FTD, a symmetrical bifrontal variation of the frontotemporal lobar dementias (FTLD) in which pathology may show tau, ubiquitin, transactive response DNA-binding protein with Mr 43 kDa (TDP-43), fused in sarcoma (FUS), or the absence of intraneuronal inclusions [11]. FTD is one of the degenerative syndromes under the category of FTLD, the others being progressive non-fluent aphasia, which involves the left frontal lobe, and semantic dementia, which involves the anterior temporal lobes. For the purpose of this discussion, we will focus on FTD [11]. FTD is a degenerative condition that usually affects patients 45–65 years of age, and consists of circumscribed degeneration of the prefrontal and anterior temporal lobes [37]. FTD is the third most common degenerative dementia behind AD and dementia with Lewy bodies [11].

The most common presenting symptom of FTD is behavioral change. Core diagnostic features for the behavioral variant of FTD (bvFTD) include decline in social cognition, impairment in regulation of personal conduct, emotional blunting, loss of insight, and utilization behavior [38]. Furthermore, bvFTD patients tend to overeat in a gluttonous manner [11].

The key components of comportment are the earliest and most prominently affected. In terms of social adaptation, patients lose respect for personal boundaries, frequently becoming overfriendly with complete strangers [11]. Patients have impaired ability to comprehend and express emotion [11]. Loss of empathy is one of the earliest and most distressing symptoms of bvFTD [8]. Patients have impaired recognition of both facial and vocal expressions of emotion, leading to difficulty inferring what other people feel or think [37]. Self-awareness is compromised, resulting in utilization behavior [37]. Interestingly, patients with predominantly right frontal atrophy exhibit greater behavioral change than those with left side atrophy.

Structural neuroimaging typically shows bilateral atrophy (often right greater than left) of the dorsolateral, orbitofrontal, insular, and medial frontal cortices [11]. Functional neuroimaging reveals hypometabolism (often left greater than right) of the anterior temporal cortex, amygdala, and insular cortex [11]. Post-mortem studies in patients with bvFTD confirm involvement predominantly of the orbitofrontal and anterior temporal cortices in socially disinhibited patients, and predominant dorsolateral involvement in those presenting with apathy [37].

Numerous studies have examined the relationship between comportmental deficits and prefrontal pathology. Patients with bvFTD perform worse on tests of emotion perception than dementia control groups without OFC damage [11]. Patients also demonstrate interpersonal coldness and poor perspective-taking. In a study of 123 patients, Rankin et al. [8] correlated empathy scores of FTLD, AD, corticobasal degeneration, and progressive supranuclear palsy as demonstrated by the Empathic Concern and Perspective-Taking Scale with anatomical findings using MRI with voxel-based morphometry. Empathy scores correlated with the volume of right temporal structures in semantic dementia and with orbitofrontal/ventral striatal volume in bvFTD. Lower levels of empathy corresponded most significantly with atrophy of the right temporal pole, the right anterior fusiform gyrus, and the right medial inferior frontal cortex. Thus, the study suggested right anterior and medial frontal regions predominantly mediate empathetic behavior [8].

Traumatic and other acquired brain injuries

In his best-selling novel, Everything is Illuminated [39], Jonathan Safran Foer recounts the story of a sawmill worker, the “Kolker,” who suffers a horrible accident while working in the fictional shtetl of Trachimibrod. One day, a disk saw blade from a chaf splitter spins from its bearings, racing through the mill and eventually imbedding itself permanently in the Kolker’s skull as he swallows a cheese sandwich. The local physician evaluates him and finds that although the Kolker appears physically intact, he has an overwhelming urge to use profanity. Over time, he becomes “undeniably different,” beating his wife repeatedly until a wall is erected to separate the two at home [39]. Despite the extraordinary nature of Foer’s descriptions, the character of the Kolker bears contemporary relevance, and is reminiscent of many patients suffering from prefrontal lesions secondary to trauma and surgery.
Like the Kolker and Phineas Gage, many victims of TBI emerge as altered individuals with an increased tendency toward aggression and violence. The OFC is a region highly susceptible to traumatic injury. Such injury may result from blunt force, intracranial hemorrhage, and/or contusion. Case studies as far back as 1835 have reported the onset of antisocial personality traits after frontal injury, particularly in the OFC [40]. German researchers described personality changes in World War I and World War II veterans with orbitofrontal lesions [40]. The Vietnam Head Injury Study (VHIS), which investigated violent and aggressive behavior in 279 head-injured veterans, found that 14% of subjects with battle-induced frontal lobe injury engaged in fights or damaged property compared with 4% of controls without head injury [41]. The study further demonstrated a significant association between increased aggression and focal mediofrontal and orbitofrontal injury as shown by brain computed tomography (CT) scan [41]. This study, however, did not make mention of a history of aggression and violence prior to head injury.

A more recent case study described a 35-year-old security guard, who after sustaining bilateral orbitofrontal lesions after an attack by a gang, engaged in frequent fights with co-workers and made sexually inappropriate overtures toward women [42]. Beer and colleagues [14] reported a group of five patients with focal bilateral OFC damage who were significantly worse than normal controls at identifying self-conscious emotions (embarrassment, shame), but not other emotions (anger, disgust, fear, happiness, sadness, contempt, surprise, or amusement) [14].

Besides blunt head trauma, surgical operations may also result in profound behavioral changes. As mentioned earlier in this chapter, Eslinger and Damasio described the case of E.V.R., a 44-year-old accountant who developed a large bilateral orbitofrontal meningioma and severe comportmental dysfunction following the tumor resection with bilateral ablation of the orbital and lower medial frontal cortices [13]. After the surgery, he engaged in reckless partnerships with individuals of questionable reputeability. Employers complained about his tardiness and disorganization. His personal life slowly disintegrated, and his wife left home with his children, filing for divorce after 17 years of marriage. Yet E.V.R. was found to have a superior range IQ. Furthermore, he performed well on tests sensitive to frontal lobe dysfunction such as the Wisconsin Card Sorting Test, memory tasks, and set shifting [13]. Interestingly, when given hypothetical scenarios with social problems such as whether a father is justified in stealing food to provide for his family, he responded appropriately. Despite this ability to solve hypothetical problems, E.V.R. appeared to have lost the ability to analyze and integrate real-life situations. E.V.R.’s case is novel in the sense that his illness did not manifest itself as the impulsiveness, disinhibition, or lack of restraint found in many TBI patients, but instead by poor decision-making in social contexts.

Prefrontal lesions that occur in childhood may also have profound social consequences, as some affected patients fail to develop skills necessary for insight, social judgment, and foresight. Price and colleagues presented a case study of two patients with early frontal lobe pathology [43]. The first was a 31-year-old man who had suffered a left perinatal subdural hematoma requiring surgical evacuation, and who subsequently developed serious behavioral problems by the age of eight. He failed to respond to parental discipline, and later was imprisoned eight times on charges of assault, forgery, grand larceny, drug involvement, and lewd behavior. On neuropsychological testing, he had a normal IQ, but had severe deficits on the Trail Making Test, the Stroop Test, the Wisconsin Card Sorting Test, the Luria hand-motor sequence, auditory go-no-go testing, and visual-verbal tests. MRI showed bilateral lesions extending from the superior medial prefrontal cortex to the caudate nuclei [43]. The other patient was a 26-year-old woman who had suffered a right frontal hematoma secondary to a car accident at the age of four. The patient later became notorious for her sexual promiscuity and bravado, frequently engaging in drug use as well. She displayed inappropriate and negligent care of her infant. She would also make poor decisions such as wandering alone through a local cemetery where she was raped on two different occasions by the same man [43]. This patient was found on neuropsychological testing to have a full scale IQ of 78 with moderate impairment in mental flexibility, abstract reasoning, the Trail Making Test, the Stroop Test, word list generation, and visual-verbal tests. MRI showed abnormal T1 and T2 signal intensities in both prefrontal regions, with dilation of the frontal horns of the lateral ventricles [43]. In both these cases, early bilateral prefrontal lesions resulted in lifelong social learning deficits. Neither patient was able to make necessary adjustments based on negative social
Schizophrenia

Schizophrenia is a brain disorder with the hallmarks of psychosis and thought disorganization. Emil Kraepelin's term for schizophrenia, *dementia praecox*, signifies the early recognition of a disease that ultimately results in intellectual dysfunction, impaired judgment, and functional decline. Individuals with schizophrenia experience positive symptoms, consisting of hallucinations, delusions, and disorganization of speech, as well as negative symptoms including blunted affect, alogia, avolition-apathy, anhedonia, and asociality [44]. Furthermore, cognitive deficits are core features of schizophrenia, primarily involving attention, verbal learning and memory, and executive function. In these key areas of cognition, patients generally show impairments between 1.5–2 deviations below healthy controls [45]. Memory and executive dysfunction may resemble that seen in FTD, which has also been correlated with hypoperfusion of the frontotemporal cortices on functional neuroimaging with single-photon emission computed tomography (SPECT) [46]. Social cognition, reasoning and problem solving, and speed of information processing are other cognitive domains that are usually measurably impaired in schizophrenia. Approximately 75% of persons with schizophrenia demonstrate impairments on standard comprehensive neuropsychological batteries [47].

Many pathological and functional neuroimaging studies demonstrate an association between schizophrenia and dysfunction of brain structures involved in comportment. Using computational morphometry, Marcelis and colleagues [48] identified several clusters of gray matter volume reduction among subjects with schizophrenia when compared with control subjects; these reductions were in the cingulate gyrus, inferior frontal gyrus, insula, and amygdala [48]. Besides these anatomical variations in schizophrenia, neurochemical variations in dopamine activity may also contribute to the dysfunction of prefrontal circuits, as the cingulate cortex receives a large projection of dopaminergic afferents [18].

On clinical evaluation, patients with schizophrenia manifest marked impairments in various aspects of comportment, including insight (particularly into one's illness), empathy, and social cognition. Lack of insight has long been considered an important clinical feature of schizophrenia. For instance, the International Pilot Study of Schizophrenia (IPSS) found the “lack of insight” item on a psychopathological inventory to be the most frequently identified problem among persons with schizophrenia [49]. This impairment of insight contributes to poor adherence to antipsychotic medication and contributes to an overall poor prognosis [50]. It has been suggested that poor insight among persons with schizophrenia may be a result of executive dysfunction, but many studies examining the association between insight and cognition have failed to show a consistent relationship [51]. However, a recent meta-analysis confirmed a relationship between insight and impairment in set shifting and error monitoring as assessed by the Wisconsin Card Sorting Test, although the correlation was weak \((r = 0.17)\) [52]. Lysaker and colleagues administered the Delis–Kaplan Executive Function System to 53 subjects with schizophrenia and found that awareness of symptoms was related to performance on verbal fluency, Stroop Test, Tower of Hanoi, and word context measures [53].

The assessment of insight in persons with schizophrenia is complicated by the dynamic nature of this faculty, which may be influenced by treatment and affective state. Unlike patients with FTD who have more static insight impairments, those with schizophrenia have been noted to have improved insight after treatment with antipsychotics [54]. Furthermore, insight has been shown to vary depending on the patient's affective state. For instance, patients with acute mania (which can occur in schizoaffective disorder) are notorious for having very poor insight during the acute episode [55]. Conversely, major depression has consistently been associated with better insight than other psychiatric disorders [56]. Freudenreich and colleagues studied 122 stable
outpatients with schizophrenia, of whom 62% had at least partial awareness of symptoms [57]. Only dysphoric affect predicted the degree of insight into the pathological nature of the patients’ symptoms. Finally, insight into illness may be also be influenced by cultural factors such as a resistance to being labeled with a mental illness or an unwillingness to take medications with a variety of side effects. Such denial of illness is a well-known psychological phenomenon in clinical medicine that can be seen in diseases unrelated to the brain (e.g., denial in patients following myocardial infarction).

Consequently, insight in schizophrenia cannot be understood as being a dichotomous variable in which the patient either does or does not have insight. Both dimensional models of insight (i.e., full insight, varying degrees of partial insight, no insight) and more complex, multidimensional conceptual models of insight have developed. David proposed a tridimensional model that conceives of insight as being comprised of three dimensions: (1) ability to recognize the pathological nature of psychological experiences (e.g., hallucinations); (2) recognition that one suffers from a mental illness; and (3) acknowledgment of the need for treatment [58].

In addition to insight deficits, many persons with schizophrenia also demonstrate impairments in the theory of mind, another likely sequel of prefrontal dysfunction. Much of the testing to support this conclusion has revolved around having patients use physical cues such as eye appearance to judge an individual’s affective state. Russell and colleagues studied subjects with schizophrenia taking antipsychotic medications whose IQ scores were similar to those of control subjects, and he assessed their ability to ascertain emotional states based on pictures of eyes [59]. Subjects with schizophrenia made more errors in mental state attribution and were found to have decreased fMRI blood-oxygen-level-dependent signal response in the left middle and inferior frontal cortex and insula compared with controls [59]. In a PET study, persons with schizophrenia receiving antipsychotic medications were matched with normal controls for verbal IQ and performed a non-verbal attribution of intention task as well as two matched physical logic tasks [60]. When compared with the control subjects, performance on these tasks was lower among those with schizophrenia; additionally, the latter group did not demonstrate blood flow responses in the right middle frontal gyrus [60].

Although persons with schizophrenia may not have obvious neuroimaging abnormalities such as those seen in FTD or TBI patients, the condition clearly affects insight and social cognition. An interesting aspect of schizophrenia is that it is one of the few comportmental disorders that can be modulated with pharmacologic treatment. Further functional and anatomical investigations are necessary to further delineate the dysfunctional circuits that result in the disorganization of both thought as well as social adaptation in these patients. A certain degree of mystery still surrounds the mechanisms underlying schizophrenia, as in autism spectrum disorders, the last topic of this section.

**Autism spectrum disorders**

In contrast to conditions affecting comportment that are acquired in adulthood, autism and AS (referred collectively to as autism spectrum disorders, or ASD) are developmental disorders that involve dysfunction in social interaction and empathy. These patients exhibit impairment in the interpretation of non-verbal behaviors (i.e., facial expressions, body posture, and gestures), fail to develop appropriate peer relationships, and lack social and emotional reciprocity [61]. The principal difference between high-functioning autism (i.e., autism with normal performance on measures of intellectual functioning) and AS is that autism is associated with language and cognitive delays [61].

Both autism and AS cause dysfunction in social cognition. Persons with these disorders do not attend normally to the affective component of facial expression [62]. In fact, Schultz and colleagues found that the brain activity of AS individuals regarding facial features was similar to that produced by these subjects viewing non-human objects [63]. Furthermore, these patients are unable to adequately perceive information about what others may think or feel, and they have impaired theory of mind. Loveland and colleagues [64] found that children and adolescents with autism were less accurate than controls in detecting whether videotaped children were willing to share candy [64]. Consequently, this failure to assess the social cues of others can lead to the expression of inappropriate behavior as well as failure to modify behavior based on social cues.

Structurally, both the frontal and temporal cortices appear to be involved in autism. In a study using voxel-based morphometry, reductions in gray matter volume in the medial frontal regions were detected [65].
Kwon and colleagues studied males with high-functioning autism, AS, and age-matched controls. Males with either autism or AS had decreased gray matter density in the ventromedial regions of the temporal cortices when compared with controls [66]. In addition, the AS group was noted to have less gray matter density in the body of the cingulate gyrus when compared with those in the autism and control groups.

Post-mortem studies of autism have shown a variety of subtle findings, including abnormal gyrification of the parietal lobe; decreased volumes of the corpus callosum, anterior cingulate, inferior frontal gyrus, and occipitotemporal junction; hypoplasia of the cerebellar vermis; and tightly packed cells in the cerebellar nuclei, amygdala, and hippocampus [6]. The amygdala appears to be consistently involved in autism. Adolphs and colleagues found that individuals with autism and those with damage to the amygdala make similar abnormal judgments of trustworthiness and approachability from faces (i.e., trusting a face with a “negative expression”) and make similar errors in recognizing emotional expression from faces [67]. Furthermore, studies of monkeys show that bilateral medial temporal lobe lesions result in reduced eye contact, inexpressive faces, decreased social encounters, and lack of play, all suggestive of an autism-like syndrome [68].

There is no single, well-accepted neuroanatomical model for autism [6]. The condition is a disorder of social cognition, which implies a neuroanatomical basis consisting of a ventral (emotion) circuit including the amygdala, anterior cingulate, OFC, and mediodorsal thalamus, and a dorsal (processing) circuit that involves the hippocampus, anterior thalamic nuclei, parietal cortex, and dorsolateral prefrontal cortex [6]. Ornitz hypothesized involvement of cerebellum, parietal cortex, brainstem, thalamus, and striatum on the basis of poor sensory modulation and selective attention in these patients [69]. Delong suggested that autism resulted from bilateral dysfunction of medial temporal lobe structures such as the hippocampus [70]. Damasio and Maurer proposed that autism resulted from dysfunction of the mesolimbic (dopaminergic) brain areas [71].

Functional MRI studies of autistic patients have suggested a neural network involving the superior temporal gyrus, amygdala, and OFC [72]. Baron-Cohen and colleagues [72] performed fMRI studies of persons with autism performing a theory of mind task in which subjects were required to judge from a person’s eyes what that individual was thinking. Not only were subjects with autism less accurate than the control subjects when judging emotion, but they also failed to activate the amygdala relative to the control subjects [72]. Critchley et al. [73] performed functional neuroimaging on persons with autism spectrum disorders during the implicit processing of facial emotions. Results revealed absent activity in the left cerebellum and left amygdalohippocampal regions in the subject group compared with the control group [73].

Clinically, autism is a developmental disease of comportment, and it stands as a clear example of how the structures responsible for comportment are not confined to the prefrontal cortex, but also depend heavily on limbic structures. The early onset of autism and its profound behavioral consequences are both related to the fact that these individuals do not learn or are unable to use effectively the rules of social interaction.

**Conclusion**

An understanding of comportment is an understanding of the qualities that define us as social beings. Successful careers, marital relationships, parental bonding, and lifelong friendships develop as a result of intact insight, judgment, self-awareness, social adaptation, and empathy. The circuitry subserving comportment, however, remains only vaguely defined, and consists of broad pathways that shuttle impulses between the frontal, temporal, and subcortical structures.

On a larger scale, comportmental dysfunction has significant ramifications for society. Many individuals with violent and antisocial behavior have dysfunction of the prefrontal cortex. For instance, individuals with antisocial personality disorder have been shown to have reduced overall prefrontal gray matter volume on MRI volumetric studies compared with control subjects [74]. Furthermore, a PET study of 41 individuals charged with murder or manslaughter demonstrated significant bilateral prefrontal hypometabolism compared with control subjects during a frontal lobe activation task [75]. It is the integrity of these regions that may distinguish the good citizen from the sociopath.

The importance of comportment in everyday function also becomes clear in illnesses that compromise the function of the prefrontal circuits. Diseases of comportment, which often culminate in increased aggression, loss of empathy, and disinhibition, challenge the very notion of true love between the patient and his
family. Whereas diseases such as amyotrophic lateral sclerosis or cancer result in distortion and atrophy of the physical body, diseases of comportment acquired during adulthood profoundly alter patients’ behaviors, changing the very psychological characteristics that previously defined them as individuals. Thus, it is the comportmental axis of the prefrontal cortex that is responsible in many ways for our humanity.

Knowledge of comportmental function leads to broader questions about good and evil. Are acts of theft and physical violence abstract psychological qualities of a criminal mind, or are they a function of abnormalities in the prefrontal circuitry? On a larger scale, could one reduce the disregard for humanity by the perpetrators of the Nazi or Rwanda genocides to an abnormality or a functional misfiring within the prefrontal cortex?

These broad questions currently seem unfathomable, but collaborative efforts between neurologists, psychiatrists, philosophers, ethicists, religious authorities, and psychologists are instrumental in arriving at solutions regarding aggressive and violent behavior. Case studies of patients with FTD and TBI with the aid of functional imaging have allowed for neuroanatomical localizations of higher mental functions such as empathy and social adaptation. With more sophisticated studies of comportment, it may even be possible to consider the eventual likelihood of modifying these circuits.

Modern advances in technology have served to recharacterize conditions such as FTD, TBI, autism spectrum disorders, and schizophrenia as anatomical and functional disorders of the brain structures responsible for comportment. The unfortunate truth is that neurologists currently serve as observers of these conditions and have limited ability to modify comportmental deficits. However, the ability to define abstract processes such as empathy and social adaptation in terms of complex neural circuitry is a resounding step forward. Perhaps one day, neurologists and psychiatrists will see diseases such as FTD and schizophrenia in the same light as Parkinson's disease, a disorder that can be eloquently modified by pharmacologic, electrical, and surgical intervention.

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