



Schizophrenia and OCD: comparative characteristics

According to contemporary psychiatric nomenclature, schizophrenia and obsessive-compulsive disorder (OCD) are distinct nosological entities characterized by non-overlapping diagnostic criteria; they have distinct clinical presentations, treatment, and prognoses. Despite these differences schizophrenia and OCD share some demographic and clinical characteristics, certain aspects of pathophysiology, and treatment strategies (Table 1.1).

Historical perspective Schizophrenia

Although case descriptions resembling schizophrenia go back hundreds of years, schizophrenia was first described as a disease in the nineteenth century. While searching for basic similarities and dissimilarities in psychotic conditions, Emil Kraepelin, one of the founders of modern psychiatry, noted that a “deteriorating process” was a common denominator for a number of psychotic disorders, such as Kahlbaum’s catatonia, Hecker’s hebephrenia, Pick’s and Sommer’s simple deterioration, and paranoid states associated with disorganization (Kraepelin, 1919). Kraepelin found it necessary to retain the above syndromes as

Table 1.1 Schematic comparative characteristics of schizophrenia and OCD

	Schizophrenia	OCD
Prevalence	~1%, narrowly defined 2–3%, broadly defined	2–3%
Gender ratio (M/F)	1/1	1/1
Age of onset	2nd–3rd decade, men earlier than women	1st–2nd decade, men earlier than women
Course	chronic with remissions	chronic, wax and wane
Involved brain regions	cortex: DLPFC, temporal, ACC; thalamus, hippocampus, striatum	cortex: OFC, ACC; thalamus, striatum
Neurotransmitter systems	Dopamine/serotonin/glutamate	Serotonin/dopamine/ glutamate
Treatment	Antipsychotic agents (add-on serotonin reuptake inhibitors)	Serotonin reuptake inhibitors (add-on antipsychotic agents)

DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex.

subdivisions of the specific disease, “dementia praecox” or premature dementia. Adolescent or early adult onset, deteriorative course, and poor outcome were distinctive characteristics of this disorder. He distinguished dementia praecox from manic–depressive illness characterized by episodic course, lack of deterioration, and relatively favorable outcome.

Eugen Bleuler introduced the term “schizophrenia” and referred to the disorder as the “group of the schizophrenias” to highlight its heterogeneous nature (Bleuler, 1911/1950). He distinguished between basic and accessory schizophrenia symptoms, and determined that disturbances of associations, affect, ambivalence, and autistic isolation (well known as the four As) were the basic symptoms, while hallucinations, delusions, and catatonic symptoms were secondary symptoms, not essential for diagnosis. Bleuler also considered “milder cases” of schizophrenia that developed in patients with a neurosis, a disorder that does not affect rational thinking and reality testing. He ascertained that for some patients who were considered neurotic, obsessive–compulsive symptoms were in fact features of schizophrenia, and emphasized the converging trajectories of the two disorders (see Chapter 2). These views were echoed by Mayer-Gross (1932) who described cases of chronic obsessive–compulsive neurosis associated with “marked autism” as actual schizophrenia.

Kurt Schneider (1959) considered first-rank symptoms (e.g., delusions of control, thought insertion, withdrawal, or broadcasting) pathognomonic to the disorder. He further developed the ideas of Karl Jaspers (1946) who claimed that “un-understandability” of the individual experience was a distinguishing feature of schizophrenia. Over time, however, the elements of un-understandability as defining psychosis have faded and these symptoms have not been found to be specific to schizophrenia (Tandon *et al.*, 2008). Schneider regarded transitory delusional ideas together with obsessive ideas as second-rank symptoms, and differentiated between genuine obsessions and symptomatic obsessions. He doubted whether a genuine obsessional neurosis could develop into schizophrenia (Schneider, 1925). In fact, the proponents of the hierarchical approach in psychiatric classifications viewed successive psychopathological symptoms as “onion-like” hierarchical layers, namely psychopathic–neurotic (including obsessive–compulsive), manic–depressive, schizophrenic, and psycho-organic; disorders of the lower layers that “superseded” disorders of the higher layers (Jaspers, 1946; Schneider, 1987). Thus, this approach to psychiatric disorders did not enable co-occurrence of the two conditions from different “layers.”

Current definitions of schizophrenia, including DSM-IV-TR (American Psychiatric Association, 2000) and ICD-10 (World Health Organization, 1992), incorporate Kraepelinian chronicity of illness, Bleulerian negative symptoms, and Schneiderian positive symptoms (Tandon *et al.*, 2008).

Obsessive–compulsive disorder

A unique syndrome characterized by the presence of obsessions and compulsions has been recognized for more than three centuries. This condition has been known as scruples, religious melancholy, *folie de doute* (insanity of doubt), *folie avec conscience* (insanity with insight), obsessive–compulsive neurosis, and finally obsessive–compulsive disorder (Berrios, 1989). As the distinction between neurotic and psychotic disorders progressed, the obsessive–compulsive syndrome became one of the prototypic neuroses. An obsession, which is an intrusive, repugnant idea recognized as senseless or irrational and experienced as internal in origin,

could thus be distinguished from a delusion, in which the senselessness is not appreciated and the idea is generally attributed to an external source. Although traditionally obsessive-compulsive phenomena have been considered neurotic, earlier descriptions depicted these symptoms with fundamental connections to a psychosis. In perhaps the earliest English language “case report,” dated 1660, Jeremy Taylor described a patient whose ego-dystonic intrusive thoughts of having sinned were replaced by a “belief that this scrupulousness of conscience is . . . a punishment of his sins” (cited in Insel and Akiskal, 1986). Similarly, German psychiatrist Westphal who offered one of the most comprehensive descriptions of the obsessive-compulsive syndrome, stressed its similarities with psychosis. He emphasized that the obsession, by its irrational content, represented a basic disorder of thinking, and classified the obsessive-compulsive syndrome as “abortive insanity” (Westphal, 1878).

Henri Legrand du Saulle, a French psychiatrist, was one of the first to recognize that patients who suffered from severe obsessive disorders also had psychotic symptoms. On follow-up some patients with obsessive disorder remained “house-bound, maintaining only a resemblance of insight and harboring darker psychotic attitudes” (cited in Berrios, 1996, p.145). Pierre Janet classified OCD under the term “psychasthenia” and provided precise clinical descriptions of the disorder in his much-cited work *Les Obsessions et la Psychasthénie* (*Obsessions and Psychasthenia*) (Janet, 1903). Among more than 300 cases, 23 patients developed psychosis: patients with primary emotional symptoms and phobias developed melancholia, and those with primary “intellectual obsessions” developed paranoia. Though Janet’s psychasthenia included cases other than obsessional neurosis, his observations hinted at the possibility of psychotic (not necessarily schizophrenic) transformation in obsessive-compulsive patients. Psychotic deterioration with affective or paranoid features, rather than schizophrenic disorder, in patients with well-established diagnoses of OCD was later substantiated (Insel and Akiskal, 1986; Eisen and Rasmussen, 1993).

From the historical perspective the consolidation of views on schizophrenia and obsessive-compulsive disorder points toward two independent but partially overlapping psychopathological trajectories. Diagnostic challenges associated with the clinical complexity of the schizophrenia-OCD interface became increasingly evident beginning with the early stages of investigation of the two disorders.

A well-known case of the patient described by Sigmund Freud (1918) in “The History of an Infantile Neurosis” under the pseudonym “Wolfman” called attention to the complex interrelationship between the two disorders and distinct diagnostic approaches of the clinicians. The patient was diagnosed and analyzed as an obsessional neurotic by Freud, but 6 years later his obsessional ideas underwent psychotic transformation into hypochondrial delusions. Before coming to Freud in Vienna, he had been treated in Munich by Emil Kraepelin, who had treated the patient’s father for manic-depressive illness and had attributed the same diagnosis to the son. This is not surprising because Kraepelin had a tendency to classify so-called “obsessional insanity” under manic depression. Eugen Bleuler would have classified chronic obsessional neurosis under the umbrella of schizophrenia (Lang, 1997).

Disease expression: signs and symptoms

Schizophrenia

Schizophrenic disorder is characterized by a diverse set of signs and symptoms, including abnormalities of perception, thinking, cognition, motor function, and affect. These disturbances are generally grouped into positive, negative, disorganized, cognitive, mood, and

motor symptom dimensions. Psychopathology is differentially expressed across patients and throughout the course of illness. Within the *positive symptom* dimension, delusions of reference and persecution, delusions of control, thought insertion, broadcasting, and withdrawal are traditionally linked to schizophrenia (Schneiderian first-rank symptoms). Although various delusions might occur, in a majority of patients delusional content focuses on a restricted set of typical themes (e.g., reference, persecution, grandeur). Additional positive symptoms, hallucinations, can occur in any of the sensory modalities, though auditory hallucinations – voices commenting or conversing, or imperative voices – are more common. Positive symptoms mark the formal onset of illness, however pathophysiological processes might begin long before. *Formal thought disorders* refer to disorganization of the logical and goal-directed thought process, and range in severity from mild circumstantiality, tangentiality, derailment, and neologisms to severe incoherence and word salad (Andreasen, 1979). According to Bleuler (1911/1950) formal thought disorder, an expression of loosening of associations, is a central deficit in schizophrenia. Disorganized thinking and behavior are prominent, particularly during acute exacerbations and are relatively persistent and associated with poor outcome. *Negative symptoms*, that are intrinsic to schizophrenia, involve restricted and blunted affect, anhedonia, avolition, apathy, and alogia (Andreasen, 1982). Negative symptoms may be detected at every stage of illness; however, they are most prominent in prodromal, post-psychotic, and residual states. Negative symptoms may have distinct pathophysiological mechanisms, remain relatively treatment-resistant, and are strongly associated with functional impairment typical to schizophrenia. *Motor symptoms* can range from simple slowness to complex stereotypic movements, mannerisms, and catatonic symptoms (waxy flexibility, posturing, echolalia, echopraxia, and negativism). *Depressive symptoms*, expressions of affective deregulation in schizophrenia, are common and may be a part of the prodromal or florid phase, follow an acute episode, or occur in remission of schizophrenia. Depressive symptoms substantially contribute to the disease burden, and are strongly associated with suicidality in schizophrenia patients. Similarly, *anxiety symptoms* are prominent features of schizophrenia and may be identified from the early stages and throughout the course of the illness.

There is no single pathognomonic symptom in schizophrenia. According to DSM-IV criteria, the diagnosis is based on a constellation of positive, negative, and disorganized symptoms, illness duration (at least 6 months, including at least 1 month of active-phase symptoms), and functional impairment, after exclusion of mood disorders, and psychoses associated with substance abuse or general medical conditions.

Obsessive–compulsive disorder

Similar to schizophrenia, OCD is associated with disturbances of thoughts, affect, somato-sensory perception, and motor function. However, typical presentations of the two disorders are basically different. OCD is most commonly characterized by the occurrence of both obsessions and compulsive rituals, but they can also occur independently (American Psychiatric Association, 2000). There are no objective tests for OCD, and the diagnosis is established based on clinical assessment. According to DSM-IV criteria, a diagnosis of OCD requires either obsessions or compulsions that cause distress, are time-consuming (more than 1 hour per day) and substantially interfere with normal functioning.

Obsessions have the following essential features: recurrent and persistent thoughts, impulses, or images that are experienced as intrusive and cause anxiety; they are not simply excessive worries about real-life issues; the affected individuals attempt to ignore, suppress, or neutralize their obsessions with other thoughts or actions; and the thoughts are recognized as products of their minds. *Compulsions* are repetitive behaviors or mental acts that the affected individuals feel compelled to perform in response to an obsession, or according to rigid rules. Compulsions are aimed at preventing or reducing anxiety and distress associated with obsessions, or at preventing dreaded events. Compulsions are excessive and not realistically connected to what they are intended to prevent (Abramowitz *et al.*, 2009).

The content and character of the obsessions and their relationships to repetitive behaviors sometimes differ. However, akin to delusions with their restricted set of distinctive themes, several typical obsessive themes have been described: contamination, symmetry or exactness, forbidden thoughts (aggressive, sexual, religious, and somatic). Specific obsessions are associated with corresponding compulsions, cleaning, ordering and arranging, checking, and hoarding, and tend to form psychopathological dimensions that are relatively stable over time (Bloch *et al.*, 2008). The content that is characteristic of obsessions and compulsions is usually readily distinguishable from the content of schizophrenic delusions. However, “bizarre” themes exhibited by a subset of otherwise typical OCD patients might complicate the distinction between the two psychopathological phenomena (see Chapter 9). The difference between OCD-related *pathological slowness* (pervasive difficulty initiating and completing routine tasks) and catatonic motor disturbances is not straightforward. *Indecisiveness* (difficulty making decisions about things that other people might not think twice about) and *pathological doubt* (uncertainty about the correctness of performed activities) are common features of OCD. Awareness of the distressful character of these symptoms, usually expressed by OCD patients, distinguishes them from schizophrenia-related ambivalence. Indeed, *insight* into the senseless nature of obsessive–compulsive symptoms is one of the hallmarks of the disorder, in contrast to lack of insight that is a cardinal feature of schizophrenia. According to the DSM-IV, at some point in the course of the illness, the patients must recognize that their obsessions and compulsions are excessive and unreasonable. In typical cases, patients readily acknowledge that their obsessive–compulsive symptoms are illogical and morbid. On the contrary, a significant majority of schizophrenia patients either do not believe that they are ill, or if they do acknowledge symptoms, they misattribute them to other causes (Amador and David, 1998). Notably, a subset of OCD patients presents with poor insight or complete conviction of the true nature of their obsessions, making differential diagnosis from delusions difficult. Nevertheless, cognitive biases that underlie high-conviction beliefs in OCD and delusions (e.g., “jumping to conclusions”) are distinct (Jacobsen *et al.*, 2012), and OCD with poor insight differs from a typical psychotic disorder (see Chapter 9). Moreover, though thought processes in OCD are disturbed by intrusive ideas and *magical thinking*, true thought derailment, thought insertion, and thought broadcasting are absent.

In general, OCD and schizophrenia have distinct but partially overlapping psychopathological features. Some, such as delusions and obsessions, most likely represent a continuum of impairments, while others, such as negative and disorganized symptoms, are more disorder-specific (Figure 1.1).

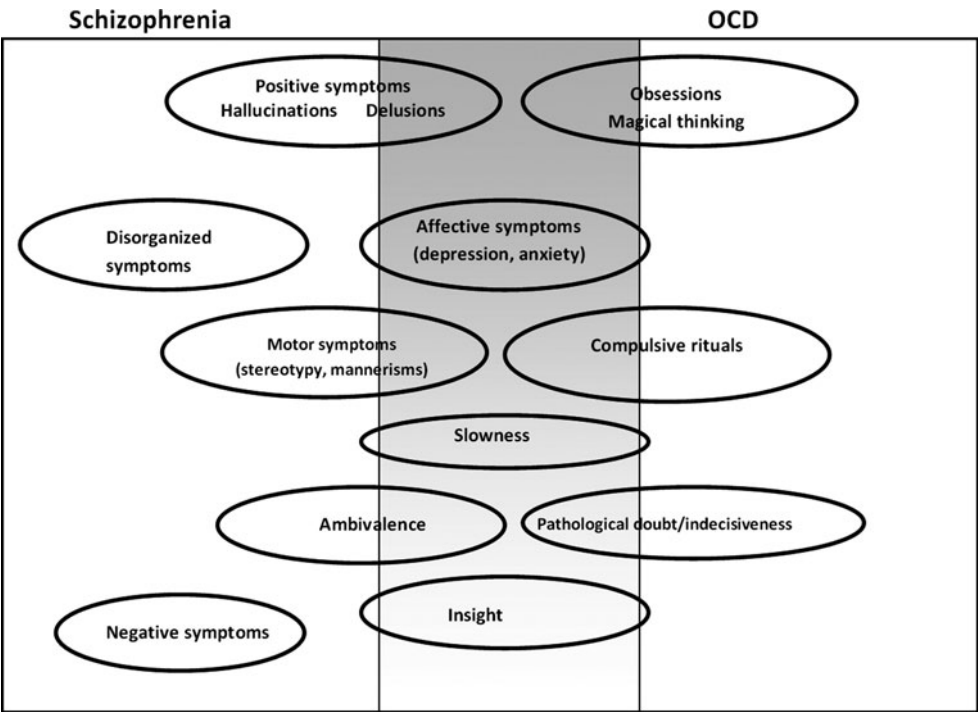


Figure 1.1 Schizophrenia versus OCD: psychopathological features.

Prevalence and demographic and clinical features

Schizophrenia

Schizophrenia is a lifelong condition that affects both men and women, though symptom expression is more severe in men. Men have earlier onset of illness, more negative symptoms, and poorer outcomes. When narrowly defined, the lifetime prevalence of schizophrenia is 0.3–0.66% (McGrath *et al.*, 2008). However, when broader diagnostic categories, such as brief psychotic disorder, delusional disorder, and psychotic disorders not otherwise specified, are included the estimated prevalence approaches 2–3% (Perala *et al.*, 2007). Demarcation between various phases of schizophrenia is imprecise; however, the disorder may be characterized by a sequential trajectory of a *premorbid stage* with non-specific cognitive, motor, and social dysfunction; *prodromal stage* with attenuated positive symptoms and declining function; *first psychotic episode* heralding formal onset of active illness; *initial decade* of illness generally marked by repeated episodes of psychosis with variable degrees of inter-episode remission and finally a *stable phase or plateau*, when psychotic symptoms are less prominent and negative symptoms and stable cognitive deficits become increasingly predominant (Tandon *et al.*, 2008).

Prognosis of the disorder is usually unsatisfactory. Sustained recovery occurs in fewer than 14% within the first 5 years following a psychotic episode, and long-term outcomes are generally only marginally better (Insel, 2010). In Europe, fewer than 20% of people with schizophrenia are employed (Marwaha *et al.*, 2007).

Obsessive–compulsive disorder

The life prevalence of OCD in the general population is estimated at 2–3% (Ruscio *et al.*, 2010), remarkably similar to the estimates of broadly defined schizophrenia. Epidemiological studies in the Americas, Europe, Asia, and Africa have confirmed the rates of occurrence of both disorders across cultural boundaries. Akin to schizophrenia, among adults, men and women are equally affected by OCD, but among adolescents, boys predominate and have an earlier age of onset. The mean age of onset in OCD is about 20 years, and onset of symptoms is before age 30 in about two-thirds of the patients. Late onset is rare. OCD and schizophrenia have similar age-at-onset distribution, with a trend towards earlier age of onset for OCD. There are evident similarities in the course of illness for both disorders: OCD is a chronic, waxing-and-waning disorder. Clinical presentations of both disorders across the lifespan are generally similar. Though the prognosis for OCD is apparently better than for schizophrenia, in comparison to people with anxiety and mood disorders, those with OCD are less likely to be married, more likely to be unemployed, and more likely to report impaired social and occupational functioning (Geller, 2006; Torres *et al.*, 2006; Pallanti, 2008; Ruscio *et al.*, 2010).

Overall, high prevalence, early age of onset, chronic course, and pervasiveness of symptoms render schizophrenia and OCD among the ten leading causes of disability (expressed by the number of years lost due to ill-health, disability, and early death). Noteworthy, when projecting the burden of disease for the year 2020, just as psychiatric disorders, primarily schizophrenia, affective disorders, and OCD, emerged as major contributors to the global disease burden in the 1990 data, mental illnesses are projected to be significant contributors to the 2020 global burden of disease. The proportion of psychiatric disorders in the total global burden of disease is expected to increase from the reported 10.5% in 1990 to 15% by 2020 (Table 1.2).

Genetic and environmental factors

Schizophrenia

Vulnerability for schizophrenia is partly genetic with heritability estimates of roughly 80%, as suggested by twin studies (McGuffin and Gottesman, 1999). Concordance in monozygotic twins is about 50% (not the 100% as might be expected for a Mendelian disorder), and considerably higher than in dizygotic twins or siblings (around 10%). Despite this genetic contribution, the identification of specific genetic associations has been challenging. A small proportion of schizophrenia cases might be explained by rare structural variations (copy-number variants occasioned by small duplications, deletions, or inversions) (Bassett *et al.*, 2010). Combining single-nucleotide polymorphism (SNP) data from several large-scale independent genome-wide studies led to identification of replicable associations with genes, including those involved in neurodevelopment and relevant to the pathophysiology of schizophrenia (Need *et al.*, 2009). Currently, at least 43 candidate genes have been identified, but individual effect sizes are consistently low, especially relative to the evidence for high heritability (Insel, 2010).

Genetic effects and environmental influences that are moderated by genes (gene–environment interaction) account for the established high heritability of schizophrenia. Environmental factors, including perinatal insults (hypoxia, maternal infection, or malnutrition) play a role in accord with genetic vulnerability (Cannon *et al.*, 2002). Advanced paternal age increases the risk of schizophrenia and possibly OCD (Wu *et al.*, 2012). Migrant ethnic groups and children raised in highly urbanized environments are also at increased risk for schizophrenia

Table 1.2 The leading causes of disability worldwide, 1990, as measured by years of life with a disability (YLD): all causes

	Total YLDs (millions)	Percent of total
1. Unipolar major depression	50.8	10.7
2. Iron-deficiency anemia	22.0	4.7
3. Falls	22.0	4.6
4. Alcohol use	15.8	3.3
5. Chronic obstructive pulmonary disease	14.7	3.1
6. Bipolar disorder	4.1	3.0
7. Congenital anomalies	13.5	2.9
8. Osteoarthritis	13.3	2.8
9. Schizophrenia	12.1	2.6
10. Obsessive–compulsive disorder	10.2	2.2

Source: Murray CJL, Lopez AD (1996) The global burden of disease. *Nature Medicine* **4**, 1241–1243. Reprinted with permission.

(van Os *et al.*, 2010). Individuals with pre-existing liability to psychosis are more susceptible to the development of transient psychotic states when exposed to cannabis than healthy controls (van Os *et al.*, 2010). The fact that only a small proportion of those exposed to cannabis, migration, or urban environment develop schizophrenia suggests that some are resilient to these environmental risk factors. The basis for this resilience is not yet clearly understood.

Obsessive–compulsive disorder

Akin to schizophrenia, twin studies have supported strong heritability for OCD, with a genetic influence of 45–65% in studies in children and 27–47% in adults (Carey and Gottesman, 2000; van Grootheest *et al.*, 2005). Monozygotic twins are concordant for OCD (80–87%), compared with 47–50% concordance in dizygotic twins. Furthermore, prevalence of OCD in first-degree relatives of OCD patients is three to five times higher than in relatives of healthy controls, clearly indicating that the disorder runs in families; and there might be a stronger familiarity in childhood-onset OCD than in cases in which the disorder develops later in life (Nestadt *et al.*, 2010). Segregation analyses of OCD implicate a gene of major effect in the etiology of OCD, and reject sporadic and environmental models. Studies of candidate genes selected on the basis of knowledge of the pathophysiology and pharmacology of the condition produced some preliminary leads for the association with the genes relevant to serotonergic, glutamatergic, and dopaminergic systems; however, there have been only few replications of these findings (e.g., the glutamate transporter gene *SLC1A1*) (Nestadt *et al.*, 2010). Large-scale genome-wide association studies that might provide further information about genetic vulnerability to the disorder, are currently underway.

Autoimmune mechanisms may also be involved in OCD. Streptococcal infection and inflammation to the basal ganglia might lead to the development of childhood-onset OCD. Such cases are grouped within a set of clinical conditions called pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS), and are sometimes successfully treated with antibiotics (Swedo *et al.*, 2001).

Cognitive dysfunction

Schizophrenia

Cognitive impairment is one of the core features of schizophrenia. Tandon and colleagues (2008) summarized the major characteristics of cognitive impairment in schizophrenia: (1) cognitive impairment is *highly prevalent* (if not *universal*) in patients with schizophrenia; (2) cognitive impairment distinguishes patients with schizophrenia from healthy comparison subjects to a *robust degree* (i.e., an effect size of approximately 1); (3) the cognitive deficit in schizophrenia is of a *generalized* nature with substantial impairments in specific domains of executive functions and working memory, attention, verbal fluency, processing speed, and episodic memory; (4) cognitive deficits are already present in the premorbid phase of illness and are observed through the long-term course of schizophrenia with a probable deterioration prior to or around the onset of psychotic symptoms, a modest improvement with treatment, and relative stability thereafter; (5) a similar pattern of cognitive impairment of lesser severity is present in non-psychotic relatives and is likely related to patient’s *genetic susceptibility* to schizophrenia; (6) cognitive impairment is a *strong predictor* of poor social and vocational outcome.

Obsessive–compulsive disorder

In contrast to generalized and pervasive cognitive impairment in schizophrenia, cognitive deficits in OCD are *more selective* and *less severe* (Table 1.3). Hence, while patients with schizophrenia have generalized deficits in all aspects of executive function, namely a poor sense of planning, impaired decision-making, and response inhibition, patients with OCD share impairment in decision-making and response inhibition, but do not display difficulties with planning (Burdick *et al.*, 2008). Perturbed declarative memory is another example of a transnosological deficit. Of its two basic forms, deficits in semantic memory are mainly restricted to schizophrenia, whereas impairment of episodic memory may also be found in OCD, however in a lesser degree (Table 1.2).

In schizophrenia, faulty social cognition is a crucial issue: it predicts conversion to full psychosis in high-risk asymptomatic individuals. Social withdrawal exacerbates negative symptoms, and false attribution to others of harmful intentions aggravates paranoia and delusions (Brune, 2005). Social cognition must be intact to appropriately decode verbal language, which is compromised in schizophrenia. Disorganization of language, perturbed verbal fluency, and a poor grasp of semantics are core features of schizophrenia. On the contrary, language function and social cognition are generally preserved in OCD (Millan *et al.*, 2012). Moreover, some cognitive domains have opposite directions of change: there is a cardinal loss of focused attention in schizophrenia, and in contrast, there is hypervigilance in OCD. Among the deficits that characterize OCD, impairment of procedural learning is of particular note. Along with other mechanisms, procedural learning underlies the principal failure to “forget” and “inhibit,” and thus might account for the occurrence of intrusive thoughts and actions characteristic of OCD (Chamberlain *et al.*, 2005; Burdick *et al.*, 2008).

Certain neurocognitive impairments (e.g., working memory in schizophrenia; response inhibition in OCD) have been found in affected probands and their unaffected first-degree relatives, thus these impairments represent heritable traits (Snitz *et al.*, 2006; Chamberlain *et al.*, 2007). These so-called intermediate phenotypes (because they are between the predisposing genes and the clinical disease phenotype) might be closer to alterations in gene function than the diagnostic category of the corresponding disease. Some of these intermediary

Table 1.3 Comparison of cognitive impairment in patients with schizophrenia and OCD

Cognitive function	Schizophrenia	OCD
Attention and vigilance	+++ (↓)	+++ (↑)
Working memory	+++	+
Executive function	+++	++
Episodic memory	+++	+
Semantic memory	++	0/+
Visual memory	+	+
Verbal memory	+++	0/+
Fear extinction	++	++
Processing speed	++	++
Procedural memory	+	++
Social cognition (theory of mind)	+++	+
Language	+++	0/+

0, essentially absent; 0/+, poorly documented, ambiguous, mid and/or variable; +, consistently present but not pronounced; ++, a common, marked characteristic; +++, a core, severe, and virtually universal characteristic of the disorder; ↑, increase.

Source: Modified from Millan *et al.* (2012) Cognitive dysfunction in psychiatric disorders: characteristics, causes, and the quest for improved therapy. *Nature Review of Drug Discovery* **11**, 141–168. Reprinted with permission.

phenotypes could be diagnostically relevant: for example the intermediary phenotype of cognitive impairment could have some specificity for the diagnostic category of schizophrenia. Indeed, meta-analytic work has indicated that relatives of patients with bipolar disorder have only minimal cognitive alterations (Arts *et al.*, 2008). Similar comparative evaluations of schizophrenia and OCD patients and their relatives have yet to be performed.

Pathophysiology: structural, functional, and neurotransmitter alterations

Schizophrenia

Structural brain imaging reports demonstrated a subtle but almost universal *decrease* in gray matter, *enlargement* of ventricles, and focal alteration of white-matter tracts in patients with schizophrenia (Glahn *et al.*, 2008; Ellison-Wright and Bullmore, 2009). Reductions have been seen primarily in temporal lobe structures, such as the hippocampus, amygdala, and the superior temporal gyri, as well as in the prefrontal cortex. At least some structural alterations appeared to be present at illness onset and then progressed during the course of illness, supporting the view that brain structural alterations in schizophrenia stem from both early and late developmental derailments (Pantelis *et al.*, 2005; DeLisi, 2008). Medication effects might be involved in some structural brain abnormalities. For example, basal ganglia volume increases might be accounted for by treatment with typical antipsychotic agents, while basal ganglia volume decreases might be attributed to treatment with atypical antipsychotics (Scherk and Falkai, 2006).