

## Section 1

## Basic Principles of Cognitive Enhancement

## Chapter

# Cognition and Its Impairment in Schizophrenia and Related Psychotic Disorders

## 1.1 Introduction

This chapter provides an overview of the diverse aspects of human cognition, including non-social cognitive functions such as attention, executive function, and memory and social cognitive functions such as emotion recognition and perspective taking. We review the nature of these functions, how they are impaired in schizophrenia and related disorders, and how to assess them. We then outline an evolving understanding of the brain circuitries underlying these functions. A detailed review of this vast literature is beyond the scope of this chapter, but we here summarize the key points a practitioner of cognitive enhancement approaches needs to keep in mind.

Emil Kraepelin (Figure 1.1), considered the father of modern psychiatry, pointed out that cognitive impairments are among the core manifestations of dementia praecox, a term originally introduced by Morel. Dementia praecox was later termed schizophrenia by Eugen Bleuler, a Swiss psychiatrist who viewed this as a group of illnesses with diverse causes which had its central feature as a “splitting” of mental functions (schism in Latin means splitting). Kraepelin described a wide range of cognitive difficulties in dementia praecox including impairments in attention, learning, and problem solving and noted the impact of these changes for independent living, social, and occupational functioning (Kraepelin, Barclay, & Robertson, 1919). However, the centrality of cognitive impairments in schizophrenia was largely ignored till the middle of the last century, perhaps because of the dominance of psychodynamic conceptualizations of this illness. Modern neuropsychological conceptualizations of psychotic disorders began in the 1950s and 1960s (Broadbent, 1958; Hemsley, 1977; McGhie & Chapman, 1961). Cognition has been continuously and extensively studied in schizophrenia over the past several decades using a wide range of traditional Neuropsychological tasks as well as paradigms developed from cognitive neuroscience and experimental psychology.

### Case Study 1.1

Jeffrey is a 26-year-old single unemployed man living with his parents. He had been diagnosed with schizoaffective disorder six years ago when he first began, during his second year of college, to experience paranoid and grandiose delusions as well as auditory hallucinations. He had begun believing that he is destined to become the President of the United States and that he was being monitored by the FBI and the CIA so that he would be “vetted” and groomed to the highest office.

Jeffrey had an unremarkable childhood, except that his early milestones were slightly delayed. He started speaking at the age of 2. He did well academically in middle school but had been evaluated by a psychologist for a possible attention deficit disorder. His grades began to decline during high school and his grades were mostly Cs by his junior year. He began college after high school but had to take a break during his first year because of academic difficulties, as well as increasing anxiety and feelings that he had more important missions in life than just getting a college degree. He could not concentrate, and could not organize his class schedules. He started becoming socially withdrawn, spending a great deal of time on Twitter where he began to post garbled political messages. It is at this time that he was hospitalized for his first psychotic episode.

Over the past 4 years, Jeffrey has been hospitalized on three occasions and he is now an outpatient at a university psychiatry clinic. His symptoms have improved but he intermittently relapses because of his poor compliance with medications (risperidone, valproate, and bupropion) as well as his forgetfulness. He does not believe that he has any illness and he is not concerned that others do not share his beliefs about his delusions; he has been unable to date or have significant friendships because his “presidential” delusions come up prominently early in his conversation. While he has been able to get job interviews, he has not been able to hold a job for longer than a few months. Jeffrey has a slow processing speed, as evidenced by performance at the 25th percentile on the BACS Symbol Coding test of the MATRICS battery (described later in this chapter). His attention is poor, as reflected by scores at the 10th percentile on the Trail Making Test - Part A and the CPT-IP. His working memory (WMS-3 Spatial Span test) was also in the low average (25th) percentile. He performed in the average range (40th percentile) on spatial reasoning (NAB Mazes test). He scored in the 20th percentile on the Managing Emotions subtest of the MSCEIT (social cognition).



**Figure 1.1** Emil Kraepelin (1856–1926), considered by many to be the father of modern psychiatry, first described dementia praecox, later termed schizophrenia

As this chapter will reveal, cognitive impairments are a core aspect of schizophrenia. An important point to remember is that schizophrenia involves impairment not just in any one of these cognitive domains, but usually a combination of many deficits; the degree to which any one domain is impaired might differ between patients, and may also differ by illness phase (Heinrichs & Zakzanis, 1998; Mesholam-Gately et al., 2009). The above patient narrative (see box) illustrates this point, and highlights how these impairments substantively affect day-to-day functioning.

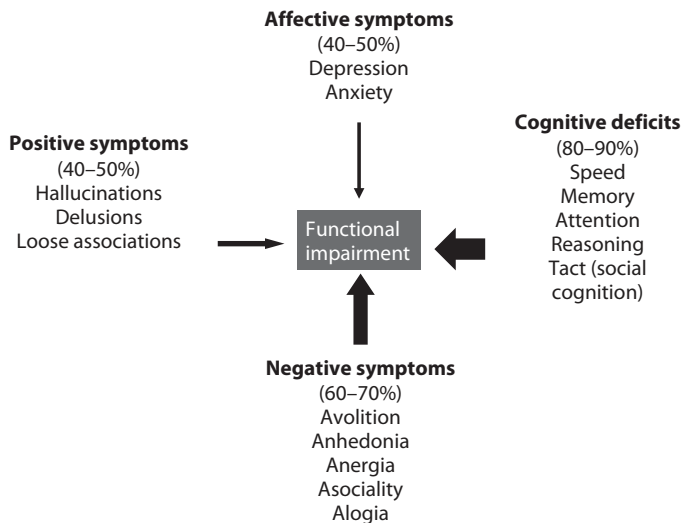
## 1.2 Nature of Cognitive Deficits in Schizophrenia

### Cognitive Impairments are Highly Prevalent in Schizophrenia

Although cognitive deficits are a core aspect of schizophrenia, many patients may appear to have normal cognitive function. In healthy individuals, cognitive function is strongly predicted by parental levels of education. Studies suggest that the majority of patients (>90%) perform at below what would be expected from the parental level of education (Keefe, Easley, & Poe, 2005), while positive and negative symptoms are present in about half to two-thirds of patients at any point in time (Figure 1.2). Thus, almost all schizophrenia patients have some degree of cognitive impairment relative to what their level of cognitive function would have been if they had never developed the illness. Over 90% of patients have impairments in at least one domain and about 75% have deficits in two domains. Cognitive impairments in schizophrenia also are more severe than in affective disorders (Hill et al., 2013).

### Cognitive Impairments May Precede the Illness, and Might Represent Premorbid Hallmarks of Schizophrenia

First degree relatives of patients with schizophrenia have cognitive impairments, albeit at a milder level, about a half a standard deviation below healthy populations (Keshavan



**Figure 1.2** Psychopathological dimensions in schizophrenia

et al., 2010; Liu et al., 2015a). Over 90% of monozygotic twins discordant for schizophrenia have cognitive impairments (Goldberg et al., 1990). Modest global cognitive deficits are often apparent in early life (premorbid) phases (Woodberry, Giuliano, & Seidman, 2008). Cognitive deficits or decline are also present in individuals at high clinical risk for schizophrenia though to a lesser extent than impairments observed in established schizophrenia (Giuliano et al., 2012) and can predict the conversion to psychosis (Seidman et al., 2010).

## Cognitive Impairments Predict Functional Outcome

Cognitive functioning reliably predicts functional outcome in schizophrenia. Functional outcome refers to independent living, as well as occupational and social functioning. Effect sizes of the relationship between cognition and outcome are medium for specific domains and larger for composite scores (Green, 2000). A meta-analysis has shown that social cognition may explain more variance in functional outcome than nonsocial cognition (Fett et al., 2011). Social cognition may be a mediator of the relationship between neurocognition and functional outcome (Couture, Penn, & Roberts, 2006). Overall, impaired cognition is a rate limiting factor for successful functional recovery.

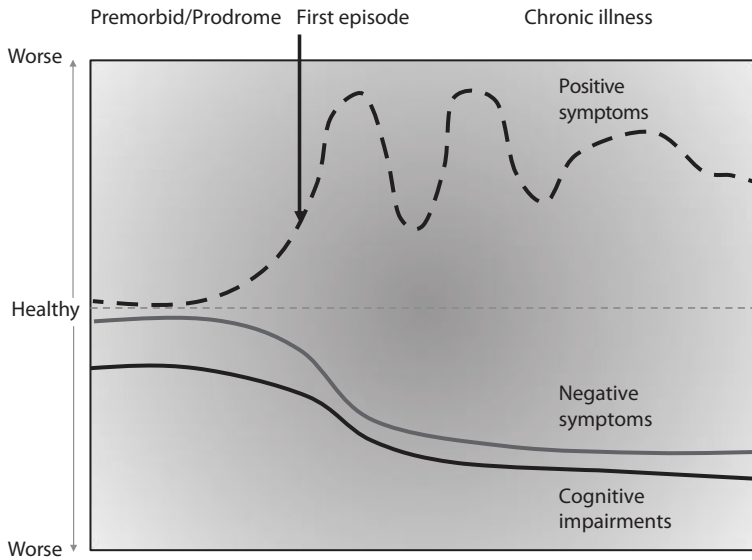
## Cognitive Impairments Persist during the Course of the Illness, and are a Trait Aspect of the Illness

Cognitive impairments are reliably and broadly seen by the first psychotic episode, tend to persist at the same or slightly increased level of deficit, and are most prominent in verbal declarative memory and processing speed (Mesholam-Gately et al., 2009). Cognitive impairments show some inconsistent relationships with negative symptoms and positive symptoms of the disorder (Bozikas et al., 2004). While psychotic symptoms fluctuate over the course of time cognitive difficulties rarely do (Figure 1.3). In general, the nature and severity of cognitive impairments are not explained by antipsychotic medications with the exception of anticholinergics (Wojtalik et al., 2012). The level of neurocognitive impairments tends to remain stable during adult life (Rund, 1998).

## Cognitive Impairments in Schizophrenia are Pervasive and Span Several Domains

Several meta-analyses have suggested that a wide range of cognitive functions are impaired in schizophrenia, at a moderate to severe degree, with effect sizes varying from the medium-to-large range (Heinrichs & Zakzanis, 1998; Mesholam-Gately et al., 2009). Notably, impaired cognitive domains include psychomotor Speed, working Memory, verbal memory and learning, Attention, Reasoning and executive functions, and Tactfulness or Social cognition; the acronym SMARTS can be used to summarize the key domains for teaching purposes.

We outline below the most important cognitive domains that are impaired in schizophrenia. Some cognitive functions, such as procedural memory, implicit learning and visual perceptual skills may be less involved (Gold et al., 2009). It is possible that the islands of preserved cognitive capability in schizophrenia may be capitalized for



**Figure 1.3** Course of cognitive impairment (black, lower line), negative (grey, lower line) and positive symptoms (black, top line) in schizophrenia.

cognitive remediation using the principles of compensatory neuroplasticity, as discussed in Chapter 2 of this volume.

## 1.3 Non-Social Cognition Deficits in Schizophrenia

### Speed of Processing

Patients with schizophrenia have significant impairments in speed of information processing (Morrens, Hulstijn, & Sabbe, 2006). A common test that taps into this domain is the Digit Symbol Coding task, which is part of the various editions of the Wechsler intelligence scales. The task requires the participant to substitute a series of numbers to symbol as rapidly as possible (e.g. within 90 seconds). Deficits in processing speed are significantly correlated with activities of daily life, occupational functioning as well as social functioning. Psychomotor speed may also be impaired by sedative antipsychotic medications, benzodiazepines and mood stabilizers.

### Memory

Broadly, memory is considered to include multiple processes. First is the working memory, which refers to the ability to hold a limited amount of information “on-line” for a short period of time, like a mental “scratch-pad.” A typical test for this cognitive domain is the Digit Span forward task (repeating a string of digits) and backward task (which requires the information to be held online as well as reordered) in the Wechsler intelligence scales. Schizophrenia patients show impairments in these tasks (Goldman-Rakic, 1994). Another common type of test is the *n*-back task, in which a sequence of stimuli are

presented and the subject has to indicate when the new stimulus (e.g. a number or letter) matches the one from  $n$  stimuli earlier in the sequence;  $n$  can be adjusted to vary the difficulty level of the task.

Explicit (or declarative) memory involves a conscious sense of remembering and recall of autobiographical or factual information. Declarative memory is of two types: semantic memory (remembering facts, such as what are the components of a thanksgiving meal) and episodic memory (remembering events, such as what one had for dinner the previous night). By contrast, implicit (or procedural) memory does not involve a conscious sense of recall; an example of the latter is not consciously recalling the steps of how to ride a bicycle but being able to do so when needed. There is no clear evidence that implicit memory is impaired in schizophrenia.

Verbal learning and retrieval, as well as recognition of previously learnt material, are all substantively impaired in schizophrenia (Heinrichs & Zakzanis, 1998). Commonly used tests involve verbal list learning, in which the person is presented with 12–16 words, and then asked to immediately recall as many as possible. After repeated learning of up to five times on 16-word lists, controls can recall at least 13 of the words, schizophrenia patients typically can only recall up to 9. There is strong evidence for an association between verbal memory and poor social and vocational outcome in schizophrenia.

## Attention

Attention is robustly impaired in schizophrenia. Two aspects of attention are: *sustained attention*, or vigilance which is the ability to maintain a continuous focus on stimuli (such as watching the train arrival times on the monitor to watch for the boarding signal for your destination), and *selective attention* which is the ability to focus on relevant stimuli and ignore competing stimuli. This is what you need in a noisy cocktail party where you have to pay attention to what your friend is saying, while ignoring all the other chatter around you. Continuous Performance Tasks (CPT) are typical tests of *sustained attention* in which a series of stimuli are presented, and the individual has to respond each time to a target stimulus appears (e.g. whenever an X appears after an A). There is evidence of impairments in sustained attention in schizophrenia and bipolar disorder (Heinrichs & Zakzanis, 1998).

*Selective attention* involves casting a spotlight on relevant external stimuli, or on internal mental representations, and ignoring competing stimuli. This may involve filtering (including desired input but excluding inputs that are not relevant), and categorizing information based on stimulus attributes such as shape or color. A classic test of selective attention is the Stroop task. In this task, the subject is asked to name the colors of the words and not read the words, as fast as he can. Thus, if the word “BLUE” is printed in red, the subject should say “RED.” Naming the color of the word takes longer and causes more errors when the color of the ink does not match the name of the color. This Stroop effect is abnormal in schizophrenia (Carter, Robertson, & Nordahl, 1992).

Another aspect of attention, impaired in schizophrenia and other related neuropsychiatric disorders, is *attention capacity*, i.e. the ability to process more than one concurrent task (like having a conversation while driving, and sipping coffee at the same time). Many patients find it difficult to multi-task because of a reduction in attention capacity (Thoma & Daum, 2008).

## Reasoning and Problem-Solving

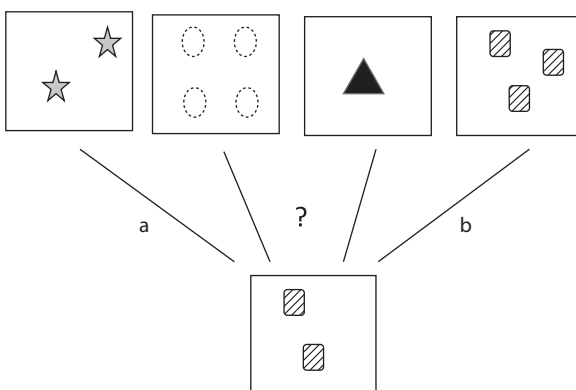
Executive functioning refers to activities such as problem-solving, planning, and shifting between two or more tasks. These abilities are critically important in day-to-day life. A common test that is used is the Wisconsin Card Sorting Test (WCST; see Figure 1.4). In this task (Heaton, 1980), the participant is asked to sort a deck of cards into groups (based on the principle of either color, number, or shape) and has to figure out the rules based on the feedback of the answers being correct or incorrect. The principle will change during the test, and the participant has to figure out the new rules and change his responses accordingly. Performance on this task – which requires conceptual flexibility and an ability to shift mental set – is consistently impaired in schizophrenia (Berman, 1987).

Another aspect of executive function – related to selective attention discussed above – is monitoring of conflict and choosing appropriate responses; a commonly used test for this is the Flanker task. In this task, a series of arrows are presented pointing to the right or left. Participants respond in the direction of the arrow pressing the right button if the arrow points to right in congruent trials while they have to press the left button when presented with a right pointing arrow in incongruent trials.

In general, aspects of “fluid” intelligence (i.e. abilities to process new information, such as working memory and executive function) are more likely to be impaired than “crystalline” intelligence (ability to use already acquired information such as vocabulary) in neuropsychiatric disorders. Both aspects of intelligence are altered in schizophrenia. However, impaired crystallized intelligence can give us a measure of premorbid abilities, while decline in fluid intelligence is likely to reflect disease-related intellectual decline.

### 1.4 Social Cognition Deficits in Schizophrenia

Social cognition is a composite term used to refer to psychological processes involved in perception, inferring about and responding in social situations (Green et al., 2008). Social cognition involves several components: emotion perception, the ability to take other people’s perspectives, and the ability to appraise the social context. Individuals with schizophrenia consistently perform poorly when asked to identify emotional expressions on peoples’ faces (Mueser et al., 1997). Schizophrenia patients also show deficits in



**Figure 1.4** Wisconsin card sorting test

perception of emotions in speech and videotaped monologues. Deficits tend to be more prominent in the perception of negative or neutral stimuli than in the perception of positive emotions (one of the authors [MSK] has observed in his practice that on days when he walks into his office with a flat facial expression, patients often ask whether he is angry with them for something!). Indeed, one of our studies has shown that emotion perception to neutral faces is impaired in adolescents at high familial risk for schizophrenia (Eack et al., 2010).

Schizophrenia patients also have difficulty in taking viewpoints of other people (*mentalizing or perspective taking*) and making inferences about their mental states based on available social context information. This process, also called “Theory of Mind” (ToM), underlies the ability to understand hints, intentions, humor, irony, and metaphor. There is some evidence that schizophrenia patients have deficits in humor perception, and this may be related to ToM impairments (Marjoram et al., 2005).

*Context appraisal* refers to a person’s ability to judge social cues from information in the social context, and awareness of the roles, rules, and norms that characterize different, sometimes ambiguous social situations. This includes the ability to perceive social cues (social perception), processing such information and choosing an appropriate response in a given social situation.

*Attributional style* refers to the way in which one makes sense of social events in life. For example, if a friend does not smile at you during a social encounter, you might assume either that you are deliberately being ignored, or that the friend may not have noticed you. The chosen explanation will clearly decide which way you react emotionally and behaviorally to this situation.

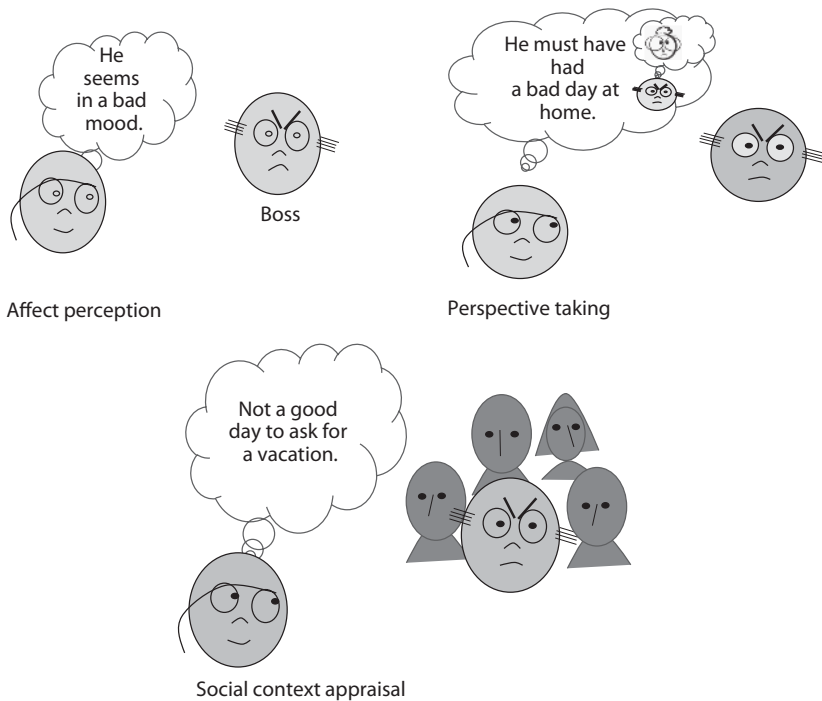
Figure 1.5 illustrates the different components of social cognition. Our patient, Jeffrey, has not been able to hold a job consistently because of his difficulty with several aspects of social cognition. As an example, if one has to navigate a work-related interaction successfully (such as asking for a day off), he has to first assess his boss’s mood (emotion recognition), figure out what his boss might be thinking (perspective taking or theory of mind), assess when might be the best time and place to make the request (social context appraisal), and make the appropriate interpretation of boss’s response (e.g. a denied request does not automatically mean the boss does not like him). In Chapter 6, we will discuss how cognition enhancement approaches target these aspects of social cognition.

## 1.5 Metacognition Deficits in Schizophrenia

Metacognition has been defined as “thinking about thinking.” This term has been used in several contexts and refers to three broad sets of function: (a) monitoring or evaluation of one’s own cognitive functions; (b) regulation of one’s own cognition, which includes executive functions and cognitive control; and (c) metacognitive knowledge, i.e. knowledge of the task difficulties, resources needed to tackle them, and alternative approaches to improve cognitive performance (Flavell, 1979). There is evidence for impairments in all of the above aspects of metacognition in schizophrenia; such impairments appear to predict functional outcome (Koren et al., 2006; Lysaker et al., 2014).

A consequence of impaired metacognition is the inability to think about one’s own delusional beliefs and the ability to change them in the context of new evidence. It has been suggested that delusions develop as a consequence of cognitive bias and in particular a tendency to “jump to conclusions” (Garety et al., 2013). This reasoning bias has been widely replicated in schizophrenia not only in people with delusions but also in people





**Figure 1.5** Components of social cognition

who have recovered from delusions and individuals at high-risk for psychoses. While the precise mechanisms underlying the *jumping to conclusions* bias remain to be understood, studies suggest that other aspects of cognitive impairment and in particular executive dysfunction may be related to such reasoning biases.

## Insight and Illness Appraisal

One of the most common problems in schizophrenia is lack of insight. Insight is a multidimensional concept and includes accurate self-awareness, correct attribution, and recognition of one's own illness and need for treatment. Patients with schizophrenia may have impairment in one or more of these dimensions. It has been found that impaired cognition is strongly related to poor insight in schizophrenia (Keshavan et al., 2004). It has even been suggested that lack of insight in schizophrenia might reflect an anosognosia, a known neurological condition with impaired awareness of one's own neurological disability (Lehrer & Lorenz, 2014).

## Foresight

A cognitive function related to insight is foresight, the ability to think of the long-term consequences of one's behavior and use this information to guide present and future actions. Foresight is critically related to functional disability in schizophrenia, as a diminished capacity for recognizing the long-term consequences of one's behavior (which has been called future "myopia"), and would likely have a negative impact on interpersonal

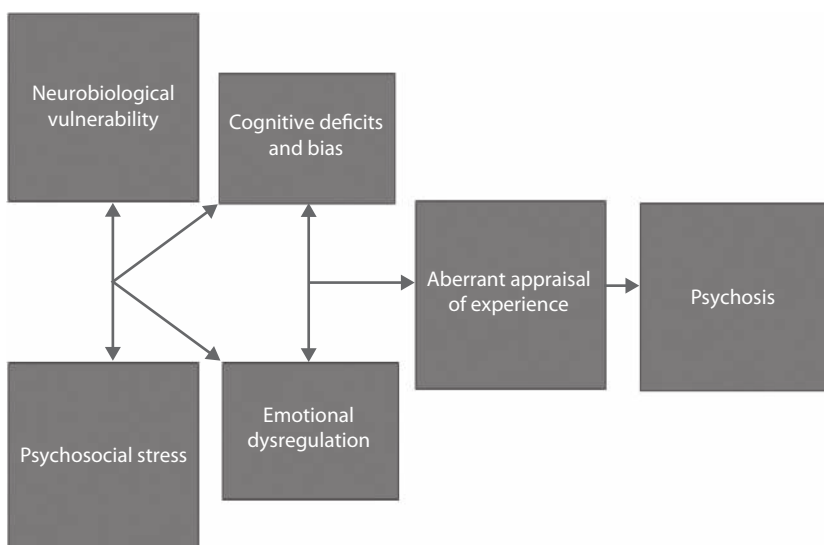
relationships in many different domains (e.g. home and work). Indeed, foresight significantly predicted functional outcome in one of our longitudinal studies (Eack & Keshavan, 2008).

In summary, cognitive deficits in schizophrenia involve multiple domains, and are central to the overall psychopathological manifestations of schizophrenia and related disorders. While the core aspects of these illnesses may at least in part be independent, it is likely that they overlap; impaired cognition, deficits in social cognition and metacognition, and affect regulation processes may interact to cause alterations in experiences and beliefs that underlie the pathogenesis of psychosis (Figure 1.6).

## 1.6 How Do We Assess Cognitive Function?

### Assessing Non-Social Cognition

A battery of cognitive tests called the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery has been developed by the National Institute of Mental Health in recent years for assessment of cognition (Green et al., 2004). The MATRICS Consensus Cognitive Battery (MCCB) is the field-standard for cognitive assessments for clinical trial studies and assesses seven domains of cognitive functions using ten tests (Table 1.1). This battery is easy to administer, has high fidelity, and takes a little over 1 hour to complete on average. In community settings with limited resources however, it may be more practical to use smaller batteries with similar reliability and validity, such as the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe, 2004). The BACS takes about 35 minutes. Both the MCCB and BACS have alternate forms available so that they can be used to minimize practice effects. Other available paper and pencil and computerized test batteries include the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph et al., 1998), Cambridge Neuropsychological Test Automated Battery (CANTAB; Sahakian et al., 1988), and the



**Figure 1.6** The intricate relationships between cognitive deficits, emotional dysregulation, and psychosis