Hot Debates in CNS Disorders

Is Cognitive Impairment in Mental Disorders an Endophenotype or an Epiphhenomenon?

16th LINF Faculty Meeting – Tallinn, Estonia, 23rd-26th May 2014
Art Contribution

Professor and artist Göran Hermerén has provided some of the illustrations for this issue of The Institute Magazine.

Since 1991, Göran Hermerén has worked as a Professor of Medical Ethics at the Faculty of Medicine, Lund University, Sweden. He is former President of the European Group on Ethics in Science and New Technologies (EGE).

At present, Göran Hermerén is chairman of the Permanent Working Group for Science and Ethics of ALLEA (All European Academies) and is involved in several EU-funded research projects.

Göran Hermerén has exhibited his abstract paintings and graphical works in Sweden and abroad (www.hermeren.nu).

Editorial

A Silent Revolution

For more than a century, it was the norm for undergraduate and postgraduate teaching of psychiatry to start with a simple classification of mental disorders into five groups: organic mental disorders, (functional) psychotic disorders, neurotic disorders, personality disorders, and mental retardation. The key difference between functional psychotic disorders and disorders due to demonstrable brain damage was that the latter were characterised by symptoms indicating cognitive damage. Psychotic and neurotic disorders were called ‘functional’ disorders because it was thought that their origin was a disruption of function, as opposed to brain damage. National and international classification systems used the presence or absence of cognitive damage as one of the main criteria for the distinction of organic mental disorders from other mental disorders. The use of this criterion to distinguish organic mental disorders from, say psychotic disorders, was somewhat illogical, and yet no one seemed to worry that a person with cognitive functions, that were presumed to be perfectly in order, could have delusions. Rational thinking is the expression of good cognitive functioning, and it would seem that the difficulty of thinking rationally must be a sign that cognitive functioning is damaged.

Towards the end of the 20th century, this zeitgeist suddenly changed without any major discussion or opposition. Psychiatrists started speaking about the cognitive symptoms of schizophrenia and bipolar disorder; it was as if the previous generally-accepted distinction of organic and functional disorders by cognitive damage had never existed. Nonetheless, the World Health Organization maintained the distinction, and the tenth revision of the International Classification of Diseases (ICD-10) still lists groups of mental disorders in the order that was proposed when it was believed that organic mental disorders had cognitive symptoms and a poor prognosis. The most durable disorders are listed first (dementia, and consequences of brain trauma), followed by psychotic disorders (which were originally considered to be more treatable since there was no demonstrable brain damage), and then neurotic disorders. The description of schizophrenia states that: “Clear consciousness and intellectual capacity are usually maintained although certain cognitive deficits may evolve in the course of time”. Thus, this description acknowledges that some cognitive symptoms may be present, but it does not see them as the key feature of schizophrenia. Cognitive symptoms are not mentioned in the general description of affective disorders, although concentration and attention difficulties are listed in the descriptions of specific disorders without being given particular prominence.

In 1999, Andreasen wrote that a variety of causes may lead to “impairment in a funda-
mental cognitive process”, which then leads to “impairment in one or more second-order cognitive processes”, which in turn produces the symptoms of schizophrenia. This model has not been generally accepted, and the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-5™) does not include cognitive impairment as a key symptom of schizophrenia. The presence of cognitive symptoms in depressive illnesses has been generally acknowledged and is usually ascribed to a lack of attention and concentration as a consequence of a preoccupation with affective symptoms.

The article by Höschl, Kane, Gaebel, Gorwood and Kennedy in this issue of the Institute Magazine takes the debate one step further. Taking for granted that cognitive symptoms are central to depression and schizophrenia, the author’s marshal arguments for and against the causal role that cognitive impairment might play in those disorders. This is an interesting issue: If, on the one hand, cognitive impairment is the cause of schizophrenia and depressive disorders, then much of our current effort to find effective treatments (and to make prevention possible) will have to change direction. If, on the other hand, cognitive impairment is just one more symptom of schizophrenia and depression, then research on cognitive impairment will have to focus on ways of dealing with it in much the same manner that we deal with other symptoms of these disorders. Thus, in either case the role of cognitive impairment in schizophrenia and affective disorders is of relevance either to direct research in new directions or to change the focus of treatment strategies from other symptoms to cognitive impairment.

This reorientation of our thinking and research from traditional targets, such as positive and negative symptoms to cognitive impairment, is a ‘silent revolution’ in our conceptualisation of schizophrenia and depressive disorders. This revolution may ultimately lead to a new understanding and successful management of these two disorders, which are among the ten most important causes of disability in our century. The Lundbeck Institute deserves credit for drawing attention to the role of cognitive impairment, both by placing it on the agenda of its faculty discussion and by paying particular attention to it in the array of courses and seminars that it organises to improve care for people with schizophrenia and affective disorders.

1 Mental retardation was also characterised by cognitive symptoms with a causal link to brain damage that occurred early in life (with consequences continuing into adulthood). The timing of the brain damage distinguished mental retardation from organic mental disorders.
“WHEN LOOKING AT THE BRAIN, IT IS IMPORTANT TO GO BEYOND ITS STRUCTURE TO ITS FUNCTION. OFTEN IN COGNITIVE DISORDERS, THE STRUCTURE OF THE BRAIN IS INTACT, BUT ITS FUNCTION IS COMPROMISED”.

ADITI SHANKARDASS
Hot Debates in CNS Disorders

Is Cognitive Impairment in Mental Disorders an Endophenotype or an Epiphenomenon?

Cognitive impairment is a clinically significant part of the symptomatology of mental disorders such as schizophrenia and major depressive disorder, but whether or not it has a causal role in the development of the disorders is debatable.

Prof. Cyril Höschl, Prague Psychiatric Center/National Institute of Mental Health, Prague, Czech Republic
Prof. John Kane, The Zucker Hillside Hospital, New York, United States
Prof. Wolfgang Gaebel, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany
Prof. Philip Gorwood, Hospital Sainte-Anne, Paris, France
Prof. Sidney Kennedy, University Health Network, Toronto, Canada

Introduction: Endophenotypes and Epiphenomena

An endophenotype, also known as an intermediate phenotype, is a measurable component which occurs along the pathway from genotype to disease (Walters & Owen, 2007). In 2003, Gottesman et Gould identified five criteria for an endophenotype in psychiatry:

1. An endophenotype is associated with illness in the population.
2. An endophenotype is heritable.
3. An endophenotype is primarily state-independent (i.e., it manifests in an individual whether or not the illness is active).
4. Within families, an endophenotype and the illness co-segregate (i.e., they are inherited together).
5. An endophenotype found in affected family members is found in non-affected family members at a higher rate than in the general population.

In contrast, an epiphenomenon, is a symptom or a function that occurs concurrently with the disease, but is not causally contributory to it. In other words, there might be shared origins, but the epiphenomenon and the phenotype do not lie on the same pathway. Thus, an epiphenomenon can be considered to be a secondary and to some extent an independent event of the disorder.

In this article, we discuss the endophenotype and epiphenomenon concepts in relation to schizophrenia and major depressive disorder (MDD) to answer the question: Is cognitive impairment in these mental disorders an endophenotype or an epiphenomenon?
Model: Four levels of pathogenesis of schizophrenia

A general model of the pathogenesis of schizophrenia was developed by Andreasen in 1999 (Figure 1) which comprises four levels. Rather than attempting to link a single aetiology to a single outcome, the model assumed that multiple aetiologies entered (risk factors such as inherited DNA, regulation of gene expression, or the influence of environmental factors), and multiple symptoms were outputted (such as hallucinations, delusions, thought disorders, disorganised speech, and disorganised behaviour). At an intermediate level, however, there was a single process which unified the concept of schizophrenia: anatomical and functional disruption in neuronal connectivity and communication. Thus, this model suggested that impairment of cognitive processes was decisive for the development of schizophrenia as well as for the heterogeneity of the clinical picture. Andreasen used the term ‘lathomenology’ to label this bottleneck in the pathogenesis of schizophrenia.

However, this opinion is not universally accepted. For example, cognitive impairment has not progressed into the schizophrenia classification systems. Even in the new Diagnostic and Statistical Manual of Mental Disorders (DSM-5™), cognitive impairment is not considered to be a mandatory criterion of schizophrenia (APA, 2013).
Figure 1. A general model of the pathogenesis of schizophrenia (Andreasen, 1999)

**Etiology**
- DNA
- Gene Expression
- Viruses
- Toxins
- Nutrition
- Birth Injury
- Psychological Experiences

**Pathophysiology**
- Neuron Formation
- Migration
- Synaptogenesis
- Pruning
- Apoptosis
- Activity-Dependent Changes

**Pathology**
- Anatomical and Functional Disruption in Neuronal Connectivity and Communication

**Phenomenology**
- Impairment in 1 or More Second-Order Cognitive Processes
  - Attention
  - Memory
  - Language
  - Executive Functions
  - Emotion

**Symptoms of Schizophrenia**
- Hallucinations
- Delusions
- Negative Symptoms
- Disorganized Speech
- Disorganized Behavior

**Impairment in a Fundamental Cognitive Process**
The Argument for Cognitive Impairment as an Endophenotype of Schizophrenia

In schizophrenia, the following evidence shows that cognitive impairment meets all five of Gottesman & Gould’s criteria for an endophenotype.

Criteria 1 & 3. Associated with illness in the population and primarily state-independent

There is a great deal of evidence to support that cognitive impairment is a core feature of schizophrenia. It is present in multiple cognitive domains as measured by standard clinical tests with effect sizes versus healthy controls ranging from 0.46 to 1.41 (Heinrichs & Zakzanis, 1998). Even after initial stabilisation of the first episode, patients show cognitive deficits relative to healthy controls (Bilder et al., 2000). Furthermore, there is considerable evidence that cognitive decline occurs prior to the onset of psychotic symptoms. In a study which retrospectively looked at the standardised scholastic test scores in 70 students who later developed schizophrenia (Fuller et al., 2002), scholastic performance declined considerably between the ages of 13 and 16 years to below state norms. Similarly, premorbid IQ deficits among individuals, who went on to develop schizophrenia, have been demonstrated in a meta-analysis (Woodberry et al., 2008) and a prospective study (Meier et al., 2014). In a follow-back study of subjects ascertained at the time of their initial episode of schizophrenia or schizoaffective disorders vs. a group of matched healthy volunteers, the standardised achievement test scores, obtained from academic records, showed a decline in estimated WAIS-R full scale IQ in the patient group. Such data suggested a substantial deficit in cognitive ability in the early infancy of people, who would later develop schizophrenia, compared to healthy controls (Bilder et al., 2006). In addition, significant differences were noted as early as the first grade with the gap between groups widening slightly over time (Figure 2). After the onset of psychosis, patients with schizophrenia suffer a further decline in cognition (Meier et al., 2014).

In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (Keefe et al., 2006), which included almost 1,500 patients with chronic schizophrenia, cognitive impairment had no correlation with positive symptoms and only a modest correlation with negative symptoms.

Criteria 2. Heritable

Recently, the Cognitive Genomics Consortium (COGENT) conducted a study with the aim of providing the first molecular genetic evidence for overlap between general cognitive ability and risk for schizophrenia (Lenz et al., 2014). Polygenic single-nucleotide polymorphism scores derived from a meta-analysis of large-scale cognitive genome-wide association studies (roughly 5,000 individuals) were applied to four schizophrenia case-control cohorts. Patients with schizophrenia had significantly lower cognitive polygenic scores compared to controls, thus confirming that there is a genetic overlap between schizophrenia and cognitive dysfunction.

Criteria 4 & 5. Overrepresentation in families

At the clinical level, a meta-analysis has clarified the mean effect size on 43 different cognitive test scores from 58 studies of cognitive performance in the unaffected adult relatives of patients with schizophrenia (Snitz et al., 2006). This study demonstrated reliable deficits in cognitive performance for unaffected relatives compared to healthy controls. Effect sizes were in the small-to-medium range over a diverse array of tasks with a largest effect sizes observed in continuous performance task, auditory verbal
learning, design copy tests, and category fluency. Thus, there are cognitive deficits not only in patients with schizophrenia, but also in their unaffected first-degree relatives.

However, despite this evidence, it has not been conclusively proven that cognitive impairment in schizophrenia meets the five criteria for an endophenotype. Although most features for endophenotypicity of cognitive impairment are confirmed, co-segregation with the illness has not been properly assessed across different domains. In addition, while most patients with schizophrenia do show some kind of cognitive impairment, it is a highly heterogeneous construct consisting of several (partly overlapping) cognitive domains (O’Carroll, 2000) and with high inter-individual variation. Our ability to sensitively and specifically measure cognitive impairment is also in question, since psychometric tests are poorly standardised and are not always domain-specific. Furthermore, there is the issue that some degree of cognitive impairment can also be observed in healthy persons. For example, a review found that more than 10 % of healthy controls had abnormal psychological measures compared to about 30 % of patients with schizophrenia and their unaffected relatives (Allen et al., 2009). Moreover, there are contradictory results regarding creative intelligence in relatives of mentally ill patients. Findings from Iceland, for example, show that first-degree relatives of psychotic patients are more successful than the general population in attaining recognition in several fields of intellectual endeavour – notably, in areas of creative and scholarly excellence (Karlsson, 1984).

The Argument for Cognitive Impairment as an Epiphenomenon of Schizophrenia

Walters & Owen (2007), who developed the model for endophenotype and epiphenomena, applied Gottesman & Gould’s five criteria for an endophenotype to a model of an epiphenomenon and found that it met each of the criteria. According to Walters & Owen, the distinguishing factor between the models is that endophenotype has a causal role in the disease, whereas the epiphenomena does not. Currently, there is no proof of a causal association between cognitive impairment and disease development in schizophrenia, and thus we cannot be certain that cognitive impairment is an endophenotype. On a related note, attempts to demonstrate that cognitive enhancers have significant antipsychotic effects have generally failed (for a review, see Harvey, 2009), although, as an add-on medication, a meta-analysis (Choi et al., 2013) found that cholinergic agents (the acetylcholinesterase inhibitors [AChEIs] donepezil, galantamine, and rivastigmine) and glutamate agonists (i.e., d-cycloserine, d-serine, and CX516) produced small improvements in measures of overall psychiatric symptoms (effect size 0.46, 95 % CI 0.04 0.88 for AChEIs, and 0.41 95 % CI 0.01 0.81 for glutamate agonists), and moderate improvements in measures of negative symptoms (effect size 0.54, 95 % CI 0.10 0.98 for AChEIs, and 0.62, 95 % CI 0.34 0.99 for glutamine agonists) with no effect on positive symptoms.

It is extremely difficult to prove whether or not a causal association exists between potential endophenotypes and schizophrenia. Candidates for endophenotypes, such as cognitive-, electrophysiological-, or neuroimaging-based measures, have a complex genetic architectures, limiting their utility for gene discovery and characterisation (Glahn et al., 2014). A study, which found associations between 46 genes and 12 neurocognitive and neurophysiological endophenotypes (Greenwood et al., 2011), also showed that half of these genes were associated with more than one endophenotype (termed ‘pleiotropy’). Thus, the heritability of cognitive dysfunction in schizophrenia is extremely complex.

Conclusion

Cognitive impairment in schizophrenia is present before the onset of clinical symptoms occurs in the majority of patients. Moreover, it is also seen in unaffected first-degree relatives. Cognitive impairment is relatively stable across clinical state changes and it is not secondary to other schizophrenia symptoms. Thus, cognitive impairment appears to meet the criteria for an endophenotype. However, cognitive impairment in schizophrenia is a heterogeneous construct encompassing several domains. Not all cognitive domains and their tests have undergone complete and rigorous testing for their endophenotype features, and studies identifying the pathophysiological pathways in schizophrenia are needed to distinguish between ‘endophenotype’ and ‘epiphenomenon’ for each domain of cognitive impairment.

The Institute Magazine | Schizophrenia
Major Depressive Disorder

The Argument for Cognitive Impairment as an Endophenotype of MDD

In MDD, the following evidence shows that cognitive impairment meets all five of Gottesman & Gould’s criteria for an endophenotype.

Criterion 1. Associated with illness in the population
Cognitive impairment, particularly executive function, is widely acknowledged as an important aspect of MDD. A meta-analysis of 113 studies (Snyder, 2013) demonstrated that MDD is reliably associated with impaired performance on neuropsychological measures of executive function with effect sizes ranging from 0.32–0.97. While processing speed is also reduced in patients with MDD, motor slowing alone was insufficient to account for these results. A second meta-analysis (Rock et al., 2014), which included publications that used the CANTAB battery in depression, found that patients with MDD had significant deficits in executive function, memory, and attention compared to healthy controls. Furthermore, a review of cognitive deficits in depression and their brain correlates (Austin et al., 2001) concluded that “the commonly held view that neuropsychological deficits in depression are simply epiphenomena of age, poor motivation, inattention, or response bias now appears somewhat dated”.

Criterion 2. Heritable
Support for the heritability of cognitive impairment in MDD comes from twin and genetic studies. Using Danish national registers, a twin study identified 94 healthy twins with a high risk for unipolar depression and 88 healthy twins with a low risk (Christensen et al., 2006). Healthy twins with a high risk for unipolar depression had a statistically significantly poorer performance on almost all measures of cognitive function, including selective and sustained attention, executive function, language processing, and working and declarative memory. This cognitive impairment appeared to be genetically transmitted as high-risk monozygotic twins had a higher level of neurocognitive impairment than high-risk dizygotic twins. In addition, a study in 71 patients with MDD has found heritable genetic markers, which may be associated with worse performance on cognitive tests (Sarosi et al., 2008).

Criterion 3. Primarily state-independent
Several studies have demonstrated that cognitive deficits are chronically associated with MDD. One study assessed cognitive function in 28 young, unmedicated, fully remitted patients with MDD compared to 23 healthy controls (Weiland-Fiedler et al., 2004). Patients with remitted MDD had significant deficits in sustained attention even after correcting for residual depressive symptoms. Similarly, another study showed that cognitive deficits persist in the remitted state of unipolar depressive disorder (Hasselbalch et al., 2012) in terms of impairment of attention, processing speed, and cognitive flexibility. The CANTAB meta-analysis (Rock et al., 2014), as described above, found that remitted patients with MDD had significant deficits in executive function and attention compared to healthy controls. Finally, a longitudinal study, in which the symptomatology of young psychiatric outpatients was followed over an average period of 21.6 months (Lee et al., 2013), showed that memory and executive functioning were independent of clinical state in early-outcome psychiatric illness.

Criterion 4 & 5. Overrepresentation in families
Cognitive deficits are also found in the non-affected family members of a person with MDD. In one study (Mannie et al., 2009), young women with a positive family history of depression, but no personal history of depression, showed decreased immediate recall and recognition memory compared to age- and sex-matched controls. The impairment in recall memory was found to be partly related to increased cortisol secretion. A second study (Clark et al., 2005) in first-degree relatives of patients with bipolar I disorder and in euthymic patients with unipolar depression demonstrated impairment of executive function (although not of memory) in relatives compared to healthy controls. Furthermore, a morphological study showed a larger right inferior frontal gyrus volume in patients with bipolar disorder and their unaffected relatives compared to healthy controls; possibly these patients ‘overexercise’ this part of the brain to compensate for cognitive or executive deficits (Hajek et al., 2013). Of note, patients treated with lithium had normal right inferior frontal gyrus volumes suggesting a neuroprotective effect of lithium.

The Argument Favouring the Epiphhenomenon Hypothesis in MDD
Cognitive impairment is undoubtedly a part of the symptomatology of MDD, but this does not mean that it is an endophenotype.

Sleep problems, for example, are a well-known risk factor for reduced cognitive skills in children and adults (Astill et al., 2012; Lim & Dinges, 2010), and MDD tends to correlate with sleep difficulties (Buysse et al., 2008). It is therefore possible that abnormal cognitive function is independently associated with major depression via comorbid sleep problems. An indirect, independent association such as this would be termed an epiphenomenon (Figure 3).

While sleep problems constitute an obvious intermediate link between depression and cognition, they are usually thought to explain only a small part of the cognitive abnormalities observed in depressed patients. Nonetheless, this heuristic finding reminds us that there are potentially many unrated or unknown third factors between depression and cognition.

One important argument in favour of the endophenotype hypothesis linking cognitive abnormalities and MDD is based on our understanding of brain functions showing that areas regulating ‘mood’ are highly connected with areas more specifically involved in cognitive function, and that depression has such a function, in particular, is highly connected with areas regulating ‘mood’. Furthermore, it is possible that abnormalities in these areas are not caused by depression itself, but rather by another factor that is causally related to depression (such as a genetic factor). Therefore, the cognitive abnormalities seen in depression may actually be epiphenomena of something else, such as a genetic factor, rather than being a direct consequence of depression itself. This would provide a better explanation for why some people with depression have cognitive abnormalities while others do not, and why cognitive abnormalities are often seen in people who do not have depression.

In conclusion, cognitive impairment is an important aspect of MDD that is likely to be genetically transmitted, primarily state-independent, and overrepresented in families. While cognitive impairment is undoubtedly related to depression, it is possible that it is an epiphenomenon of something else, such as a genetic factor, rather than being a direct consequence of depression itself. This would help to explain why some people with depression have cognitive abnormalities while others do not, and why cognitive abnormalities are often seen in people who do not have depression.
Figure 3. Modelling cognitive impairment as an epiphenomenon

Causation: if << 1 >> does not exist, then << 2 >> does not occur, << a >> is only in parallel

But temporality might be misleading: as << 1 >> does not occur, << 2 >> and << a >> will not... although with no causality

1=Risk factors of MDD
2=Emotion
a=Cognition

Figure 4. Therapeutic strategies to address cognitive impairment (Modified from Millan et al., 2012)

<table>
<thead>
<tr>
<th>Influence on Emotional Symptoms</th>
<th>Influence on Cognitive Impairment</th>
<th>Psychiatric Disorders Treated</th>
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<tr>
<td>Cognitive Behavioural Therapy</td>
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<td>Primarily Depression, also Anxiety Disorders</td>
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functions. However, these models are misleading, because many non-specific regions of the brain are involved in emotional processes, including the amygdala, nucleus accumbens, hypothalamus, orbitofrontal cortex, anterior cingulate cortex, and ventromedial prefrontal cortex (Pessoa, 2008). There is in fact a considerable overlap between these 'emotion' parts of the brain and the 'cognitive' parts of the brain. For example, the amygdala, which is extremely important for fear processing, also has an important role in attention and is extensively connected to other cognitive regions of the brain (for a perspective, see Pessoa, 2008; Young et al., 1994). The lateral prefrontal cortex provides another interesting example as it is playing an important role in working memory and in reward expectancy (Watanabe, 1996) and is thus demonstrating an ability to process different kinds of information in parallel, which could be seen as cognitive-based (assessing potential reward of cues) and emotion-based (reward is a core component of pleasure).

As a result of this large overlap between areas in charge of emotion and cognition and the absence of real anatomical or network specificities, some authors boldly propose that "true integration of emotion and cognition takes place, strongly blurring the distinction between the two" (Pessoa, 2008). According to this point of view, emotion would be a spreading, contaminating, self-perceived type of cognition. This reinforces the hypothesis that cognition cannot be artificially differentiated from the emotional disorder of depression and that it constitutes an epiphénoménon.

Different treatment strategies can have varying effects on cognition and emotion (Figure 4) (Millan et al., 2012). For example, some psychotropic drugs may improve cognition via emotional improvement, whereas rapid transcranial magnetic stimulation may improve mood via cognitive improvement. In cognitively intact patients, however, the AChEI, donepezil appears to have no clear benefit for preventing recurrence of depression (Reynolds et al., 2011). Demonstrating that mood disorders are being resolved through cognitive improvement is extremely difficult, and the risk of spurious association is difficult to avoid.

Conclusion

Cognitive impairment represents a core feature of depression. Due to its complex interplay with mood symptoms, and the difficulty in ruling out the possibility that cognitive abnormalities are explained by unknown third, cognitive impairment in MDD may have several explanations. These two concepts might either be a. associated, b. being a risk factor or c. a stigmata of each other.

However, there are strong arguments in favour of neurocognitive abnormalities being an endophenotype of MDD with fewer arguments favouring the possibility that neurocognitive specificities of depressed patients are just an epiphenomenon.

We have to remember that MDD is a heterogeneous disorder, when reconciling these discrepant statements.
Discussion

The definition of an endophenotype is not fixed, but it is generally thought that it must have a causal role in the development of the disease. In other words, an endophenotype lies on the disease pathway and is a pre-stage of the manifest illness. One way to demonstrate this causality would be to show that treatment of cognitive dysfunction prevents the subsequent onset of symptoms; however, to date, no one has done this. It is noteworthy that, in everyday practice, cognitive symptoms are not adequately assessed in non-elderly non-demented patients, particularly in those suffering 'only' from depression. The cognitive impairment in well-functioning depressed patients, and those who are still working, is usually not assessed at all. In most cases, cognitive symptoms are screened only by clinical impression together with general questions about functioning. Screening tools to assess neurocognitive impairment are not largely available in routine psychiatric practice.

An alternative way to demonstrate causality is to find a robust genetic link between cognitive dysfunction and the disease. To date, genetic studies have demonstrated an association, but the effect size is too small to show causality. Even in the COGENT meta-analysis (Lencz et al., 2014), where the statistical evidence for an association was strong, the overall amount of variance explained was modest (<0.5%). Moreover, trying to determine if endophenotypes have a distinguishable genetic component may be a wasted effort. Nowadays, the notion of separating genetic and environmental factors has become meaningless, since we know through the ENCODE project that 80% of the human genome may be functional (ENCODE Project Consortium, 2012), and that epigenetic effects can be transmitted across several generations. Thus, everything may be heritable to a certain extent.

Causality itself may be a misleading concept, because conditions such as schizophrenia and MDD correspond to parallel dysfunctions in intrinsic connectivity networks. To know which dysfunction is hierarchically dominant is impossible and to impose a hierarchy would be misleading. Cognitive test aptitude has a very complex heritability and a high level of pleiotropy. The important detail to ascertain for cognitive symptoms is to which intrinsic connectivity networks the dysfunction corresponds. Following this, it can be established whether the dysfunction is stable or reversible, whether it is sensitive to drugs, and whether it can contaminate other networks.

In addition, there may be a temporal influence as to whether or not we consider something to be an endophenotype. Genetics can exert an effect over time as a result of epigenetic factors. According to the stage of the illness, the proportion of the effect that is due to epigenetic or endophenotype effects may change. Early on, cognition might look like an endophenotype, but later, when all of the effects have accumulated, it might appear to be more epigenetic. The dynamics of the entire disease must be considered before coming to a conclusion regarding epiphenomena or endophenotypes.

Two other issues have been neglected this far: First, that not all patients with depression or with schizophrenia are the same, and second, that patients in clinical studies may not be representative of all patients. In schizophrenia, patient subtypes vary from simple, slowly developing schizophrenia to acute, late-onset schizophrenia. The range of symptoms is wide and there is currently no proof that this range represents a single disorder. Likewise, depression ranges from mild to suicidal, psychotic depression. It would be interesting to look at the endophenotype concept in subtypes of these diseases. In addition, the schizophrenia populations in the studies presented are mostly not representative of schizophrenia as a whole, but rather of patients with schizophrenia (similarly for depression). In Europe, about 20% of patients with schizophrenia have never been treated and the number is even higher in non-European countries (Kohn et al., 2004). So when deciding between an epiphenomenon and an endophenotype, additional refinement of study samples is necessary. Similarly, we should focus on specific domains of cognition, rather than cognitive decline as a global phenomenon because of its heterogeneity.

It is noteworthy that cognitive impairments converge in several different disease pathologies (i.e., in dementias, depression, schizophrenia, and bipolar disorder), but that there are also differences between the pathologies. In premorbid states, patients, who will later develop schizophrenia, already have some cognitive impairment; this does not apply in patients with depression or bipolar disorder.

Overall, it is difficult to decide whether cognitive impairment is an endophenotype or an epiphenomenon, not least because the concept of an endophenotype is not fixed and may need to be changed.