Peggy M.P.C. Bosch
Maurits W.M.L. van den Noort

Schizophrenia, Sleep, & Acupuncture

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Schizophrenia, Sleep, and Acupuncture

We would like to dedicate the book to all patients with schizophrenia.

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Peggy M.P.C. Bosch
Maurits W.M.L. van den Noort
(Editors)

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Table of Contents

Preface

In 2005, after having done some literature research on the use of acupuncture in the treatment of schizophrenia, we (Peggy Bosch and Maurits van den Noort) came up with the idea that it might be interesting to gather experts from both fields and to publish a book. The aim of the book should be to combine the background and all important theories from both Traditional Chinese Medicine (TCM) as well as from Western medicine, which are involved in schizophrenia, acupuncture, and the acupuncture treatment of patients with schizophrenia. Being psychologists ourselves, and being involved in TCM (Peggy Bosch studied acupuncture in Amsterdam, The Netherlands) made us realize how large the misunderstandings between Chinese medicine and Western medicine really are. Moreover, we realized what a pity it is that there is so little cooperation between the two fields. Both traditions have something to offer and might be used simultaneously, creating more positive results for the patients. In short, we thought it necessary to try to build a bridge between Western and Chinese medicine.

We had our first talk with some of the staff from Hogrefe & Huber at the 9th European Congress of Psychology in Granada (2005), Spain, where we learned that they were interested in publishing an innovative book on this intriguing subject. This talk was the start of the book that lies in front of you now. From that moment in Granada on, we continued to do research into this highly interesting field, finding that hardly any serious research had been conducted on the combination of schizophrenia and acupuncture outside of China.

The theoretical concept behind the treatment of schizophrenia with acupuncture has to date almost always been described from a Chinese medicine point of view, which is not really something that Western scientists or psychiatrists are able to grasp. We, therefore, decided to try to edit a book on this subject, which might shed some light on its background from both Western and Chinese points of view.

After continuing our own research, we came to the conclusion that sleep disorders are an essential aspect of many mental disorders, which acupuncture has a very strong and positive effect upon. Sleep disorders are, in fact, a key symptom in most patients with schizophrenia and we, therefore, decided that sleep and its related disorders needed to have an essential place in this book.

One goal of the present book is to be an introduction for Western MDs, psychiatrists, and psychologists who might be interested in a possible cooperation with acupuncturists, as well as for acupuncturists who wish to know more about the Western medicine's concept and understanding of schizophrenia and sleep disorders, and the relationship between these disorders. Moreover, we hope to be

a source of information for patients with schizophrenia and their families and friends.

We hope that, by editing and publishing this book, we will create more understanding and stimulate cooperation across the borders of the system of medicine we were taught, in order to create better treatments for our patients. In line with this "East-West" cooperation, we have gathered experts from both traditions of medicine; moreover, the various contributions came from a range of different countries: Belgium, China, Denmark, Germany, Israel, Korea, Macedonia, The Netherlands, Norway, Switzerland, the United Kingdom, and the United States of America.

In selecting the contributors, it was our intention to attract experts in all the fields that we thought appropriate to include in the book. We aimed to include authors from universities, but also some practitioners who are in direct and daily contact with patients. For some chapters practitioners joined forces with researchers. At this point, we would like to briefly introduce our authors to you.

Part I focuses on schizophrenia and Western research into this area so far. We found Prof. Hugo A. Jørgensen and Dr. Erik Johnsen from the University of Bergen, Norway, willing to write an introductory chapter on schizophrenia. Prof. Jørgensen is an internationally known (Danish) author and researcher in the field of schizophrenia. Although he has had a critical attitude when it comes to the idea of using acupuncture in patients with schizophrenia, he has kept an open mind and supported the idea of testing it thoroughly. We truly appreciate this point of view and are honored to have him contribute to the book. Dr. Johnsen is one of his gifted pupils. In his clinical work, he shows a warm heart toward his patients. He recently finished his PhD at the University of Bergen, Norway.

We the Editors (Dr. Maurits van den Noort and Peggy Bosch, MA) have written Chapter 2 on schizophrenia and what has been discovered from neuroimaging research. Dr. Van den Noort is a Dutch researcher who received his PhD at the University of Bergen, Norway. He was a member of the Bergen fMRI Group for several years and since neuroimaging research on schizophrenia is a subject that has an emphasis in this group, he is well suited for this chapter. Ms. Bosch has a masters in clinical psychology. Moreover, she is an acupuncturist and she is currently working as a PhD student on the Schizophrenia, Sleep, and Acupuncture project at the Radboud University Nijmegen, The Netherlands. She also works as a clinical psychologist with an emphasis on patients with schizophrenia.

For Chapter 3, Dr. Bart Ellenbroek from Evotec Hamburg, Germany, joined the team to add his expertise in the field of pharmacotherapy and schizophrenia. Dr. Ellenbroek is a researcher who formerly worked at the Radboud University Nijmegen, The Netherlands. He is very fond of and gifted in research with rats, and he has a very broad view when it comes to research. He is a person who is always willing to help, and who usually has great practical ideas when it comes to methods of research or applying for grants. We hope that our collaboration will

stay as inspiring as it has been over the last year and we thank him for his input and advice. Moreover, I (Peggy Bosch) thank him for his involvement in my project. His support in the preparation has meant more to me than he will ever know.

Dick J. Brouwer, MD, Annita Bosveld, MA, Ineke van der Lans, and Dzelal Dani, MSc, are a group of colleagues from GGNet Groenlo (The Netherlands). They wrote Chapter 4 on their practical experiences in the treatment of patients with schizophrenia. Dr. Brouwer is a psychiatrist with many years of experience in the field of schizophrenia. Together with Ms. Van der Lans, he is in charge of the Hearing Voices project that is run at this department. Ms. Bosveld is the Head of the Department of Support and Psychosis, and has many years of experience in the field. Mr. Dani works as a clinical physician at this department and has gained a lot of international experience in the field over the years. We are happy that we are able to present to you a chapter out of the daily lives of patients with schizophrenia and thank the authors for their input.

Last, but not least, we asked Dr. Leila Kozak, from Bastyr University, Kenmore, WA, Dr. Lorin Boynton from the University of Washington, Seattle, WA, Dr. Arushi Sinha from Big Think Media, and Jacob Bentley, MA from Harborview Medical Center and Seattle Pacific University, Seattle, WA (all in the United States) to shed some light upon the cross-cultural differences in schizophrenia, and the way this disease is treated across different countries and cultures. Dr. Kozak has, among other things, done important research in the area of consciousness and health. We have come to know her as a very compassionate and enthusiastic person. She has been an absolute inspiration in the preparation of this book. Dr. Boynton's main interest lies in work with immigrants and refugees, which is why she is an expert in the field of cross-cultural treatments. Apart from the bridge that has to be built between Chinese and Western medicine, we need many more bridges, some of them between practitioners and patients who have different cultural backgrounds. This is why cross-cultural issues need their place in this book as well. Dr. Sinha and Mr. Bentley joined them in order to create a more complete overview. Mr. Bentley is currently completing his doctoral dissertation project examining cross-cultural assessment of trauma and posttraumatic stress disorder (PTSD) in East African populations. Dr. Sinha is a medical anthropologist whose award-winning research focuses on the intersection of technology and healthcare. She is the President of Big Think Media, Inc., a healthcare communications company whose clients include leading nonprofit and biotech organizations. We thank the authors for their input.

For Part II on sleep and related topics we found a very enthusiastic contributor in Prof. Anton Coenen from the Radboud University Nijmegen, The Netherlands. He wrote an introductory chapter on sleep, in particular sleep and schizophrenia. Prof. Coenen has studied sleep during his long and very successful career and we are happy and honored that he decided to share his extensive knowledge with us. Besides being a Professor at the Radboud University Nijmegen, he is a very warm-

hearted person who is always willing to listen, give a hand, or to give advice when needed. He truly is someone to look up to. I (Peggy Bosch) thank him for all his support in my project.

For Chapter 7 we asked Prof. Vadim Rotenberg from Tel Aviv University in Israel to contribute. He has done a lot of work on sleep in schizophrenia, part of which focused on melatonin treatment. We have the highest respect for his work and are very grateful that he accepted our request to write a chapter in the book, and we trust that you will all read it with the same enthusiasm that we felt when we received it. This chapter gave us all great ideas for cooperation, and we would like to express the wish that it may be fruitful and lasting.

In Part III, on acupuncture (TCM), we found it necessary first to introduce our Western readers who may be less experienced with TCM to the Chinese ideas behind acupuncture. We decided to ask two practitioners who have been teaching acupuncture to Western people for a long time. The first of these introductory chapters was written by Ms. LiPing Han, MB, the teacher that introduced me (Peggy Bosch) to the fascinating study of Chinese herbs. She truly knows a great deal about diagnostics and, in my opinion, about teaching. Even though most of the class did not understand a word of Chinese, she was able to introduce us to the remarkable world of Chinese herbs, which she combined with a profound knowledge of TCM diagnostics.

Chapter 9 concerns the philosophy behind TCM, which is a topic that deserves a place in this book in order to explain a bit further the complexities and fascinating aspects behind TCM. This chapter was written by Dr. Stan Switala, who is, in my (Peggy Bosch) personal opinion, one of the most inspiring and stimulating teachers I have ever had. He introduced me to TCM and, after some lessons with him, complex theories suddenly seemed logical and easy to comprehend. We hope that this chapter has the same effect on our readers.

To make clear what modalities are used at this moment in acupuncture research and practice, we asked Prof. Brigitte Ausfeld-Hafter from the University of Bern, Switzerland, to cooperate with us. Prof. Ausfeld-Hafter is an influential researcher and teacher; moreover, she is an absolute expert on laser acupuncture. We are very grateful to have her on the team and would like to express the wish to cooperate more closely, as was planned from our first meeting on.

We found that it was necessary to add two chapters on more recent Western research on acupuncture. Chapter 11 is a review of neuroimaging results on acupuncture, written by Peggy Bosch, MA, and Dr. Maurits van den Noort.

For Chapter 12 we contacted Prof. Sabine Lim from Kyung Hee University in Seoul, South Korea. Prof. Lim is a researcher who is at the very top of her field. She is especially famous for her work on acupuncture in the treatment of Parkinson's disease, a disease that is related to schizophrenia because of the fact that dopamine levels are disturbed. Chihyoung Son, MD, from the Department of Applied Korean Medicine, Kyung Hee University and Seung Youn, MD, a Diplo-

mate of the American Chiropractic Neurology Board, a Diplomate of the International Board of Applied Kinesiology, Board Certified Teacher of Applied Kinesiology, and connected to the AK Medical/Oriental Medical Integrative Clinic joined Prof. Lim in her work on the chapter. We are proud and honored to have them in the book.

Chapter 13 is the first officially published teamwork by Peggy Bosch, MA, Dr. Maurits van den Noort, Prof. Anton Coenen, and Dr. Bart Ellenbroek (see above). It is the start of an extensive research project on schizophrenia, sleep, and acupuncture at the Radboud University Nijmegen, The Netherlands.

For Chapter 14 we contacted Dr. Yifan Yang, who is internationally known for her books on Chinese herbal medicine and her work on psychological problems in relation to Chinese medicine. She is a teacher, writer, and practitioner and we hold her in high esteem. For this book, she wrote a chapter on acupuncture in psychological disorders and we trust that it will help readers understand more of the Chinese background on which treatments are based.

For Chapter 15 we have the unique opportunity to present to you a chapter by the famous Chinese Professor, Prof. Qing-Zhang Ding, together with two of his colleagues. Prof. Qing-Zhang Ding works at the College of Chinese Medicine at the Hebei Medical Sciences University, China. He is also the executive director of Hebei Jikang hospital, China, and he specializes in the treatment of schizophrenia with TCM. He was the first person to publish on the integration of Western and Chinese diagnosis for schizophrenia. More specifically, he published on several possible Chinese diagnoses that can be seen in the different Western subtypes of schizophrenia and he did this in a Western journal. It is a great honor for us that he agreed to write a chapter in this book. He cooperated with two of his colleagues: Ma Yixiong and Yan Junying, and their chapter was translated by Michael Helme with help of Xin Gong.

For Chapter 16 we found a very enthusiastic team from England: Patricia Ronan, MSc, Dominic Harbinson, Lic.Ac., and Neil Quinton, Lic.Ac., who are doing research on psychosis and acupuncture and are one of the very few research groups that have so far focused on this research in practice (out of China). We are happy to say that we will be cooperating with them in our future research. We hope this might be the start of a great collaboration.

It is our sincere hope that this book will contribute to a continued interest in one of the most promising fields of new research for patients with schizophrenia.

In addition to thanking the authors of the chapters, we would like to acknowledge the contributions of several other people without whose help and assistance this book would not have been published. Our thanks first go to Michael Helme and Xin Gong, who translated Chapter 15 (by Prof. Ding and his colleagues) for us, and furthermore were a source of inspiration and encouragement. In addition, we would like to thank Dominic Harbinson and Patricia Ronan for their help with the editing of some of the chapters.

Moreover, we would like to thank Robert Dimbleby, Christina Sarembe, Gundula von Fintel, and Lisa Bennett at Hogrefe & Huber specifically, for assisting in all stages of the editorial process. We would also like to thank all of the other staff at Hogrefe & Huber, who have helped and advised us.

In this line of acknowledgments, we thank our family and friends for their continuous support and inspiration.

Finally, we wish all our readers pleasure in reading this book. We hope that it will contribute to building a bridge between Eastern and Western medicine because what can not be achieved alone might be achieved when working together . . .

Peggy Bosch and Maurits van den Noort

Note on the Translation of Chinese Medical Terms

The terminology used in this book generally follows that used in the volume *Foundations of Chinese Medicine* (Maciocia, 1989). As in that book, we have decided to translate all Chinese medical terms with the exception of yin, yang, qi, shen, and a small number of others that you will find clearly described in the chapters in the third part of the book (on TCM). We have also continued using capitals when it comes to meridian and Chinese organ names, thereby Liver would refer to the Liver meridian, whereas liver (lower case) would refer to the Western organ. Please note that we have chosen to use the Pinyin names (with Unicode) as well as the Western names for the acupuncture points in order to be as complete as possible.

Reference

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1

An Introduction to Schizophrenia

Hugo A. Jørgensen and Erik Johnsen

Abstract. The present chapter is a condensed introduction to schizophrenia as a severe mental illness. The condition is placed both in a historical and in an updated diagnostic context with regards to the characteristic symptoms and clinical features. The common belief that the occurrence of schizophrenia is the same around the world is challenged by an overt variation in reported incidence and prevalence. Environmental and genetic risk factors are briefly discussed and examples of their interaction given. The changes in brain structure and function are discussed in relation to psychosocial strain and stress and in relation to the stress-vulnerability model considered to be an integrative way of understanding the premises for the functional outcome.

Keywords: schizophrenia, symptoms, epidemiology, risk factors, neuropathology

Schizophrenia (literally: splitting of the mind) is a clinical syndrome with severe psychopathology within several domains including cognition, emotion, and behavior. For more than a hundred years, divergent concepts have been discussed. Today, schizophrenia is classified descriptively according to criteria outlined by either the World Health Organization (1992) or the American Psychiatric Association (1994). The two systems have developed to be quite similar (see Table 1a and Table 1b) but there are some differences.

ICD-10 emphasizes the character of the symptoms and DSM-IV gives weight to course and functional impairment. The present concept(s) of schizophrenia delineates a group of patients that is heterogeneous with respect to the extent of psychopathology, impairment of function and ability to manage a role in society. Some will suffer from one episode and be able to manage their lives after recovery, others will have several relapses with autonomous function in between, but the majority will need treatment and support more or less continuously for the rest of their lives.

The main clinical features consist of delusions, hallucinations, and thought disturbances, often called positive symptoms; and lack of drive, slowness, paucity of speech, blunted emotional responses, and social withdrawal, often called negative

Table 1a. **Diagnostic criteria for schizophrenia according to the ICD-10 classification of mental and behavioral disorders.**

1) thought echo, thought insertion or withdrawal, and thought broadcasting;

2) delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception;

3) hallucinatory voices giving a running commentary on the patient's behavior, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body;

4) persistent delusions of other kinds that are culturally inappropriate and completely impossible, such as religious or political identity, or superhuman powers and abilities (e.g., being able to control the weather, or being in communication with aliens from another world);

5) persistent hallucinations in any modality, when accompanied either by fleeting or half-formed delusions without clear affective content, or by persistent over-valued ideas, or when occurring every day for weeks or months on end;

6) breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech, or neologisms;

7) catatonic behavior, such as excitement, posturing, or waxy flexibility, negativism, mutism, and stupor;

8) "negative" symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses, usually resulting in social withdrawal and lowering of social performance, it must be clear that these are not due to depression or to neuroleptic medication;

9) a significant and consistent change in the overall quality of some aspects of personal behavior, manifested as loss of interest, aimlessness, idleness, a self-absorbed attitude, and social withdrawal.

Diagnostic guidelines: One very clear symptom (and usually two if less clear-cut) from any of the groups listed as (1) to (4) above, or symptoms from at least two of the groups listed as (5) to (8), should have been clearly present for most of the time during a period of 1 month or more. Symptoms from group (9) applies only to the diagnosis of simple schizophrenia, and a duration of at least 1 year is required.

The diagnosis of schizophrenia should not be made in the presence of overt brain disease, during states of drug intoxication or withdrawal, or in the presence of extensive depressive or manic symptoms unless it is clear that schizophrenic symptoms antedated the affective disturbance.

Table 1b. **Diagnostic criteria for schizophrenia according to DSM-IV**

A. Delusions,
hallucinations,
disorganized speech (e.g., frequent derailment or incoherence)
grossly disorganized or catatonic behavior,
negative symptoms (e.g., affective flattening, alogia, or avolition)

B. Social or occupational dysfunction for a significant portion of the time since onset

C. Continuous signs of the disturbance persisting for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A and may include periods of prodromal or residual symptoms.

D. Schizoaffective and mood disorders should be ruled out.

E. The disturbance should not be due to the direct physiological effects of a substance or a general medical condition.

F. In case of a history of Autistic Disorder or another Pervasive Developmental Disorder, the diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 month (or less if successfully treated).

Diagnostic guidelines: One symptom will satisfy Criterion A if delusions are bizarre or auditory hallucinations consist of running commentary on the person's behavior or thoughts. Otherwise, at least two should be present for a significant portion of time during a 1-month period (or less if successfully treated). All criteria A-F are required for the diagnosis.

symptoms. Such disturbances have been described since ancient times, but it is uncertain whether they were associated with one condition corresponding to a modern definition of schizophrenia. The symptoms are not unique to schizophrenia and in the past such a condition was described as insanity or madness. The doctors of the Antique, Hippocrates and Galen, considered insanity as a disorder of the brain and a responsibility for the medical profession. At the end of the Roman Empire and during the Middle Ages in Europe this belief was replaced by mysticism and religious understanding. The mentally disturbed were considered possessed and accordingly the treatment was exorcism. The clergy used all means to fight the devil in the insane, sometimes including mutilation, torture, and execution. After the Reformation the situation gradually improved but psychiatry was not considered part of medicine until the 19th century (Von Krafft-Ebing, 1888). At that time psychiatrists started to study the central nervous system (CNS) in order to differentiate conditions and to find etiologic explanations. The cause of syphilitic insanity was found, and at the end of the century the German psychiatrist, Emil Kraepelin (1856–1926) grouped to-

gether hebephrenia, paranoia, and catatonia in the diagnostic category of dementia praecox (dementia of the young), differentiated from affective psychosis. He emphasized the deteriorating course of the disorder with loss of intellectual capacity, emotionality, and mastery of volition and sense of reality. In the beginning of the 20th century, Eugen Bleuler (1857–1939) argued that dementia was not characteristic of dementia praecox and suggested the term schizophrenia. He considered the variety of symptoms one could observe in the patients as manifestations of a common underlying process. The primary symptoms reflecting this process were loosening of associations (thought disorder), dysregulated affect, ambivalence, autism, and loss of mastery of attention and will. These fundamental symptoms could give rise to secondary symptoms as delusions and hallucinations. Bleuler's schizophrenia concept was wider than dementia praecox and was further widened in the years to come, especially in the USA. In 1957 an important contribution to diagnostics was provided by Kurt Schneider (1887–1967). In order to increase the diagnostic reliability he identified a group of symptoms he considered to be of particular value in characterizing schizophrenia. These so-called first rank symptoms have formed the basis for the present ICD-10 and DSM-IV criteria and a more unifying concept of schizophrenia. The classical division of schizophrenia into hebephrenic, paranoid, catatonic, and simple subtypes is now an artefact and of no practical value.

Differential diagnostic difficulties may arise particularly in the distinction of schizophrenia from organic syndromes, mood disorder, and personality disorder. Lysergic acid diethylamide (LSD), phencyclidine, but also cocaine and amphetamine may result in hallucinations and delusions; the same is true in a state of withdrawal from alcohol. If the patient knows that he or she is influenced by a substance or withdrawal from a substance and understands the cause of this, the condition is classified as drug intoxication or withdrawal with hallucinations and delusions. If the patient has no insight and is otherwise orientated, with clear consciousness, the condition is classified as psychosis caused by psychoactive substance use. Drug-induced psychoses should be fully resolved within 6 months. If not, a diagnosis of schizophrenia should be considered.

The Onset and Course of Schizophrenia

The onset can be insidious with signs of unspecific abnormality already observable in infancy. The child may differ from siblings in responsiveness and motor performance. In school the child may be shy, introverted, and tend to be socially isolated. At the same time, intellectual performance is often below normal standards (Jones, Rodgers, Murray, & Marmot, 1994). In adolescence or early adulthood the condition may drift to a more deviant life style with odd ideas and neglect of personal hygiene and needs, sometimes even with flashes of psychotic

experiences. Such unspecific prodromal symptoms may further develop to manifest schizophrenia with delusions and hallucinations. The prodromal phase may, however, be of varying length and sometimes the psychosis becomes manifest after only a few weeks of dysphoric mood, irritability, and disturbed concentration and sleep. In some instances the debut of psychosis is related to intake of elicit drugs or a life event of great individual impact. For men the peak age of onset is about 22, and for women it is 5 years later.

According to a summary by Liddle (1998), less than 20% of first-episode patients have a complete recovery without any residual impairment and 20–30% have an episodic course with minor disability between the episodes. These patients are typically more sensitive to demands and stress and may possess minor behavioral oddities or lack of initiative. They are able to sustain a relationship but many have lost their friends during hospitalization and their acquaintances are often restricted to the family. They are able to perform an occupation but at a lower level than otherwise expected. Some of these patients may have delusions or hallucinations that interfere minimally with their daily lives.

About 50% suffer from substantial disability and some have such extensive symptoms and functional impairment that they need intensive treatment and continuous support.

Factors that indicate a good prognosis include female sex, good premorbid function, abrupt and late onset, and the presence of mood disturbances at the onset. A poor prognosis is indicated by insidious and early onset, marked structural abnormality in the brain, and marked cognitive impairment.

Impaired cognitive function is not an explicit part of the present diagnostic criteria. The significance of cognitive function was emphasized by Kraepelin when he described dementia praecox. During the 20th century, however, the focus moved toward the positive symptoms, probably as a result of the discovery of antipsychotic medication that especially targets these symptoms. In the last part of the century cognitive impairment in schizophrenia again attracted research interest. The vast majority of patients have more or less cognitive impairment and it was shown that in stabilized patients, cognitive function is the most important predictor for future function in the community (Green, 1998). In a synthesis of findings by Weickert and Goldberg (2000) there is evidence for low IQ in children and adolescents prior to the development of psychotic symptoms and schizophrenia, with impairment affecting multiple cognitive domains. In some patients the cognitive deficits become manifest concurrently with the psychotic symptoms and with a pattern of deficits encompassing executive functions, attention, and memory. These prefrontal functions have been suggested as "core" deficits in the development of schizophrenia.

Epidemiology

It is a common belief that schizophrenia is fairly evenly distributed around the globe and affects females and males equally. There are quite large variations in both point prevalences and annual incidences, however. Based on extensive reviews of available studies, McGrath and collaborators (McGrath, 2005, 2006) found that the median incidence was 15.2 per 100,000, with a range between the 10th and the 90th percentile of 7.7 to 43.0 per 100,000, which is a five-fold variation. Males were found to develop schizophrenia more often than females (median male to female risk ratio = 1.4). Based on studies from 1965 to 2002 (Saha, Chant, Welham, & McGath, 2005) median point prevalence was 4.6/1000 with a range between the 10th and 90th percentile of 1.9 to 10 per 1,000, a five-fold variation. Some of the variance may be explained by variation in methodology, but chances are that the rates of schizophrenia differ across time, space, and sexes. There is compelling evidence that the risk of schizophrenia is a result of a genotype-by-environment interaction and there are reasons to believe that the distribution of genes and environmental risk factors differ across human populations and time periods.

The mean lifetime risk for schizophrenia is close to 1% in a Western European population. If both parents or a monozygotic twin have the diagnosis the risk is close to 50%, falling to approximately 10% if the diseased relative is a dizygotic twin/sibling. Interestingly, some studies have shown that older age of the father will increase the risk of schizophrenia for the offspring (Sipos et al., 2004). Epidemiologic studies, including family, twin, and adoption studies, provide evidence both for a high degree of genetic heritability and for the importance of the environment. The search for genes implicated in schizophrenia has been difficult and despite an estimated total heritability of approximately 80% it has been hard to find susceptibility genes with more than small effects. At the same time, more powerful environmental factors have been identified (Cannon & Clarke, 2005).

In Table 2 several environmental factors found to increase the risk of schizophrenia above the population risk are listed. The prenatal period seems to be especially vulnerable around the second trimester. In this period, prenatal risk factors may double the risk for the offspring. Obstetric complications also double the risk. Winter birth has a much smaller effect (5–8% increase). In the context of risk factors for schizophrenia, cannabis has become a drug of increasing importance (Di Forti, Morrison, Butt, & Murray, 2007). It is consumed by approximately 4% of the adult population. Particularly, European countries have seen a rise in consumption of high potency preparations in a still younger population. The CB1 receptors in the brain are normally activated by the endocannabinoids. The active ingredient of cannabis, [DELTA][9] – tetrahydrocannabinol appears to disrupt normal CB1 mediated signaling, increases dopaminergic neuronal firing, and many heavy users will develop problems. Until recently, it was not clear

Table 2. **Environmental risk factors and susceptibility genes repeatedly associated with schizophrenia**

Environmental factors	Susceptibility genes
Prenatal:	Strong evidence:
severe famine	DTNBP1 – dysbindin1
infection	NRG1 – neuregulin 1
catastrophic events	Less evidence:
Perinatal/neonatal:	COMT – Catechol-o-methyl transferase
bleeding	RGS4 – regulator of G protein signaling 4
diabetes	DAAO – D-amino acid oxidase
rhesus incompatibility	G72 – activator of DAAO
pre-eclamsia	DISC1 – disrupted-in-schizophrenia gene 1
abnormal growth	GRM3 – metabotropic glutamate receptor 3
asphyxia	
winter birth	
Others:	
cannabis use	
migration	
urbanicity	

whether psychosis was a cause or a consequence of cannabis use. Now there is compelling evidence that cannabis use overall doubles the risk of schizophrenia. The risk increases dose-dependently, with younger age, a positive family history for psychosis, and variation in the COMT gene that codes for the enzyme cathechol-o-methyl transferase. If a cannabis user has the Val/Val alleles the enzyme will exert high activity in the catabolism of dopamine, especially in the forebrain, and the risk of psychosis increases five-fold, an example of a gene-by-environment interaction predisposing for schizophrenia. In a recent review of the risk of schizophrenia associated with migration (Cantor-Graae & Selten, 2005), it was found that a personal or family history of migration increases the risk 2.7 times among first-generation migrants and 4.5 times among second-generation migrants, respectively. No difference was found between sexes. The high figures cannot be explained by selection and it is poorly understood why the risk is so high among the second-generation migrants. The review also revealed significant associations of risk of schizophrenia with black skin color and with level of economic development in the region of birth, which points to the importance of psychosocial factors. The findings that the incidence of schizophrenia increases with increased level of "urbanicity" (Mortensen et al., 1999) are probably along the same line. It has been hypothesized that the big cities convey more exposure to toxic agents, infections, and health risk behaviors like smoking, drinking, and substance abuse. However, the increased risk of schizophrenia in an urban envi-

ronment has not been satisfactorily explained by such factors. Psychosocial factors, including discrimination and social exclusion, have been pointed to as more likely explanations. So far, urbanicity, as a proxy for known and unknown aspects of being brought up in a big city, seems to be the most powerful environmental risk-factor for schizophrenia (Van Os, Krabbendam, Myin-Germeys, & Delespaul, 2005).

The susceptibility genes listed in Table 2 have been associated repeatedly with schizophrenia and some also with bipolar disorder. The effect sizes are typically small to modest (1.2–3). Children with a rare chromosomal abnormality, 22q11 deletion syndrome (DiGeorge syndrome or Velo-cardio-fascial syndrome), have a risk of 24% for developing schizophrenia, however. Several genes are identified in the chromosomal area of interest including COMT but the link to the high risk for schizophrenia is not revealed. There are reasons for scepticism in the area of gene finding. Although the listed genes repeatedly have been found to be associated with schizophrenia, there are also negative findings, and the specific risk alleles have not been replicated (Harrison & Weinberger, 2005). Nevertheless, the total weight of evidence is increasing that susceptibility genes will provide insight into the pathology of schizophrenia and probably other psychoses, too. Genetic variation may change the structure of the encoded protein or the expression of the gene and, thereby, the amount and distribution of the protein. Most of the actual candidate genes have impact on mechanisms active during development of the brain and the regulation of synapse function, especially glutamatergic synapses and processes. There are also links to the dopaminergic and GABAergic systems. However, an understanding of how the specific risk alleles, solely or in combination with environmental factors, relate to the observed pathology in brain structure and function still remains obscured.

Neuropathology

According to a recent summary (Harrison & Weinberger, 2005) the best replicated macroscopic findings are ventricular enlargement and small reductions in brain volume and weight. This applies in particular to the hippocampus, prefrontal region, superior temporal region, and thalamus. There are also reported structural abnormalities in cortical thickness, cortical gyrification, hippocampal shape, and cerebral asymmetry. Some of these findings exist before the onset of psychosis and occur in unaffected relatives. There are great methodological problems related to post-mortem studies and modern imaging studies have added significantly to our knowledge about structural and functional pathology related to schizophrenia (for more details see Chapter 2). As a mirror of the heterogeneity at the level of symptoms and behavior, the neuropathology findings are far from consistent, not specific,

and the magnitude of changes are relatively small and with considerable overlap between schizophrenia and comparison groups. At the histological level there are no signs of a recognized neurodegenerative disorder. The most noteworthy observations are those of misplaced neurons in the entorhinal cortex and in neocortical white matter, indicative of early developmental disturbances. Findings of small cell bodies and reduced amount of dendrites and spines may be indicative of reduced connectivity. In line with this, the thalamus may have a reduced number of neurons. At the level of neurochemistry, glutamatergic and dopaminergic transmission seems altered in several brain regions.

Neurochemistry

The dopamine hypothesis in schizophrenia links a deficient stimulation of dopaminergic D1 receptors in prefrontal cortex to negative symptoms and intermittent excess of subcortical D2-receptor stimulation to positive symptoms. Imaging studies and the effect of antipsychotics are generally consistent with this model. The mechanism behind the imbalance in dopamine (DA) transmission is not well elucidated but the failure may involve dysfunction in the glutamate (NMDA) system. The role of glutamate and the NMDA receptors in schizophrenia is largely based on the observation that the NMDA antagonists phencyclidine ("angel dust") and ketamine induce both positive and negative symptoms in both healthy individuals as well as individuals with schizophrenia. Another observation is that long-term NMDA antagonism alters DA transmission in the direction observed in patients. After synthesizing the findings Abi-Dargham and Laruelle (2005) suggested three interrelated neurochemical dysfunctions in the brains of patients with schizophrenia: sustained deficit in NMDA and D1 transmission affecting cortical connectivity and intermittent excess of D2 transmission affecting subcortical regions. The glutamatergic and dopaminergic dysregulations may have a negative impact on each other and result in symptoms. According to this notion, classical D2-blocking antipsychotics will have a fast effect on patients with positive symptoms and excess of D2 transmission. The atypical antipsychotics have a weaker subcortical D2 blockade but increase DA in the prefrontal region and stimulate D1 and NMDA transmission with a potential effect on negative symptoms.

Neurophysiological Changes

On a group level, people with long-term schizophrenia often demonstrate several neurophysiological abnormalities (Siever & Davis, 2004). Event-related potentials

(ERP) are electromagnetic signals from cortical regions that reflect processing of sensory stimuli, usually auditory. The amplitude of the signal may be positive (P) or negative (N) and it is further named according to the stimulus – signal interval in milliseconds. At least in chronic schizophrenia, there is a reduced ability to inhibit overloading of sensory input, measured as a failure of P50 suppression and reduced P300 and P400 as indications of impaired auditory attention and recurrent inhibition associated with pathology in the left posterior superior temporal gyrus and ventral temporal regions, respectively. Mismatch negativity (MMN) is a short-latency (150–250 ms after stimulus presentation) negative ERP indicating a sudden deviance in a sequence of stimuli, for example, a sudden change in tone pitch or tone duration. MMN seems to be dependent on normal glutamatergic activity in the cortex. A recent interest in glutamate in relation to schizophrenia has actualized this type of studies and 40–50% of the patients with schizophrenia seem to demonstrate reduced MMN. In the backward masking test, early visual processing seems to be altered, demonstrated by masking at an interstimulus interval that is easy to handle for normal subjects. There is also deficit in prepulse inhibition in a blink startle paradigm, reflecting impaired adaptation to the environment, a capacity related to the cortico-striatal-thalamo-cortical loop. The patients also demonstrate problems with motion detection and smooth-pursuit eye movement, leading to difficulties in focusing on a moving target, a capacity localized to the frontal and temporal cortex together with the brainstem. The anatomical lack of asymmetry is mirrored on the functional level by impairment of the right ear advantage demonstrated in the dichotic listening paradigm (Løberg et al., 2006), which tests the functional lateralization of language perception and the functional integrity of the posterior superior temporal region. Several of the mentioned abnormalities can also be found in clinically unaffected relatives of the patients, indicative of genetic factors contributing to vulnerability to schizophrenia.

Cognitive Impairment

There is a relatively large variation in cognitive abilities within the population of people with schizophrenia, even among chronic patients (Weickert & Goldberg, 2000). People with premorbid deficits seem to exhibit deficits in nearly all domains tested, including attention, memory, executive function/working memory, language, oculomotor speed, and visuospatial perception, implicating pan-cortical impairment. Chronic patients, not clearly premorbidly affected, may have an intellectual decline after onset of the psychosis without visuospatial and reading abilities being compromised. Others seem cognitively preserved and may only display mild impairments of executive function/working memory and attention,

Table 3. **Cognitive deficits and function**

Cognitive domain	Function
Declarative memory Vigilance	Social functions
Executive functions Declarative memory Working memory Vigilance	Occupational functioning
Executive functions Declarative memory Working memory	Living independently

implicating the importance of prefrontal functions. In some materials these patients do not differ significantly from normal controls. Interestingly, auditory hallucinations are reported to be the most intense in the premorbidly compromised group (Weickert & Goldberg, 2000). As is the case with the neuropathological findings, the cognitive deficits in schizophrenia are not specific for the diagnosis but usually more pronounced than if they occur in other psychiatric conditions. Not all cognitive deficits are consistently found to predict functional outcome for the patients. Table 3 shows the cognitive domains in which deficits are found to be important for functional aspects of life (Harvey & Sharma, 2002).

General Physical Health

An increasing number of patients with schizophrenia live in the community or in facilities alternative to hospitals. At the same time, it seems as if somatic diseases and physical problems are increasing (Salokangas, 2007). In comparison with the general population there is an increased morbidity of obesity/overweight, dyslipidemia, diabetes, heart diseases, lung diseases, gastrointestinal diseases, and cancer (mostly in the lungs). In addition, mortality resulting from suicides and accidents is markedly increased. The result is that life expectancy is reduced by 10–20% in comparison to the general population.

Hyperlipidemia and diabetes, which have been associated with the use of atypical antipsychotics, are also independently associated with schizophrenia. In general, people with schizophrenia seem to demonstrate poor health behavior. In a study of health habits among patients with schizophrenia living in the commu-

nity (Roick et al., 2007) it was found that in comparison to the general population they consumed a little less alcohol (the males) but smoking was increased. In addition, they had less healthy food and were less physically active. The authors concluded that schizophrenia patients are an appropriate target group for public health interventions.

The Role of Stress

Relatively powerful risk factors, such as migration and urbanicity, have already been discussed. High rates of schizophrenia in big cities and among migrants, especially second-generation, have not been satisfactory explained. Strain and stress caused by frustrating psychosocial circumstances have been mentioned as elements of potential importance. There is, in fact, a literature that might give us some hints about the relationship between social factors and schizophrenia. A review of "a disappearing literature" (Jarvis, 2007) reminds us that 50 years ago it was observed that blacks in Chicago had higher rates of hospital admissions of psychosis except in parts of the city where blacks were the majority. These findings were recently replicated in the UK (Boydell et al., 2001) suggesting that the strain of being a minority group under adverse social circumstances may be a risk factor for schizophrenia. Based on the review (Jarvis, 2007) the author makes the case that psychosis and schizophrenia may arise from social factors as poverty, migration, and racial discrimination.

Life-events studies have focused on both onset of first episode schizophrenia and relapse. In a review of studies using a different methodology (Phillips, Francey, Edwards, & McMurray, 2007), some evidence for the increasing amount of life events prior to the onset of psychosis was found. There were also indications of a greater reactivity to even trivial events among schizophrenia patients. The findings were, however, equivocal, and cross-sectional studies of young people at risk and people in the prodromal phase could not find increased reactivity to life events (Phillips et al., 2007).

After the Second World War, psychoanalysts proposed the notion of the "schizophrenogenic mother." Later, focus was removed toward the role of the patient in the parental relationship and the problems with individuation in the family. Family communication resulting in contradictory signals to the recipient was suggested to be pathogenic and resulted in the "double bind" hypothesis by Bateson and co-workers. Many family studies were done but no clear message emerged before the Finnish adoptive-family study of schizophrenia by Tienari (Tienari et al., 1994), which demonstrated both the effect of genetics and the deteriorating effect of a disturbed family environment.

Another source of stress in relation to psychosis comes from the family of high