

Genetic and nongenetic studies of schizophrenia

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Chapter 10

Summary

Schizophrenia is a severe mental illness, and despite the fact that a lot of research has been dedicated to identifying its aetiology, what exactly causes schizophrenia is still unknown. But from research findings so far, one can confidently say that in the aetiology of schizophrenia there are both genetic and environmental factors. This thesis is on the aetiology of schizophrenia, and thus it contains studies both on genetic and non genetic factors, and suggests a possible model of how the interaction between them in the aetiology of schizophrenia is studied further. 'Chapter 1' is a General Introduction to the thesis. 'Chapters 2, 3 and 4', focus on the genetic component of schizophrenia, and are family studies. 'Chapters 5, 6, 7 and 8' are studies on nongentic factors in the aetiology of schizophrenia, and 'Chapter 9' is a General Discussion.

'Chapter 1' starts with a short overview of the literature that supports the genetic element in the aetiology of schizophrenia. It then presents the notion of the use of 'Endophenotypes'. It defines what 'Endophenotypes' are, and the possible advantages of their use instead of clinically defined schizophrenia in genetic studies. It presents literature that shows that in schizophrenia there are structural brain abnormalities and neuropsychological impairments, and thus their potential to be used as 'Endophenotypes' of schizophrenia. 'Chapter 1' continues with literature review of studies on the possible roles prenatal exposure to Influenza, Urbanicity, Social Class and Cannabis in the development of schizophrenia. This chapter then concludes with a summary of the studies presented in this thesis.

In the studies presented in 'Chapter 2 and 3' we examined structural brain changes found in patients with schizophrenia and their relatives. These two studies were designed to provide a gradient of genetic risk for schizophrenia in first degree relatives of probands who have a diagnosis of schizophrenia.

In the study of 'Chapter 2' we examined if the structural brain changes found in patients with schizophrenia and their relatives are due to genetic factors or obstetric complications. Brain structures studied were: whole brain, lateral ventricles, third ventricle, cerebellum and temporal lobes. We studied two sets of families. One set consisted of probands with a diagnosis of schizophrenia of families multiply affected by schizophrenia and their unaffected relatives. The other set consisted of families with no other affected individual with schizophrenia. Controls were also used. This study showed that lateral ventricle enlargement correlated with the likelihood of carrying susceptibility genes for schizophrenia, and thus highlighting the potential of lateral ventricles being used in studies as 'Endophenotypes' of schizophrenia.

The study presented in 'Chapter 3', is a family study with the same design as the study presented in 'Chapter 2' and focused on if the reported loss of the normal fronto-occipital asymmetry in patients with schizophrenia and in their non-affected relatives could be associated with genetic susceptibility. The result of this study did not find any association between the loss of this torque and genetic susceptibility

for schizophrenia, and thus it did not support its use as a potential 'Endophenotype' of schizophrenia.

The study of 'Chapter 4' assessed if the neuropsychological deficits found in schizophrenia can constitute a familial, probably genetic, risk for schizophrenia. The study consisted of a family study where we examined the correlation between structure and function of the brain, and if this correlation had particular characteristics in patients with schizophrenia or their relatives. Neuropsychological assessments were done by an extensive battery of tests, and the brain structures measured by MRI were for whole brain, prefrontal region, lateral ventricles, third ventricles, temporal lobes, hippocampi and cerebellum. This study had interesting findings on correlations between whole brain and structures of brain volumes and results of neuropsychological tests. But in terms of search for endophenotypic markers, all findings were negative.

The study of 'Chapter 5' studied if the proportion of persons with a diagnosis of paranoid schizophrenia would increase with an increase in the level of influenza exposure during gestation. The number of deaths attributed to influenza was used as a proxy measure of the prevalence of influenza, and the exposure months (i.e. the fifth month prior to birth) were divided into quartiles of increasing exposure to influenza according to the frequency of these deaths. Crude analysis in the study showed that an increase in exposure to influenza during the fifth month of gestation was accompanied with an increase in the proportion of persons with a diagnosis of paranoid schizophrenia. But when allowance was made for sex, seasonality and birth period, this association was lost.

'Chapter 6' is a whole population prospective cross sectional study based in the Maltese Islands. All patients with first onset psychosis admitted to one of the psychiatric units in the Maltese islands during a one year period were included in the study. This study replicated results of previous studies that lower social class and exposure to urban living are associated with psychosis.

'Chapters 7' is a study on the influence of cannabis use on outcome of recent onset psychosis. It is a 4-year follow up study of a cohort of patients in South London with psychosis who had onset within 5 years of index admission. The patients followed-up were divided into four groups according to duration of cannabis use, taking index admission as reference point. The patients in this study who continued to use cannabis had more positive (but not negative) symptoms and more continuous illness.

'Chapter 8' is a whole population based study conducted in the Maltese Islands on patients with first episode psychosis. The aim of this study was to assess if cannabis can hasten the age of onset of patients with psychosis, and thus implying that it has an aetiological role. The results of this study showed that the mean age of first admission to hospital for psychosis in patients whose urine at admission was posi-

tive to cannabis was significantly less than those whose urine at admission was negative to cannabis.

'Chapter 9' is a discussion which highlights and integrates the results of the studies presented in this thesis. There is discussion on how according to the studies presented in the thesis enlarged lateral ventricles are the only potential 'Endophenotype' of schizophrenia out of all the structural brain abnormalities and neuropsychological deficits studied, and that further research to confirm this is required. The negative and positive findings of the nongenetic studies in the thesis are also discussed. In the last section of this chapter I discuss a possible better model than previous ones, to be used for studying the interaction between genes and environment in the aetiology of schizophrenia. How the findings of the studies presented in this thesis can help in further research, by means of this model, is also discussed.