Chapter 1

Introduction: Neuropsychiatry of hallucinations
Chapter 1

Schizophrenia

Schizophrenia is one of the most severe psychiatric disorders. Generally, it profoundly affects an individual's ability to think clearly, distinguish reality from fantasy, react in an emotionally appropriate way, and interact with others. One of the most tragical features of the disorder is the early appearance of the symptoms, usually between ages 20 to 35, with devastating effects on social relationships, education, and starting a professional career, thereby ruining all promises of early adulthood. Approximately 15% of patients with schizophrenia commits suicide. The general population lifetime prevalence of schizophrenia is 1.0 - 1.5 %, and the annual incidence rate is between 0.16 and 0.42/ 1000 persons at risk (Jablensky, 1995). Although text-books state that schizophrenia affects men and women equally (e.g., Kaplan, Sadock & Grebb, 1994), evidence is accumulating that men are at higher risk for schizophrenia (Iacono & Beiser, 1992; Goldacre et al., 1994; Schelin et al., 2000).

Phenomenology

Symptoms of schizophrenia include delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, affective flattening, alogia, and avolition. None of these symptoms is pathognomonic for schizophrenia. Table 1 lists the diagnostic criteria for schizophrenia from the DSM-IV (American Psychiatric Association, 1994), the currently most widely used psychiatric classification system. Symptoms of schizophrenia have been characterized to be “waxing and waning”, referring to the acute and chronic nature of different symptoms. Acute symptoms are usually so-called “positive” symptoms (which are present in schizophrenia but not in healthy individuals), such as delusions and hallucinations. On the other hand, negative symptoms (the absence of functions that are present in healthy individuals), such as affective flattening and avolition, are more persistent and are probably of more serious prognostic importance (Andreasen, 1990; Murray, 1997).

Surprisingly, although a hallmark of schizophrenia, cognitive dysfunction is not listed among the symptoms of schizophrenia in DSM-IV (it is expected that the next revision of the DSM will correct for this omission). Numerous neuropsychological investigations have established that patients with schizophrenia suffer from significant deficits in attention, memory, executive functioning and general intellectual abilities (Randolph et al., 1993; Heinrichs &
**Introduction**

Table 1. Diagnostic criteria for schizophrenia (DSM-IV).

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| A | **Characteristic symptoms:** Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):  
  (1) delusions  
  (2) hallucinations  
  (3) disorganized speech (e.g., frequent derailment or incoherence)  
  (4) grossly disorganized or catatonic behavior  
  (5) negative symptoms, i.e., affective flattening, alogia or avolition |
| B | **Social/occupational dysfunction:** For a significant portion of time since the onset of the disturbance, one or more areas of functioning, such as work, interpersonal relations, or self-care are markedly below the level achieved prior to onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement) |
| C | **Duration:** Continuous signs of the disturbance persist for at least six months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet criterion A (i.e., active phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual symptoms, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in criterion A present in attenuated form (e.g., odd beliefs, unusual perceptual experiences) |
| D | **Schizoaffective and Mood Disorder exclusion:** Schizoaffective Disorder and Mood Disorder with Psychotic features have been ruled out because either (1) no Major Depressive, Manic, or Mixed Episodes have occurred during active-phase symptoms; or (2) if mood episodes have occurred during active phase symptoms, their total duration has been brief relative to the active or residual periods. |
| E | **Substance/general medical condition exclusion:** The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition. |
| F | **Relationship to a Pervasive Developmental Disorder:** If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated). |

Zakzanis, 1998; Bilder et al., 2000; Weickert et al., 2000). Moreover, such cognitive dysfunction has been shown to relate to outcome, e.g. verbal memory predicts social and vocational outcome in schizophrenia (Green, 1996). Again, it is important to note that a minority of patients does not show neuropsychological dysfunction (Palmer et al., 1997; Weickert et al., 2000).
Etiology

The precise cause of schizophrenia is not known. Despite decades of huge research efforts, schizophrenia remains a poorly understood disorder. This is not to say, however, that there is no information on the pathophysiology implicated in schizophrenia. From 1976, when the first study appeared in which enlarged cerebral ventricles were demonstrated in schizophrenia (Johnstone et al., 1976), a large number of studies have reported structural and functional brain abnormalities in schizophrenia (cf. Cannon, 1996; Deakin, 1996; Lawrie & Abukmail, 1998; Harrison, 1999; Liddle, 1996; Nelson et al., 1998; Sommer et al., 2001; Staal et al., 1999; Zakzanis & Heinrichs, 1999). The most consistent neuroanatomical changes are the enlargement of the lateral and third ventricles (Raz & Raz, 1990), and a decrease in volume of the temporal lobe and certain temporal structures (Nelson et al., 1998; but see Zakzanis et al. [2000] for a critical review). In addition, volume decrements have been reported for the thalamus (Andreasen et al., 1994; Staal et al., 1998), and cortical grey matter (Lawrie & Abukmail, 1998). It is not clear to which extent such changes may be progressive. Neuroimaging studies of patients during their first episodes of the illness show similar abnormalities, and most studies do not find evidence of progression when patients are followed up for longer periods (Harrison, 1999). This suggests that the abnormalities reflect a static lesion present at or before the onset of psychosis, and that the abnormalities are not artefacts of treatment or chronicity. On the other hand, recent studies have reported evidence of a progressive decline (Hulshoff Pol et al., submitted; McCarley et al. 1999), and effects of antipsychotic treatment (Scheepers et al., 2001). At the neuropil level, abnormalities have also been reported. For example, a recent study by Kalus et al. (2000) observed a marked decrease in the length of the basilar dendrites of pyramidal cells in layer 3 of the prefrontal cortex, coupled to a decrease in the number of their distal segments (the findings were based on a classic Golgi stain analyzed with modern imaging techniques).

It is well established that schizophrenia has a hereditary component (Gottesman, 1991). For example, identical twins show average concordance rates of 50%. This does not only imply an important genetic contribution (dizygotic twins have an average concordance rate of 17%) but also points to a substantial environmental contribution. No genes have been positively and definitively identified as “schizophrenia genes”, although some suggestive evidence has been reported for candidates at a number of chromosomal loci (Faraone et al., 1998). Very recently, Brzustowicz et al. (2000) conducted a genome-wide scan for
schizophrenia susceptibility loci in 22 extended families with high rates of schizophrenia, which provided highly significant evidence of linkage to chromosome 1 (1q21-q22). The authors interpret their finding as strong evidence for genetic predisposition to schizophrenia.

Some environmental risk factors have been established: seasonality of birth (Torrey et al., 1997), urban birth (Marcelis et al., 1998), prenatal or perinatal viral infection of the nervous system (Jones & Cannon, 1998), and complications during pregnancy and delivery (specifically preeclampsia in the mother, resulting in fetal hypoxia; Cannon, 1996). Psychosocial factors, such as dysfunctional family environment, may also act as adverse environmental factors (Wahlberg et al., 1997).

An important hypothesis with regard to the etiology of schizophrenia is the neurodevelopmental hypothesis (Lewis & Murray, 1987; Weinberger, 1987), which has gained increasing popularity in recent years. This hypothesis states that a disturbance in the orderly development of the brain, decades before the symptomatic phase of the illness, may ultimately lead to the expression of schizophrenia. This disturbance in orderly development would include alterations in neuronal size and synaptic and dendritic organization, and additional or alternative abnormalities regarding cell adhesion, myelination and synaptic pruning (cf. Akbarian et al., 1996; McGlashan & Hoffman, 2000; Weinberger, 1996). Although the principle remains largely unchallenged, the neurodevelopmental model (like all other models) has problems in explaining the onset (typically during adolescence), relapsing and remitting course, and outcome of schizophrenia (Harrison, 1999).

**Cognitive Neuropsychiatry**
The cognitive neuropsychiatry approach (David, 1993) concerns research in psychiatry using cognitive neuropsychological methods (Shallice, 1988). The aim is to uncover dysfunctions in cognitive mechanisms that may account for clinical phenomena. From this perspective, investigators do not concentrate on syndromes, such as “Alzheimer’s Disease”, “epilepsy”, or “stroke”, but on psychological constructs such as “phonological dyslexia”, or “prosopagnosia” (e.g., De Haan et al., 1991). This approach converges largely with the “symptom-oriented” approach to psychiatric research (Persons, 1986; Bentall, 1990; Costello, 1992). The symptom-oriented perspective argues that, in order to understand the nature of psychological processes underlying such psychologic
phenomena as formal thought disorder, delusions and hallucinations, research concentrating directly on such individual phenomena will be more successful than studying diagnostic categories (e.g., "schizophrenia"). The following advantages of studying symptoms rather than syndromes have been advanced in the literature (cf. Persons, 1986; Mojlabai & Rieder, 1998): 1) the symptom approach permits the isolation of single elements of pathology for study; 2) the symptom approach is less vulnerable to the lack of adequate reliability and validity of diagnostic categories; 3) the symptom approach avoids misclassification and confounding associated with diagnostic categories; 4) symptom-oriented theories are clearer, easier to test, and more likely to lead to an explanation of psychopathology; 5) the symptom approach recognizes the continuity of clinical phenomena and mechanisms with normal phenomena and mechanisms.

Another characteristic of the cognitive neuropsychiatry approach is the use of case-studies. Shallice et al. (1991) and David (1993) have advocated the rationale of this methodology and list several advantages of the case-study approach (cf. Caramazza, 1986). An important issue regards the heterogeneity of schizophrenia and the consequences for interpretation of cognitive performance results. In studies of large groups of patients, the heterogeneity of schizophrenia will lead to group means which may not reflect the behavior of any individual. In the case-study approach, multiple tests are administered to a few selected patients (on the basis of a priori criteria), where the within-subject comparison of differential test performance may reveal specific domains of dysfunction characteristic to the condition studied.

Nevertheless, the cognitive neuropsychiatry approach, with its emphasis on symptom-oriented research and case-studies, has its limitations (which were already recognized by David, 1993). With regard to the symptom-oriented approach, such limitations have recently been critically reviewed by Mojlabai & Rieder (1998). These problems mainly concern whether and to which extent the findings can be generalized, and whether the results have implications for etiology. Moreover, the symptom-approach cannot explain why some cognitive deficits remain present in asymptomatic episodes.

Given the advantages of the cognitive neuropsychiatry approach described above, a substantial part of this thesis takes the cognitive neuropsychiatry, symptom-oriented approach. However, because of its limitations, a number of chapters (specifically, chapter 2 and 3) are primarily based on a syndrome-oriented, classical neuropsychological approach. In this way, we have intended to work towards a balanced scientific analysis. We will combine
the cognitive neuropsychiatry approach with the “levels of explanation” approach to schizophrenia, described by Mortimer & McKenna (1994). This approach assumes that the cognitive level is intermediate between symptoms and neuropathology, and that the neuropsychology of schizophrenia may thus have the capability to connect neurology with phenomenology.

Outline and aims of the studies
Hallucinations are a characteristic feature of schizophrenia. Little is known about the mechanisms that give rise to hallucinations. In this thesis, research is reported on the cognitive and neuroanatomical basis of hallucinatory experiences. To set the stage for the more specific cognitive neuropsychiatric investigations, the cognitive sequelae of schizophrenia are explored first. The substantial body of evidence that exists in this area has been brought together and quantitatively analysed using meta-analytical procedures. Subsequently, the studies are aimed specifically at the neuropsychological and neuroanatomical basis of hallucinatory experiences in the normal population and in patients with schizophrenia. Although a number of cognitive functions will be examined, we will mainly concentrate on mental imagery and its possible role in hallucinatory experiences. Of the cognitive processes that have been hypothesized to be implicated in hallucinations (inner speech, speech perception, verbal self-monitoring, reality monitoring, mental imagery), least is known about the role of mental imagery, as very few studies have applied adequate behavioral measures. In the present thesis, such methods are developed, and a range of studies is carried out in order to elucidate the relation between mental imagery and hallucinations, and their neural basis.

A number of controversies surround cognitive research in schizophrenia, with regard to methodological and conceptual issues. At the end of each section of this thesis, we illustrate this by including a critical evaluation of a controversial issue, relevant to the subject of the section.

Cognitive dysfunction in schizophrenia
Before focusing on a particular symptom and its associations with cognitive function, it is important to have clear insight into the cognitive deficits associated with schizophrenia. A wide range of cognitive deficits have been suggested, but few attempts have been made at quantitative integration of the research findings. A notable exception is the meta-analysis reported by Heinrichs & Zakzanis.
(1998), who statistically combined the results of a large number of studies, in which schizophrenia versus control differences were indexed on multiple measures of memory, attention, intelligence, executive function, language, and motor performance. The results indicated that schizophrenia is characterized by a broad range of cognitive impairments, with varying degrees of severity in the different ability domains. Of these domains, the most pronounced deficits were observed for memory tasks. In chapter 2, we report more detailed meta-analyses in which the performance of patients with schizophrenia versus normal controls was contrasted on multiple tasks of memory performance.

In the late eighties, Liddle (1987) proposed a three-factor model of symptoms of schizophrenia, as a refinement of the classical positive/negative dichotomy. The three factors were based on the solution of factor-analyses: besides negative symptoms the subdivision of positive symptomatology into symptoms of disorganisation and reality distortion was suggested. Indeed, it has been suggested that these symptom-dimensions are differentially related to neurocognitive dysfunction (Green, 1998), and would provide a more parsimonious explanation of the cognitive basis of schizophrenia than the examination of individual symptoms. The aim of the study reported in chapter 3 was to examine whether there would be a differential relation between these three symptom dimensions and executive and attentional function. This was investigated by meta-analyses of the published literature on performance on the Wisconsin Card Sorting and the Continuous Performance Test in schizophrenia.

**Hallucinatory experiences and mental imagery in non-psychiatric individuals**

An important advantage of studying hallucinatory experiences and their cognitive basis in non-psychiatric individuals is that it avoids the confounding factors associated with psychopathology. Indeed, hallucinatory experiences have been reported in non-psychiatric subjects from the normal population. Most research in normal subjects uses the Launay-Slade Hallucination Scale (LSHS) as a measure of hallucinatory predisposition. In chapter 5 we report the factor structure of the LSHS in a normal sample, in order to provide insight into the nature of hallucinatory predisposition.

The aim of chapter 6 is to investigate whether, in a group of non-selected college students (N=74), subjects with relative high LSHS scores will show more vivid mental imagery than low scoring subjects. Mental imagery vividness was measured with an introspective questionnaire and with a behavioral measure.
Chapter 7 concerns a more thorough investigation of this hypothesis. From a large group of college students who completed the LSHS, two groups were selected, the first from the highest and lowest quartiles. The hallucination-prone group was then contrasted with the comparison group on multiple measures of auditory and visual imagery and perception. The prediction on the basis of the vivid-imagery hypothesis of hallucinations was that hallucination-prone individuals would show smaller imagery-perception differences which may be indicative of increased perceptual characteristics of mental images.

Mental imagery, hallucinations, and the brain
Data regarding the neuroanatomical basis of mental imagery and hallucinations may either support or refute the plausibility of the imagery hypothesis of hallucinations. The aim of chapter 9 is to provide indirect evidence that auditory mental imagery may share brain structures with auditory perception, by focusing on the relation between music processing and auditory imagery. (Studies regarding brain areas involved in hallucinations will subsequently be discussed in more detail in chapter 13).

Chapter 10 is a thorough investigation of the neuroanatomy of visual imagery, in which the role of sensory visual areas is contrasted with parietal association cortex, using two state-of-the-art neuroimaging techniques, functional Magnetic Resonance Imaging (fMRI), and repetitive TMS (rTMS). Finally, the study reported in chapter 11 was intended as an exploratory investigation of the effect of rTMS over the left auditory cortex on hallucinations and neurocognition in schizophrenia. Besides having implications for understanding the functional neuroanatomy of hallucinations, such a study may also have clinical relevance with regard to treatment of auditory hallucinations.

Cognitive basis of hallucinations in schizophrenia
In chapter 13 an overview is given of theory and findings regarding hallucinations in schizophrenia. Besides providing a general introduction to hallucinations in schizophrenia, the aim of this chapter is to critically discuss neurocognitive theories that have been proposed in recent years. To this end, behavioral and neuroimaging evidence is extensively reviewed. Subsequently, applying the cognitive neuropsychiatric approach, chapter 14 investigates whether a distorted balance between imagery and perception could underlie hallucinations. A continuously hallucinating patient is contrasted with five non-hallucinating
patients on multiple behavioral measures of imagery and perception. As an extension of this design, chapter 15 reports a group study in which patients with and without hallucinations are compared on measures of imagery/perception and reality monitoring. Specifically, the aim of this study is to replicate the finding of reality monitoring errors in relation to hallucinations, and, more importantly, to investigate whether differences in imagery vividness underlie such errors.

Finally, chapter 17 provides a summary and discussion of the findings reported in this thesis.

In sum, this work starts from the assumption that hallucinations can be studied in isolation using a cognitive neuropsychiatric approach. The main hypothesis that is investigated states that hallucinations form a continuum from subjective experiences that are common in the normal population to those reported by patients with schizophrenia (and other patients), and are, at least partly, secondary to cognitive distortions that are common in such patients. In addition, these cognitive alterations can be related to certain brain areas that may be compromised in schizophrenia. More specifically, the hypothesis is tested that abnormal mental imagery may be crucial in the false attribution of internally generated messages or other types of information as coming from the outside.
References


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