Cognitive neuropsychiatry of hallucinations in schizophrenia

How the brain misleads itself

Cognitieve neuropsychiatrie van hallucinaties bij schizofrenie: hoe het brein zichzelf misleidt

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de Rector Magnificus, Prof. Dr. W.H. Gispen, ingevolge van het besluit van het College voor Promoties in het openbaar te verdedigen, op D.V. vrijdag 6 april 2001 des ochtends te 10.30 uur

door

Andreas Aleman

geboren op 20 juni 1975, te Leiden

Promotores: Prof. Dr. E.H.F. de Haan
Prof. Dr. R.S. Kahn

Co-promotores: Dr. K.B.E. Böcker
Dr. R. Hijman

The research reported in this thesis was made possible by a grant from the Netherlands Organisation for Scientific Research (NWO), MaG 575-25-007.

The studies were conducted at the Psychological Laboratory (Department of Psychonomics), Utrecht University; Department of Psychiatry, University Medical Center Utrecht; and the Helmholtz Instituut (accredited by the Royal Netherlands Academy of Arts and Sciences, KNAW).

Publication of this thesis was financially supported by: NWO, AstraZeneca B.V., Neotonus Inc., and UCB Pharma B.V.

Cognitive neuropsychiatry of hallucinations in schizophrenia

How the brain misleads itself

André Aleman

ISBN 90-393-2667-3

Printed in the Netherlands by Ridderprint Offsetdrukkerij B.V.
Cover illustration: Alline Aleman

Aan mijn ouders
Voor Finnie

Immers wandelt de mens als in een beeld...

PSALM 39:7

Table of contents

Chapter 1

Introduction: Neuropsychiatry of hallucinations

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 &

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

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 succesfully 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 lenght 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 succesful 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 confouding 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 allready 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 primary 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 neuroscience 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

Akbarian, S., Kim, J.J., Potkin, S.G. et al. (1996). Maldistribution of interstitial neurons in prefrontal white matter of the brain of schizophrenic patients. *Archives of General Psychiatry, 53,* 425-436.

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.* Washington, DC: APA.

Andreasen, N.C., Flaum, M., Swayze, V. et al. (1990). Positive and negative symptoms in schizophrenia. A critical reappraisal. *Archives of General Psychiatry, 47,* 615-621.

Andreasen, N.C., Arndt, S., Swayze, V. et al. (1994). Thalamic abnormalities in schizophrenia visualized through magnetic resonance image averaging. *Science, 266,* 294-298.

Bentall, R.P. (1990). The syndromes and symptoms of psychosis: or why you can't play twenty questions with the concept of schizophrenia and hope to win. In R.P. Bentall (Ed), *Reconstructing schizophrenia* (pp. 23-60). London: Routledge.

Bilder, R.M., Goldman, R.S., Robinson, D., et al. (2000). Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *American Journal of Psychiatry, 157,* 549-559.

Brzustowicz, L.M., Hodgkinson, K.A., Chow, E.W., Honer, W.G., & Bassett, A.S. (2000). Location of a major susceptibility locus for familial schizophrenia on chromosome 1q21-q22. *Science, 288,* 678-682.

Cannon, T.D. (1996). Abnormalities of brain structure and function in schizophrenia: implications for aetiology and pathophysiology. *Annals of Medicine, 28,* 533-539.

Caramazza, A. (1986). On drawing inferences about the structure of normal cognitive systems from the analysis of patterns of impaired performance: the case for single-patient studies. *Brain and Cognition, 5,* 41-66.

Costello, C.G. (1992). Research on symptoms versus research on syndromes: arguments in favour of allocating more time to the study of symptoms. *British Journal of Psychiatry, 160,* 304-308.

David, A.S. (1993). Cognitive neuropsychiatry? *Psychological Medicine, 23,* 1-5.

Deakin, J.F.W. (1996). Neurobiology of schizophrenia. *Current Opinion in Psychiatry, 9,* 50-56.

De Haan, E.H.F., Young, A.W., & Newcombe, F. (1991). Covert and overt recognition in prosopagnosia. *Brain, 114,* 2575-2591.

Faraone, S.V., Matise, T., Svrakic, D. et al. (1998). Genome scan of European-American schizophrenia pedigrees: results of the NIMH Genetics Initiative and Millennium Consortium. *American Journal of Medical Genetics, 81,* 290-295.

Goldacre, M., Shiwach, R., & Yeates, D. (1994). Estimating incidence and prevalence of treated psychiatric disorders from routine statistics: the example of schizophrenia in Oxfordshire. *Journal of Epidemiology and Community Health, 48,* 318-22.

Gottesman, I.I. (1991). *Schizophrenia genesis: The origins of madness.* New York (NY): W. H. Freeman and Co, Publishers.

Green, M.F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? *American Journal of Psychiatry, 153,* 321-330.

Green, M.F. (1998). *Schizophrenia from a neurocognitive perspective: Probing the impenetrable darkness.* Boston: Allyn & Bacon.

Harrison, P.J. (1999). The neuropathology of schizophrenia: a critical review of the data and their interpretation. *Brain, 122,* 593-624.

Heinrichs, R.W., & Zakzanis, K.K. (1998). Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology, 12,* 426-445.

Hulshoff Pol, H.E., Schnack, H.G., Mandl, R.C.W., van Haren, N.E.M., Koning, H., Collins, D.L., Evans, A.C. & Kahn, R.S. *Focal gray matter density changes in schizophrenia..* (Manuscript submitted for publication).

Iacono, W.G. & Beiser, M. (1992). Are males more likely than females to develop schizophrenia? *American Journal of Psychiatry, 149,* 1070-1074.

Jablensky, A. (1995). Schizophrenia: the epidemiological horizon. In S.R. Hirsch & D.R. Weinberger (Eds.), *Schizophrenia.* (pp. 206-252). Oxford: Blackwell.

Johnstone, E.C., Crow, T.J., Frith, C.D., et al. (1976). Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet, ii,* 924-926.

Jones, P. & Cannon, M. (1998). The new epidemiology of schizophrenia. *Psychiatric Clinics of North America, 21*, 1-25.

Kalus, P., Muller, T.J., Zuschratter, W. et al. (2000). *Neuroreport, 11,* 3621-3625.

Kaplan, H.I., Sadock, B.J., & Grebb, J.A. (1994). *Synopsis of Psychiatry.* Baltimore: William & Wilkins.

Lawrie, S.M., & Abukmeil, S.S. (1998). Brain abnormality in schizophrenia: a systematic and quantitative review of volumetric magnetic resonance imaging studies. *British Journal of Psychiatry, 172,* 110-120.

Lewis, S.W., & Murray, R.M. (1987). Obstetric complications, neurodevelopmental deviance, and risk of schizophrenia. *Journal of Psychiatric Research, 21,* 413-421.

Liddle, P.F. (1996). Functional imaging – schizophrenia. *British Medical Bulletin, 52,* 486-494.

Marcelis, M., Navarro-Mateu, F., Murray, R., Selten, J.P., & Van Os, J. (1998). Urbanization and psychosis: a study of 1942-1978 birth cohorts in the Netherlands. *Psychological Medicine, 28,* 871-879.

McCarley, R.W., Wible, C.G., Frumin, M. et al. (1999). MRI anatomy of schizophrenia. *Biological Psychiatry, 45,* 1099-1119.

McGlashan, T.H. & Hoffman, R.E. (2000). Schizophrenia as a disorder of developmentally reduced synaptic connectivity. *Archives of General Psychiatry, 57,* 637-648.

Mojtabai, R., & Rieder, R.O. (1998). Limitations of the symptom-oriented approach to psychiatric research. *British Journal of Psychiatry, 173*, 198-202.

Mortimer, A.M. & McKenna, P.J. (1994). Levels of explanation – symptoms, neuropsychological deficit and morphological abnormalities in schizophrenia. *Psychological Medicine, 24,* 541-545.

Murray, R.M. (1997). Schizophrenia. In R. Murray, P. Mill & P. McGuffin (Eds.), *The essentials of postgraduate psychiatry*. Cambridge: Cambridge University Press. (pp. 281-309).

Nelson, M.D., Saykin, A.J., Flashman, L.A., & Riordan, H.J. (1998). Hippocampal volume reduction in schizophrenia as assessed by magetic resonance imaging: a meta-analytic study. *Archives of General Psychiatry, 55,* 433-440.

Palmer, B.W., Heaton, R.K., Paulsen, J.S. et al. (1997). Is it possible to be schizophrenic yet neuropsychologically normal? *Neuropsychology, 11*, 437-446.

Persons, J.B. (1986). The advantages of studying psychological phenomena rather than psychiatric diagnoses. *American Psychologist, 41,* 1252-1260.

Randolph, C., Goldberg, T.E., & Weinberger, D.R. (1993). The neuropsychology of schizophrenia. In K.M. Heilman & E. Valenstein, *Clinical Neuropsychology*. Oxford: Oxford University Press. (pp. 499-522).

Raz, S. & Raz, N. (1990). Structural brain abnormalities in the major psychoses: A quantitative review of the evidence from computerized imaging. *Psychological Bulletin, 108,* 93-108.

Scheepers, F.E., De Wied, C.C., Van de Flier, W., Van der Linden, J.A., & Kahn, R..S. (2001). The effect of clozapine on caudate nucleus volume in schizophrenic patients previously treated with typical antipsychotics. *Neuropsychopharmacology, 24*, 47-54.

Schelin, E.M., Munk-Jorgensen, P., Olesen, A.V., & Gerlach, J. (2000). Regional differences in schizophrenia incidence in Denmark. *Acta Psychiatrica Scandinavica, 101,* 293-299.

Shallice, T. (1988). *From neuropsychology to mental structure.* Cambridge University Press: Cambridge.

Shallice, T., Burgess, P.W., & Frith, C.D. (1991). Can the neuropsychological case-study approach be applied to schizophrenia? *Psychological Medicine, 21,* 661-673.

Staal, W.G., Hulshoff Pol, H.E., & Kahn, R.S. (1999). Outcome of schizophrenia in relation to brain abnormalities. *Schizophrenia Bulletin, 25,* 337-347.

Staal, W.G., Hulshoff Pol, H.E., Schnack, H., Van der Schot, A.C., & Kahn, R.S. (1998). Partial volume decrease of the thalamus in relatives of patients with schizophrenia. *American Journal of Psychiatry, 155,* 1784-1786.

Sommer, I.E., Aleman, A., Ramsey, N.F., Bouma, A., & Kahn, R.S. (2001). Handedness, laterality and asymmetry in schizophrenia: a review and meta-analysis. *British Journal of Psychiatry,* in press.

Torrey, E.F., Miller, J., Rawlings, R., & Yolken, R.H. (1997). Seasonality of births in schizophrenia and bipolar disorder: a review of the literature. *Schizophrenia Research, 28,* 1-38.

Tsuang, M. (2000). Schizophrenia: genes and environment. *Biological Psychiatry, 47*, 210-220.

Wahlberg, K.E., Wynne, L.C., Oja, H., Keskitalo, P., Pykalainen, L., Lahti, I., et al. (1997). Gene-environment interaction in vulnerability to schizophrenia: Findings from the Finnish adoptive family study of schizophrenia. *American Journal of Psychiatry, 154*, 355-362.

Weickert, T.W., Goldberg. T.E., Gold, J.M., Bigelow, E.B., Egan, M.F., & Weinberger, D.R. (2000). Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. *Archives of General Psychiatry, 57,* 907-913.

Weinberger, D.R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry, 44,* 660-670.

Weinberger, D.R. (1996). On the plausibility of "the neurodevelopmental hypothesis" of schizophrenia. *Neuropsychopharmacology, 14(Suppl 3),* 1S-11S.

Zakzanis, K.K., & Heinrichs, R.W. (1999). Schizophrenia and the frontal brain: A quantitative review. *Journal of the International Neuropsychological Society, 5,* 556-566.

Zakzanis, K.K., Poulin, P., Hansen, K.T., & Jolic, D. (2000). Searching the schizophrenic brain for temporal lobe deficits: a systematic review and meta-analysis. *Psychological Medicine, 30,* 491-504.

Chapter 2

Memory impairment in schizophrenia

Summary

We present meta-analyses of the published literature on recall and recognition memory performance in patients with schizophrenia compared with normal controls. Tests of categorical models were used in analyses of potential moderators (clinical variables and study characteristics). Our findings (integrating the results of 70 studies) reveal a significant and stable association between schizophrenia and memory impairment. The composite effect size for recall performance was large, d=1.21. Recognition showed less, but still significant, impairment, d=0.64. The magnitude of memory impairment was not affected by age, medication, duration of illness, patient status, severity of psychopathology or positive symptoms. Negative symptoms showed a small, but significant relation with memory impairment. In conclusion, this meta-analysis documents significant memory impairment in schizophrenia. The impairment is stable, wide ranging and not substantially affected by potential moderating factors such as severity of psychopathology and duration of illness.

Aleman, A., Hijman, R., De Haan, E.H.F., & Kahn, R.S. (1999). Memory impairment in schizophrenia: a meta-analysis. *American Journal of Psychiatry, 156*, 1358-1366.

During the last decades, evidence has accumulated that schizophrenia is associated with significant impairment in cognitive functioning. Specifically, deficits in attention, memory and executive functions have been consistently reported in patients with schizophrenia (1-3). In contrast, formal assessment of perceptual processes and basic language functions does not show gross impairment (3). Memory has been regarded as one of the major areas of cognitive deficit in schizophrenia (4). Although the pioneers of schizophrenia research, Kraepelin (5) and Bleuler (6), considered memory functions to be relatively preserved in schizophrenia, numerous studies conducted in the second half of this century have shown patients with schizophrenia to perform poorly on a wide range of memory tasks (3, 7, 8). Recent studies indicate memory impairment in schizophrenia to be common and disproportionate to the overall level of intellectual impairment (9, 10). McKenna and colleagues (11) have even suggested the existence of a “schizophrenic amnesia”.

However, other authors consider the memory impairment to be relatively small in magnitude, or secondary to attentional dysfunction (12-15). In addition, the specificity of memory impairment in schizophrenia is unclear. It has been suggested that, in schizophrenia, some aspects of memory may be affected to a greater extent than others. This would be the case, for example, for active retrieval (free recall) of declarative information from long-term memory, which would be significantly more impaired in schizophrenics than retrieval from short-term memory, e.g. digit span (16). Also, some authors have proposed that encoding of information may be more affected than memory processes such as retrieval and recognition (17, 18). In contrast, other studies report that the memory deficit in schizophrenia encompasses a broad range of memory processes, as evidenced by poor scores in multiple task paradigms (7, 10, 19, 20). Other important issues regarding schizophrenia and memory performance which remain unclear are whether memory functioning in schizophrenia is stable over time, whether chronic patients exhibit greater memory impairment than acutely ill schizophrenics, and whether effects of medication may account for a significant portion of the observed memory impairment.

Meta-analysis represents a type of reviewing that applies a quantitative approach with statistical standards comparable to primary data analysis. A meta-analytical approach has several advantages above traditional narrative ways of reviewing. By quantitatively combining the results of a number of studies, the power of the statistical test is increased substantially. Also, studies are differentially weighted with varying sample size. Finally, by extracting information quantitatively from existing studies, meta-analysis allows one to examine more precisely the influence of potential moderators of effect size.

The aim of the present study was twofold. First, to determine the magnitude, extent and pattern of the memory impairment in schizophrenia by meta-analytically synthesizing the data from existing studies published during the past two decades. The second purpose was to examine the effect of potential moderator variables like clinical variables (e.g. age, patient status, medication) and study characteristics (e.g., matching of controls, year of publication) on the association between schizophrenia and memory impairment.

Method

Literature search

Articles for consideration were identified through an extensive literature search in PsycLIT and Medline, from 1975 through july 1998. Key words were 'memory' and 'schizophrenia'. The search produced over 750 unique studies. Titles and abstracts of the articles were examined for possible inclusion in our analysis. Additional titles were obtained from the bibliographies of the obtained articles and a journal-by-journal search for all months of 1997 and the first half of 1998 of journals that to our perception most frequently publish articles in the targeted domain. This strategy was adopted in order to minimize the possibility of overlooking studies that may not yet have been included in the computerized databases. The journals included *American Journal of Psychiatry*, *Archives of General Psychiatry*, *Journal of Abnormal Psychology*, *Psychological Medicine*, *Schizophrenia Bulletin*, and *Schizophrenia Research.*

The identified studies had to meet the following inclusion criteria. First, each study had to include valid measures of explicit memory performance. We included the following paradigms: digit span (forward and backward), cued and free list recall and word list recognition, paired-associate recall, prose recall, and nonverbal (visual pattern) recall and recognition. Second, studies had to compare performance of a healthy normal control group with performance of patients with schizophrenia. Studies with a control group consisting of nonpsychotic subjects with a higher risk for schizophrenia (e.g. first degree relatives or subjects with schizotypal traits) were not included in the analyses. Finally, studies had to include sufficient data for the computation of a d value, which implies that means and SDs, exact p values, t values or exact F values and relevant means should be reported. We obtained 70 studies (refs. 21-84) that met the criteria for inclusion in our meta-analysis.

Data collection and analysis

By comparing measures of free recall, cued recall and recognition, we examined the effect of retrieval support on memory performance in schizophrenic patients compared to normal controls. In free recall measures, retention is measured in the absence of any cues, while in cued recall tests a portion of the encoding context is presented at the time of retrieval. In recognition, the target material is presented along with distracters, and the subject is required to differentiate between target material and distracters. The learning curve refers to the increase in recall of information with different learning trials. Furthermore, we investigated the influence of the nature of the stimuli used in the memory tasks (verbal vs. nonverbal). Finally, we evaluated the role of retention interval, which could be immediately after presentation of the to-be-learned material, or after a delay.

From the data reported in each study, we calculated effect sizes for the difference in memory performance between schizophrenic patients and normals. The effect size estimate used was Hedges g (85), the difference between the mean of the schizophrenic group and the mean of the control group, divided by the pooled standard deviation. From these g's an unbiased estimation, d, was calculated, to correct for upwardly biased estimation of the effect in small sample sizes (85, 86). The direction of effect size was positive if the performance of schizophrenic patients on memory measures was worse than that of controls.

The combined d value is an indication of the magnitude of associations across all studies. In addition to d, we calculated another statistic, Stouffer's Z weighted by sample size, with a corresponding probability level (86). This statistic provides an indication of the significance of the difference between memory performance in the schizophrenic and the control group, and thus indicated whether the results could have arisen by chance. We also calculated a chi-square statistic, Q, indicating the homogeneity of results across studies (87). Significance of the Q-statistic points to heterogeneity of the set of studies, in which case a further search of moderator variables is needed. In the moderator analyses, Q_W denotes heterogeneity of studies within categories. The Q_B-statistic refers to a test of differences between categories. This between-group homogeneity statistic is analogous to the F statistic. All analyses were performed with the statistical package META (88).

When more than one dependent measure was used as an indication of memory performance, a pooled effect size was computed in order to prevent data from one study from dominating the outcome of the overall meta-analysis. For example, in studies reporting data on free and cued recall of verbal and nonverbal stimuli, for each study a combined d was calculated for inclusion in the overall analysis. However, in subsequent analyses, we only included the data pertaining to the specific category of our aim. Thus, for example, in the meta-analysis of differences between schizophrenic patients and controls in cued recall performance, only data of cued recall measures were included in the analysis. In a similar way, when a study reported data for subgroups like first-episode versus chronic schizophrenic patients, in the overall analysis the d's were pooled, but in the moderator analysis of duration of illness the d's were included separately in the analysis.

In the case of twin studies (e.g. Goldberg et al. [44]) the patients were compared with normal control twins. Thus, the unaffected siblings of identical twins discordant for schizophrenia were not included in the analyses. Furthermore, in studies wherein data were reported for different subgroups (e.g., male/female, paranoid/nonparanoid), data were pooled across subgroups, which were then compared as one group with performance of the control group.

When we encountered different studies in which data were reported concerning the same sample of subjects, only one of the studies was included in the analysis, in order to avoid the problem of dependent data (i.e. to prevent one sample from dominating the outcome). For example, in the study by Goldberg et al. (89) the same subjects were included as in Goldberg et al. (44). We only included Goldberg et al. (44) in the analysis, because the sample in this study contained more subjects than the sample in Goldberg et al. (89).

Publication bias

In order to examine the possibility of publication bias, we computed a fail-safe N (90, 86). Publication bias implies that studies with no effect may not get published and remain in file drawers, and may pose a threat to the stability of the obtained effect size. The fail-safe N statistic indicates the number of studies with null effects that must reside in file drawers before the results of the obtained effect sizes are reduced to a negligible level (which we set at 0.2). Publication bias can also be inspected graphically in a funnel plot (91). The total sample size of each study is plotted with its effect size. As larger studies will more influence the population effect size, small studies should be randomly scattered about the central effect size of the larger studies. Thus, scatter will increase when study size decreases, which gives rise to an inverted funnel appearance. When the portion of the funnel near effect size 0 is not present, this may be an indication of publication bias due to studies with nonsignificant effects and small samples not being published.

Moderator variables

The literature suggests a number of variables that may affect memory performance of schizophrenic patients. We evaluated the potential influence on effect size of several such factors using categorical models. The moderator variables we studied can be divided in two groups: clinical variables and study characteristics. The clinical variables included age of subjects, patient status (inpatient or outpatient), medication status, duration of illness, severity of psychopathology and the influence of positive and negative symptoms. For the analysis of severity of psychopathology we only included studies reporting Brief Psychiatric Rating Scale (BPRS) scores. Other psychopathology measures such as the Positive and Negative Syndrome Scale (PANSS) were not included because of a lack of studies. For positive and negative symptoms the scales included in the analysis were the Scale for Assessment of Positive Symptoms (SAPS) and the Scale for Assessment of Negative Symptoms (SANS), respectively. The groups were divided by means of a median split.

Study characteristics were year of publication (before and after 1986, the median of the period covered in the literature search), sample size, and whether schizophrenic and control groups were matched for age and level of education. Unfortunately, sex differences, differential performance of diagnostic subgroups (e.g., paranoid/nonparanoid), task difficulty and reliability, and moderating effects of attentional dysfunction could not be studied, due to the very small number or total lack of studies reporting exact results for these parameters.

Results

Table 1 displays the results of meta-analyses on schizophrenia/control differences in performance on several memory measures: verbal and nonverbal, cued and free recall, delayed and immediate; verbal and nonverbal recognition; short-term memory (digit span) and encoding (learning curve).

Combined schizophrenia-memory effect sizes

As can be seen in table 1, memory is significantly impaired in schizophrenia. All analyses yielded highly significant Z-values for the difference in memory performance between patients with schizophrenia and controls. The magnitude of the overall effect size of the composite long-term recall measures was large, d=1.21. In this overall analysis, 60 studies were included with a total sample size of 3315 (with study sample ranging from N=16 to N=254). Effect sizes ranged from 0.44 to 3.10. The homogeneity statistic showed significant heterogeneity among studies. The funnel plot (figure) demonstrates the characteristic inverted funnel. However, the lower left portion of the funnel is less pronounced than the right part, suggesting some bias in not publishing small studies with no effect. The fail-safe N, at a critical d of 0.20, was 303. This implies that 303 unpublished null-effect studies are necessary to reduce our effects to a size of 0.20. Fail-safe N's for the other analyses were also large enough to lend credence to our findings.

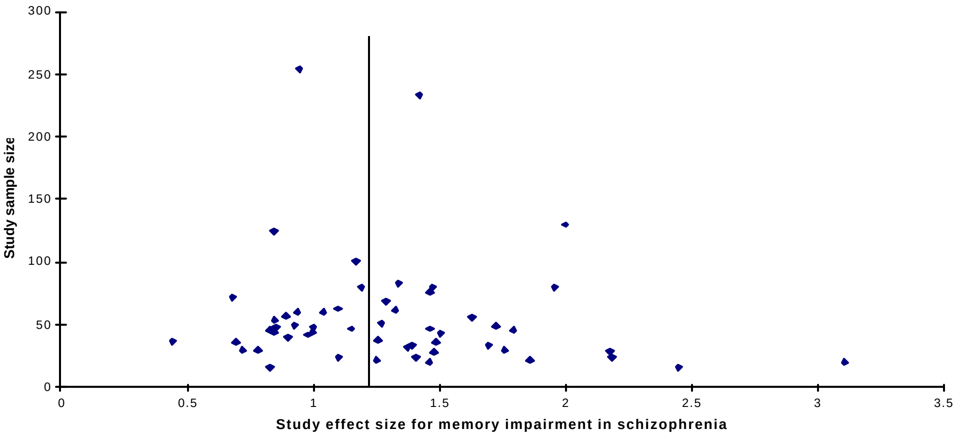

Figure. Funnel plot for the meta-analysis on composite recall measures. Each point represents the position of a single study. The vertical line indicates the mean weighted effect size.

Analyses of short-term memory (digit span) and encoding also revealed significant memory impairment, although to a considerable lesser degree than for recall measures. The difference between forward (d=0.71) and backward (d=0.82) digit span was not significant (Q_B=0.6, df=1, p>0.10).

Effects of task characteristics

Level of retrieval support. Schizophrenic patients show significantly better memory performance when retrieval cues are provided, as evidenced by the d of 1.20 in delayed free recall versus a d of 0.78 in cued recall (Q_B=11.6, df=1, p<0.001). However, the difference in performance on cued recall measures between normals and schizophrenics remains considerable. Recognition also showed significant less impairment than recall (Q_B=58.1, df=1, p<0.0001), but the difference with control performance remains substantial (d=0.64). As can be seen in table 1, the Q_W statistics indicate homogeneous within group d values.

Stimulus type. Verbal and nonverbal recall both show significant d values (p<0.0001). Although impairment for verbal material in the delayed recall condition (d=1.20) seemed larger than for nonverbal material (d=1.09), this difference was not significant. This was also the case for the immediate condition. For the recognition measures, the reverse pattern was observed: retrieval of verbal material (d=0.61) appeared to be less impaired than retrieval of nonverbal material (d=0.73), but again the difference did not reach significance.

Retention interval. The length of the retention interval did not affect the magnitude of d values. The difference between delayed (d=1.20) and immediate (d=1.22) verbal recall was not significant.

Table 1. Results of meta-analyses of schizophrenia/control differences in memory performance

	k	N	d	Z[a]	95%CI	Q_W[b]	Fail Safe-N
Total recall	60	3315	1.21	20.5	1.09-1.33	101.6[d]	303
verbal							
delayed	35	1910	1.20	17.5	1.06-1.33	61.4[d]	175
free	33	1740	1.20	18.9	1.08-1.33	42.2[c]	165
cued	7	342	0.78	5.7	0.51-1.05	9.25[c]	0
immediate	33	1734	1.22	11.7	1.01-1.42	79.8[d]	168
free	31	1666	1.27	11.3	1.05-1.48	81.5[d]	165
cued	11	722	0.95	10.4	0.77-1.12	10.4[c]	1
nonverbal							
delayed	11	800	1.09	7.8	0.82-1.37	21.0[d]	49
immediate	7	294	1.00	5.3	0.62-1.36	8.9[c]	28
Total recognition[f]	17	1024	0.64	9.6	0.51-0.77	15.7[c]	37
verbal							
Hit rate	12	771	0.61	7.8	0.45-0.76	13.4[c]	24
False alarm	3	381	0.58	5.3	0.36-0.80	2.5[c]	6
Discriminability	5	436	0.72	7.0	0.52-0.93	2.8[c]	13
nonverbal							
Hit rate	8	347	0.73	5.1	0.45-1.00	5.8[c]	21
Digit Span							
forward	18	881	0.71	9.2	0.56-0.86	17.8[c]	46
backward	7	306	0.82	4.8	0.49-1.16	11.8[c]	22
Learning curve	4	399	0.60	3.3	0.24-0.94	9.43[c]	8

k=number of studies; N=total number of subjects; d=mean weighted effect size; Z=Stouffer's Z for significance of effect size; 95%CI=95% confidence interval; Q_W=within category homogeneity statistic; Fail-safe N=the number of unrecovered studies with null results that would be required to reduce d to 0.20. [a]All Z values are significant, $p<0.0001$. [b]df=k-1. [c]Not significant. [d]Significant, $p<0.01$. [f]Verbal + nonverbal, hit-rate only.

Potential moderators of effect size

Clinical variables. Table 2 shows the influence of potential moderator variables. The Q_B statistic only reveals a significant effect of negative symptoms, $Q_B=4.1$, df=1, $p<0.05$. Negative symptoms affected memory performance negatively. Age was not associated with memory impairment in schizophrenia in the categorical analysis. We also examined the exact correlation between age and *d* values, which was nonsignificant, r=0.14, N=57, p>0.10. Although in the categorical analyses the two groups differed significantly in age (p<0.001), the range of the group as a whole was rather restricted (mean=32.4 years, SD=5; range from 15.7 to 42.8).

Table 2. Analyses of potential moderators of effect size, clinical variables

	k	N	d	Z	95% CI	QW	QB
Age (yrs)							
<30	18	1040	1.13	10.1	0.91-1.35	30.7[d]	1.6[d]
30	39	2264	1.23	16.9	1.09-1.38	96.1[e]	
Medication							
Yes	50	2629	1.19	18.4	1.06-1.32	77.2[e]	1.3[d]
No	6	467	1.32	7.5	0.98-1.67	10.6[d]	
Duration of illness							
2 yrs	15	792	1.17	11.5	0.97-1.37	21.3[d]	0.1[d]
>2 yrs	36	2093	1.19	16.0	1.04-1.33	50.4[d]	
Patient status							
Inpatient	37	1755	1.27	15.4	1.11-1.43	61.3[e]	2.2[d]
Outpatient	8	508	1.11	10.5	0.90-1.32	8.3[d]	
Severity of psychopathology							
BPRS 35	6	536	1.30	7.8	0.97-1.63	13.3[d]	0.8[d]
BPRS>35	8	534	1.18	7.8	0.88-1.47	10.1[d]	
Positive symtomps							
SAPS 7	5	539	1.11	7.3	0.81-1.40	6.4[d]	0.1[d]
SAPS>7	6	576	1.16	13.7	1.16-1.55	5.9[d]	
Negative symptoms							
SANS 12.5	6	707	1.11	9.02	0.87-1.34	6.8[d]	4.1[f]
SANS>12.5	7	507	1.37	13.5	1.17-1.57	5.9[d]	

k=number of studies; N=total number of subjects; d=mean weighted effect size; Z=Stouffer's Z for significance of effect size; 95%CI=95% confidence interval; Q_W=within homogeneity statistic, Q_B=between homogeneity statistic. [a]All Z values are significant, p<0.0001. [b]df=k-1. [c]df=1. [d]Not significant. [e]Significant, p<0.01. [f]p=0.04.

Medication status, duration of illness, severity of psychopathology and positive symptoms were not associated with memory impairment. For duration of illness it was not possible to calculate a correlation coefficient because a great number of studies did not report exact values, and studies differed in their definition of disease onset. For the other parameters, the number of studies was to small in order to interpret meaningfully the r value.

Study characteristics. Studies that did not match controls for age and education showed a greater association between schizophrenia and poor memory performance than matched-control studies, Q_B=5.7, df=1, p=0.02. Notwithstanding, the d for matched-control studies remained considerable, d=1.17. For the other study characteristics, number of subjects and year of publication, no relation was found with d values (table 3).

Table 3. Analyses of potential moderators of effect size, study characteristics

	k	N	d	Z	95% CI	Q_W	Q_B
Matched controls							
Yes	38	2290	1.17	19.2	1.05-1.29	51.6[d]	5.7[f]
No	16	780	1.39	9.4	1.10-1.86	36.2[d]	
Number of subjects							
N 50	33	1132	1.21	13.1	1.03-1.40	45.2[d]	0.1
N>50	20	1846	1.24	14.1	1.06-1.41	50.1[e]	
Year of publication							
1985	14	485	1.31	7.0	0.94-1.68	28.9[e]	0.99
>1985	45	2829	1.18	70.4	1.08-1.28	70.4[e]	

k=number of studies; N=total number of subjects; d=mean weighted effect size; Z=Stouffer's Z for significance of effect size; 95%CI=95% confidence interval; Q_W=within homogeneity statistic, Q_B=between homogeneity statistic. [a]All Z values are significant, $p<0.0001$. [b]df=k-1. [c]df=1. [d]Not significant. [e]Significant, $p<0.01$. [f]$p=0.02$.

Discussion

The purpose of this study was to investigate whether and to what extent schizophrenia is associated with memory impairment and whether this association is influenced by potential moderator variables. The results of the meta-analysis indicate that schizophrenia and memory dysfunction are significantly associated, as evidenced by moderate to large effect sizes.

Our meta-analysis corroborates and extends the findings of a recent meta-analysis (92) in which performance on multiple measures of neurocognitive function was contrasted between schizophrenic patients and normal controls. With regard to differences in memory performance, Heinrichs and Zakzanis (92) also report moderate to large effect sizes for the memory variables they studied, which included verbal and nonverbal long-term memory.

The d for recall was 1.21, which indicates a large effect size according to the nomenclature of Cohen (93). Thus, performance of schizophrenic patients is more than 1 SD lower than that of normal controls on tasks of recall memory. A recent meta-analysis on memory impairment in depression (94) revealed a d of 0.56 (54 studies) for recall performance of depressive patients compared with normal controls. When comparing these results with our present analysis, the memory deficit in schizophrenia appears to be substantially greater than in depression. The d for recognition was 0.64, which can be considered a moderate effect size (93). The difference in recall versus recognition performance may point to a retrieval deficit, in addition to less effective consolidation of material.

Alternatively, the recall-recognition difference may be an artifact of the differences in difficulty between recall and recognition tests. However, studies in which tasks were matched for difficulty level also report greater impairment in recall than recognition (33, 34). The finding of a considerable memory deficit in schizophrenia supports the view that memory belongs to the cognitive domains which show major impairment in schizophrenia (3, 4). However, the lack of difference between immediate and delayed recall does not appear to be in accordance with schizophrenia as an "amnestic syndrome" (11). Measures of short-term memory performance showed significant impairment. This result appears to contradict the assertion by Clare et al. (40) that short-term memory is preserved in schizophrenia. The divergence may result from the fact that Clare et al. base their conclusion on one study only, while the present study concerns a quantitative integration of multiple studies. Furthermore, our meta-analysis provides evidence that the learning curve (which reflects explicit encoding of information) is significantly affected in schizophrenia. The large difference between recall of information after a delay (composite delayed recall, d=1.20) and learning curve (d=0.60) suggests that the memory dysfunction in schziophrenia is not entirely due to deficient learning processes (as has been argued by Heaton et al.[17]), but that retrieval processes may also be affected. However, caution is needed in interpreting this finding, considering that digit span and learning curve indices may not reflect all "encoding" processes.

The results failed to reveal a difference in memory impairment for verbal and nonverbal (visual pattern) stimuli. Thus, the memory impairment in schizophrenia does not appear to be modality specific.

The present meta-analysis indicates memory impairment in schizophrenia to be wide ranging and consistent across task variables such as level of retrieval support (free recall, cued recall or recognition), stimulus type (verbal vs. nonverbal) and retention interval (immediate vs. delayed). The extent of the memory impairment may appear to be in accordance with a pattern of generalized dysfunction rather than a differential deficit (95). However, our study was restricted to memory functions, whereas conclusions regarding the generalized versus differential nature of neurocognitive dysfunction in schizophrenia must also include evaluation of functioning in other cognitive domains. Indeed, the recent meta-analysis by Heinrichs and Zakzanis (92) in which schizophrenia versus control differences were indexed on multiple measures of memory, attention, intelligence, executive function, language, and motor performance indicated that schizophrenia is characterized by a broadly based cognitive impairment, with varying degrees of deficit in the different ability domains.

On the basis of our results, it is not possible to establish the cause or underlying mechanism of the memory impairment in schizophrenia. For example, we were not able to examine moderating effects of attentional dysfunction. However, given the magnitude and extent of the memory impairment revealed by the meta-analysis, the possibility that the memory impairment may be secondary to attentional dysfunction does not seem very plausible. Moreover, in case of an important attentional contribution to the memory impairment, one would expect performance on the backward digit span test to show a significant greater impairment than the forward digit span test. This was not the case, however. Our findings are in agreement with the study by Kenny and Meltzer (55), who controlled for the influence of attention by analysis of covariance. Controlling for attention had very little effect on the differences in performance on long-term memory recall between schizophrenic patients and controls.

Although the meta-analysis did not address the relation between memory impairment and brain pathology in schizophrenia, the pattern of impairment may be indicative of specific brain dysfunction. Impairments in encoding and consolidation have been associated with hippocampal and temporal lobe dysfunction (96, 97). Brain imaging studies have provided evidence for pathology or reduced volume of these structures in schizophrenia (98). In addition, frontal lobe systems, which may also be affected in schizophrenia, have been shown to be involved in active retrieval of declarative memories (99, 100). More research into the relation between brain dysfunction and memory impairment in schizophrenia is needed before firm conclusions can be drawn on this issue.

Of the potential moderator variables, only negative symptoms affected the schizophrenia-memory association. Although this effect was rather small, it is consistent with previous research examining the relation between negative symptoms and cognitive function in schizophrenia (101, 102). Specifically, negative symptoms have been associated with more pronounced frontal lobe dysfunction, which may account for larger retrieval deficits (102). No relation was found between age and the magnitude of memory impairment. Unfortunately, as all subjects included in the analyses were less than 45 years old, no conclusions can be made regarding the relation between cognitive aging and memory in schizophrenia.

Clinical variables such as medication, duration of illness, patient status, severity of psychopathology and positive symptoms did not appear to influence the magnitude of memory impairment. Thus, the memory impairment in schizophrenia is of a considerable robustness and is not readily moderated by variables that may seem relevant. This is an important finding, as a number of authors have emphasized the role of medication, symptom severity, and chronicity in memory performance of schizophrenic patients (8, 26). Frith (103) even suggested that medication may principally account for the memory deficits observed in schizophrenia. It is instructive to note that our meta-analysis does not address the relation between medication and memory performance directly, but compares performance of unmedicated samples with medicated samples. Differences in medication status may be due to unspecified differences in clinical factors. Our results are consistent, however, with studies examining this relation directly by experimentally controlling for medication (104, 105). It must be emphasized that medication in the studies in our analysis consisted of conventional neuroleptics. Evidence is emerging that novel antipsychotics may have beneficial effects on memory function (106).

As the present meta-analysis demonstrates, there is no evidence of progressive decline associated with age or duration of illness in schizophrenia. Our failure to find an effect of chronicity on memory impairment is in accordance with the view of cognitive deficits in schizophrenia as a “static encephalopathy” (107). The fact that schizophrenic patients with a long duration of illness do not perform worse than more acutely ill patients on memory tasks implies that the concept of “dementia praecox” (5) may not be accurate in the sense of progressive deterioration during the long-term course of the illness. On the other hand, considering the substantial memory deficit in schizophrenia revealed by our analysis, the term dementia praecox may be even more appropriate than Kraepelin himself may have anticipated.

The findings of our meta-analysis have important clinical implications. The substantial memory deficit in schizophrenia is likely to have repercussions on therapy and rehabilitation. A thorough understanding of the cognitive deficits in schizophrenia may prevent future treatment failures (108). For example, insight-related or other therapies that require advanced learning and memory functions are almost certain to turn out ineffective.

The extent and stability of the association between schizophrenia and memory impairment suggest that the memory dysfunction may be a trait rather than a state characteristic. Hypothetically, some degree of memory dysfunction may already be present in subjects at risk for schizophrenia. Future research must concentrate on this issue in order to explore the possible implications with regard to prescreening for schizophrenia.

There is evidence that verbal memory is a rather strong predictor of functional outcome in schizophrenia (109). Improving memory may result beneficial for every day functioning. Therefore, given the considerable memory impairment revealed by our meta-analysis, research focusing on pharmacological treatment and rehabilitation strategies in order to improve memory functioning in patients with schizophrenia is necessary.

References

(References marked with an asterisk indicate studies included in the meta-analysis)

1. Pantelis C, Nelson HE, Barnes TRE, eds: Schizophrenia: a Neuropsychological Perspective. Chichester, Wiley, 1996
2. Bilder RM: Neuropsychology and neurophysiology in schizophrenia. Curr Op Psychiatry 1996;9:57-62
3. Goldberg TE, Gold JM: Neurocognitive functioning in patients with schizophrenia, in Psychopharmacology: the Fourth Generation of Progress. Edited by Bloom FE, Kupfer DJ. New York, Raven, 1995, pp 1245-1257
4. McKenna P, Clare L, Baddeley AD. Schizophrenia, in Handbook of Memory Disorders. Edited by Baddeley AD, Wilson BA, Watts FN. New York, Wiley, 1995, pp 271-292
5. Kraepelin E [Barclay RM, trans-ed.]: Dementia Praecox and Paraphrenia. Edinburgh, Scotland, E & S Livingstone, 1919 (reprinted, Huntington, NY, Krieger, 1971)

6. Bleuler E [Zinkin J, trans-ed.]: Dementia Praecox, or the Group of Schizophrenias. New York, International Universities Press, 1911
7. Landrø NI. Memory function in schizophrenia: Acta Psychiatr Scand 1994;90 (suppl 384):87-96
8. Stip E: Memory impairment in schizophrenia: perspectives from psychopathology and pharmacotherapy. Can J Psychiatry 1996;41 (Suppl 2):27S-34S
9. *Gold JM, Randolph C, Carpenter CJ, Goldberg TE, Weinberger DR: Forms of memory failure in schizophrenia. J Abnorm Psychol 1992;101:487-494
10. *Rund BR: Distractibility and recall capability in schizophrenics: a 4 year longitudinal study of stability in cognitive performance. Schizophr Res 1989;2:265-275
11. McKenna PJ, Tamlyn D, Lund CE, Mortimer AM, Hammond S, Baddeley AD: Amnesic syndrome in schizophrenia. Psychol Med 1990;20:967-972
12. Cutting J: The Psychology of Schizophrenia. Edinburgh, Churchill Livingstone, 1985
13. Nuechterlein KH, Dawson ME: Information processing and attention in the development of schizophrenic disorders. Schizophr Bull 1984;10:160-203
14. Gjerde P: Attentional capacity dysfunction and arousal in schizophrenia. Psychol Bull 1983;93:57-72
15. *Culver LC, Kunen S, Zinkgraf SA: Patterns of recall in schizophrenics and normal subjects. J Nerv Ment Dis 1986;174:620-623
16. *Koh SD, Marusarz TZ, Rosen AJ: Remembering of sentences by schizophrenic young adults. J Abnorm Psychol 1980;89:291-294
17. Heaton R, Paulsen JS, McAdams LA, Kuck J, Zisook S, Braff D, Harris MJ, Jeste DV: Neuropsychological deficits in schizophrenics; relationship to age, chronicity and dementia. Arch Gen Psychiatry 1994;51:469-476
18. McClain L: Encoding and retrieval in schizophrenic free recall. J Nerv Ment Dis 1983;171:471-479
19. *Calev A, Venables PH, Monk AF: Evidence for distinct verbal memory pathologies in severely and mildly disturbed schizophrenics. Schizophr Bull 1983;9:247-263
20. *Saykin AJ, Gur RC, Gur RE, Mozley D, Mozley LH, Resnick SM, Kester DB, Stafiniak P: Neuropsychological function in schizophrenia. Arch Gen Psychiatry 1991;48:618-624
21. *Abbruzzese M, Scarone S: Memory and attention dysfunctions in story recall in schizophrenia: evidence of a possible frontal malfunctioning. Biol Psychol 1993;35:51-58
22. *Albus M, Hubmann W, Mohr F, Scherer J, Sobizack N, Franz U, Hecht S, Borrmann M, Wahlheim C: Are there gender differences in neuropsychological performance in patients with first-episode schizophrenia? Schizophr Res 1997; 28:39-50
23. *Bauman E, Kolisnyk E: Interference effects in schizophrenic short-term memory. J Abnorm Psychol 1976;85:303-308
24. *Bazin N, Perruchet P: Implicit and explicit associative memory in patients with schizophrenia. Schizophr Res 1996; 22:241-248
25. *Binder J, Albus M, Hubmann W, Scherer J, Sobizack N, Franz U, Mohr F, Hecht S: Neuropsychological impairment and psychopathology in first-episode schizophrenic patients related to the early course of illness. Eur Arch Psychiatry Clin Neurosci 1998;248:70-77
26. *Blanchard JJ, Neale JM: The neuropsychological signature of schizophrenia: generalized or differential deficit? Am J Psychiatry 1994;151:40-48
27. *Bornstein RA, Nasrallah HA, Olson SC, Coffman JA, Torello M, Schwarzkopf SB: Neuropsychological deficit in schizophrenic subtypes: paranoid, nonparanoid, and schizoaffective subgroups. Psychiat Res 1990;31:15-24
28. *Braff DL, Heaton R, Kuck J, Cullum M, Moranville J, Grant I, Zisook S: The generalized pattern of neuropsychological deficits in outpatients with chronic schizophrenia with heterogeneous Wisconsin Card Sorting test results. Arch Gen Psychiatry 1991;48:891-898
29. *Brebion G, Smith MJ, Gorman JM, Amador X: Discrimination accuracy and decision biases in different types of reality monitoring in schizophrenia. J Nerv Ment Dis 1997;185:247-253
30. *Brebion G, Amador X, Smith MJ, Gorman JM: Mechanisms underlying memory impairment in schizophrenia. Psychol Med 1997;27:383-393
31. *Broga MI, Neufeld RWJ: Multivariate cognitive performance levels and response styles among paranoid and nonparanoid schizophrenics. J Abnorm Psychol 1981;90:495-509
32. *Buchanan RW, Strauss ME, Kirkpatrick B, Holstein C, Breier A, Carpenter WT: Neuro-psychological impairments in deficit vs nondeficit forms of schizophrenia. Arch Gen Psychiatry

1994;51:804-811
33. *Buckley PF, Moore C, Long H, LarkinC, Thompson P, Mulvany F, Redmond O, Stack JP, Ennis JT, Waddington JL: 1H-Magnetic resonance spectroscopy of the left temporal and frontal lobes in schizophrenia: clinical, neurodevelopmental, and cognitive correlates. Biol Psychiatry 1994; 36:792-800
34. *Calev A: Recall and recognition in mildly disturbed schizophrenics: the use of matched tasks. Psychol Med 1984;14:425-429
35. *Calev A: Recall and recognition in chronic nondemented schizophrenics: use of matched tasks. J Abnorm Psychol 1984;93:172-177
36. *Calev A, Berlin H, Lerer B: Remote and recent memory in long-hospitalized chronic schizophrenics. Biol Psychiatry 1987;22:79-85
37. *Calev A, Nigal D, Kugelmass, Weller MPI, Lerer B: Performance of long-stay schizophrenics after drug withdrawal on matched immediate and delayed recall tasks. Br J Clin Psychol 1991;30:241-245
38. *Calev A, Edelist S, Kugelmass S, Lerer B: Performance of long-stay schizophrenics on matched verbal and visuospatial recall tasks. Psychol Med 1991;21:655-660
39. *Cannon T, Zorrilla LE, Shtasel D, Gur RE, Gur RC, Marco EJ, Moberg P, Price RA: Neuropsychological functioning in siblings discordant for schizophrenia and healthy volunteers. Arch Gen Psychiatry 1994;51:651-661
40. *Cantor-Graae E, Warkentin S, Nilsson A: Neuropsychological assessment of schizophrenic patients during a psychotic episode: persistent cognitive deficit? Acta Psychiatr Scand 1995;91:283-288
41. *Clare L, McKenna PJ, Mortimer AM, Baddeley AD: Memory in schizophrenia: what is impaired and what is preserved? Neuropsychologia 1993;31:1225-1241
42. *Colombo C, Abbruzzese M, Livian S, Scotti G, Locatelli M, Bonfanti A, Scarone S: Memory functions and temporal-limbic morphology in schizophrenia. Psychiat Res: Neuroim 1993;50:45-56
43. *Everett J, Laplante L, Thomas J: The selective attention deficit in schizophrenia. J Nerv Ment Dis 1989;177:735-738
44. *Frame CL, Oltmanns TF: Serial recall by schizophrenic and affective patients during and after psychotic episodes. J Abnorm Psychol 1982;91:311-318
45. *Ganzevles PGJ, Haenen M-A: A preliminary study of externally and self-ordered task performance in schizophrenia. Schizophr Res 1995;16:67-71
46. *Goldberg TE, Weinberger DR, Pliskin NH, Berman KF, Podd MH: Recall memory deficit in schizophrenia: a possible manifestation of prefrontal dysfunction. Schizophr Res 1989;2:251-257
47. *Goldberg TE, Hyde TM, Kleinman JE, Weinberger DR: Course of schizophrenia: neuro-psychological evidence for a static encephalopathy. Schizophr Bull 1993;19:797-804
48. *Goldberg TE, Torrey EF, Gold JM, Ragland JD, Bigelow LB, Weinberger DR: Learning and memory in monozygotic twins discordant for schizophrenia. Psychol Med 1993;23:71-85
49. *Granholm E, Morris SK, Sarkin AJ, Asarnow RF, Jeste DV: Pupillary responses index overload of working memory resources in schizophrenia. J Abnorm Psychol 1997;106:458-467
50. *Gras-Vincendon A, Danion J-M, Grange D, Bilik M, Willard-Schroeder D, Sichel J-P, Singer L: Explicit memory, repetition priming and cognitive skill learning in schizophrenia. Schizophr Res 1994;13:117-126
51. *Hagger C, Buckley P, Kenny JT, Friedman L, Ubogy D, Meltzer HY: Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. Biol Psychiatry 1993;34:702-712
52. *Harvey PD, Earle-Boyer EA, Wielgus MS, Levinson JC: Encoding, memory, and thought disorder in schizophrenia and mania. Schizophr Bull 1986;12:252-261
53. *Harvey PD, Serper MR: Linguistic and cognitive failures in schziophrenia: a multivariate analysis. J Nerv Ment Dis 1990;178:487-494
54. *Hoff AL, Riordan H, O'Donnell DW, Morris L, DeLisi LE: Neuropsychological functioning of first-episode schizophreniform patients. Am J Psychiatry 1992;149:898-903
55. *Hutton SB, Puri BK, Duncan L-J, Robbins TW, Barnes TRE, Joyce EM: Executive function in first-episode schizophrenia. Psychol Med 1998;28:463-473
56. *Kenny JT, Friedman L, Findling RL, Swales TP, Strauss ME, Jesberger JA, Schulz SCS: Cognitive impairment in adolescents with schizophrenia. Am J Psychiatry 1997;154:1613-1615

57. *Kenny JT, Meltzer HY: Attention and higher cortical functions in schizophrenia. J Neuropsychiatry 1991;3:269-275
58. *Koh SD, Kayton L, Peterson RA: Affective encoding and consequent remembering in schizophrenic young adults. J Abnorm Psychol 1976;85:156-166
59. *Kolb B, Whishaw IQ: Performance of schizophrenic patients on tests sensitive to left or to right frontal, temporal, or parietal function in neurological patients. J Nerv Ment Dis 1983;171:435-443
60. *Kwapil TR, Chapman LJ, Chapman JP: Monaural and binaural story recall by schizophrenic subjects. J Abnorm Psychol 1992;101:709-716
61. *Landrø NI, Ørbeck AL, Rund BR: Memory functioning in chronic and non-chronic schizophrenics, affectively disturbed patients and normal controls. Schizophr Res 1993;10:85-92
62. *Lutz J, Marsh TK: The effect of a dual level word list on schizophrenic free recall. Schizophr Bull 1981;7:509-515
63. *Nathaniel-James DA, Brown R, Ron MA: Memory impairment in schizophrenia: its relationship to executive function. Schizophr Res 1996;21:85-96
64. *Park S, Holzman PS: Schizophrenics show spatial working memory deficits. Arch Gen Psychiatry 1992;49:975-982
65. *Paulsen JS, Heaton RK, Sadek JR, Perry W, Delis DC, Braff D, Kuck J, Zisook S, Jeste D: The nature of learning and memory impairments in schizophrenia. J Int Neuropsychol Soc 1995;1:88-99
66. *Radant AD, Claypoole K, Wingerson DK, Cowley DS, Roy-Byrne PP: Relationships between neuropsychological and oculomotor measures in schizophrenia patients and normal controls. Biol Psychiatry 1997;42:797-805
67. *Ragland JD, Censits DM, Gur RC, Glahn DC, Gallacher F, Gur RE: Assessing declarative memory in schizophrenia using Wisconsin Card Sorting Test stimuli: the Paired Associate Recognition Test. Psychiatry Res 1996;60:135-144
68. *Randolph C, Gold JM, Kozora E, Cullum CM: Estimating memory function: disparity of Wechsler Scale- Revised and California Verbal Learning Test indices in clinical and normal samples. Clin Neuropsychol 1994;8:99-108
69. *Russell PN, Beekhuis ME: Organization in memory: a comparison of psychotics and normals. J Abnorm Psychol 1976;85:527-534
70. *Rizzo L, Danion J-M, Van der Linden M, Grange D: Patients with schizophrenia remember that an event has ocurred, but not when. Br J Psychiatry 1996;168:427-431
71. *Salamé P, Danion J-M, Peretti S, Cuervo C: The state of functioning of working memory in schizophrenia. Schizophr Res 1998;30:11-29
72. *Saykin AJ, Shtasel DL, Gur RE, Kester DB, Mozley LH, Stafiniak P, Gur RC: Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. Arch Gen Psychiatry 1994;51:124-131
73. *Schwartz BL, Rosse RB, Deutsch SI: Limits of the processing view in accounting for dissociations among memory measures in a clinical population. Memory and Cognition 1993;21:63-72
74. *Seidman LJ, Stone WS, Jones R, Harrison RH, Mirsky AF: Comparative effects of schizophrenia and temporal lobe epilepsy on memory. J Int Neuropsychol Soc 1998;4:342-352
75. *Shedlack K, Lee G, Sakuma M, Xie S-H, Kushner M, Pepple J, Finer DL, Hoff AL, DeLisi LE: Language processing and memory in ill and well siblings from multiplex families affected with schizophrenia. Schizophr Res 1997;25:43-52
76. *Shoqueirat MA, Mayes AR: Spatiotemporal memory and rate of forgetting in acute schizophrenics. Psychol Med 1988;18:843-853
77. *Speed M, Toner BB, Shugar G, Di Gasbarro I: Thought disorder and verbal recall in acutely psychotic patients. J Clin Psychol 1991;47:735-744
78. *Stefánsson SB, Jónsdóttir TJ: Auditory event-related potentials, auditory digit span, and clinical symptoms in chronic schizophrenic men on neuroleptic medication. Biol Psychiatry 1996;40:19-27
79. *Stirling JD, Hellewell JSE, Hewitt J: Verbal memory impairment in schizophrenia: no sparing of short-term recall. Schizophr Res 1997;25:85-95
80. *Stone M, Gabrieli JDE, Stebbins GT, Sullivan E: Working memory deficits in schizophrenia. Neuropsychology 1998;12:278-288

81. *Stratta P, Daneluzzo E, Prosperini P, Bustini M, Mattei P, Rossi A: Is Wisconsin Card Sorting Test performance related to 'working memory' capacity? Schizophr Res 1997;27:11-19
82. *Sullivan EV, Shear PK, Zipursky RB, Sagar HJ, Pfefferbaum A: Patterns of content, contextual, and working memory impairments in schizophrenia and nonamnesic alcoholism. Neuropsychology 1997;11:195-206
83. *Traupmann KL: Encoding processes and memory for categorically related words by schizophrenic patients. J Abnorm Psychol 1980;89:704-716
84. *Traupmann KL, Anderson LT: Imagery and the short-term recall of words by schizophrenics. Psychol Record 1981;31:47-56
85. Hedges LV, Olkin I: Statistical Methods for Meta-analysis. Orlando, FL, Academic Press, 1985
86. Rosenthal R: Meta-analytic Procedures for Social Research. London: Sage, 1991
87. Shaddish WR, Haddock CK: Combining estimates of effect size. In The Handbook of Research Synthesis. Edited by Cooper H, Hedges V. New York, Sage,1994, pp 261-285
88. Schwarzer R: Meta-analysis programs. Behav Res, Methods, Instr & Computers 1988;20:338
89. Goldberg TE, Ragland D, Torrey EF, Bigelow LB, Gold JM, Weinberger DR: Neuropsychological assessment of monozygotic twins discordant for schizophrenia. Arch Gen Psychiatry 1990;47:1066-1072
90. Orwin RG: A fail-safe N for effect size in meta-analysis. J Ed Statistics 1983;8;157-159
91. Egger M, Davey-Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-634
92. Heinrichs RW, Zakzanis KK: Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 1998;12:426-445
93. Cohen J: Statistical Power Analysis for the Behavioral Sciences. Hillsdale, NJ, Erlbaum,1988
94. Burt DB, Zembar MJ, Niederehe G: Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. Psychol Bull 1995;117:285-305
95. Blanchard JJ, Neale JM: The neuropsychological signature of schizophrenia: generalized or differential deficit? Am J Psychiatry 1994:151:40-48
96. Squire LR: Memory and the hippocampus: a synthesis from findings with rats, monkeys and humans. Psychol Rev 1992;99:192-231
97. Hijman R: Memory processes and memory systems: fractionation of human memory. Neurosci Res Comm 1996;19:189-196
98. Lawrie SM, Abukmeil SS: Brain abnormality in schizophrenia: a systematic and quantitative review of volumetric magnetic resonance studies. Br J Psychiatry 1998;172:110-120
99. Wheeler MA, Stuss DT, Tulving E: Frontal lobe damage produces episodic memory impairment. J Int Neuropsychol Soc 1995;1:525-536
100. Ungerleider LG: Functional brain imaging studies of cortical mechanisms for memory. Science 1995;270:769-775
101. Liddle PF: Schizophrenic syndromes, cognitive performance and neurological dysfunction. Psychol Med 1987;17:49-57
102. Liddle PF, Morris DL: Schizophrenic syndromes and frontal lobe performance. Br J Psychiatry 1991;158:340-345
103. Frith CD: Schizophrenia, memory and anticholinergic drugs. J Abnorm Psychol 1984;93:339-341
104. Goldberg TE, Weinberger DR: Effects of neuroleptic medication on the cognition of patients with schizophrenia: a review of recent studies. J Clin Psychiatry 1996;57 (Suppl 9):62-65
105. Mortimer AM: Cognitive function in schizophrenia: do neuroleptics make a difference? Pharmacol Biochem Behav 1997;56:789-795
106. Green MF, Marshall MD, Wirshing WC, Ames D, Marder SR, McGurk S, Kern R, Mintz J: Does risperidone improve verbal working memory in treatment-resistant schizophrenia? Am J Psychiatry 1997;154:799-804
107. Goldberg TE, Hyde TM, Kleinman JE, Weinberger DR: Course of schizophrenia: neuropsychological evidence for a static encephalopathy. Schizophr Bull 1993;19:797-804
108. Keefe RSE: The contribution of neuropsychology to psychiatry. Am J Psychiatry 1995;152:6-15
109. Green MF: What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 1996;153:321-330

Chapter 3

Schizophrenia syndromes in relation to executive and attentional function

Summary

In this article, we quantitatively review the published literature on the relationships between symptom dimensions in schizophrenia and performance on the two most widely applied tests of executive functioning and sustained attention, the Wisconsin Card Sorting Test and the Continuous Performance Test. Results of meta-analyses showed statistically significant relationships of negative symptoms with worse performance on the WCST (perseverations) and the CPT. Disorganisation symptoms correlated with persevations on the WCST, but not with CPT performance. In contrast, reality distortion symptoms and general scores for all positive symptoms did not correlate with either measure. However, the observed associations between psychiatric symptoms and cognitive performance were typically weak, suggesting relative independence of these disease processes.

Nieuwenstein, M.R., Aleman, A., De Haan, E.H.F. (in revision). Relationship between schizophrenia syndromes and neurocognitive functioning: a meta-analysis of CPT and WCST studies.

Introduction

Deficits in executive functioning and vigilance are considered core neurocognitive abnormalities in schizophrenia (Randolph et al., 1993; Green, 1998). Impaired performance on the most widely applied neuropsychological tests of executive functioning and vigilance, the Wisconsin Card Sorting Test and the Continuous Performance Test, respectively, has been associated with psychosis-proneness (Franke et al., 1992; Nelson et al., 1998) and worse functional outcome (Green and Nuechterlein, 1999; Harvey et al., 1999). Although patients with schizophrenia have often been reported to perform worse than normal controls on these tests a recent quantitative review indicated that these differences may be attributed to a subgroup of patients (Heinrichs and Zakzanis, 1998). Since performance on both tests has been associated with deficits of prefrontal functioning, these findings suggest the existence of a subtype of schizophrenia in which pathology of the neural networks involving the frontal lobes is most pronounced (Zakzanis and Heinrichs, 1999). Following Crow's two syndrome hypothesis (Crow, 1980), many researchers have adopted a symptom-based approach in attempting to identify the dimensions along which these patients may be discerned from others (eg. Liddle, 1987).

Executive functions involve such abilities as abstract reasoning, concept formation, decision making and planning of behavior. Based on a rule learning paradigm which invokes these abilities the Wisconsin Card Sorting Test (WCST; Milner, 1963) has been one of the most widely applied neuropsychological measures of executive functioning (Heaton, 1993). Although schizophrenic patients have consistenty been shown to perform worse than normal controls on the WCST (Heinrichs and Zakzanis, 1998), research relating WCST performance to symptom dimensions has produced inconsistent results. Some authors reported findings indicating that predominantly negative symptoms are related to poor performance (Addington et al., 1991; Berman et al., 1997; Perry and Braff, 1998; Rosse et al., 1993). Others, however, have failed to replicate this finding (Cuesta et al., 1995; Himelhoch et al., 1996; Ragland et al., 1996). The relation of WCST performance to positive symptomatology is even less clear, with findings indicating relations varying from better (e.g. Hammer et al., 1995) to worse (e.g. Perry and Braff, 1998) performance on the WCST. However, the positive dimension of schizophrenia symptomatology has been shown to be heterogeneous, with accumulating findings suggesting the subdivision of positive symptomatology into symptoms of disorganisation and reality distortion (Liddle, 1987; Andreasen et al., 1994). It has been argued that disorganisation symptoms may be strongly related to multiple cognitive deficits, whereas reality distortion symptoms such as hallucinations and delusions have been associated with relatively intact cognitive functioning (Green, 1998).

The CPT is a well-known measure of vigilance, which refers to sustaining attention on a stimulus or a certain dimension of that stimulus over a period of time (Nuechterlein et al., 1994). The typical variable measured is the decrement in signal/noise discrimination within the vigilance period, termed sensitivity. Poor performance on the CPT has been identified as a vulnerability marker to schizophrenia (Nuechterlein et al., 1994), thereby suggesting performance to be independent of clinical state. Nuechterlein's contention has been supported by Cornblatt et al.'s failure to find significant relations between CPT performance and either positive or negative symptoms (Cornblatt et al., 1997). Others, however, have suggested an important role of impaired attention in the genesis of positive symptoms and psychosis in general (Nelson et al., 1998; Berman et al., 1997; Addington et al., 1997). Finally, findings have also been reported that CPT impairment is related to negative symptoms (Strauss, 1993).

There are two factors that may have contributed to the inconsistencies in reported associations between symptom dimensions and neuropsychological test performance. First, the studies that report these relations differ with respect to the clinical state of the studied patients. Specifically, some studies concern acute schizophrenic patients (eg. Addington et al., 1991), whereas other studies included only chronic patients (eg. Liddle et al., 1991). Baxter and Liddle (1998) have suggested that associations between symptoms dimensions and performance on neuropsychological tests may differ for patients in different phases of the illness. Second, methodological differences may contribute to the inconsistencies in reported associations. Specifically, the use of different symptom scales such as the BPRS, SANS and PANSS may result in different correlations between cognitive deficits and clusters of symptoms that were derived from these scales through factor-analysis.

The aim of the present study was to provide a quantitative review of the literature on symptom dimensions and performance on the WCST and CPT. By performing a meta-analysis on all studies in this domain, we investigated the validity of claims about differential relations between symtpom dimensions and cognitive deficits (Crow, 1980; Green, 1998). In addition, the use of meta-analysis enables an evaluation of the role of between-study differences in sample characteristics and symptom scales in accounting for the inconsistencies in reported associations.

Method

Literature search Articles for consideration were identified through an extensive literature search in the Psychlit and Medline databases, from 1980 through december 1999. The key words were: "schizophrenia and executive functions", "schizophrenia and Wisconsin*", "schizophrenia and WCST", "schizophrenia and sustained attention", "schizophrenia and continuous*" and "schizophrenia and CPT". In order to minimize the possibility of overlooking studies due to the limited purview of computer databases we paged through the volumes of relevant journals published in 1999. The selection of journals was based on the frequency of the publication of relevant articles. The journals included *American Journal of Psychiatry, Biological Psychiatry, Journal of Nervous and Mental Disease, Psychiatry Research, Schizophrenia Bulletin and Schizophrenia Research.* The search produced over 250 unique studies from which titles and abstracts were examined for possible inclusion in our analysis.

Criteria for inclusion The identified studies were included if they met the following criteria. First, the study had to include patients with a diagnosis of schizophrenia (based on DSM, ICD or RDC criteria). Studies that also included patients with schizoaffective or schizotypical disorders were excluded if the data on schizophrenic patients were not reported separately.

Second, each study had to include valid measures of symptomatology. Measures included were: Scale for the Assessment of Negative Symptoms (SANS: Andreasen, 1983), the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), the positive and negative component scales of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and the positive and negative component scales of the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962). In addition, we included studies that computed scores for clusters of symptoms based on factor-analyses of the SANS, SAPS, PANSS and BPRS scales. These studies often included descriptive statistics for measures of reality distortion and disorganisation subsyndromes, thereby enabling meta-analysis of the relation with WCST and CPT performance. From studies reporting correlations for separate symptoms we computed scores for the disorganisation, negative, positive and reality distortion dimensions by averaging the scores for symptoms constituting these dimensions. Third, the studies had to report valid measures of the Wisconsin Card Sorting Task (Heaton et al., 1993) or the Continuous Performance Task (Nuechterlein and Dawson, 1984). We included perseverative errors, perseverative responses and the number of categories completed as WCST performance measures. Factor-analytical findings indicate that these variables load on a factor termed perseveration (PE) which has been reported to differentiate well between schizophrenic patients and normals (Cuesta et al., 1995; Koren et al., 1998). When a study reported separate correlations between symptom dimensions and multiple WCST variables we computed the pooled effect size. The measure of the Continuous Performance Task included for meta-analysis was the measure of sensitivity, d'. If selected studies presented measures for different experimental conditions (e.g. neuroleptic naive versus neuroleptic free) we computed a pooled effect size. Fourth, the studies had to report correlational statistics, which are suitable for meta-analysis by providing direct measures of the relation between scores on scales of symptomatology and neuropsychological test performance. Finally, the population samples from the studies included had to be independent.

For the WCST meta-analysis 16 studies that met the criteria could be included, whereas 6 studies were included in the CPT meta-analysis (studies included in the analyses are marked with an asterisk in the reference list). Tables 1 and 2 list sample and study characteristics of the studies included in the WCST and CPT meta-analyses, respectively.

Data collection and analysis We performed meta-analyses on the correlational data reported in the selected studies. Analyses were performed on relations of negative, positive, disorganisation and reality distortion symptomatology with the CPT measure of sensitivity, d', and WCST-PE. From studies reporting measures of multiple versions of the CPT we selected results for the versions that most resembled the CPT paradigm developed by Nuechterlein and Dawson (Nuechterlein and Dawson, 1984).

For computation of population effect sizes we used mean r-values weighted for sample size (Hunter, Schmidt, & Jackson, 1982; Hunter & Smidt, 1990). The combined r-value is an indication of the strength of associations across all selected studies. The corresponding z-value and significance level provide an indication of the significance of the association.

For WCST-PE, a positive correlation indicated an association between symptomatology and worse performance, whereas for the CPT variable d', positive correlations indicated that more symptoms were associated with better performance. In addition we calculated a χ^2 statistic for an indication of the heterogeneity of results across studies in a single category (Hunter et al., 1982; Rosenthal, 1991). A significant χ^2 statistic indicates that the observed variance in study effect sizes is significantly greater than would be expected by chance if all studies shared a common population effect size. Thus, if homogeneity is rejected, the mean weighted r-value should not be interpreted as an estimate of a single effect parameter that gave rise to the sample observations, but rather simply as describing a mean of observed effect sizes, which of course limits a reliable interpretation and generalization. If there is significant heterogeneity, categorical moderator analyses may be performed by grouping studies into appropriate categories until homogeneity is not rejected within those categories. In the present context, heterogeneity would signify the role of possible confounding factors such as phase of illness.

Analyses were performed using the statistical software package META (Schwarzer, 1988).

Results

As can be seen in table 3, negative and disorganisation symptoms correlated significantly with WCST-PE (r=0.27 and r=0.25, respectively, both p's <0.01). The magnitude of the correlations is small to modest, in the nomenclature of Cohen (1988). Composite scores for all positive symptoms and the cluster of reality distortion symptoms did not correlate with WCST-PE. Vigilance performance measured with CPT-d' only correlated with negative symptoms, r=-0.31, p<0.01. Associations of total positive symptoms on one hand, or disorganisation and reality distortion on the other hand, with either WCST or CPT performance were not significant. As can be seen in table 3, there was no significant heterogeneity of effect sizes within the analyses. Although the results failed to indicate significant heterogeneity, we performed additional analyses using the sample and study characteristics listed in Tables 1 and 2 as moderator variables. None of these analyses reached significance.

Table 3. Results of meta-analyses on all studies for WCST-perseveration and CPT-d'

Variable	Dimension	N	k	r	Z	95% Cl	χ^2
WCST	Negative	699	15	0.27	7.23*	0.13 – 0.40	18.9
	Positive	487	9	0.06	1.24	-0.15 – 0.27	13.3
	Disorganisation	273	6	0.25	4.22*	0.24 – 0.26	6.0
	Reality distortion	194	4	0.04	0.60	-0.22 – 0.30	7.4
CPT	Negative	250	6	-0.31	-4.94*	-0.41 - -0.21	6.8
	Positive	188	4	-0.01	-0.10	-0.10 – 0.09	4.5
	Disorganisation	98	2	-0.06	-0.54	-0.04 - -0.08	1.1
	Reality distortion	98	2	0.04	0.39	0.02 – 0.06	0.0

* $p<0.01$; k=number of studies; N=total number of subjects; r=mean weighted correlation; Z=Stouffer's Z for significance of effect size; 95%CI=95% confidence interval; χ^2=heterogeneity between studies

Discussion

The goal of the present study was to provide a quantitative review of the relations between dimensions of schizophrenia symptoms and performance on neuropsychological tests of executive functioning and vigilance. Negative symptoms were significantly associated with impairments in both domains of cognitive functioning. In contrast, general scores for all positive symptoms and separate scores for reality distortion symptoms were not associated with either WCST or CPT performance. Disorganisation symptoms showed a significant correlation with worse WCST performance, but not with CPT performance. The observed significant correlations were in the small to modest range. In addition, these relations were shown to be stable across studies that differed in sample and study characteristics.

The present results confirm the existence of differential, albeit weak, relations between the symptom dimensions of schizophrenia and deficits in executive functioning and vigilance (Baxter and Liddle, 1998; Liddle, 1996; Strauss, 1993). These differential syndrome-cognition relations can be linked to evidence showing that different anatomical structures are associated with the negative, positive and reality distortion syndromes of schizophrenia. Results from brain imaging studies have demonstrated that negative symptoms are associated with abnormalities of the frontal cortex (Andreasen et al. 1998; Schröder et al. 1996). Our observation of significant relationships between negative symptoms and impaired performance on neuropsychological tests that have been associated with frontal lobe functioning is in accordance with these neuroanatomical findings. Disorganisation symptoms have been shown to have similar relations with with frontal lobe functioning (Crider, 1997; Liddle et al., 1992). In contrast, reality distortion symptoms have been associated with abnormalities of the temporal lobes (Liddle et al., 1992; Kaplan et al., 1993; Wright et al., 1995).

The present findings adress two important issues regarding the use of syndrome-based approaches in the study of cognition in schizophrenia. First, the fact that disorganisation and reality distortion showed differential relations with neurocognitive performance supports the notion that positive symptoms do not form a homogeneous syndrome (Liddle, 1987). Indeed the fact reality distortion symptoms did not correlate with WCST nor CPT performance, whereas disorganisation did correlate with WCST performance, is in agreement with findings from several factor-analytical studies of schizophrenia symptoms which have shown that these symptoms constitute a distinct dimension of schizophrenia symptoms (see Grube et al., 1998, for a meta-analysis). Taken together, these findings favor a three syndrome model over the two syndrome model as proposed by Crow (1980).

A second issue concerns the degree to which these syndromes can account for heterogeneity in performance on neuropsychological tests. Although we found significant associations between some symptom dimensions and performance on the WCST and the CPT, the magnitude of the weighted mean correlations indicated that these dimensions account for less than 10% of the variance in performance on these tests. Taken together with the observed differential nature of the correlations, this suggests that, although symptom dimensions and their neurocognitive correlates may be remotely related to a common pathophysiological alteration, they do not necessarily co-occur across the time-course of schizophrenia. This interpretation is in agreement with the model of schizophrenia recently proposed by Green and Nuechterlein (1999). According to this model, neurocognitive deficits are central to the chronic disabilities of patients with schizophrenia and relatively independent of symptomatic expressions of schizophrenia. Indeed, neurocognitive deficits have been shown to be more closely related to the schizophrenia genotype than symptomatic expressions, with several findings indicating the presence of cognitive deficits both before the onset and throughout the course of schizophrenia (Goldberg et al., 1993; Green and Nuechterlein, 1999), as well as in schizotypic relatives of schizophrenic patients (Franke et al., 1992; Nelson et al., 1998). Conversely, symptomatic expressions fluctuate considerably across the time-course of schizophrenia (Carpenter et al., 1988; Murray, 1997), with negative symptoms constituting relatively enduring traitlike characteristics (Arndt et al., 1995). Cognitive deficits and negative symptoms may thus both reflect a trait-like pathophysiology in schizophrenia.

In conclusion, the present study provides some evidence for the hypothesis that dimensions of schizophrenia symptoms may be distinctly related to neurocognitive function. Negative symptoms and disorganisation symptoms show associations with impaired performance on neuropsychological tests sensitive to frontal functioning, whereas reality distortion symptoms do not. By obtaining differential correlations between symptom dimensions and neurocognitive performance, to a certain extent our meta-analysis can be taken to support the external validity of the symptom-dimensions model. However, the association between symptoms and neurocognition must not be overstated. The present findings of relatively weak correlations seem to favor a model of schizophrenia in which symptom dimensions and performance on classical neuropsychological tests are relatively independent (Green & Nuechterlein, 1999). This is not to say that cognitive functioning may not act as intermediate level between phenomenology (symptoms) and neurobiology, as has been proposed by Mortimer & McKenna (1994). However, fine-grained studies with experimental tasks aimed at specific cognitive processes in relation to individual symptoms may have more explanatory power than relating syndromes to classical neuropsychological tests (which are typically involve more than one cognitive process). Without doubt, however, the understanding of the heterogeneous features of schizophrenia is likely to benefit importantly from further elaboration of the neurocognitive basis of distinct clinical phenomena characteristic of this disabling condition.

References

(Studies included in meta-analysis are indicated with an asterisk)

Aleman A, Hijman R, De Haan EHF, Kahn RS. Memory impairment in schizophrenia: a meta-analysis. Am J Psychiat 1999;156:1358-1366.

*Addington J, Addington D, Maticka-Tyndale E. Cognitive functioning and positive and negative symptoms in schizophrenia. Schizophr Res 1991;5:123-134.

*Addington J, Addington D. Attentional vulnerability indicators in schizophrenia and bipolar disorder. Schizophr Res 1997;23:197-204.

Andreasen NC. Scale for the assessment of negative symptoms (SANS). The university of Iowa, Iowa City, 1983.

Andreasen NC.Scale for the assessment of positive symptoms (SAPS). The university of Iowa, Iowa City, 1984.

Andreasen NC, Nopoulos P, Schultz S, Miller D, Gupta S, Swayze V, Flaum M. Positive and negative symptoms: Past, present, and future. Acta Psychiatrica Scandinavica 1994;90 (suppl 384):51-59.

Andreasen NC, Paradiso S, O'Leary DS. "Cognitive dysmetria" as an integrative theory of schizophrenia: A dysfunction in the cortical-subcortical-cerebellar circuitry? Schizophr Bull 1998;24:203-218.

Arndt S, Andreasen NC, Flaum M, Miller D, Nopoulos P. A longitudinal study of symptom dimensions in schizophrenia: prediction and patterns of change. Arch Gen Psychiatry 1995;52, 352-360.

*Basso MR, Nasrallah HA, Olson SC, Bornstein RA. Neuropsychological correlates of negative, disorganized and psychotic symptoms in schizophrenia. Schizophr Res 1998;31:99-111.

Baxter RD, Liddle PF. Neuropsychological deficits associated with schizophrenic syndromes. Schizophr Res 1998;30:239-249.

*Berman I, Viegner B, Merson A, Allan E, Pappas D, Geen AI. Differential relationships between positive and negative symptoms and neuropsychological deficits in schizophrenia. Schizophr Res 1997;25:1-10.

*Braff DL, Heaton R, Kuck J, Cullum M, Moranville J, Grant I, Zisook S. The generalized pattern of neuropsychological deficits in outpatients with chronic schizophrenia with heterogeneous Wisconsin Card Sorting Test results. Arch Gen Psychiat 1991;48:891-898.

Brébion G, Amador X, Smith MJ, Malaspina D, Sharif Z, Gorman JC. Opposite links of positive and negative symptomatology with memory errors in schizophrenia. Psychiat Res 1999;88:15-24.

Cardo AG, Holmans PA, Harvey I, Williams MB, Owen MJ, McGuffin P. Factor-derived subsyndromes of schizophrenia and familial morbid risks. Schizophr Res 1997;23:231-238.

Carpenter WT Jr, Heinrichs DW, Wagman AMI. Deficit and nondeficit forms of schizophrenia: the concept. Am J Psychiatry 1988;145, 578-583.

Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale, NJ, Erlbaum, 1988.

*Cohen RM, Nordahl TE, Semple WE, Andreason P, Pickar D. Abnormalities in the distributed network of sustained attention predict neuroleptic treatment respons in schizophrenia. Neuropsychopharmacology 1998;19:36-47.

*Collins AA, Remington GJ, Coulter K, Birkett K. Insight, neurocognitive function and symptom clusters in chronic schizophrenia. Schizophr Res 1997;27:37-44.

Cornblatt BA, Obuchowski M, Schnur DB, O'Brien JD. Attention and clinical symptoms in schizophrenia. Psychiatric Quarterly 1997;68:343-359.

Crider A. Perseveration in schizophrenia. Schizophr Bull 1997;23:63-73.
Crow TJ. Molecular pathology of schizophrenia: More than one disease process? British Medical Journal 1980;280:66-68.
Cuesta MJ, Peralta V. Cognitive disorders in the positive, negative nad disorganisation syndromes of schizophrenia. Psychiat Res 1995;58:227-235.
*Cuesta MJ, Peralta V, Caro F, De Leon J. Schizophrenic syndrome and Wisconsin Card Sorting Test card dimensions. Psychiat Res 1995;58:45-51.
*Franke P, Maier W, Hain C, Klinger T. Wisconsin Card Sorting Task: An indicator of vulnerability to schizophrenia? Schizophr Res 1992;6:243-249.
Franke P, Maier W, Hardt J, Hain C, Cornblatt BA. Attentional abilities and measures of schizotypy: Their variation and covariation in schizophrenic patients, their siblings, and normal control subjects. Psychiat Res 1994;54:259-272.
Frith, CD. The cognitive neuropsychology of schizophrenia. Lawrence Erlbaum, 1992.
Gold JM, Harvey PD. Cognitive deficits in schizophrenia. Psychiatric Clinics of North America 1993;16:295-312.
Green MF. Schizophrenia from a neurocognitive perspective; Probing the impenetrable darkness. Allyn & Bacon, 1998. p. 83-103.
Green MF, Nuechterlein KH. Should schizophrenia be treated as a neurocognitive disorder? Schizophr Bull 1999;25:309-319.
Grube, BS, Bilder, RM, Goldman, RSTI. Meta-analysis of symptom factors in schizophrenia. Schizophr Res 1998;25:113-20.
*Hain C, Maier W, Klingler T, Franke P. Positive/negative symptomatology and experimental measures of attention in schizophrenic patients. Psychopathology 1993;26:62-68.
*Hammer MA, Katsanis J, Iacono WG. The relationship between negative symptoms and neuropsychological performance. Biol Psychiat 1995;37:828-830.
Harvey PD, Parrella M, White L, Mohs RC, Davidson M, Davis KL. Convergence of cognitive and adaptive decline in late-life schizophrenia. Schizophr Res 1999;35:77-84.
Heaton RK, Chelune GJ, Kay KK, Curtiss G. Wisconsin Card Sorting Test Manual: Revised and expanded. Los Angeles. CA: Western Psychological Services, 1993.
Hemsley DR. Schizophrenia: A cognitive model and its implications for psychological intervention. Behavior Modification 1996;20:139-169.
Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. Neuropsychology 1998;12:426-445.
*Himelhoch S, Taylor SF, Goldman RS, Tandon R. Frontal lobe tasks, antipsychotic medication, and schizophrenia syndromes. Biol Psychiat 1996;39:227-229.
Hunter JE, Schmidt FL, Jackson GB. Meta-analysis. Cumulating research findings across studies. Beverly Hills, CA: Sage, 1982.
Hunter JE, Smidt FL. Methods of meta-analysis: Correcting error and bias in research findings. Newbury Park, CA: Sage, 1990.
*Ito M, Kanno M, Mori Y, Shin-ichi Niwa. Attention deficits assessed by Continuous Performance Test and Span of Apprehension test in japanese schizophrenic patients. Schizophr Res 1997;23:205-211.
Keefe RSE, Arnold MC, Bayen UJ, Harvey PD. Source monitoring deficits in patients with schizophrenia; a multinomial modelling analysis. Psychol Med 1999;29:903-914.
Kay SR, Opler LA, Fiszbein A. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261-276.
Koren D, Harrison RH, Kremen WS, Goldstein JM, Faraone SV, Seidman LJ, Lyons MJ, Caplan B, Tsuang MT. Factor structure of the Wisconsin Card Sorting Test: Dimensions of deficit in

schizophrenia. Neuropsychology 1998;12:289-302.
*Lees-Roitman S, Keefe RSE, Harvey PD, Siever LJ, Mohs RC. Attentional and eye-tracking deficits correlate with negative symptoms in schizophrenia. Schizophr Res 1997;26:139-145.
Liddle PF. The symptoms of chronic schizophrenia: A re-examination of the positive-negative dichotomy. Br J Psychiatry 1987;151:145-151.
*Liddle PF, Morris DA. Schizophrenic syndromes and frontal lobe performance. Br J Psychiatry 1991;158:340-345.
Liddle, PF, Friston, KJ, & Frith, CD. Patterns of cerebral blood flow in schizophrenia. Br J Psychiatry 1992;160, 179-186.
Liddle PF. Syndromes in schizophrenia and their neuropsychological and neuroanatomical correlates; In C. Pantelis, H.E. Nelson, T.R.E. Barnes, Schizophrenia: a neuro-psychological perspective. Chicester: John Wiley & Sons, 1996. p299-316.
Milner B. Effects of different brain lesions on card sorting. Arch Neurol 1963; 9:100-110.
Mortimer, A.M. & McKenna, P.J. (1994). Levels of explanation – symptoms, neuropsychological deficit and morphological abnormalities in schizophrenia. *Psychological Medicine*, *24*, 541-545.
Murray RM. Schizophrenia. In R. Murray, P. Mill & P. McGuffin (Eds.), *The essentials of postgraduate psychiatry*. Cambridge: Cambridge University Press. (pp. 281-309), 1997.
Nelson EB, Sax KW, Strakowski MS. Attentional performance in patients with psychotic and nonpsychotic major depression and schizophrenia. Am J Psychiat 1998;155:137-139.
Nuechterlein KH, Dawson ME. Information processing and and attentional functioning in the developmental course of schizophrenics disorders. Schizophr Bull 1984;10:160-203.
*Nuechterlein KH, Edell WS, Norris M, Dawson ME. Attentional vulnerability indicators, thought disorder, and negative symptoms. Schizophr Bull 1986;12:408-424.
Nuechterlein KH, Buchsbaum MS, Dawson ME. Neuropsychological vulnerability to schizophrenia. In: David A.S., Cutting J.C. The neuropsychology of schizophrenia. Lawrence Erlbaum Associates Ltd, 1994. p53-73.
Overall JE, Gorham DR. The brief psychiatric rating scale. Psychol Rep 1962;10:799-812.
Peralta V, Cuesta MJ. Dimensional structure of psychotic symptoms: an item-level analysis of SAPS and SANS symptoms in psychotic disorders. Schizophr Res 1999;38:13-26.
*Perry W, Braff DL. A multimethod approach to assessing perseverations in schizophrenic patients. Schizophr Res 1998;33:69-77.
*Ragland JD, Censits DM, Gur RC, Glahn DC, Gallacher F, Gur RE. Assessing declarative memory in schizophrenia using Wisconsin Card Sorting Test stimuli: The paired associate recognition test. Psychiat Res 1996;60:135-145.
Randolph C, Goldberg TE, Weinerger DR. The neuropsychology of schizophrenia. In K.M. Heilman, E. Valenstein, Clinical Neuropsychology. New York: Oxford University Press, 1993. p499-522
Rosenthal R. Meta-analytic procedures for social research. London: Sage, 1991.
*Rosse RB, Schwartz BL, Kim SY, Deutsch SI. Correlation between antisaccade and Wisconsin Card Sorting Task performance in schizophrenia. Am J Psychiat 1993;150:333-335.
*Rossi A, Mancini F, Stratta P, Mattei P, Gismondi R, Pozzi F, Casacchia M. Rispiridone. Negative symptoms and cognitive deficit in schizophrenia: an open study. Acta Psychiatrica Scand 1997;95:40-43.
*Rowe EW, Shean G. Card-sort performance and syndromes of schizophrenia. Genetic Soc Gen Psychological Monograms 1997;123(3):197-209.
Schröder J, Buchsbaum MS, Siegel BV, Geider FJ, Lohr J, Tang C, Wu J, Potkin SG. Cerebral metabolic activity correlates of subsyndromes in chronic schizophrenia. Schizophr Res 1996;19:41-53.

Schwarzer R. Meta-analysis programs. Behav Res, Methods, Instr & Computers 1988; 20:338.

Strauss ME. Relations of symptoms to cognitive deficits in schizophrenia. Schizophr Bull 1993;19:215-231.

*Strauss ME, Buchanan RW, Hale J. Relations between attentional deficits and clinical symptoms in schizophrenic outpatients. Psychiat Res 1993;47:205-213.

*Vorungati LNP, Heslegrave RJ, Awad AG. Neurocognitive correlates of positive and negative syndromes in schizophrenia. Can J Psychiatry 1997;42:1066-1071.

Zakzanis KK, Heinrichs RW. Schizophrenia and the frontal brain: A quantitative review. J Int Neuropsychol Soc 1999;5:556-566.

Chapter 4

Controversies and Discussions 1

Medication and cognition in schizophrenia

Aleman A, De Haan EHF. (2000). Antipsychotics and working memory in schizophrenia. *Science, (July 7) 289*, 56-57.

Patients with schizophrenia suffer from substantial cognitive deficits, notably in the realm of memory functioning (Aleman, Hijman, De Haan & Kahn, 1999), which warrants considerable research efforts aimed at developing pharmacological treatment strategies. Castner, Williams and Goldman-Rakic (2000) report reversal of antipsychotic-induced working memory deficits in monkeys by short-term dopamine D1 receptor stimulation. They emphasize that the results of their study may have important therapeutic implications for schizophrenia. However, we think that the putative implications for treatment of cognitive dysfunction in schizophrenia may be somewhat overstated.

Castner et al. explicitly propose that chronic haloperidol treatment should induce severe working memory impariments. Although they cite some studies that reported haloperidol-induced cognitive impairment in patients with schizophrenia, most studies do not find haloperidol to influence cognitive function significantly, as three recent reviews of the literature have concluded (King, 1990; Mortimer, 1997; Sharma, 1999). In a review on adverse neurobiological effects of long-term use of neuroleptics, Jeste et al. (1998) conclude that "persistent cognitive impairment associated with long-term use of typical neuroleptics has not been well documented" (p. 201) . In addition, two recent well-controlled studies that appeared after these reviews also indicate that haloperidol does not worsen working memory performance in schizophrenia (Lee et al., 1999; Purdon et al., 2000). Indeed, in a multicenter, double blind study with random assignment, Purdon et al. (2000) observed a near-significant *improvement* on the Wisconsin Card Sorting Test (decline in number of perseverative errors) after 12 months of treatment with haloperidol (effect size –0.46, $p=0.06$).

Castner *et al.* have provided strong evidence that haloperidol can induce working memory deficits in monkeys, which can be reversed by short-term dopamine D1 receptor stimulation. However, as haloperidol does not seem to impair working memory significantly in patients with schizophrenia, the clinical implications of Castner *et al.*'s findings remain unclear.

References

Aleman, A., Hijman, R., De Haan, E.H.F., & Kahn, R.S. (1999). Memory impairment in schizophrenia: a meta-analysis. *American Journal of Psychiatry, 156,* 1358-1366.

Castner, S.A.,Williams, G.V., & Goldman-Rakic, P.S. (2000). Reversal of antipsychotic-induced working memory deficits by short-term dopamine D1 receptor stimulation. *Science, 287,* 2020-2022.

King, D.J. (1990). The effect of neuroleptics on cognitive and psychomotor function. *British Journal of Psychiatry, 57,* 799-811.

Mortimer, A.M. (1997). Cognitive function in schizophrenia--do neuroleptics make a difference? *Pharmacology, Biochemistry and Behav*.ior, *56,* 789-95.

Sharma, T. (1999). Cognitive effects of conventional and atypical antipsychotics in schizophrenia. *British Journal of Psychiatry, suppl 38,* 44-51.

Jeste, D.V., Lohr, J.B., Eastham, J.H., Rockwell, E., & Caligiuri, M.P. (1998). Adverse neurobiological effects of long-term use of neuroleptics: human and animal studies. *Journal of Psychiatric Research, 32,* 201-14.

Lee, M.A., Jayathilake, K., Meltzer, H.Y. (1999). A comparison of the effect of clozapine with typical neuroleptics on cognitive function in neuroleptic-responsive schizophrenia. *Schizophrenia Research, 37,* 1-11.

Purdon, S.E., et al. (2000). Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. The Canadian Collaborative Group for research in schizophrenia. *Archives of General Psychiatry, 57,* 249-258.

Chapter 5

Multi-dimensionality of hallucinatory predisposition

Summary

A substantial percentage of normal people has been documented to report hallucinatory experiences. We investigated the multi-dimensionality of such experiences in 243 subjects from the normal population who completed the Launay-Slade Hallucination Scale. Principal components analysis with oblique rotation was performed on the data. Three factors were obtained loading on items reflecting (1) tendency towards hallucinatory experiences, (2) subjective externality of thought, and (3) vivid daydreams. An additional exploratory factor analysis revealed highly similar factors. The results support the concept of hallucinatory disposition as a multi-dimensional construct.

Aleman, A., Nieuwenstein, M., Böcker, K.B.E., De Haan, E.H.F. (2001). Multidimensionality of hallucinatory predisposition: factor structure of the Launay-Slade Hallucination Scale in a normal sample. *Personality and Individual Differences, 30,* 287-292.

Introduction

Hallucinatory experiences have been reported to occur not only in psychiatric patients, but in a substantial percentage of normal subjects as well. A number of studies have established that 10 to 25% of subjects from the normal population may have the experience of hearing voices without any objective basis (Posey & Losch, 1983; Young et al., 1986; Tien, 1991). Such auditory-verbal hallucinatory experiences may, to an important degree, resemble the hallucinations characteristic of schizophrenia (Barrett & Caylor, 1998). A frequently applied questionnaire for measuring hallucinatory experiences is the Launay-Slade Hallucination scale (Launay & Slade, 1981, modified version Bentall & Slade, 1985), which was developed based on the assumption that hallucinatory experiences form a continuum with normal psychological functioning (Slade & Bentall, 1988). For example, the scale includes items related to daydreaming (e.g. “The sounds I hear in my daydreams are usually clear and distinct”), but also includes items related to psychotic hallucinations (e.g. “I have heard the voice of the Devil”). The items of the LSHS can be found in table 1.

In the original scale (Launay & Slade 1981) subjects had to respond with true/false to each of the twelve items, of which two were negatively stated. A principal components analysis on the data of 54 normal controls, 42 psychiatric patients and 200 prisoners (Launay & Slade, 1981) revealed two factors: “tendency to hallucinatory experiences” and “negative response set”. All items except items 9 and 11 loaded on the first factor, with items 9 and 11 (which were negative response items) loading on the second factor.

Bentall & Slade (1985) modified the LSHS by introducing a 5 point Likert scale instead of the simple true/false response dichotomy, and by changing the negative response items to positive ones. For research purposes, the LSHS is mainly used in subjects from the normal population (e.g., Aleman et al., 1999; Rankin & O’Carroll, 1995). The multi-dimensionality of hallucinatory disposition has not been studied yet in a sample from the normal population using the modified LSHS. Levitan et al. (1996) investigated the factor structure of the modified LSHS in a sample of 169 psychiatric patients. Principal component analysis yielded four factors, characterised as “vivid daydreams” (items 1, 3, 5, 6 and 9), “clinical auditory hallucinations” (items 7, 9, 10, 11 and 12), “intrusive thoughts” (items 1, 3, 4 and 12), and “sub-clinical auditory hallucinations” (items 8 and 9), respectively.

The aim of the present study was to investigate the multi-dimensionality of hallucinatory experiences in a normal sample of 243 undergraduate students in order to shed more light on the nature of the concept of hallucinatory predisposition.

Method

Subjects were 243 undergraduate students from Utrecht University, who completed the Dutch translation of the modified version of the LSHS (Bentall & Slade, 1985). Mean age was 22.6 years (SD=5.6). One hundred and eighty nine subjects were female, and the other 58 subjects were male. LSHS items were scored on a five point scale as follows: 0="certainly does not apply to me", 1="possibly does not apply to me", 2="unsure", 3="possibly applies to me" and 4="certainly applies to me". Factor structure of the data was examined by principal component analysis (PCA). The number of components to be retained was determined by Kaiser's criterion (eigenvalue greater than 1) followed by inspection of the scree plot in order not to miss possible relevant factors with smaller eigenvalues. An oblique rotation (Oblimin with Kaiser normalisation) was then carried out since the phenomena under investigation may well not lead to independent factors. In order to check the fit of the PCA we also performed an exploratory factor analysis in which common variance is explored by principal axis factoring. All analyses were performed with SPSS 8.0 (SPSS Inc, Chicago).

Results

The mean total score of the subjects was 13.9, SD=6.7 (range from 0 to 36); there was no evidence of sex differences in LSHS-ratings, t=0.23, $p>0.8$. The distribution was positively skewed, comparable to the distributions reported by Bentall & Slade (1985). A substantial percentage of subjects responded affirmative ("possibly applies" or "certainly applies") to typical hallucination-items such as item 7 (7 and 4.1%) and item 8 (25.5 and 5.3%). All items correlated significantly with the total test score ($p<.01$). The internal consistency coefficient (equivalent to Cronbach's alpha; Murphy & Davidshofer, 1994) was 0.82.

The PCA revealed three factors (eigenvalues>1) which accounted for 50% of the variance. Table 1 shows loadings of items on the three factors. The first factor accounted for 29.8% of the variance and can be characterised as general hallucinatory tendency (e.g., item 7). The second factor (accounting for 10.8% of the variance) concerned subjective externality of thought (e.g., item 3), and the third factor (9.5% of the variance) may be described as vividness of daydreams (e.g., item 6). Correlations between factors were r=0.29 for I-II, r=0.30 for I-III and r=0.12 for II-III.

Table 1. LSHS items and factor loadings (only loadings >0.4 are shown)

		Factor		
	Item	1	2	3
1	No matter how hard I try to concentrate, unrelated thoughts always creep into my mind	0.70		
2	In my daydreams I can hear the sound of a tune almost as clearly as if I were actually listening to it	0.46		
3	Sometimes my thoughts seem as real as actual events in my life		0.79	
4	Sometimes a passing thought will seem so real that it frightens me		0.65	
5	The sounds I hear in my daydreams are usually clear and distinct			0.82
6	The people in my daydreams seem so true to life that some-times I think they are			0.84
7	I often hear a voice speaking my thoughts aloud	0.74		
8	In the past I have had the experience of hearing a person's voice and then found that no one was there	0.51		
9	On occasions I have seen a person's face in front of me when no one was in fact there	0.61		
10	I have heard the voice of the devil	0.71		
11	In the past I have heard the voice of God speaking to me		0.63	
12	I have been troubled by hearing voices in my head	0.61		0.41

The results of the principal factor analysis with oblique rotation revealed the same factors as the PCA, with small differences in the items loading on these factors. Items that loaded higher than 0.40 on factor I were items 1, 7, 8, 9, 10 and 12, on factor II items 3 and 11, and on factor III items 5 and 6. The differences with the results of the PCA are mainly that item 2 did not load on factor I in this analysis and that item 4 did not load on factor II. Correlations between factors were r=0.41 for I-II, r=0.45 for I-III and r=0.20 for II-III.

Given the skewed distribution and the possibility that outliers (e.g., the few individuals that may endorse the more pathological items) may strongly influence the factor structure, we conducted a third analysis. This analysis was identical to the first one (i.e., PCA with oblique rotation) with exception that ln-transformation was performed on the data prior to analysis, and outliers were excluded (defined as $z>4$ [Stevens, 1996], which concerned five datapoints). This analysis again yielded the same three factors, with the following items loading higher than 0.40: items 1, 2, 7, 8, 9, 10 and 12 on factor I; items 3, 4, and 11 on factor II; and items 5, 6, 9 and 12 on factor III. The difference with the first PCA was that item 9 also loaded on factor III (items 4 and 5 remained loading the highest on this factor).

Discussion

In this study we investigated the multi-dimensionality of hallucinatory predisposition as measured by the Launay-Slade Hallucination Scale (LSHS) in normal subjects. A small, but clearly noticeable percentage of subjects reported hallucinatory experiences (for example item 8), which is in accordance with previous findings in college students in Great Britain (Young et al., 1986). However, the mean total rating on the LSHS was lower than that reported in previous studies (e.g. 13.9 in our study versus 19.6 reported by Bentall & Slade [1985] in a very similar sample). The observation of a small, but substantial, number of subjects from the normal population reporting hallucinatory experiences is in accordance with the view of hallucinations as existing on a continuum with normal mental events (Slade & Bentall, 1988; Aleman & De Haan, 1998).

The multi-dimensionality of the LSHS was investigated with principal component analysis, yielding three factors, which we characterised as (1) tendency towards hallucinatory experiences, (2) subjective externality ("realness") of thought, and (3) vivid daydreams. These results indicate that hallucinatory predisposition can be regarded to be a multi-dimensional construct, which is consistent with the findings of Levitan et al. (1996) who investigated the factorial structure of the LSHS in psychiatric patients. Levitan et al. (1996) also found evidence for a vivid daydreams factor and for a factor related to vivid thoughts. However, in addition to these factors, they report two hallucination factors, "clinical auditory hallucinations" and "sub-clinical auditory hallucinations" (as described in the introduction). In contrast, our analysis revealed only one general hallucinatory tendency factor. Our failure to find two distinct hallucination factors may be explained by the different subject group: normal subjects in our study versus psychiatric patients in the study by Levitan et al. (1996). Indeed, the subjects in the Levitan et al. (1996) study scored much higher overall and showed a greater range of LSHS scores. The finding of only one hallucination factor in normal subjects suggests that the distinction between clinical and sub-clinical hallucinations may be specific to psychiatric patients.

A number of authors have associated high scores on the LSHS with psychosis-proneness (Bentall et al., 1989; Kendler & Hewitt, 1992; Vollema & Van den Bosch, 1995). It could be hypothesised that the factors underlying the LSHS, as established in the present study, may be differentially related to vulnerability to psychopathology. For example, high ratings on items loading on factor 1 (tendency towards hallucinatory experiences) or factor 2 (subjective externality of thought) may be a better predictor of the occurrence of subsequent psychopathological symptoms than high ratings on factor 3 (vivid daydreams). Future research may be directed at such questions and should also concentrate on the cognitive processes involved in hallucinatory experiences.

References

Aleman, A., & De Haan, E.H.F. (1998). On redefining hallucination [Letter]. *American Journal of Orthopsychiatry, 68,* 656-658.

Aleman, A., Böcker, K.B.E., & De Haan, E.H.F. (1999). Disposition towards hallucination and subjective versus objective vividness of imagery in normal subjects. *Personality and Individual Differences, 27,* 707-714.

Barrett, T.R., & Caylor, M.R. (1998). Verbal hallucinations in normals, V: perceived reality characteristics. *Personality and Individual Differences, 25,* 209-221.

Bentall, R.P. & Slade, P.D. (1985). Reliability of a scale measuring disposition towards hallucination: a brief report. *Personality and Individual Differences, 6,* 527-529.

Bentall, R.P., Claridge, G.S., & Slade, P.D. (1989). The multi-dimensional nature of schizotypal traits: a factor analytic study with normal subjects. *British Journal of Clinical Psychology, 28,* 363-375.

Launay, G., & Slade, P.D. (1981). The measurement of hallucinatory predisposition in male and female prisoners. *Personality and Individual Differences, 2,* 221-234.

Kendler, K.S. & Hewitt, J.K. (1992). The structure of self-report schizotypy in twins. *Journal of Personality Disorders, 6,* 1-17.

Levitan, C., Ward, P.B., Catts, S.V., & Hemsley, D. R. (1996). Predisposition toward auditory hallucinations: The utility of the Launay-Slade Hallucination Scale in psychiatric patients. *Personality and Individual Differences, 21,* 287-289.

Murphy, K.R., & Davidshofer, C.O. (1994). *Psychological testing; principles and applications*. New Jersey: Prentice Hall.

Posey, T.B., & Losch, M.E. (1983). Auditory hallucinations of hearing voices in 375 normal subjects. *Imagination, Cognition and Personality, 2,* 99-113.

Rankin, P.M., & O'Carroll, P.J. (1995). Reality discrimination, reality monitoring and disposition towards hallucination. *British Journal of Clinical Psychology, 34,* 517-528.

Slade, P.D., & Bentall, R.P. (1988). *Sensory deception; a scientific analysis of hallucination*. Baltimore: John Hopkins University Press.

Stevens, J. (1996). *Applied mulivariate statistics for the social sciences*. Mahwah (N.J.): Lawrence Erlbaum.

Tien, A.Y. (1991). Distribution of hallucinations in the population. *Social Psychiatry and Psychiatric Epidemiology, 26,* 287-292.

Vollema, M.G., & Van den Bosch, R.J. (1995). The multi-dimensionality of schizotypy. *Schizophrenia Bulletin, 21,* 19-31.

Young, H.F., Bentall, R.P., Slade, P.D., & Dewey, M.E. (1986). Disposition towards hallucination, gender and IQ scores. *Personality and Individual Differences, 7,* 247-249.

Chapter 6

Disposition towards hallucination and imagery vividness

Summary

In the present study we investigated the relation between subjective and objective indices of vividness of imagery and disposition towards hallucination in 74 college students. Self-reported imagery vividness was measured with the visual and auditory subscales of the Betts Vividness of Imagery Scale. The objective task concerned the difference between a perceptual and an imagery condition of judgment of visual similarity of named objects. In addition, subjects completed a hallucination questionnaire (the Launay-Slade Hallucination Scale). After assigning subjects to a high and a low scoring group on the basis of scores on the hallucination scale, analysis of variance revealed a significant interaction between group and the two vividness of imagery measures. Subjects reporting hallucinatory experiences tended to show higher imagery vividness ratings on the Betts Scale than nonhallucinating subjects. In contrast, the reverse relation was found on the experimental imagery task. Implications of these findings for the validity of self-report imagery vividness measures are discussed.

Aleman, A., Böcker, K.B.E. & De Haan, E.H.F. (1999). Disposition towards hallucination and subjective versus objective vividness of imagery in normal subjects. *Personality and Individual Differences, 27,* 707-714.

Introduction

Hallucinations are perceptions in the absence of corresponding stimulation of the senses and are usually associated with the presence of psychopathology (Asaad & Shapiro, 1986). The idea that increased vividness of mental imagery may be associated with hallucinatory experiences was already expressed more than hundred years ago by Francis Galton (1883). The results of subsequent research examining this hypothesis remain inconclusive. Roman & Landis (1945), Mintz & Alpert (1972), and Slade (1976) report more vivid imagery in hallucinating psychiatric patients as compared with nonhallucinating patients. Other studies failed to find a relation between more vivid imagery and occurence of hallucinations. Cohen (1938), Seitz & Molholm (1947), Brett & Starker (1977) and Starker & Jolin (1982) found no evidence of increased vividness of imagery in hallucinating patients. Starker & Jolin (1982) even go so far as to argue that hallucinating patients have less vivid imagery compared to nonhallucinating patients. All these studies employed introspective measures of imagery vividness. In a review of theory and research on hallucinations, Bentall (1990) concluded that the vividness of imagery hypothesis of hallucinations lacks convincing empirical evidence. Recently, however, Barrett (1992) demonstrated high-scoring college students on a verbal hallucination scale to have more self-rated imagery vividness than low scoring subjects. Barrett (1992) interpreted these results as support for the increased imagery vividness hypothesis of hallucinations.

An important distinction between percepts and images is that percepts, which are based on externally presented stimuli, are characterized by more detailed sensory, contextual and semantic information than images, which are based on internal generated information (Johnson & Raye, 1981). Following this distinction, the vividness of an image may be operationally defined as the degree of resemblance of a mental image to the corresponding perceptual qualities; the more vivid an image, the closer the experience is to actual perception of sensory input. According to this definition an objective index of imagery vividness can be obtained by comparing performance on a perceptual and an imagery condition of an experimental task. The more vivid the images are, the smaller will be the difference between performance on the imagery and the perception condition.

It was the same Galton (1883) who stated that hallucinatory experiences may be much more widespread under the normal population than generally expected. In recent years, there is increasing evidence supporting this claim. Several studies have documented the occurence of hallucinations in some 10% of normal healthy subjects (Posey & Losch, 1983; Young, Bentall, Slade & Dewey, 1986; Tien, 1991). In a study of hallucinations in college students, Barrett and Etheridge (1992) found that at least 25% reported verbal hallucinations. From these studies it may be concluded that hallucinations can be seen as existing on a continuum with normal mental events (Slade & Bentall, 1988).

Up to now, most studies examining the relation between vividness of imagery and hallucination have made use of introspective measures. The validity of these measures is unclear. The present study addressed two questions. First, is greater imagery vividness related to increased reports of hallucinations? If so, we would expect to replicate Barrett's (1992) finding, and also find a relationship between an objective imagery measure and reports of hallucinatory disposition. The second question concerned the validity of self-report measures of imagery vividness. We examined whether an objective task of imagery vividness would yield the same results in relation to hallucinatory disposition as a self-report questionnaire. Convergence with an objective task of imagery vividness would support the validity of subjective measures of imagery vividness.

Method

Subjects

Subjects were 74 undergraduate students from Utrecht University. The mean age of the participants was 21.2 years (SD=1.8). Fifty-four subjects were female and twenty were male.

Materials

Two questionnaires and one experimental task were used. The auditory and visual subscales of the Betts QMI Vividness of Imagery Scale (Richardson, 1969) consist of nine verbal descriptions, such as "the sun as it is sinking below the horizon" (visual) and "the miaowing of a cat" (auditory). The Launay-Slade Hallucination Scale (LSHS; Launay & Slade, 1981) consists of 12 descriptions of hallucinatory experiences, e.g. "I often hear a voice speaking my thoughts aloud". The experimental vividness of imagery task concerned a quantitative comparison between imagery and perception, and was adapted from Mehta, Newcombe & De Haan (1992). The task consisted of 22 object names printed on cards and 22 triads of line drawings of common objects (Snodgrass & Vanderward, 1980).

Procedure

All 74 subjects were given the two questionnaires and the experimental task. Subjects first completed the hallucination questionnaire. For each of the 12 statements, subjects had to indicate if the statement was "true" or "false" for their case. The questionnaire was scored by summing the number of “true” statements. A high score on the LSHS indicates increased predisposition to hallucinations. Subsequently, subjects completed the two Betts subscales. They were asked to rate their imagery vividness on a 7-point scale, ranging from 1: "Perfectly clear and as vivid as the actual experience" to 7: "No image present at all, you only 'knowing' that you are thinking of the object". The questionnaire was scored by summing the ratings. A low score indicated more vivid imagery. The experimental imagery vividness task had two conditions: a perceptual condition and an imagery condition. From the triads of line drawings, the item that was most deviant in terms of visual form characteristics had to be indicated. In the perceptual condition the line drawings were actually presented, whereas in the imagery condition the object names were read from cards. For example, in the perceptual condition pictures of the following three objects were presented: “pumpkin”, “lettuce” and “tomato”, whereas in the imagery condition only the names of these three objects were presented to the subject. Thus, the imagery condition required the subjects to form mental images in order to be able to make a correct judgement (which in the example given would be “lettuce”). A difference-score was calculated by subtracting the correct responses in the imagery condition from the correct responses in the perceptual condition. The more vivid the images are, the smaller will be the difference between performance on the imagery and the perception condition. Hence, the difference-score between both conditions was considered an objective index of imagery vividness.

Results

Mean scores of the group as a whole (N=74) were 3.0 (SD=1.9) for the LSHS, 25.7 (SD=7.0) for the summed subscales of the Betts Scale, 21.0 (SD=1.0) for the perception condition of the imagery perception comparison task, 18.9 (SD=1.5) for the imagery condition, and 2.1 (SD=1.6) for the difference between perception and imagery.

A high and a low hallucination group was formed on the basis of scores on the hallucination questionnaire, using a median-split. Subjects with a hallucination score equal to the median value were not included in the analysis (N=17). The mean rating on the LSHS of the high hallucination group (N=26) was 5.2 (SD=1.3), the mean for the low hallucination group (N=31) was 1.3 (SD=0.8). The difference between both groups was significant, $t=14.2$, *p*<0.0001. Analysis of variance (ANOVA) was performed with Measure as within-subjects factor consisting of two levels: objective and subjective imagery scores. The scores on the Betts Scale and the imagery perception comparison task were transformed to z-values before performing the analysis, as the scale units are not comparable. Group was taken as between-subjects variable. The effect of Gender was also considered, as some studies have shown more vivid imagery ratings in females compared to males (Campos & Sueiro, 1993).

Table 1 shows means and SDs for the high and low hallucination groups on the imagery vividness measures, and z-transformed means and SDs. The ANOVA with z-transformed objective and subjective imagery scores as a two-level within-subjects variable did not reveal a significant main effect of Group ($F<1$), due to the difference in direction of the imagery measures (as can be seen in table 1). However, the Group × Measure interaction was significant, $F(1, 55)=8.0$, $p=0.006$.

Table 1. Means scores (and standard deviations) for ratings on the Betts QMI Vividness of Imagery (summed auditory and visual subscales, and visual subscale only) and difference between perception and imagery performance on the imagery perception comparison task by hallucination group as defined on the Launay-Slade Hallucination Scale. Lower scores indicate more vivid imagery.

	High LSHS group (N=26)	Low LSHS group (N=31)
Betts Scale, visual + auditory	23.7 (5.4)	27.1 (7.1)
Betts Scale, visual only	13.0 (3.3)	14.6 (3.9)
Imagery-perception comparison task	2.5 (1.4)	1.7 (1.7)

In Figure 1 the relation between the two measures and the high and low LSHS group are plotted. Post-hoc t-tests (on the scores without z-transformation) were performed in order to examine differences between the hallucination groups on each of the imagery measures separately. Subjects in the high hallucination group reported more self-rated imagery vividness on the Betts Scale than subjects in the low hallucination group. However, this difference just failed to attain significance ($t=1.95$, $p=0.056$). In contrast, subjects in the high hallucination group tended to show less imagery vividness as measured by performance on the imagery perception comparison task than subjects in the low hallucination group, although the difference between the high and low hallucination group failed to reach significance, t=-1.85, p=0.069. No significant effect nor interaction of Gender was observed.

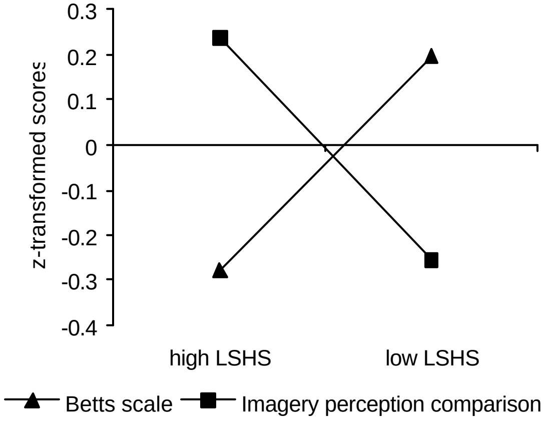

Figure 1. Z-transformed scores on the Betts QMI Vividness of Imagery Scale (summed visual and auditory subscales) and the imagery perception comparison task for high (N=26) and low (N=31) LSHS groups. Lower scores indicate more vivid imagery.

We also performed an ANOVA including only the visual subscale of the Betts Scale, given that the experimental vividness measure is visual in nature. Thus, the Imagery factor consisted of two levels, z-transformed scores on the Betts visual subscale and on the imagery perception comparison task. Again, the Group × Measure interaction was significant, $F(1,55)=5.78$, $p=0.02$, demonstrating a dissociation between objective and subjective vividness of imagery scores in relation to hallucinatory disposition. Although nonsignificant ($p>0.08$), post hoc t-tests showed trends in the same opposite direction for the Betts scale versus the imagery perception comparison task as in the first analysis.

Discussion

The aim of this study was to examine whether vividness of mental imagery as measured with a self-report measure (the visual and auditory subscales of the Betts QMI Vividness of Imagery Scale) and with an experimental task (the Mehta imagery perception comparison task) would be related to hallucinatory disposition in normal subjects. Our results demonstrate a dissociation between self-report and objective vividness of imagery in relation to hallucinatory disposition, as shown by the significant Group × Measure interaction.

The results do not permit straightforward conclusions regarding our first research question, whether a relation exists between vividness of imagery and disposition towards hallucination, given the divergence between the subjective and objective imagery vividness measure. Nevertheless, the present findings may have important implications for understanding possible relations between vividness of imagery and hallucinations. Subjects reporting hallucinatory experiences tended to show higher imagery vividness ratings on the Betts scale than nonhallucinating subjects. Thus, we replicated the finding by Barrett (1992) of a positive relation between hallucinatory disposition and self-report imagery vividness. The observation that our results were less significant can be attributed to the fact that Barrett (1992) included more extreme groups, with a larger difference in hallucination ratings. Barrett (1992) employed a different hallucination scale, the Verbal Hallucination Scale (Barrett & Etheridge, 1992). Our replication of Barrett's finding with the Launay-Slade Hallucination Scale provides additional support for the hypothesized relation between hallucinations and self-report imagery vividness. In contrast, the reverse relation was found for the experimental vividness of imagery task, which brings us to our second research question, regarding the validity of self-report vividness of imagery measures.

To our knowledge, this is the first study which contrasts subjective and objective measures of imagery vividness in relation to hallucinatory disposition in normal subjects. The divergence between objective and subjective measures of imagery vividness observed in the present study is consistent with the study by Kosslyn, Brunn, Cave & Wallach (1984), who failed to find a relation between performance on an objective task of acuity of visual images and a self-report imagery measure, the Vividness of Visual Imagery Questionnaire (VVIQ; Marks, 1973). These findings suggest that self-report imagery questionnaires are not simply measures of imagery vividness but may reflect different sets of processes.

A clear advantage of investigating the relation between imagery and hallucinations with experimental "objective" tasks in which analyses are restricted to cognitive processes is the avoidance of the methodological problems associated with introspection. This advantage may be especially important when investigating subjects with hallucinatory experiences, in which insight into the subjects' own psychological functioning may be distorted.

The lack of convergence between self-report imagery ratings and an experimental measure of imagery vividness indicates that studies including only self-report measures must be interpreted with caution. Situational demand characteristics may contribute importantly to the associations between self-report imagery vividness and hallucination ratings, due to the similarity in content and format of the hallucination and imagery vividness questionnaire. In addition, self-report questionnaires concern the subject's naive thinking about mental imagery, which is influenced by certain meta-cognitive processes such as the subjects theory of imagery and his or her idea of vividness (Cornoldi, 1995). The use of the vividness rating scale may reduce the validity of self-report measures as different people employ different criteria in considering the vividness of an image.

On the other hand, one might argue that it is not "objective" imagery vividness that counts in whether or not a person classifies an internal generated experience as externally presented (resulting in a hallucinatory experience) but that the person's subjective bias may play a more important role. Thus, persons biased in making high vividness ratings of their own internally generated thoughts, may as a result thereof tend to misclassify an internal generated experience as externally presented - a process which has been referred to as "reality discrimination" (Bentall & Slade, 1985; Mintz & Alpert, 1972). However, with self-report measures it is not possible to differentiate between constructs as reality discrimination and vividness of imagery, whereas objective tasks can be designed to be specifically aimed at measuring one of these constructs, which is a major advantage (e.g. Böcker, Van der Lee, Hijman & De Haan, 1996; Mintz & Alpert, 1972).

An important consideration with regard to objective measures is that they may be restricted to a limited part of the concept of imagery vividness, by not taking into account the content of imagery. For example, phenomenological differences in the content of mental images may even explain our failure to observe a relation between imagery vividness as measured by the experimental task and hallucinatory predisposition. The possibility must be considered that the hallucination group is producing more vivid images than the other group but that these images are more idiosyncratic, so that in the imagery condition, the most deviant image occasionally might not be the same named thing as in the perception condition.

These concerns highlight the importance of validation of experimental imagery vividness tasks as well as of self-report measures. Clearly, more research is needed into the relation between vividness of imagery and hallucinations, both in the general population and in psychotic illnesses, with multiple objective tasks in the visual as well as the auditory modality. The results of a preliminary study (Böcker et al., 1996) in which such experimental tasks are employed have indicated that schizophrenic patients who experience auditory hallucinations have more vivid auditory than visual imagery, compared to nonhallucinating patients.

We conclude that subjective and objective measures of imagery vividness may not converge in predicting hallucinatory disposition. This finding calls for a more thorough evaluation of the validity of measures of imagery vividness. Future research focusing on multiple objective and subjective measures of imagery vividness in relation to hallucinatory experiences may further elucidate the cognitive basis of hallucinations.

References

Asaad, G., & Shapiro, B. (1986). Hallucinations: theoretical and clinical overview. *American Journal of Psychiatry, 143*, 1088-1097.

Barrett, T.R. (1992). Verbal hallucinations in normals-II: self-reported imagery vividness. *Personality and Individual Differences, 15*, 61-67.

Barrett, T.R., & Etheridge, J.B. (1992). Verbal hallucinations in normals, I: People who hear 'voices'. *Applied Cognitive Psychology, 6*, 379-387.

Bentall, R.P. (1990). The illusion of reality: a review and integration of psychological research on hallucinations. *Psychological Bulletin, 107*, 82-95.

Bentall, R.P., & Slade, P.D. (1985). Reality testing and auditory hallucinations: a signal detecion analysis. *British Journal of Clinical Psychology, 24*, 213-222.

Böcker, K.B.E., Van der Lee, J., Hijman, R., & De Haan, E.H.F. (1996). Perception, mental imagery and reality discrimination in hallucinating and nonhallucinating schizophrenic patients. *Journal of the International Neuropsychological Society, 2*, 204-205.

Brett, E.A., & Starker, S. (1977). Auditory imagery and hallucinations. *Journal of Nervous and Mental Disease, 164*, 394-400.

Campos, A., & Sueiro, E. (1993). Sex and age differences in visual imagery vividness. *Journal of Mental Imagery, 17*, 91-94.

Cornoldi, C. (1995). Imagery and meta-imagery in the VVIQ. *Journal of Mental Imagery, 19*, 131-136.

Galton, F. (1883). *Inquiries into human faculty and its development*. London: McMillan.
Johnson, M.K., & Raye, C.L. (1981). Reality monitoring. *Psychological Review, 88*, 67-85.
Kosslyn, S.M., Brunn, J.R., Cave, K.R., & Wallach, R. (1984). Individual differences in mental imagery ability: a computational analysis. *Cognition, 18*, 195-243.
Launay, G., & Slade, P.D. (1981). The measurement of hallucinatory predisposition in male and female prisoners. *Personality and Individual Differences, 2*, 221-234.
Marks, D.F. (1973). Visual imagery differences in the recall of pictures. *British Journal of Psychology, 64*, 17-24.
Mehta, Z., Newcombe, F., & De Haan, E.H.F. (1992). Selective loss of imagery in a case of visual agnosia. *Neuropsychologia, 30*, 645-655.
Posey, T.B., & Losch, M.E. (1983). Auditory hallucinations of hearing voices in 375 normal subjects. *Imagination, Cognition and Personality, 2*, 99-113.
Richardson, A. (1969). *Mental imagery*. New York: Springer.
Roman, R., & Landis, C. (1945). Hallucinations and mental illness. *Journal of Nervous and Mental Disease, 102*, 327-331.
Seitz, P.F.D., & Molholm, H.B. (1947). Relation of mental imagery to hallucinations. *Archives of Neurology and Psychiatry, 57*, 469-480.
Slade, P.D. (1976). An investigation of psychological factors involved in the predisposition to auditory hallucinations. *Psychological Medicine, 6*, 123-132.
Slade, P.D., & Bentall, R.P. (1988). *Sensory deception; a scientific analysis of hallucination*. Baltimore: John Hopkins University Press.
Snodgrass, J.G., & Vanderward, M. (1980). A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity and visual complexity. *Journal of Experimental Psychology: Human Learning and Memory, 6*, 174-215.
Starker, S., & Jolin, A. (1982). Imagery and hallucinations in schizophrenic patients. *Journal of Nervous and Mental Disease, 170*, 448-451.7
Tien, A.Y. (1991). Distribution of hallucinations in the population. *Social Psychiatry and Psychiatric Epidemiology, 26*, 287-292.
Young, H.F., Bentall, R.P., Slade, P.D., & Dewey, M.E. (1986). Disposition towards hallucination, gender and IQ scores. *Personality and Individual Differences, 7*, 247-249.

Chapter 7

Mental imagery and perception in hallucination-prone individuals

Summary

College students screened for hallucination-proneness using the Launay-Slade Hallucination Scale (LSHS) were compared on measures of self-report vividness of imagery and on behavioral measures of imagery and perception (visual and auditory). Specifically, we tested the hypothesis whether hallucination-prone individuals would show smaller differences between imagery and perception performance, which may be indicative of increased sensory characteristics of mental images. We replicated earlier findings of higher self-report imagery ratings in the high hallucination-prone group. However, the two groups did not differ on five of six behavioral imagery-perception comparisons. Although vividness of mental images may be subjectively associated with mild hallucinatory experiences, we suggest that cognitive processes associated with reality discrimination rather than increased perceptual characteristics of mental images may play a role at the information processing level.

Aleman, A., Nieuwenstein, M., Böcker, K.B.E., De Haan, E.H.F. (2000). Mental imagery and perception in hallucination-prone individuals. *Journal of Nervous and Mental Disease, 188,* 830-836.

Introduction

Despite decades of research, the exact mechanisms underlying the puzzling phenomenon of hallucination remain poorly understood. As a working definition, hallucinations may be considered "sensory experiences that occur in the absence of external stimulation of the relevant sensory organ, have the compelling sense of reality of a true perception, are not amenable to direct and voluntary control by the experiencer, and occur in an awake state" (Aleman and De Haan 1998; see also Slade and Bentall 1988). Hallucinations may occur in a wide range of medical and psychiatric conditions (Asaad and Shapiro 1986; Brasic 1998; Slade and Bentall 1988) and are one of the characteristic disturbing symptoms of schizophrenia (Schneider 1962). Slade and Bentall (1988) estimated the prevalence of auditory hallucinations to be 60% in schizophrenia, based on 16 published reports including 2924 cases. However, hallucinations are not always indicative of pathology, as indicated by numerous studies which have established the occurrence of hallucinatory experiences in a substantial number of persons from the normal population (Aleman et al. 2000; Barrett and Etheridge 1992; Bentall and Slade 1985; Tien 1991). Such auditory-verbal hallucinatory experiences may, to an important degree, resemble the hallucinations characteristic of schizophrenia (Barrett and Caylor 1998; Honig et al. 1998). Indeed, it has been proposed that psychosis-like experiences may be thought of as existing on a continuum, ranging from very mild expressions in the normal population to the bizarre symptoms characteristic of severe mental illness (Crow 1998; Slade and Bentall 1988). Thus, the study of cognitive mechanisms underlying hallucinatory experiences in individuals from the normal population may provide important information about the possible mechanisms underlying hallucinations in mental disorders.

Although theories of hallucination differ considerably (e.g. Bentall 1990; David 1994; Frith and Done 1988; Hoffman 1986), some consensus is emerging that hallucinations are a result of the confounding of internally-generated experiences with externally-generated events (Slade 1994). It has been hypothesized that such confounding may arise from biases in reality monitoring, i.e., the processes involved in discriminating memories of internal generated information from memories of external derived information (Bentall et al. 1991; Morrison and Haddock 1997). However, a recent study (Keefe et al. 1999) showed that hallucinating and nonhallucinating patients with schizophrenia did not differ on measures of reality monitoring, although both groups showed significant more reality monitoring errors compared with a healthy comparison group.

Alternatively, it may be hypothesized that the erroneous attribution of internally-generated events to external sources may result from mental images having more perceptual characteristics than expected by the cognitive system. The idea that hallucinations are extreme vivid manifestations of mental imagery was allready stated by Galton more than a century ago (Galton 1883). Results from studies in which this claim was investigated are contradictory. For example, Mintz and Alpert (1972), Roman and Landis (1945), and Slade (1976) found evidence of more vivid imagery in hallucinating patients compared to non-hallucinating patients. Moreover, Barrett (1992) compared high-scoring college students on a verbal hallucination scale with low scoring participants and found high scoring participants to report more vivid self-rated imagery. In contrast, Brett and Starker (1977), Seitz and Molholm (1947), and Starker and Jolin (1982) failed to find evidence of increased imagery vividness in hallucinating schizophrenic patients. However, these studies all concerned introspective measures of imagery, which are limited to the subjective experience of imagery.

The aim of the present study was twofold. First, to replicate the relation reported by Barrett (1992) between hallucination-proneness in subjects from the normal population and self-rated imagery vividness. Second, to investigate whether a relation would be found between hallucination-proneness and imagery on behavioral comparisons of measures of imagery and perception. According to Johnson and Raye (1981) percepts, which originate from externally presented stimuli, are characterized by more detailed sensory, contextual and semantic information than internally generated images. Evidence that mental images are less rich in perceptual details than 'real' percepts and that, as a consequence, images are more difficult to perform mental operations upon, was recently presented by Kosslyn et al. (1999). The hypothesis that imagery and perception are more alike (and therefore harder to discern from each other) due to increased sensory characteristics of mental images in individuals that experience hallucinations thus predicts that these subjects will show smaller performance differences between a perception and an imagery condition of the same task.

Methods

Subjects were two groups selected out of 243 undergraduate students (mean age 22.6 years, SD=5.6) from Utrecht University, who completed the Launay-Slade

Hallucination scale[1] (LSHS; Launay and Slade, 1981; revision Bentall and Slade, 1985). The LSHS consists of 12 descriptions of hallucinatory experiences, e.g. "I often hear a voice speaking my thoughts aloud". LSHS items were scored on a five point scale as follows: 0=”certainly does not apply to me”, 1=”possibly does not apply to me”, 2=”unsure”, 3=”possibly applies to me” and 4=”certainly applies to me”. The questionnaire was scored by summing the ratings. A high score on the LSHS indicates increased predisposition towards hallucination. We selected 19 high scoring participants (from the upper 15%) and 17 low scoring participants (from the lower 15%) from the sample of 243 students. The mean LSHS rating of the high group was 26.7(SD=3.6), and the mean rating of the low LSHS group was 4.0 (SD=1.9). The difference between the two groups was significant, t = 23.7, $p < .0001$. The male/female ratio was comparable in both groups, 6:13 for the high LSHS group and 5:12 for the low LSHS group.

Procedure

Two questionnaires and six experimental tasks were used. The questionnaires concerned the Betts QMI Vividness of Imagery Scale, and the Marks Vividness of Visual Imagery Questionnaire (VVIQ). The experimental tasks concerned a visual and auditory version of a triad imagery perception comparison task, a visual and auditory version of an imagery-perception interaction task, a letter imagery task (visual), and a Musical imagery task (auditory). A more detailed description of the measures follows.

Betts QMI Vividness of Imagery Scale. The auditory and visual subscales of the shortened Betts QMI Vividness of Imagery Scale (Richardson 1969) consist of nine verbal descriptions, such as "the sun as it is sinking below the horizon" (visual) and “the meowing of a cat” (auditory). Participants are asked to rate their imagery vividness on a 7-point scale, ranging from 1: "Perfectly clear and as vivid as the actual experience" to 7: "No image present at all, you only 'knowing' that you are thinking of the object". The questionnaire is scored by summing the ratings. A low score indicates more vivid imagery.

Vividness of Visual Imagery Questionnaire. The Marks Vividness of Visual Imagery Questionnaire (VVIQ; Marks, 1973) is an extension of the visual subscale of the Betts scale. It consists of 16 descriptions which must be rated on a 5-point

[1] Several studies have reported evidence in favour of the reliability and validity of the Launay-Slade Hallucination Scale (Launay and Slade, 1981; Bentall and Slade, 1985; Rankin and O’Carroll, 1995; Levitan, Wards, Catts and Hemsley, 1996; Morrison, Wells and Nothard, 2000)

Likert-scale, in an identical way as the Betts scale. However, the subject must rate the items once with eyes open, and once with eyes closed. The questionnaire is scored by summing the ratings. Lower scores indicate more vivid imagery.

Object imagery. The object imagery task concerns a quantitative comparison between imagery and perception of visual form characteristics of common objects (this task was adapted from Mehta et al. 1992) or sound characteristics of common sounds (auditory version). *Visual modality.* The task consists of 22 object names printed on cards and 22 triads of line drawings of common objects (Snodgrass and Vanderward, 1980). From the triads of line drawings, the item that is most deviant in terms of visual form characteristics has to be indicated. In the perceptual condition the line drawings are actually presented, whereas in the imagery condition the object names are read from cards. For example, in the perceptual condition pictures of the following three objects are presented: “pumpkin”, “lettuce” and “tomato”, whereas in the imagery condition only the names of these three objects were presented to the subject. Thus, the imagery condition requires the participants to form mental images in order to be able to make a correct judgement (which in the example given would be “lettuce”). A difference-score was calculated by subtracting the correct responses in the imagery condition from the correct responses in the perceptual condition. *Auditory modality.* The auditory task was similar to the visual version in that a triad of common sounds was presented, and participants had to indicate the item that is most deviant in terms of acoustic characteristics. In the perceptual condition the sounds were actually presented (by the computer), whereas in the imagery condition the names of the sounds were read from cards. An example of a sound triad that was presented is “crying baby”, “laughing baby” and “meowing cat”, where “laughing baby” was regarded the deviant item.

Imagery-perception interaction. Imagery is known to affect certain aspects of perceptual processes, which makes it possible to obtain an indirect measure of imagery qualities by recording objective perceptual processes. Farah (1989) demonstrated that, in the visual modality, near-threshold stimuli are more easily detected if they are presented on an image (say of a letter H) than when presented off the image in a forced choice psychophysical paradigm. This effect has also been found in the auditory modality; tones presented at absolute perception threshold are detected more often when they are also imaged (Farah and Smith, 1983). *Visual modality.* In this test, first the absolute threshold for duration of dot presentation was determined by use of the staircase method. Second, two series of 32 trials were presented, while the participants was imagining one of the two letters (capital T or H in a 5 x 5 grid). In 25% of the trials the stimuli were “on-image” and in another 25% the stimuli were “off-image”. For the other 50% no stimuli were present. The difference in the number of detected stimuli in the on-image condition compared to the off-image condition is a measure for the interaction between imagery and perception. In contrast to the other behavioral measures, a larger difference value implies a greater effect of imagery, which is expected in participants with hallucinatory experiences according to the hypothesis that increased perceptual characteristics of mental images are associated with hallucination. *Auditory modality.* The auditory version of this task was identical to the visual version, with the difference that the absolute threshold was determined for the loudness of two tones in 74 dB(A) white noise, and that the stimuli presented during the experiment consisted of tones which could be at a frequency of 440 or 1000 Hz. A tone at one of these frequencies had to be imaged (e.g. 440 Hz), while a tone at one of either frequency was presented as stimulus during the experiment, with 25% of the stimuli being “on-image” (in this case 440 Hz) and 25% “off-image” (1000 Hz).

Letter imagery. We adapted the letter imagery task used by Kosslyn et al. (1988). The subject is asked whether an X-mark, presented in a 4x5 grid, falls on a capital letter. In the imagery condition, the letter is not actually presented in the grid, but must be imaged by the subject. For example, after a fixation point a lowercase letter ‘f’ is presented, followed by an empty grid with the X-mark at the lower right corner. The subject must decide whether the target would fall on an uppercase letter ‘F’ or not. In the perception condition, the letter actually appeared in the grid. Eight letters were randomly presented during the task: ‘c’, ‘f’, ‘h’, ‘j’, ‘l’, ‘p’, ‘s’, ‘u’. Each condition of the task consisted of 32 trials, 4 trials for each of the letters (two “on” and two “off” trials for each letter). We modified the task slightly, in that we allowed the X-mark to appear only in cells in which the chance that the X-mark would cover a letter was equal (thus, no X-marks appeared in the most left column, as most capital letters would cover these cells). The difference in number of correct responses between the imagery and perception condition was the dependent measure.

Musical imagery. This task of musical imagery requires participants to mentally compare pitches of notes corresponding to song lyrics, and was adapted from Halpern (1988; experiment 2). Participants viewed the lyrics from the first line of a familiar Dutch song on a screen and were asked to decide whether, of two indicated lyrics (which were marked on both sides with asterisks and appeared in uppercase letters), the pitch of the second lyric was higher or lower than that corresponding to the first lyric. Lyric refers here to a monosyllabic word, or one syllable of a two-syllabic word. An English language example would be: "*OH* say can *YOU* see", taken from the American national anthem. Participants responded by means of a key press. In the perceptual condition, participants were actually presented with the song, which was played via a tape-recorder. The imagery condition was identical, with the exception that the song was not presented, and participants had to rely on their musical imagery in order to be able to perform the task correctly. Again, the difference in number of correct responses between the imagery and perception condition was calculated.

Statistical analyses. Analysis of variance was performed to investigate between group differences on vividness of imagery ratings and performance differences on imagery and perception conditions of the behavioral tasks. The level of significance was set at $p<.05$ (two-tailed). In addition, non-parametric correlation coefficients for the relation between imagery and perception performance were calculated within each group.

Results

Table 1 presents means and SDs for the high and low LSHS group on the imagery measures.

Self-rated imagery vividness

For the ratings on the VVIQ, the groups differed significantly, $F(1, 34)=4.7$, $p<.05$. Participants in the high LSHS group reported more vivid images than participants in the low group (table 1). No significant differences were observed between the high and low LSHS group on the Betts visual subscale ($F[1, 34]=3.1$, $p<.10$), nor on the Betts auditory subscale ($F[1, 34]=1.6$, $p>.10$). The Betts visual subscale as well as the VVIQ correlated significantly with ratings on the LSHS (for both $r=-0.40$, $p<.05$). The correlation between the Betts auditory subscale and the LSHS was not significant ($r=0.21$, $p>.10$).

Behavioral measures of imagery and perception

Of the behavioral measures, only the visual object imagery task showed a significant group difference in imagery/perception difference-scores. A significant larger difference between imagery and perception performance was observed in the low LSHS group compared with the high group, $F(1, 34)=7.0$,

$p<.05$ (see table 1). The other five behavioral measures failed to reveal significant differences between the high and the low LSHS group. There was no significant difference between imagery scores in the visual and auditory modality in either group (This was evaluated with ANOVA's on z-transformed scores as the scales of the different measures are not comparable).

Table 1. Means and SDs for the high LSHS and the low LSHS group on measures of imagery vividness (lower scores indicate higher imagery)

Imagery vividness measure		High LSHS group (N=19)	Low LSHS group (N=17)
VVIQ		34.1 (6.2)	37.5 (8.6)
Betts visual subscale		12.7 (3.7)	15.1 (4.6)
Betts auditory subscale		11.1 (3.9)	12.6 (3.3)
Object imagery	visual	2.5 (1.7)	0.8 (2.2)
	auditory	3.9 (2.0)	3.2 (2.6)
Imagery-perception interaction	visual*	0.7 (2.2)	0.4 (3.3)
	auditory*	2.2 (3.5)	1.9 (5.0)
Letter Imagery		3.0 (2.7)	2.1 (2.7)
Musical imagery		2.5 (3.1)	2.0 (3.8)

*higher scores indicate higher imagery performance

When performance on the perception and imagery conditions was analyzed independently, no difference between the high and low group was found on any of the six behavioral tasks (all *p*'s>.10). In addition, the two groups did not differ in perceptual acuity as indicated by the auditory and visual threshold measures of the imagery-perception interaction task ($p>.70$).

Correspondence between imagery and perception

As table 2 demonstrates, correlations between performance (number of correct responses) on the imagery and perception tasks were substantial higher in the high LSHS than in the low LSHS group for the object imagery task (visual and auditory) and the musical imagery-perception task. No differences were observed for the letter imagery-perception task. For the imagery-perception interaction task no correlations were computed, as this task, measuring the interaction between imagery and perception, does not have strictly distinct imagery and perception conditions.

Table 2. Nonparametric correlations (Spearman's rho) between performance on imagery and perception conditions of the behavioral measures for the high LSHS and the low LSHS group

Imagery measure		High LSHS group (N=19)	Low LSHS group (N=17)
Object imagery	Visual	.64**	-.11
	Auditory	.45*	.10
Musical imagery		.62**	.50*
Letter Imagery		.34	.39

*$p<.05$, **$p<.01$

Discussion

The present study was designed to replicate the previously reported relation between self-reported vividness of mental imagery and hallucination-proneness, and more importantly, to investigate whether a relation between imagery and hallucination-proneness would be observed on behavioral measures of information processing. Subjects from the normal population with high ratings on a questionnaire for hallucination-proneness (the Launay-Slade Hallucination Scale) were contrasted with low hallucination-prone subjects on multiple behavioral measures of imagery-perception comparisons in both the visual and the auditory modality.

Consistent with earlier observations (Barrett 1992; Aleman, Böcker et al. 1999), the high group showed higher imagery vividness ratings than the low group on the self-report measures. We thus replicated the relation between hallucinatory predisposition and self-report imagery vividness in normal subjects (Barrett 1992) using a different hallucination questionnaire (LSHS in stead of Verbal Hallucination questionnaire) and including a different imagery questionnaire (the VVIQ, in addition to the Betts scale). It is important to note that the experiences considered in the LSHS as well as the imagery vividness questionnaires are highly similar phenomenologically, which may contribute to the observed association between these measures.

In contrast, there were no important differences between the high and low hallucination-prone groups in imagery-perception comparisons as measured with behavioral tests of imagery and perception. The groups differed on only one of the six behavioral measures, the visual object imagery-perception task. For this task, the difference between perception and imagery scores was larger in high LSHS participants, indicating a possible decrease rather than increase in perceptual characteristics of mental images. Cognitive dysfunction has been consistently documented in schizophrenia (Aleman, Hijman et al. 1999;

Heinrichs & Zakzanis 1998) and may to some extent be found in subjects with high ratings on schizotypy scales (Lenzenweger 1998). The LSHS has been considered a scale that provides an indication of positive schizotypy (Vollema and Van den Bosch 1995). It could thus be argued that subjects in the high hallucination-prone group may have a higher incidence of mild cognitive problems which could explain a lower performance compared to low hallucination-prone subjects. It is important to note, however, that the two groups did not differ significantly on the perception nor on the imagery condition of this task, implying that the difference between the groups can not be attributed to attentional or motivational factors. It was the relative score of the difference between perception and imagery that showed a significant difference between groups, with high hallucination-prone subjects showing larger differences between imagery and perception performance than subjects in the low group. In an earlier study, in which the object imagery task was the only behavioral measure, also a negative relation between imagery-perception differences and LSHS ratings was observed (Aleman, Böcker et al. 1999). Horowitz (1975) hypothesized that hallucinators have less vivid imagery than non-hallucinators which would lead an occasional "vivid" image to be misinterpreted as a perception. Indeed, it could be argued that there is no absolute increase in imagery vividness in hallucinating individuals, but a relative increase of imagery vividness in the modality of hallucination, caused by a decrease of vividness in other modalities. It is therefore interesting to note that the lower imagery vividness performance in the hallucination-prone group was only in found on a visual imagery task, and that the LSHS mainly concerns auditory hallucinatory experiences. This is consistent with the finding by Böcker et al. (in press) of a modality-specific imagery difference in auditory hallucinating patients (larger imagery-perception interaction in an auditory, but not in a visual condition of an imagery task), which was not observed in a control group of patients without hallucinations. Certainly, more detailed investigation of imagery-perception comparisons with behavioral measures in psychiatric patients with more severe and bizarre hallucinations characteristic of psychosis is needed before strong final conclusions can be reached.

Our finding of a larger correlation between imagery and perception in the high LSHS group than in the low LSHS group may support the plausibility of an explanation in terms of cognitive processes that are involved in distinguishing internal and external sources of perceived events, which has been termed "reality discrimination" (cf. Bentall 1990). The observation may imply that the cognitive processes involved in perception and imagery operate separately to a significant extent in low hallucination-prone participants, but are more closely related in high hallucination-prone participants. According to Johnson and Raye (1981), errors in discriminating internal from external information are more likely to occur when the cognitive processes involved are highly similar. Indeed, Rankin and O'Carroll (1995) have provided evidence of deficient reality discrimination in high LSHS participants compared to low LSHS participants.

Conclusion

In the present study, we replicated the finding of a positive relation between hallucination-proneness and self-report vividness of mental imagery. However, this relation was not observed on multiple behavioral measures of auditory and visual imagery and perception. A higher correlation between imagery and perception was observed in high hallucination-prone individuals compared to the low group, which may imply that the cognitive processes involved in imagery and perception may result less distinctive from each other in the high group, thus making reality discrimination errors more likely. Future research in psychiatric patients must be aimed at disentangling these complex relations to provide a more detailed account of the cognitive basis of hallucinations.

References

Aleman A, Böcker KBE, De Haan EHF (1999) Disposition toward hallucination and subjective versus objective imagery in normal subjects. *Pers Individ Diff* 27:707-714.

Aleman A, De Haan EHF (1998) On redefining hallucination [letter]. *Am J Orthopsychiatry,* 68:656-658.

Aleman A, Hijman R, De Haan EHF, Kahn RS (1999) Memory impairment in schizophrenia: a meta-analysis. *Am J Psychiatry* 156:1358-1366.

Aleman A, Nieuwenstein MR, Böcker KBE, De Haan EHF (2000) Multidimensionality of hallucinatory predisposition: factor structure of the Launay-Slade Hallucination Scale in a normal sample. *Pers Individ Diff* In press.

Asaad G, Shapiro B (1986) Hallucinations: theoretical and clinical overview. *Am J Psychiatry,* 143, 1088-1097.

Barrett TR (1992) Verbal hallucinations in normals-II: self-reported imagery vividness. *Pers Individ Diff* 15:61-67.

Barrett TR, Caylor MR (1998) Verbal hallucinations in normals, V: perceived reality characteristics. *Pers Individ Diff* 25:209-221.

Barrett TR, Etheridge, JB (1992) Verbal hallucinations in normals, I: People who hear 'voices'. *Appl Cogn Psychol* 6, 379-387.

Bentall RP (1990) The illusion of reality: a review and integration of psychological research on hallucinations. *Psychol Bull* 107:82-95.

Bentall RP, Baker G, Havers S (1991) Reality monitoring and psychotic hallucinations. *Br J Clin Psychol* 30:213-222.

Bentall RP, Slade PD (1985) Reliability of a scale measuring disposition towards hallucination: a brief report. *Pers Individ Diff* 6:527-529.

Böcker KBE, Hijman R, Kahn RS, De Haan EHF (in press) Perception, mental imagery and reality discrimination in hallucinating and nonhallucinating schizophrenic patients. *Br J Clin Psychol*.

Brasic JR (1998) Hallucinations. *Percept Motor Skills* 86:851-877.

Brett EA, Starker S (1977) Auditory imagery and hallucinations. *J Nerv Ment Dis* 164:394-400.

Crow TJ (1998) From Kraepelin to Kretschmer leavened by Schneider. *Arch Gen Psychiatry* 55:502-504.

David AS (1994) The neuropsychological origin of auditory hallucinations. In: A.S. David & J.C. Cutting (Eds), *The neuropsychology of schizophrenia.* Hove: Psychology Press.

Farah MJ, Smith AF (1983) Perceptual interference and facilitation with auditory imagery. *Percept Psychophys* 33:475-478.

Farah MJ (1989) Mechanisms of imagery-perception interaction. *J Exp Psychol: Hum Percept Perform* 15:203-211.

Frith CD, Done DJ (1988) Towards a neuropsychology of schizophrenia. *Br J Psychiatry* 153:437-443.

Galton F (1883) *Inquiries into human faculty and its development.* London: McMillan.

Halpern R (1988) Mental scanning in auditory imagery for songs. *J Exp Psychol: Learn Mem Cogn* 10:496-512.

Heinrichs RW, Zakzanis KK (1998) Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology* 12:426-445.

Hoffman RE (1986) Verbal hallucinations and language production processes in schizophrenia. *Behav Brain Sci* 9:503-548.

Honig A, Romme MAJ, Ensink BJ, Escher SD, Pennings MHA, deVries MW (1998) Auditory hallucinations: A comparison between patients and nonpatients. *J Nerv Ment Dis* 186:646-651.

Horowitz MJ (1975) Hallucinations: an information processing approach. In RK Siegel and LJ West (Eds) *Hallucinations: Behavior, experience and theory* (pp. 163-196). New York: Wiley.

Johnson MK, Raye CL (1981) Reality monitoring. *Psychol Rev* 88:67-85.

Keefe RSE, Arnold MC, Bayen UJ, Harvey PD (1999) Source monitoring deficits in patients with schizophrenia; a multinomial modelling analysis. *Psychol Med* 29:903-914.

Kosslyn SM (1994) *Image and brain.* Cambridge, MA: The MIT Press.

Kosslyn SM, Cave CB, Provost D, Von Gierke S (1988) Sequential processes in image generation. *Cogn Psychol,* 20:319-343.

Kosslyn SM, Sukel KE, Bly BM (1999) Squinting with the mind's eye: effects of stimulus resolution on imaginal and perceptual comparisons. *Mem Cogn* 27:276-287.

Launay G, Slade PD (1981) The measurement of hallucinatory predisposition in male and female prisoners. *Pers Individ Diff* 2:221-234.

Lenzenweger MF (1998) Schizotypy and schizotypic psychopathology: mapping an alternative expression of schizophrenia liability. In MF Lenzenweger and RH Dworkin (Eds) *Origins and development of schizophrenia; advances in experimental psychopathology* (pp 93-122). Washington, DC: American Psychological Association

Levitan C, Ward PB, Catts SV, Hemsley DR (1996) Predisposition towards auditory hallucinations: the utility of the Launay-Slade Hallucination Scale in psychiatric patients. *Pers Individ Diff* 21:287-289.

Marks DF (1973) Visual imagery differences in the recall of pictures. *Br J Psychol* 64:17-24.

Mehta Z, Newcombe F, De Haan EHF (1992) Selective loss of imagery in a case of visual agnosia. *Neuropsychologia*, 30:645-655.

Mintz S, Alpert M (1972) Imagery vividness, reality testing, and schizophrenic hallucinations. *J Abn Psychol* 79:310-316.

Morrison AP, Haddock G (1997) Cognitive factors in source monitoring and auditory hallucinations. *Psychological Med* 27:669-679.

Morrison AP, Wells A, Nothard S (2000) Cognitive factors in predisposition to auditory and visual hallucinations. *Br J Clin Psychol* 39:67-78.

Rankin PM, O'Carroll PJ (1995) Reality discrimination, reality monitoring and disposition towards hallucination. *Br J Clin Psychol* 34:517-528.

Richardson A (1969) *Mental imagery*. New York: Springer.

Roman R, Landis C (1945) Hallucinations and mental illness. *J Nerv Ment Dis* 102:327-331.

Schneider K (1962) *Klinische Psychopathologie* (6e Auflage). Stuttgart: Georg Thieme.

Seitz PFD, Molholm HB (1947) Relation of mental imagery to hallucinations. *Arch Neurol Psychiatry*, 57:469-480.

Slade PD (1976) An investigation of psychological factors involved in the predisposition to auditory hallucinations. *Psychological Med* 6:123-132.

Slade PD (1994) Models of hallucination: from theory to practice. In: A.S. David & J.C. Cutting (Eds), *The neuropsychology of schizophrenia.* Hove: Psychology Press.

Slade PD, Bentall RP (1988) *Sensory deception; a scientific analysis of hallucination*. Baltimore: John Hopkins University Press.

Snodgrass JG, Vanderward M (1980) A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity and visual complexity. *J Exp Psychol: Learn Mem Cogn* 6:174-215.

Starker S, Jolin A (1982) Imagery and hallucinations in schizophrenic patients. *J Nerv Ment Dis* 170:448-451.7

Tien AY (1991) Distribution of hallucinations in the population. *Soc Psychiatry Psychiatric Epidemiol* 26:287-292.

Vollema MG, Van den Bosch RJ (1995) The multi-dimensionality of schizotypy. *Schizophr Bull* 21:19-31.

Chapter 8

Controversies and Discussions 2

Definition of hallucination

Aleman, A., & De Haan, E.H.F. (1998). On redefining hallucination. *American Journal of Orthopsychiatry, 68*, 656-658.

In his interesting and thought-provoking article “Toward a new definition of hallucination”, Liester (1998) proposed a revised definition of the concept of hallucination. Taking the widely applied DSM-IV definition as a starting point, Liester argued that there are important shortcomings in current definitions of hallucination. DSM-IV defines hallucinations as follows:

> “A sensory perception that has the compelling sense of reality of a true perception but that occurs without external stimulation of the relevant sensory organ.”

Liester (1998) mainly focused on two flaws: the failure to distinguish between pathological and nonpathological experiences and the lack of appropriate consideration to cultural beliefs of the individual experiencing the hallucination. Liester formulated a revised definition of hallucination in which these notions are incorporated. He proposed the following definition of hallucination:

> “A sensory experience that has the compelling sense of reality of an “objective” perception, but that occurs without external stimulation of the relevant sensory organ; that occurs in conjunction with and is believed to be etiologically related to, a physical or mental disorder; and that is not ordinarily experienced or accepted by other members of the culture or subculture.”

To our perception, however, the definition is not adequate, as it is based on certain assumptions regarding the nature of psychopathology that remain unjustified. In our comment we will address this issue, and will specifically pay attention to the question whether a definition of hallucination must be restricted to psychopathological experiences, as advocated by Liester (1998).

As recognized by Liester (1998), numerous reports have by now established the occurence of hallucinatory experiences in the normal population (Posey & Losch, 1983; Young et al., 1986; Tien, 1991; Barrett & Etheridge, 1992; Aleman, Böcker & De Haan, 1998). Moreover, the percentage of normal subjects reporting hallucinatory experiences is substantial, ranging from 10% (Tien, 1991) to 25% (Barrett & Etheridge, 1992). The hallucinatory events reported by these people are very similar to the auditory-verbal hallucinations characteristic of schizophrenia. For example, in the study by Bentall & Slade (1985), 17.7% of the subjects (N=136) scored the item “I often hear a voice speaking my thoughts aloud” as “Certainly applies” and 15.4% scored the item “In the past I have had the experience of hearing a person’s voice and then found that there was no one there” as “Certainly applies”. These studies strongly suggest that hallucinations can be seen as existing on a continuum with normal mental events. As Slade &

Bentall (1988) have stated: "…Hallucinations should be studied in their own right, rather than as part of larger psychiatric syndromes" (p.56).

Liester (1998) is particulary concerned with "the difficult problem of distinguishing "pathological" from "normal" hallucinations." This conception of hallucination is based on a medical model of psychiatric illness in which a categorical distinction is assumed between "healthy" conditions and "ill" conditions. However, there is considerable debate about the validity of such an approach to the classification of abnormal behavior (Blashfield, 1984; Bentall, 1990a). As an alternative, abnormal experiences might be seen as existing on a continuum with normal mental events, differing only in degree of severity. Or, as Crow (1998) recently put it: "…The phenomena of psychosis can be regarded as a component (albeit an extreme or "boundary" condition) of the diversity of human psychological structure…" (p. 504). In this approach it is not necessary to distinguish between "pathological" and "normal" hallucinations. Rather, it is the task of the clinician to evaluate whether the hallucinations arise in the context of a psychiatric condition or not.

There is no a priori reason, therefore, nor is there a theoretical justification for limiting the definition of hallucinations to psychopathological experiences. Restricting the definition of hallucination to psychopathology may result in a rather arbitrary classification practice. Consider the following example. John and Mark both often experience "a voice speaking their thoughts aloud". A psychiatrist conducts a psychiatric examination on both, and concludes that John, in contrast to Mark, presents some (other?) symptoms of psychopathology. Is the same hallucinatory experience, shared by John and Mark, to be defined hallucination in John, but not in Mark? And, if so, what is the hallucinatory experience of Mark to be called?

We also doubt whether the elimination from the definition of hallucination of hallucinatory events that are accepted within certain cultural contexts will prove to be valuable. Whether occurring in a particular cultural context, in a general medical condition or in a psychiatric disorder, the phenomenology of hallucination is similar. As long as the social, cognitive and neurobiological mechanisms underlying hallucinatory experiences are not fully specified, and the etiology thus remains unknown, it does not seem reasonable to term the same phenomenological event as "hallucination" in one instance (e.g. within a psychopathological context), but not in another (e.g. within a cultural context).

Therefore, we are more at ease with the working definition given by Slade & Bentall (1988):

> "Any percept-like experience which (a) occurs in the absence of an appropriate stimulus, (b) had the full force or impact of the corresponding actual (real) perception, and (c) is not amenable to direct and voluntary control by the experiencer."

However, a shortcoming of the definition by Slade & Bentall (1988) might be that vivid dreams (with clear and lively imagery) fulfill the criteria of the definition, and must hence be termed "hallucinations". It does not seem appropriate to consider vivid dreams as hallucinations, as the possibility of hallucination implies the possibility of adequate discrimination between perceptual events with and without an objective ("real") basis. This latter ability requires a conscious, awake state. We would therefore like to propose the following revised working definition of hallucination:

> "A sensory experience which occurs in the absence of external stimulation of the relevant sensory organ, but has the compelling sense of reality of a true perception, is not amenable to direct and voluntary control by the experiencer, and occurs in an awake state."

This definition specifies the unique phenomenological characteristics of hallucinations and differentiates hallucinations from vivid mental imagery ("not amenable to direct and voluntary control") and from vivid dreams ("in an awake state").

Future research aimed at elucidating the exact mechanisms that give rise to hallucinations is necessary. Increasing knowledge of hallucinatory phenomena may indeed lead to a revised conception of these perceptual "illusions of reality" (Bentall, 1990b). For the moment, however, in order to achieve a better understanding of hallucinations, a working definition confined to the phenomenological level is the best we have.

References

Aleman, A., Böcker, K.B.E. & De Haan, E.H.F. (1998). Disposition toward hallucination and subjective versus objective vividness of imagery in normal subjects. Submitted.

Barrett, T.R. & Etheridge, J.B. (1992). Verbal hallucinations in normals, I: People who hear 'voices'. *Applied Cognitive Psychology, 6*, 379-387.

Bentall, R.P. (1990a). The syndromes and symptoms of psychosis. In R.P. Bentall (Ed.), *Reconstructing schizophrenia* (pp 23-60). London: Routledge.

Bentall, R.P. (1990b). The illusion of reality: a review and integration of psychological research on hallucinations. *Psychological Bulletin, 107*, 82-95.

Bentall, R.P. & Slade, P.D. (1985). Reliability of a scale measuring disposition towards hallucination: a brief report. *Personality and Individual Differences, 6*, 527-529.

Blashfield, R.K. (1984). *The classification of psychopathology; neo-Kraepelinian and quantitative approaches*. New York: Plenum Press.

Böcker, K.B.E., Van der Lee, J., Hijman, R. & De Haan, E.H.F. (1996). Perception, mental imagery and reality discrimination in hallucinating and nonhalucinating schizophrenic patients. *Journal of the International Neuropsychological Society, 2*, 204-205.

Crow, T.J. (1998). From Kraepelin to Kretschmer leavened by Schneider. *Archives of General Psychiatry, 55*, 502-504.

Liester, M.B. (1998). Toward a new definition of hallucination. *American Journal of Orthopsychiatry, 68*, 305-312.

Posey, T.B. & Losch, M.E. (1983). Auditory hallucinations of hearing voices in 375 normal subjects. *Imagination, Cognition and Personality, 2*, 99-113.

Slade, P.D. & Bentall, R.P. (1988). *Sensory deception; a scientific analysis of hallucination*. Baltimore: John Hopkins University Press.

Tien, A.Y. (1991). Distribution of hallucinations in the population. *Social Psychiatry and Psychiatric Epidemiology, 26*, 287-292.

Young, H.F., Bentall, R.P., Slade, P.D. & Dewey, M. (1986). Disposition towards hallucination, gender and EPQ scores. *Personality and Individual Differences, 7*, 247-249.

Chapter 9

Music training and mental imagery

Summary

Neuroimaging studies have suggested that the auditory cortex is involved in music processing as well as in auditory imagery. We hypothesized that music training may be associated with improved auditory imagery ability. In this study, performance of musically trained and musically naive subjects was compared on 1) a musical mental imagery task (in which subjects had to mentally compare pitches of notes corresponding to lyrics taken from familiar songs), 2) a non-musical auditory imagery task (in which subjects had to mentally compare the acoustic characteristics of every-day sounds) and 3) on a comparable measure of visual imagery (in which subjects had to mentally compare visual forms of objects). The musically trained group did not only perform better on the musical imagery task, but also outperformed musically naive subjects on the non-musical auditory imagery task. In contrast, the two groups did not differ on the visual imagery task. This finding is discussed in relation to theoretical proposals about music processing and brain activity.

Aleman A, Nieuwenstein M, Böcker KBE, De Haan EHF (2000). Music training and mental imagery ability. *Neuropsychologia, 38,* 1664-1668.

Introduction

Musical mental imagery, or the ability to "hear" melodic sound-sequences with the "mind's ear" in the absence of external stimulation, plays an important role in musical performance [2]. Musicians often rely on musical imagery to guide their performance and to memorize or compose new music. Moreover, the ability to read written music silently is an acquired skill that often involves mental imagery. Halpern [4] devised a task aimed at measuring mental scanning in auditory imagery for songs, modeled on the visual scanning study by Kosslyn et al. [6]. Subjects were asked to mentally compare pitches of notes corresponding to lyrics taken from familiar songs (e.g. "The Star Spangled Banner"). Results showed that reaction times increased as a function of the distance between two beats and as a function of the starting point of the earlier lyric [4], and thus provided evidence that auditory imagery is not only a strong subjective experience, but, analogous to visual imagery, can be quantified to a certain extent.

It has been suggested that music training and listening to music may have beneficial effects on other cognitive processes. For example, Rauscher et al. [12] reported that college students who listened to the first ten minutes of Mozart's Sonata for Two Piano's in D Major (K.448) subsequently scored significantly higher on a spatial-temporal task than after listening to ten minutes of progressive relaxation instructions or after ten minutes of silence (although this effect has not always been replicated for other cognitive tasks, cf. ref. 15). Indeed, evidence has also been provided that music training may improve preschool children's spatial-temporal reasoning [14].

The putative effects of music training on cognitive performance may not be limited to spatial-temporal tasks, however. Chan *et al.* [1] recently reported higher verbal but not visual memory performance in subjects with at least six years of music training before the age of twelve compared to a control group without music training. These authors argued that the improved verbal memory in musically trained subjects may be due to a larger planum temporale in the left hemisphere relative to the right hemisphere in musicians, as has been shown in previous MRI-studies [17]. However, there is no evidence of involvement of the planum temporale in memory processing [18] and in a recent review on structure and function of the planum temporale [18] it is concluded that "the functional significance of asymmetrical planum temporale remains obscure" (p.41).

A more straightforward approach would be to predict which cognitive processes may be enhanced in musically trained individuals compared to non-trained individuals by taking into account the neural structures activated in music processing. Two studies using positron emission tomography (PET) have been reported [19, 5], in which basically the same auditory cortical areas (in the temporal lobes, bilateral) were activated during musical imagery and musical perception, and it has been proposed that these areas are involved in auditory imagery in general [19]. A related finding was recently reported in an fMRI-study of vivid auditory imagery associated with auditory hallucinations in patients with schizophrenia, which activated sensory auditory cortex [20]. In the present study we compared performance of subjects with and without music training on tasks of musical auditory imagery, non-musical auditory imagery and visual imagery. If music training leads to more proficient processing of mental images in auditory cortical areas, better performance of musically trained subjects on musical imagery may well extend to non-musical auditory imagery. This is not a trivial prediction, as there is evidence that music (the domain in which the training occurs) concerns a very specific type of auditory information processing and representation, that may dissociate with other types of auditory information [11]. According to our hypothesis, musically trained subjects will *not* perform better on a visual object imagery task compared to subjects without musical training, as visual imagery activates different cortical areas [6].

Method

Subjects

Thirty-five college students from Utrecht University participated in the study. Subjects were assigned to either a “musically-trained” group (fifteen subjects) or a “non-trained” group (twenty subjects). Subjects in the musical group had to 1) actively play a musical instrument at the moment of testing, and 2) have received at least two years of formal music training. The two groups differed significantly ($P < 0.01$) in number of years of music training (musicians 5.4; non-musicians 1.5). The two groups did not differ in terms of age (musicians 22.5 yrs; non-musicians group 21.1 yrs; $t = 1.25$) or number of years of education (musicians 16.3; non-musicians 16.0; $t = 0.49$). The male/female ratio was 6/9 in the trained group and 5/15 in the non-trained group.

Measures

Musical auditory imagery task. Musical imagery was assessed with a pitch comparison task (based on the task described by Halpern [4]) that consisted of a perception and an imagery condition and required subjects to compare the pitches of notes corresponding to song lyrics. Subjects viewed the lyrics from the first phrase of a familiar Dutch song on a screen and were asked to decide whether, of two highlighted lyrics which appeared in uppercase letters, the pitch of the second lyric was higher or lower than that of the first lyric. An English-language example of a song-line would be “OH say can you SEE”, taken from the American national anthem. Lyric refers here to a monosyllabic word, or one syllable of a two-syllabic word. Subjects responded by means of a key-press and were asked to respond as fast as possible. In the perceptual condition, subjects were actually presented with the song, which was played on a tape-recorder, and thus viewed the lyrics and heard the song at the same time. The imagery condition was identical, with the exception that the song was not presented, and subjects had to rely on their musical imagery in order to be able to perform the task correctly. The task consisted of 31 trials, divided over five well-known Dutch songs. Number of correct responses and reaction times were recorded.

Non-musical auditory imagery task. This task was modeled on the visual imagery object comparison task developed by Mehta et al. [9], described below. The task concerned a quantitative comparison between imagery and perception of acoustic characteristics of common sounds. A triad of common sounds was presented, and subjects had to indicate the most deviant item in terms of acoustic characteristics. In the perceptual condition, the sounds were actually presented (with use of a personal computer), whereas in the imagery condition the names of the sounds were read from cards, which required subjects to form mental images in order to be able to make a correct judgement. An example of a sound triad that was presented is “crying baby”, “laughing baby” and “meowing cat”, where “laughing baby” was regarded the deviant item. The task consisted of 23 triads.

Visual imagery task. This task was adapted from Mehta et al. [9] Subjects had to indicate the odd-one-out in terms of visual form characteristics of a triad of common objects. The task consisted of 24 object names printed on cards and 24 triads of line drawings of common objects [18]. From the triads of line drawings, the item that was most deviant in terms of visual form characteristics had to be indicated. In the perceptual condition the line drawings were actually presented, whereas in the imagery condition the object names were read from cards. For example, in the perceptual condition pictures of a “pumpkin”, “lettuce” and “tomato” were presented, whereas in the imagery condition only the names of these three objects were presented to the subject. Thus, the imagery condition requires the subjects to form mental images in order to be able to make a correct judgement of the odd-one-out (in the example given, “lettuce”).

Results

We conducted a 2 (Group: musicians, non-musicians) × 2 (Condition: perceptual, imagery) × 3 (Measure: musical, non-musical, visual) multivariate analysis of variance (MANOVA). Number of correct responses was the dependent variable included in the analysis for the three imagery measures. A z-tranformation was applied to the scores before analysis, as the scales of the different measures are not comparable. Only the between-subjects factor Group was significant, $F(1, 33) = 6.6$, $P < 0.02$. Table 1 shows the means and SDs of both groups on the different measures.

Table 1. Means (and SDs) of subjects in the musically trained group and in the non-trained group on measures of auditory and visual imagery and perception

Task	Condition	Trained group (N=15)	Non-trained group (N=20)
musical pitch comparison	perception	29.0 (1.7)	27.8 (2.9)
	imagery	28.1 (3.4)	24.3 (4.0)
everyday-sound comparison	perception	20.6 (1.3)	19.8 (1.9)
	imagery	17.6 (1.6)	15.8 (2.8)
visual form comparison	perception	21.2 (1.3)	20.7 (1.8)
	imagery	19.5 (2.0)	19.1 (2.4)

In a subsequent MANOVA on only the imagery measures, again only a significant effect of Group was obtained, $F(3, 31) = 3.6$, $P < 0.03$. Follow-up univariate analyses of variance (ANOVAs) revealed a significant difference between the musically trained and the non-trained group on the musical imagery task, $F(1, 33) = 8.6$, $P < 0.01$. Musically trained subjects had more correct responses for this task. The groups did not differ in reaction time, $F(1, 33) = 0.04$, $P > 0.10$. The difference between both groups was also significant for the non-musical auditory imagery task, $F(1, 33) = 4.9$, $P < 0.05$. Again, musically trained subjects performed better. There was no difference between the groups for performance on the visual imagery task, $F(1,33) = 0.3$, $P > 0.10$. In Figure 1 mean percentage correct responses of both groups are presented graphically for the three imagery tasks.

The MANOVA with perceptual conditions of the three tasks as dependent variables did not reveal significant differences between the musically trained and the non-trained group, although a trend seemed to emerge, $F(3, 31) = 3.6$, $P < 0.07$.

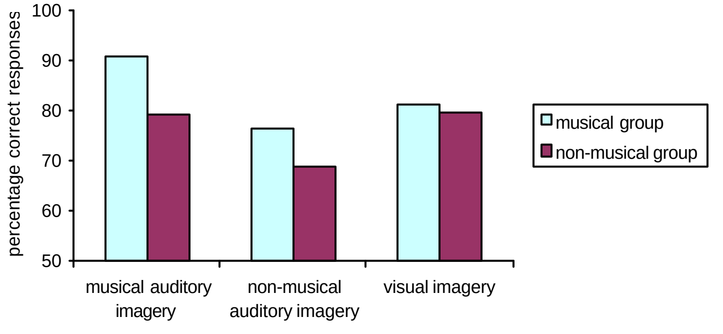

Figure 1 Mean percentage correct responses given by subjects with and without music training on the musical auditory imagery task, the non-musical auditory imagery task and the visual imagery task.

Follow-up ANOVA's, in order to examine the direction of this trend, failed to reach significance (all P 's> 0.10). We also performed within-group analyses to examine whether subjects within a group differed on the three tasks. No significant differences were found (all P 's> 0.20), indicating that the three measures did not differ importantly in difficulty level.

Discussion

In this study the hypothesis was tested whether musically trained subjects would perform better than non-trained subjects on a musical imagery task and whether this better performance would extend to a non-musical auditory imagery task. The results suggest that music training may improve both musical and non-musical auditory imagery but not visual imagery, consistent with the evidence of temporal association cortical involvement in auditory imagery [11].

The musically trained group did not differ from the non-trained group on the perceptual condition of the musical imagery task. The fact that people with little musical training performed as well as trained subjects on this task may be due to the use of relatively easy stimuli: familiar songs with well-known melodies. This could likewise explain why the non-trained group also performed fairly well on the imagery task. Indeed, as most of us will confirm from personal experience, the experience of having "tunes running through ones head" is not confined to musicians only. Notwithstanding, the musically trained group performed significantly better than the non-trained group on the imagery condition of the musical imagery task, suggesting more efficient processing of musical image representations in people with musical training.

Alternatively, one could argue that this is not a result of better processing of auditory image representations, but rather of an enhanced ability to organize and manipulate musical information in working memory. For example, analogous to expertise in chess, extensive music training may lead to the use of effective strategies involving abstract schemata, in this case regarding pitch relationships within melodic sound-sequences. However, the fact that trained subjects did not perform better than the non-trained subjects on the perception condition of the musical task is at odds with this possibility. More importantly, such an explanation would not predict better performance of musical trained subjects on non-musical auditory imagery tasks with everyday sounds (e.g., "a train passing") as stimuli. However, this was exactly what we found in the present study: musically trained subjects also performed better on a non-musical auditory imagery task than non-trained subjects.

An alternative explanation for the observed relation between music training and auditory imagery ability could be that it may be due to other variables, such as attention and memory, on which the two groups may differ and that may influence imagery performance. However, the subjects were drawn from a group (college students of identical age) that is relatively homogeneous in terms of cognitive abilities. In addition, the fact that the two groups did not perform differently on the visual imagery task, which has similar cognitive processing demands as the auditory tasks, suggests that the groups did not differ importantly on such variables. Another possibility would be that the musically trained subjects might be more interested in auditory tasks, thus causing more attention to this condition. However, if musicians are more interested in auditory tasks than in visual tasks, one would expect higher performance on the auditory tasks than on the visual tasks, which was not the case.

The possibility could also be considered that music training leads to a general improvement of imagery ability, regardless of the modality involved. Contrary to this hypothesis, the musically trained group did not perform better on a visual imagery task that was comparable to the non-musical auditory imagery task in terms of task-related characteristics. This finding is consistent with theoretical proposals regarding the neural basis of auditory imagery as involving auditory cortical areas in the temporal lobe [11] and visual imagery as involving occipital cortical areas [6]. Music training, which involves musical mental imagery, may thus lead to more proficient processing of imagery representations in auditory cortical areas, which may eventually result in a general enhancement of auditory imagery ability. It is important to note that the lack of a difference between musicians and non-musicians on the visual imagery task is not in contradiction with the findings by Rauscher et al. [12]. As Rauscher and Shaw [15] have explicitly pointed out, the Mozart effect is only observed on tasks which strongly require spatial-temporal processing (e.g., paperfolding tasks). Thus, measures that mainly require visual object recognition or imagery (i.e. without the temporal component of image transformation) may not show improvement after listening to music.

Rauscher et al. [13] proposed a neurophysiological basis for the enhancement of spatial-temporal task performance after listening to a Mozart piano sonata. Their model is based on Mountcastle's [10] organizational principle in which the cortical column is the basic neural network of the cortex. These networks have a large repertoire of inherent, periodic spatial-temporal firing patterns which can be excited in specific symmetries. The computation by symmetry operations among the inherent brain patterns is considered a key property of higher brain function and, more specifically, of spatial-temporal tasks, and may be enhanced and facilitated by music. To complement this account, we suggest that this effect may be especially pronounced in localized networks, which may explain why non-musical auditory imagery is enhanced in musically trained subjects. This is consistent with the study by Sarnthein et al. [16] who observed enhanced synchrony between the neural activity in right frontal and left temporoparietal cortical areas in an EEG coherence study of the Mozart effect. Indeed, recent studies have shown that training in a specific domain alters structure and function of localized brain areas [8]. Without doubt, more research is needed on the relation between music training and mental imagery and the neural correlates involved before strong conclusions can be reached. For example, it would be interesting to compare musicians and non-musicians in a functional magnetic resonance imaging (fMRI) design on patterns of brain activation during various imagery tasks.

References

1. Chan, A.S., Ho, Y-C., Cheung, M-C. Music training improves verbal memory. *Nature*, 1998, 396, 128.
2. Deutsch, D., Pierce, J.R., The climate of auditory imagery and music. In Reisberg D (Ed.), *Auditory imagery*. (pp. 237-260). Hillsdale: Lawrence Erlbaum (1992).
3. Dierks, T., Linden, D.E., Jandl, M., Formisano, E., Goebel, R., Lanfermann, H., Singer, W., Activation of Heschl's gyrus during auditory hallucinations. *Neuron*, 1999, 22, 615-621.
4. Halpern, A.R., Mental scanning in auditory imagery for songs. *Journal of Experimental Psychology: Learning Memory and Cognition*, 1988, 14, 193-202.
5. Halpern, A.R., Zatorre, R.J., When that tune runs through your head: a PET investigation of auditory imagery for familiar melodies. *Cerebral Cortex*, 1999, 9, 697-704
6. Kosslyn, S.M., Ball, T.M., Reiser, B.J., Visual images preserve metric spatial information: evidence from studies of image scanning. *Journal of Experimental Psychology: Human Perception and Performance*, 1978, 4, 47-60.
7. Kosslyn, S.M., Thompson, W.L., Kim, I.J., Alpert, N.M., Topographical representations of mental images in primary visual cortex. *Nature*, 1995, 378, 496-98.
8. Maguire, E.A., Gadian, D.G., Johnsrude, I.S., Good, C.D., Ashburner, J., Frackowiak, R.S.J., Frith, C.D., Navigation-related structural change in the hippocampi of taxi drivers. *Proceedings of the National Academy of Sciences of the United States of America*, in press.
9. Mehta, Z., Newcombe, F., De Haan, E.H.F., Selective loss of imagery in a case of visual agnosia. *Neuropsychologia*, 1992, 30, 645-55.
10. Mountcastle, V.B., The columnar organisation of the neocortex. *Brain*, 1997, 120, 701-722.
11. Peretz, I., Kolinsky, R., Tramo, M., Labrecque, R., Hublet, C., Demeurisse, G., Belleville, S., Functional dissociations following bilateral lesions of auditory cortex. *Brain*, 1994, 117, 1283-1301.
12. Rauscher, F.H., Shaw, G.L., Ky, K.N., Music and spatial task performance. *Nature*, 1993, 365, 611.
13. Rauscher, F.H., Shaw, G.L., Ky, K.N., Listening to Mozart enhances spatial-temporal reasoning: towards a neurophysiological basis. *Neuroscience Letters*, 1995, 185, 44-47.
14. Rauscher, F.H., Shaw, G.L., Levine, L.J., Wright, E.L., Dennis, W.R., Newcomb, R., Music training causes long-term enhancement of preschool children’s spatial-temporal reasoning. *Neurological Research*, 1997, 19, 2-8.
15. Rauscher, F.H., Shaw, G.L., Key components of the Mozart effect. *Perceptual and Motor Skills*, 1998, 86, 835-841.
16. Sarnthein, J., VonStein, A., Rappelsberger, P., Petsche, H., Rauscher, F.H., Shaw, G.L., Persistent patterns of brain activity: an EEG coherence study of the positive effect of music on spatial-temporal reasoning. *Neurological Research*, 1997, 19, 107-116.
17. Schlaug, G., Jäncke, L., Huang, Y., Steinmetz, H., In vivo evidence of structural brain asymmetry in musicians. *Science*, 1995, 268, 699-701.
18. Shapleske, J., Rossell, S.L., Woodruff, P.W.R., David, A.S., The planum temporale: a systematic, quantitative review of its structural, functional and clinical significance. *Brain Research Reviews*, 1999, 29, 26-49.
19. Snodgrass, J.G., Vanderward, M., A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity and visual complexity. *Journal of Experimental Psychology: Human Learning and Memory*, 1980, 6, 174-215.
20. Zatorre, R.J., Halpern, A.R., Perry, D.W., Meyer, E., Evans, A.C., Hearing in the mind’s ear: a PET investigation of musical imagery and perception. *Journal of Cognitive Neuroscience*, 1996, 8, 29-46.

Chapter 10

Neuroanatomy of visuospatial imagery: evidence from fMRI and rTMS

Summary

A major debate in functional brain imaging research concerns the functional organisation, in the human brain, of internally reproduced images. By using two complementary techniques, functional MRI and repetitive Transcranial Magnetic Stimulation, we determined the nature of the involvement of visual and parietal cortex, two areas that have been hypothesized to be necessary in the mediation of visuospatial mental imagery. The results clearly indicate that the posterior parietal cortex is essential for visuospatial mental imagery, not the visual cortex.

Aleman, A., Ramsey, N., Van Honk, J.E., Kessels, R.P.C., Hoogduin, J., Schutter, D.L.G., Postma, A., Kahn, R.S., De Haan, E.H.F. (submitted). Parietal cortex mediates visuospatial imagery: evidence from fMRI and rTMS.

Introduction

Which brain areas are involved in visual mental imagery, or “seeing with the mind’s eye”? The results of numerous neuroimaging studies conducted over the past decade are inconclusive.[1] Some studies reported activation of Area 17 (primary visual cortex), whereas other studies only observed activation of parietal cortex. Kosslyn et al.[2] hypothesised that Area 17 may subserve depictive rather than spatial imagery (which may primarily involve parietal cortex), and provided evidence of Area 17 involvement in depictive imagery. Using functional magnetic resonance imaging (fMRI) and repetitive transcranial magnetic stimulation (rTMS), we demonstrate that spatial mental imagery relies on activation of the posterior parietal cortex.

Method and Results

Two experiments were conducted: one with fMRI and one with rTMS. fMRI reveals the cortical structures activated during a cognitive task, but cannot establish whether this activation is essential to task performance. By transiently disrupting neural activity in cortical areas, rTMS can provide evidence of a causal relation. Five healthy subjects performed a behaviorally controlled visuospatial mental imagery task[3] during fMRI brain scanning. Subjects had to indicate whether a crossmark, presented in a 4 by 5 grid on a computer screen, would fall on an imaginary letter or not. A lowercase letter was presented before the grid, and subjects were asked to image the corresponding uppercase letter into the grid. The control task used the same stimuli, but did not invoke imagery: subjects had to indicate whether the crossmark appeared in the lower or in the upper half of the grid. Regions of interest were bilateral primary visual cortex and right superior parietal lobule. Right-hemisphere parietal lobe was taken as region of interest, as most studies imply the right parietal cortex to be involved in spatial processing.[4] fMRI activation was measured in a single-session experiment on a 1.5 Tesla Philips ACS-NT scanner with the BOLD-sensitive 3D PRESTO fMRI pulse sequence (functional scan TE/TR 36.8/23.8 ms; flip angle 9º; FOV 256x208x88; matrix 64x52x22; slice thickness 4 mm; scan time 2 s). Difference images (active – control condition) were analysed for regions of interest using multiple regression analysis with detrending factors,[6] resulting in a t-value for each voxel. Significance threshold was set at $t=3.5$ (corresponding to $\alpha=0.05$, after Bonferroni correction). Subtraction analysis of the individual fMRI datasets revealed that right parietal cortex was active during spatial imagery in all subjects

(Fig. 1). In contrast, there was no evidence of primary visual cortex activation in any of the subjects. One could argue that fMRI was not sensitive enough for visual cortex activity, but the detection of parietal activity at the same significance threshold does not support this.

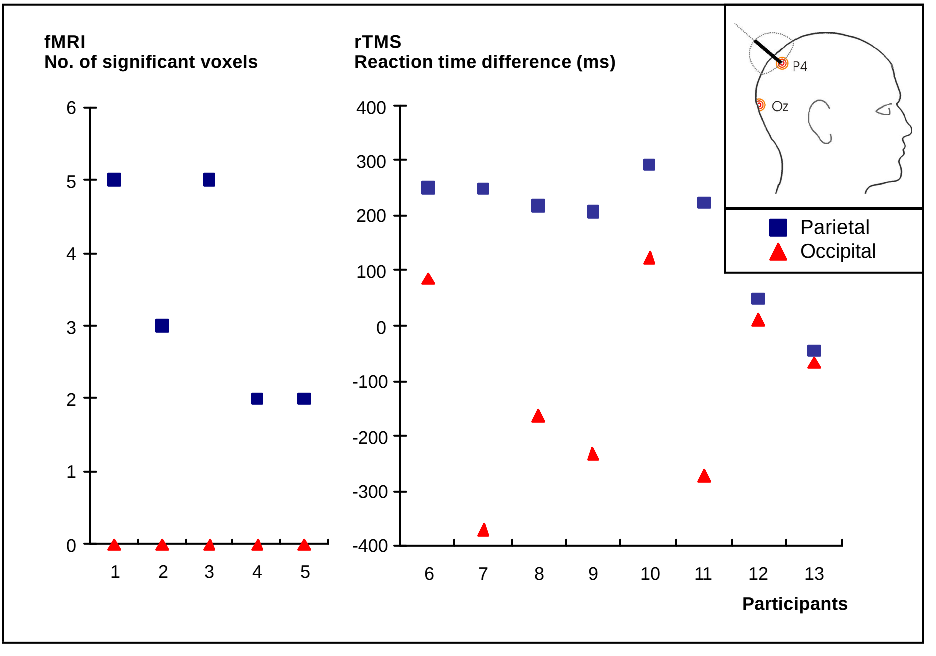

Figure 1. Number of significantly activated voxels revealed by fMRI for right Brodmann area 7 (superior parietal lobule); and Brodmann area 17 (occipital cortex), and difference reaction times between the real rTMS and sham rTMS conditions for the Oz (Area 17) and P4 (Area 7) positions.

In the second experiment, eight healthy subjects were stimulated continuously with 2Hz-TMS for 20 min., after which they performed the imagery task. rTMS was carried out with a Neopulse stimulator (Neotonus Inc., iron-core coil) at a frequency of 2 Hz and intensity of 90% of each subject's motor threshold. Real rTMS and sham rTMS (which controlls for the characteristic sound and sensation on the scalp of real rTMS) were applied to the Oz scalp position (corresponding to Area 17) and to the P4 position (Area 7, right hemisphere). Subjects were tested in four sessions, each session on a different day: 1) real rTMS at the Oz position, 2) sham rTMS at the Oz position, 3) real rTMS at the P4 position, and 4) sham rTMS at the P4 position. The order of the conditions was counterbalanced over participants, to control for practice effects. Real rTMS conditions were compared with the sham condition of the other location to avoid type 2 errors due to the possibility of slight effects of sham rTMS on information processing in the targeted brain area.[7] The results revealed a significant effect (increase in reaction time, RT) of rTMS at P4, compared to sham rTMS (ÄRT = 181 ms, P = 0.003), and compared to real rTMS at Oz (ÄRT = 208 ms, P = 0.006). There was no effect of real rTMS at Oz compared to sham. None of the conditions affected the number of correct responses. The overall mean reaction time on the imagery task was 870 ms (standard deviation: 240).

Discussion

We describe two experiments in which the functional organization of visuospatial mental imagery is investigated: one with fMRI and one with rTMS. Results from both neuroimaging methods converged, and provide strong evidence for parietal mediation of spatial mental imagery. Thus, our finding is consistent with the hypothesis that depictive visual mental imagery may involve activation of visual areas in the occipital lobe[2], whereas visual imagery that requires a spatial decision would depend on parietal structures. The fMRI experiment confirms the only fMRI study reported to date with a behaviorally controlled visuospatial imagery task, in which evidence was presented of posterior parietal cortex but not occipital activation.[5] Extending beyond this, our rTMS results now demonstrate a causal link between such parietal activation and spatial imagery.

References

1. Mellet E, Petit L, Mazoyer B, Denis M, Tzourio N. Reopening the mental imagery debate: lessons from functional anatomy. NeuroImage 1998;8:129-139.
2. Kosslyn SM, Pascual-Leone A, Felician O, et al. The role of area 17 in visual imagery: convergent evidence from PET and rTMS. Science 1999;284:167-170.
3. Podgorny P, Shepard RN. Functional representations common to visual perception and imagination. J Exp Psychol: Hum Percept Perform. 1978;4:21-35.
4. Kessels RPC, D'Alfonso AAL, Postma A, De Haan EHF. Spatial working memory performance after high-frequency repetitive transcranial magnetic stimulation of the left and right posterior parietal cortex in humans. Neurosci Lett 2000;287:68-70.
5. Trojano L, Grossi D, Linden DEJ, et al. Matching two imagined clocks: The functional anatomy of spatial analysis in the absence of visual stimulation. Cereb Cortex 2000;10:473-481.
6. Ramsey NF, van den Brink JS, van Muiswinkel AM, et al. Phase navigator correction in 3D fMRI improves detection of brain activation: quantitative assessment with a graded motor activation procedure. NeuroImage 1998;8:240-248.
7. Loo CK, Taylor JL, Gandevia SC, et al. Transcranial magnetic stimulation (TMS) in controlled treatment studies: are some "sham" forms active? Biol. Psychiatry 2000;47:325-331.

Chapter 11

Effects of rTMS on hallucinations and neurocognition in schizophrenia

Summary

We investigated the effects of transcranial magnetic stimulation (TMS) of left auditory cortex on hallucination severity and neurocognition in medication-resistant hallucinating patients. Nine hallucinating patients with schizophrenia were stimulated 20 minutes daily at the left auditory cortex with TMS at 1Hz for ten treatment days. At baseline, after 5 days and after 10 days a standardized hallucination rating scale was completed. In addition, at baseline and after the treatment a wide range of verbal and nonverbal neuropsychological measures was administered. A statistically significant improvement was observed on the hallucination scale and on a measure of auditory imagery. No difference between pre- and post-treatment testing was observed on the other neuropsychological variables. We conclude that TMS may have the potential to improve hallucination severity, without having adverse effects on cognitive functioning.

D'Alfonso, A.A.L., Aleman, A., Kessels, R.P.C., Schouten, E.A., Postma, A., Van der Linden, J.A., Cahn, W., Greene, Y., De Haan, E.H.F., Kahn, R.S. (in revision). TMS of left auditory cortex in schizophrenia: effects on hallucinations and neurocognition.

Hoffman et al.[1, 2] recently reported beneficial effects of low-frequency TMS of left temporo-parietal cortex in medication-resistant hallucinating patients. In the first study, patients were stimulated during four days with TMS (the mean duration of stimulation was 10 minutes daily). All three patients demonstrated considerable improvement in hallucination severity as rated on a visual analogue scale after the 4-day period. In the second study[2], 12 medication-resistant hallucinating patients with schizophrenia were treated with TMS, and again active stimulation reduced ratings of hallucination severity relative to sham stimulation. Four patients could be classified as nonresponders, because they did not improve or the improvement was negligible.

The rationale of Hoffman et al. [1, 2] to stimulate left temporo-parietal regions in their TMS studies originated from the hypothesis that brain regions underlying speech perception contribute to auditory hallucinations. However, although there is some evidence for the involvement of left temporo-parietal cortex in hallucinations[3], most brain imaging studies of hallucinating patients indicate the auditory cortex (middle and superior temporal gyri) to be mainly involved in the experience of auditory hallucinations[3-5]. Therefore, in this study we investigated whether TMS at the auditory cortex would improve severity of hallucinations. In addition, we stimulated for a longer period, i.e. two weeks, and included a standardized hallucination rating scale. Finally, we evaluated the effect of low-frequency TMS treatment on a wide range of neurocognitive functions.

Method

Nine medication-resistant patients with auditory hallucinations participated in the study after giving written informed consent. The study was approved by the medical committee of the UMC. All patients had DSM-IV diagnosis of schizophrenia (as established with the Comprehensive Assessment of Symptoms and History [CASH]). All patients had a stable medication status and used atypical antipsychotics. None of the patients received concomitant anticonvulsant drugs or benzodiazepines, which may reduce TMS effects. Further patient characteristics are given in table 1.

Patients were stimulated daily with TMS for 20 min. during two weeks consecutively (only workdays, in total 10 days) in an open trial. Stimulation was carried out with a Neopulse stimulator (Neotonus Inc.) at a frequency of 1 Hz and an intensity of 80% of the motor threshold. For one patient (patient #1) the intensity was lower, approximately 50%, because of painful muscle contraction at higher intensities. The location of stimulation was approximately 2 cm above T3 electrode position (10-20 international system). The definition of this stimulation position was based on Tailarach Atlas coordinates (coronal plane) in order to influence predominantly the superior temporal gyrus. At base-line, after one week, and at the end of the treatment a standardized hallucination scale, the Topography of Voices Rating Scale[6], was completed by each patient. This scale measures frequency, audibility, clarity and affective response to auditory-verbal hallucinations, and consists of 5 items which are rated on a 5-point scale by the patient. The author who carried out the stimulation (AALd'A) was not involved in collecting the data.

Sensitive neuropsychological measures were included that were primarily aimed at auditory and verbal functions: an auditory imagery test[7] in which subjects were asked to mentally compare acoustic characteristics of every-day sounds, Rey Auditory-Verbal Learning Test (verbal memory), Token Test, short form (verbal comprehension), and tests of verbal fluency and phoneme detection. The following nonverbal measures were also included: Judgment of Line Orientation, Line Bisection Test, Benton Visual Retention Test and the Test for Facial Recognition, short form (for description of all neuropsychological tests see ref. 8).

Nonparametric statistical analysis (Friedman's test) was performed in the analysis of hallucination ratings, as the measurement scale was ordinal.

Results

One patient was excluded from the analysis because of discontinuing medication, after which symptoms aggravated. Symptom ratings of the remaining 8 patients are listed in table 1. A significant effect of TMS treatment was observed on the Topography of Voices Rating Scale between baseline and at the end of the treatment, $\div^2=4.5$, df=1, $p=0.034$ (Means and SDs: 13.4 ±2.8 at baseline and 14.6±1.8 at end of treatment). We also computed the corresponding effect size, which was $r=0.65$. The difference between baseline and week 1 showed the same trend, but failed to reach significance, $\div^2=3.6$, df=1, $p=0.070$. Of the neurocognitive measures, only the auditory imagery test revealed a significant performance difference, $t=-2.6$, df=5, $p=0.046$ (for this test baseline data were not available for two patients). Performance was significantly better at post-treatment (M=17.7 correct out of 21) than at baseline (M=15.3).

Table 1. Patient characteristics and ratings of hallucination severity on the Topography of Voices Rating Scale at baseline, after 1 week and after 2 weeks of daily TMS treatment

Patient	Age	Sex	Medication	Handed-ness	Duration of illness[a]	PANSS[b]	Topography of Voices Rating Scale[c]		
							Baseline	1 week	2 weeks
1	43	F	425 mg clozapine	Right	18	103	13	15	17
2	29	M	300 mg clozapine	Left	5	83	12	13	13
3	19	M	400 mg clozapine	Right	3	70	12	12	17
4	32	M	400 mg clozapine	Right	7	109	14	20	16
5	31	M	500 mg clozapine	Right	13	143	12	14	13
6	33	M	400 mg clozapine	Right	13	72	11	25	13
7	32	M	350 mg clozapine	Right	14	143	13	13	15
8	22	M	15 mg olanzapine	Right	5	75	20	16	13

[a]number of years; [b]Positive and Negative Syndrome Scale, total psychopathology; [c]sum of ratings on individual items; higher scores indicate less severity of hallucinations, maximum=25, minimum=5

Discussion

The present study was designed to investigate whether two weeks of daily 1Hz transcranial magnetic stimulation (TMS) of left auditory cortex would influence hallucination severity and neurocognition in medication-resistant hallucinating patients. A statistically significant effect was observed on hallucination severity ratings as measured with a standardized scale. Thus, our results are in accordance with the findings of Hoffman et al.[1, 2] who also reported beneficial effects of TMS on hallucinations in schizophrenia. However, in the present study, all patients still experienced hallucinations after the treatment. Indeed, considering that the location of stimulation was based on the weight of the neuroimaging evidence and that we stimulated for 20 minutes daily during two weeks, we had expected more promising results.

Examination of the individual data revealed that hallucination severity improved in seven out of eight patients at week 2; in 5 patients this was an improvement of 2 points or more on the standardized scale. The fact that a few patients did not seem to respond substantially to TMS (and one actually deteriorated), is in accordance with Hoffman et al's study[2] in which 4 out of 12 patients were classified as nonresponders because they did not improve more than one point on a ten-point visual analog scale. We observed individual differences in the onset of the improvement, whereas a previous study[2] revealed large individual differences in the duration of the TMS-effect. These data suggest that there may be a complex interaction between number of treatments, brain location of treatment, and improvement that differs from patient to patient, which deserves further exploration.

In the neurocognitive domain, only auditory imagery showed improvement after TMS treatment. Speculatively, the concurrent improvement of hallucination severity and auditory imagery may be seen as in accordance with theories that have implicated deficient imagery processes in hallucination. Alternatively, improvement on the imagery task may be attributed to a test-retest effect, although such effects would then also be expected on the other neurocognitive tests.

A limitation of this explorative study was the lack of a placebo-control group. Clearly, larger double-blind placebo-controlled trials are needed before strong conclusions about TMS treatment of auditory hallucinations can be reached. To our knowledge, the present study is the first study to use TMS in patients using clozapine. It would be interesting to investigate possible interaction between type of medication and effectiveness of TMS. Future research must also evaluate the effect of TMS of the right hemisphere.

Finally, an important finding of this study was that daily TMS stimulation during two weeks did not have adverse effects on cognitive functioning. This is specifically important, as TMS is known to be able to transiently disrupt processing in brain areas. With regard to clinical safety, our results on cognitive function thus converge with recent MRI studies which indicate no structural brain changes in humans after high-dose repetitive TMS.[9]

References

1. Hoffman RE, Boutros NN, Berman RM, et al.: Transcranial magnetic stimulation of left temporo-parietal cortex in three patients reporting hallucinated “voices”. Biol Psychiatry 1999; 46:130-132
2. Hoffman RE, Boutros NN, Hu S, Berman RM, Krystal JH, Charney, DS. Transcranial magnetic stimulation and auditory hallucinations in schizophrenia. Lancet 2000; 355:1073-5.
3. Silbersweig DA, Stern E, Frith C, et al: A functional neuroanatomy of hallucinations in schizophrenia. Nature 1995; 378:176-179
4. Dierks T, Linden DE, Jandl M, et al: Activation of Heschl's gyrus during auditory hallucinations. Neuron 1999; 22:615-621
5. Weiss AP, Heckers S: Neuroimaging of hallucinations: a review of the literature. Psychiat Res: Neuroimaging 1999; 92:61-74
6. Hustig HH, Hafner RJ: Persistent auditory hallucinations and their relationship to delusions of mood. J Nerv Ment Dis 1990; 178:264-267
7. Aleman A, Nieuwenstein M, Böcker KBE, De Haan EHF. Mental imagery and perception in hallucination-prone individuals. J Nerv Ment Dis 2000;188:830-836.
8. Lezak MD: Neuropsychological assessment. Oxford: Oxford University Press, 1995.
9. Niehaus L, Hoffmann KT, Grosse P, Roricht S, Meyer BU: MRI study of human brain exposed to high-dose repetitive magnetic stimulation of visual cortex. Neurology 2000; 54:256-258

ACKNOWLEDGEMENTS

We would like to thank Anke Jongen, Claudy Oomen and Esther Caspers for their assistance in this study.

Presented at the third annual meeting of the International Society for Transcranial Magnetic Stimulation (ISTS), Chicago, IL, May 10, 2000.

Chapter 12

Controversies and Discussions 3

Cognitive processes and hallucination

Aleman, A. & De Haan, E.H.F. (2000). Non-language cognitive deficits and hallucination in schizophrenia. *American Journal of Psychiatry, 157*, 487.

Ralph E. Hoffman, M.D., and colleagues (Hoffman et al., 1999) reported impaired performance of hallucinating schizophrenic patients on a narrative speech perception task and a sentence repetition task relative to both non-hallucinating patients and normal subjects. However, the hallucinating and non-hallucinating groups did not differ on a measure of continuous performance, indicating that the differences in speech perception were not due to deficits in sustained attention. Hoffman et al. concluded: “Results support the hypothesis that hallucinated voices in schizophrenia arise from disrupted speech perception and verbal working memory systems rather than from non-language cognitive or attentional deficits” (p. 393). We think that the first part of the conclusion is adequate (i.e., it is supported by the data), but the latter part of the conclusion may be premature. Specifically, the two non-language cognitive functions that have figured most prominently in cognitive theories of hallucination, namely reality monitoring and imagery vividness, were not assessed by the authors. Previous studies have revealed differences between hallucinating and non-hallucinating patients on tasks measuring these functions (e.g., Mintz & Alpert, 1972; Morrison & Haddock, 1997; Böcker et al. 1996). Although, as Hoffman et al. point out, one PET-study of hallucinations failed to find activation of Broca’s area, which challenges the reality monitoring account that hallucinations are misidentified thoughts, all studies of functional brain imaging during auditory hallucinations (e.g., Silbersweig et al., 1995) have demonstrated activation of temporal areas, consistent with as well speech perception as imagery accounts (auditory imagery has been shown to activate temporal auditory association areas [Zatorre et al., 1996]). In addition, the speech perception tasks used by Hoffman et al. may involve mental imagery to a significant extent. The process of “filling in the blanks” during speech perception in order to reduce acoustically ambiguous speech is clearly dependent upon imagery. Indeed, Kosslyn and Sussman (1995) have argued that “immaculate perception” does not exist: in most circumstances perception and imagery are intimately intertwined. This underscores the importance of a thorough investigation of differences between patients with and without hallucinations on multiple tasks aimed at measuring language-specific (e.g. speech perception) as well as non-language-specific (e.g. reality monitoring and mental imagery) cognitive functions that may be involved in the cognitive basis of hallucination. It is too early yet to discard the possible contribution of disruptions in nonlanguage cognitive functions to the occurence of hallucinations in schizophrenia.

References

Böcker, K.B.E., Van der Lee, J., Hijman, R., De Haan, E.H.F. (1996). Perception, mental imagery and reality discrimination in hallucinating and nonhallucinating schizophrenic patients [Abstract]. *Journal of the International Neuropsychological Society, 2,* 204-205.

Hoffman, R.E., Rapaport, J., Mazure, C.E., Quinlan, D.M. (1999). Selective speech perception alterations in schizophrenic patients reporting hallucinated “voices”. *American Journal of Psychiatry, 156,* 393-399.

Kosslyn SM, Sussman L: Roles of imagery in perception: or, there is no such thing as immaculate perception. In MS Gazzaniga, ed: The cognitive neurosciences (pp. 1035-1041). Cambridge, MA: MIT Press, 1995.

Lennox, B.R., Bert, S., Park, G., Jones, P.B., Morris, P.G. (1999). Spatial and temporal mapping of neural activity associated with auditory hallucinations. *Lancet, 353,* 644.

Mintz, S., Alpert, M. (1972). Imagery vividness, reality testing, and schizophrenic hallucinations. *Journal of Abnormal Psychology, 793,* 10-316.

Morrison, A.P., & Haddock, G. (1997). Cognitive factors in source monitoring and auditory hallucinations. *Psychological Medicine, 27,* 669-79.

Zatorre, R.J., Halpern, A.R., Perry, D.W., Meyer, E., & Evans, A.C. (1996). Hearing in the mind’s ear: a PET investigation of musical imagery and perception. *Journal of Cognitive Neuroscience, 8,* 29-46.

Chapter 13

Hallucinations in schizophrenia : theory and findings

Summary

Hallucinations are a mysterious psychological phenomenon. In this paper, current theory and research on the neurocognitive basis of hallucination are reviewed. The phenomenology of hallucinations in schizophrenia is discussed, followed by an overview of functional brain imaging studies of cortical areas involved in hallucination. Theories addressing the putative cognitive mechanisms underlying hallucination are critically reviewed. Hypotheses concerning the role of inner speech, speech perception, reality monitoring, mental imagery, verbal self-monitoring and top-down perceptual expectations are discussed in light of the published evidence. Proposals for integration of various cognitive models are described and future directions for research are outlined.

Revision and translation of Aleman, A. (2000). Hallucinaties bij schizofrenie: hoe het brein zichzelf misleidt. *De Psycholoog, 35,* 154-159.

Hallucinations are an intriguing psychological phenomenon. The brain perceives something: a sound, a voice, an image. However, there is no corresponding source in the world outside.

Where do hallucinations come from? In non-western cultures, the answer usually is: from gods and ghosts (Al-Issa, 1995). This is also the case for ancient Greece literature, such as the Illias. In our culture, hallucinations are mostly associated with the use of stimulants, and with medical and psychiatric conditions. A hallucination can be defined as a perceptual experience in the absence of sensory stimulation. In order to distinguish this from mental imagery and dreaming (cf. Slade & Bentall, 1988; Aleman & De Haan, 1998), it is instructive to add to this definition that hallucinations are not under voluntary control of the individual (contrary to mental imagery), and occur in a wakeful state (contrary to dreaming). Hallucinations may occur in a wide range of circumstances. For example, Brasic (1998) lists more than 40 medical and psychiatric conditions in which hallucinations may occur. This paper will be restricted to hallucinations in schizophrenia, on which cognitive research has concentrated over the past few decades (David, 1999). After a description of the phenomenology of hallucinations, neuroimaging studies of patterns of cerebral activation associated with hallucination will be reviewed, and cognitive theories of hallucination will be discussed.

Phenomenology

Hallucinations may occur in any sensory modality: auditory, visual, somatosensory, gustatory and olfactory. In schizophrenia, auditory hallucinations are by far most frequent, 65% of patients with schizophrenia has suffered at least once from auditory hallucinations (Slade & Bentall, 1988). Visual hallucinations are less frequent, some 20% of patients. Less than 5% of patients reports hallucinations in the other modalities.

Auditory hallucinations may differ considerably in their phenomenology. They may consist of simple sounds, such as “tapping on the scalp” or ringing of deathbells. In other cases, music is heard. Predominant, however, are verbal hallucinations or “hearing voices”. A well-known classification of these are the hallucinations designated “first-rank” symptoms of schizophrenia by Kurt Schneider (Schneider, 1962). He distinguished three types of hallucination: 1) the patient hears ongoing commentary on his behavior, 2) the patient hears voices talking about him in the third person, and 3) the patient hears his own thoughts spoken aloud.

There is significant inter-individual variability between patients in formal characteristics of hallucinations (Junginger & Frame, 1985). This concerns the frequency (which varies from almost never to continuously), location (inside or outside the head), clearness (wich varies from unclear and not understandable to very clear) and loudness (which varies from very soft, almost inaudible, to very loud, screaming). Despite this variability, a study conducted with 54 hallucinating patients (Junginger & Frame, 1985) revealed that a majority of patients can understand the voices clearly, with a volume comparable to normal conversation. With regard to the location, a small majority reported that this was "outside the head". Nayani & David (1996) replicated these results in a study with 100 patients.

In a large number of cases, the "voices" heard by patients with schizophrenia are experienced as hostile. For example, the voices may continuously criticize the patient's behavior, or command the patient to behave against his will. Nayani & David (1996) observed that the most frequent expressions in auditory-verbal hallucinations concerned abusive language. Such hallucinations are a stressful experience which may severly impair the patient's ability to function normally in daily life.

Visual hallucinations may also tend to be of bizar content. An example is the case described by Silbersweig et al. (1995). This patient saw moving, colorful scenes, with rolling heads without body, adnd heard these heads speak to him, giving him instructions.

Are hallucinations pathologic?

In the absence of a direct cause, such as use of stimulants, or a medical condition such as a brain-tumor, hallucinations are usually taken to imply some form of mental illness. However, a number of studies has demonstrated that a substantial part of individuals from the normal population (varying from 5-25%) reports hallucinatory experiences (Aleman et al. 2001; Morrison et al. 1999; Young et al. 1986; Barrett & Etheridge, 1992). For example, a British study among 203 college students reported that 13% of the respondents answered "certainly applies to me" to the item "In the past I have had the experience of hearing a person's voice and then found that no one was there" (Young et al. 1986). Such hallucinatory events have not only been reported by college students but have been corroborated by large epidemiological studies (Tien, 1991). On the basis of these studies, it can be concluded that hallucinatory experiences form a continuum with normal psychological processes (cf. Slade & Bentall, 1988). An important distinction with hallucinations in schizophrenia is that, in individuals from the normal population, hallucinatory events rarely are experienced as unpleasant, emotional threathening or hostile (Barrett & Caylor, 1998). In much cases a person only hears his or her name, while no one is around.

Brain activity during hallucinations

Which brain areas are involved in experiencing a hallucination? Researchers have tried to answer this question with the use of modern functional neuroimaging techniques, such as PET and fMRI (for a recent review, see Weiss & Heckers, 1999). In the first study (McGuire et al. 1993), 13 patients were scanned with PET in an episode of their illness in which they experienced hallucinations. They were scanned again on a second occassion, when the hallucinations were absent. Compared to the second measurement, hallucination-related activity was observed in language-related areas, especially Broca's area (involved in speech production). Although to a lesser extent, activity was also found in the anterior cingulate (involved in attentional processes), and in the left temporal cortex (a.o. auditory perception and memory processes). In a comparable design, Suzucki et al. (1993) observed an increase in regional bloodflow in the left temporal lobe (auditory association cortex) in five hallucinating patients. Silbersweig et al. (1995) reported activation of subcortical structures, the parahippocampal gyrus and the middle temporal gyrus in five patients during auditory hallucinations. One of their patients also hallucinated in the visual modality. For these hallucinations, activation was observed in visual areas (lingual, fusiform and occipital gyri).

Lennox et al. (1999) imaged a hallucinating patient with fMRI. This patient hallucinated with consequent intervals: approximately for 26 seconds he heard a "voice", followed by a comparable period in which hallucinations were absent. The patient indicated with a key press when he heard the "voice". This was an ideal condition for a controlled fMRI study, in which a within-subject comparison could be made between hallucinatory periods and hallucination-free periods. The results revealed strong activity in the right middle temporal gyrus. In the same way, using the "button-pressing method", Dierks et al. (1999) managed to scan three patients with fMRI. They observed activity in Broca's area, in the temporal gyri, and in the primary auditory cortex (Heschls gyrus). Studies by David et al. (1996) and Woodruff et al. (1997) also indicate that primary sensory areas may be involved in the experience of hallucination. These investigators found that the primary auditory cortex is less responsive to auditory stimuli during hallucinations compared to absence of hallucinations. This is an indication that the primary auditory cortex is actively involved in hallucinations, and therefore no “resources” are left for additional processing of auditory stimuli. For visual hallucinations, an identical finding has been reported (Howard et al., 1995). In the most recent study, Shergill et al. (2000) used a novel fMRI method to measure brain activity during hallucinations in 6 patients. In this “random sampling” method, a large number of individual scans is acquired at unpredictable intervals in each subject while they are intermittently hallucinating. Immediately after each scan, subjects report whether they had been hallucinating at that instant. Neural activity is then compared for the scans when patients were and were not experiencing hallucinations. The results revealed a distributed network of cortical and subcortical activity associated with auditory hallucinations: inferior frontal/insular, temporal cortex bilaterally, right thalamus and inferior colliculus, and left hippocampus and parahippocampal cortex.

To summarize, neuroimaging studies reveal a distributed network of cortical and subcortical areas involved in the experience of hallucinations. Although the exact role of these areas is not clear yet, it could be hypothesized that hallucinations are triggered by activity in subcortical and frontal areas, which in turn project to modality-specific association cortex, thereby leading to a conscious perceptual experience. With respect to auditory hallucinations, some studies observe activity in language-production areas during auditory hallucinations, some studies observe activity in the primary auditory cortex, but all studies report activity in the temporal lobe, more specifically in the middle or superior gyri. For visual hallucinations, activity is observed in secondary visual cortex.

Cognitive theories

Four approaches can be distinguished in recent cognitive theories regarding the mechanism of hallucination. These approaches focus respectively on 1) “inner speech”, 2) speech perception, 3) reality discrimination, and 4) mental imagery. In contrast to the latter, the first two approaches are confined to auditory-verbal hallucinations.

Inner speech

Most individuals report the experience of “inner speech” (either occasionally or continuously) when they think. Some hallucinating patients indicate that they cannot distinguish well between their inner speech and the “voices” they hear. In addition, subvocal muscle activity has been reported, associated with hallucinations (Green & Kinsbourne, 1990). The “inner-speech” hypothesis of hallucinations holds that some distortion in the production of inner speech leads to the erroneous interpretation that the “inner speech” is of non-self origin. A cognitive neuropsychological study by David & Lucas (1993) was not able to confirm the inner speech hypothesis. On the basis of Baddeley’s working memory model (Baddeley & Hitch, 1974; Baddeley, 1986) these authors argued that inner speech is mediated by phonological processes in short-term memory (the “phonological loop” in Baddeley’s terms). If hallucinations and inner speech both call on resources in the phonological loop, a dual task will disrupt either process, given the limited nature of processing resources in working memory. David & Lucas (1993) went on to demonstrate that phonological processing during auditory-verbal hallucinations was not affected in a continuously hallucinating patient. The authors suggest that their finding implies that inner speech and auditory-verbal hallucinations are different processes. Moreover, in contrast to what the inner speech hypothesis would predict, Haddock et al. (1996) did not find specific impariments in phonological processing which could underly distortions in inner speech in hallucinating patients as compared to non-hallucinating patients.

McGuire et al. (1993) and Dierks et al. (1999) reported activity of Broca’s area during hallucinations, which may be consistent with the inner speech theory. However, other PET and fMRI studies failed to find Broca area involvement (Silbersweig et al., 1995; Lennox et al., 1999).

Speech perception

According to Hoffman (Hoffman et al., 1999) a dysfunction of the speech perception system underlies auditory-verbal hallucinations. In the analysis of every-day sound characteristics, there is an important degree of acoustic ambiguity, due to background noise, and due to the “pasting” of phonemes (also called “blurring”). Syntactical and semantical expectations, based on earlier learnt words, therefore play a crucial role in speech perception. Hoffman’s hypothesis is that hallucinations arise from an impairment in verbal working-memory, which leads to pronounced linguistic expectations that could generate spontaneous perceptual "outputs".

Evidence for this hypothesis comes from a study in which hallucinating and non-hallucinating patients were compared on a speech perception task in which the presented speech was so distorted that it was difficult to recognize (Hoffman et al., 1999). As predicted, hallucinating patients performed significantly worse than their non-hallucinating comparison patients. On a measure of verbal working-memory (sentence repetition), the hallucinating group also performed worse, but not on a measure of sustained attention, indicating that the performance differences could hardly be ascribed to attentional deficits.

However, on the basis of his theory Hoffman (1986) predicted that hallucinating patients would have more difficulties in the production and processing of speech than non-hallucinating patients, but subsequent research has failed to confirm this prediction (Slade & Bentall, 1988). Nevertheless, PET and fMRI studies of brain activity during hallucinations are consistent with the speech-perception hypothesis: all studies report acitivation in temporal auditory-linguistic association areas.

Reality monitoring

"Source monitoring" refers to the ability to distinguish between different sources of information, e.g., whether something was read in a newspaper, or whether it was told by a friend (Johnson, Hashtroudi & Lindsay, 1993). Reality discrimination and reality monitoring (Johnson & Raye, 1981) are considered to belong to this category of processes. *Reality discrimination* refers to distinguishing between internally generated information and externally presented information (e.g., imagination and perception), whereas *reality monitoring* refers to memories of whether information was or internal or external origin (e.g., did I imagine it, or did it really occur?). Thus, reality discrimination refers to the "online" distinguishing of external versus internal sources, whereas reality monitoring refers to information that was presented or generated in the past. Reality discrimination measured with a signal detection task was reported by Bentall & Slade (1985), who found that hallucinating patients made significantly more errors than non-hallucinating patients (specifically, the hallucinating patients erroneously indicated that a word had been presented in a burst of white noise). An example of a reality monitoring task is a memory task in which the subject is asked to remember words that have either been said by the experimenter or have been generated by the subject himself (after indications by the experimenter). Subsequently, the subject is asked to indicate, from a list of words, whether a word was a) previously read by the experimenter, b) generated by the subject himself, or c) whether the word is new. According to the reality monitoring hypothesis (Bentall, 1990), hallucinating patients will more frequently erroneously assign self-generated words to an external source (by indicating that the word was presented by the experimenter). A number of behavioral studies has provided evidence for such a relation between reality monitoring errors and the occurence of hallucinations (Bentall, Baker & Havers, 1991; Morisson & Haddock, 1997; Brébion et al., 2000). However, the question remains as to how specific disorders in reality monitoring are to hallucinations. Keefe et al. (1999), for example report that patients without hallucinations (but with other positive symptoms) made the same errors as hallucinating patients.

According to Johnson, Hashtroudi & Lindsay (1993), areas in the frontal lobe are crucially involved in reality monitoring. Only a few neuroimaging studies have revealed frontal activity associated with hallucinations, however (McGuire et al., 1993; en Dierks et al. 1999).

Mental imagery

In the 19th century, Fancis Galton wrote that mental imagery exists as a continuum in the population, ranging from a total absence of mental images (subjectively) to imagery of great intensity and vividness, ending in pure hallucination (Galton, 1883). A number of studies investigated the imagery hypothesis (e.g., Roman & Landis, 1945; Mintz & Alpert, 1972; Starker & Jolin, 1982), but with inconsistent results. The fact that none of the studies included adequate behavioral measures may account for this inconsistency. Indeed, Slade & Bentall (1988) have drawn attention to the fact that explaining hallucinatory experiences with a phenomenologically highly similar event – subjectively rated imagery vividness – borders to circularity.

However, it is not easy to think of a method to measure vividness of mental imagery behaviorally. A possible approach could be the one first described by Aleman et al. (1999; cf. Aleman et al., 2000), in which performance is compared on a perception and on an imagery condition of the same behavioral task. According to Johnson and Raye (1981) percepts, which originate from externally presented stimuli, are characterized by more detailed sensory, contextual and semantic information than internally generated images. Evidence that mental images are less rich in perceptual details than 'real' percepts and that, as a consequence, images are more difficult to perform mental operations upon, was recently presented by Kosslyn et al. (1999). The hypothesis that imagery and perception are more alike (and therefore harder to discern from each other) due to increased sensory characteristics of mental images in individuals that experience hallucinations thus predicts that these subjects will show smaller performance differences between a perception and an imagery condition of the same task.

Using this method, Böcker et al. (2000) compared hallucinating and non-hallucinating patients on two measures of auditory and two of visual imagery and perception. No differences were found between both groups when performance on the imagery measures relative to perception performance was compared. However, after performing within-group comparisons, the authors observed more vivid auditory than visual imagery in patients that hallucinated in the auditory modality. Evans et al. (2000) also reported a lack of differences between hallucinating and non-hallucinating patients with schizophrenia on a number of auditory imagery measures. However, these authors did not include perception conditions, nor measures in another non-hallucination modality.

It is interesting to note that it has also been argued that hallucinating patients may suffer from an imagery *deficit*, rather than a general increase in vividness. For example, Horowitz (1975) hypothesized that hallucinating patients have less vivid mental images, which leads them to attribute occasional vivid images to an external source. However, in both instances of imagery theory, a vivid mental image ultimately gives rise to the hallucinatory experience.

Neuroimaging studies are consistent with activation that would be predicted by the imagery hypothesis: both auditory hallucinations and auditory imagery appear to activate auditory association areas (Dierks et al., 1999; Zatorre et al., 1996). The same holds for visual hallucinations and visual imagery (ffytche et al. 1999; Kosslyn et al. 1999).

Integrating the various perspectives

Despite the differences between these four cognitive approaches, there is also some conceptual overlap, which makes the possibility of integration especially attractive. Indeed, it could be argued that two earlier theories, namely the proposals of Frith (1992) and of Grossberg (1999) incorporate elements of more than one approach.

Frith's theory (Frith & Done, 1988; Frith, 1992) can be seen as an integration of the "inner speech" hypothesis and the reality monitoring hypothesis. According to Frith, hallucinations arise from failures in the monitoring of own intentions during inner speech (sometimes called 'self-monitoring' by Frith). As a consequence, the cognitive system does not recognize that inner speech originates from the self, and thus erroneously attributes it to a non-self source. Thus, this approach does not consider the *production* of inner speech to be impaired, but rather states that auditory hallucinations are derived from defective *monitoring* of inner speech. Evidence for this hypothesis was recently presented by Johns & McGuire (1999). Hallucinating patients, non-hallucinating patients and normal control subjects were asked to speak presented words out aloud in a microphone. Ocassionally, the spoken word was distorted by the experimenter (by modulating the pitch). Participants heard the words in their headphones and were asked to indicate if the source of the heard word: "myself", "somebody else", or "unsure". The hallucinating group made significantly more errors by attributing own (distorted) speech to someone else. Indeed, this study was inspired by the "speech-monitoring" approach, but is clearly also consistent with the speech perception hypothesis of Hoffman (1999). A problem for the verbal self-monitoring theory concern the results reported by Leudar, Thomas & Johnston (1994). These authors investigated whether schizophrenic patients have deficient internal error detection in speech repairs (especially when these occur rapidly, before external acoustic feedback can have come into play). Although patients with schizophrenia showed less internal error detection than controls, consistent with a failure of verbal self-monitoring, there was no difference between patients with and without hallucinations.

In accordance with Frith's speech-monitoring hypothesis, McGuire et al. (1995) found reduced temporal activation during verbal self-monitoring tasks in hallucinating patients. Other neuroimaging studies have implied this region in self-monitoring in healthy subjects (e.g., McGuire et al., 1996). Shergill et al. (2000) also argue that their findings are consistent with Frith's verbal self-monitoring theory. However, they relate this to the attenuated activation of the supplementary motor area (SMA) during hallucinations. As the SMA has been implicated in the deliberate generation of inner speech, and lesions in this region have been associated with the alien limb syndrome (in which a patient attributes self-generated movements to someone else), the paucity of SMA activation during hallucinations might be related to a lack of awareness that inner speech has been generated.

A different approach to hallucinations has been described by Grossberg (2000), based on the finding that top-down perceptual expectations can importantly affect the detection of stimuli (Coren, Wards & Enns, 1994). Indeed, such top-down mechanisms play an important role in perception, by modulating, priming and matching incoming bottom-up information (cf. Kosslyn, 1994). Thus, for example, an expected stimulus will be detected better than an unexpected stimulus. The neurophysiological basis of this effect has been well studied (Grossberg 1999), and includes feedback circuits in which a balance is reached between top-down excitation and inhibition (e.g. by feedback into information flow in visual cortex layers via an on-center, off-surround pathway). However, although such top-down expectations can modulate, sensitize, or prime the processing of bottom-up information, they cannot by themselves cause supra-threshold activation of their target cells. Nevertheless, as Grossberg (2000) recently hypothesized, under normal behavioral conditions, a volitional signal can be phasically turned on that can alter this balance to favor top-down excitation, which can create conscious experiences in the absence of bottom-up information. In this way, conscious mental imagery can arise. In addition, Grossberg (2000) proposes a mechanism by which hallucinations in schizophrenia could arise, namely when the phasic volitional signal becomes chronically hyperactive. As a result, top-down sensory expectations can generate conscious experiences that are not under the volitional control of the individual who is experiencing them. The net effect is a hallucination. Further details on the possible neurophysiological mechanisms can be found in Grossberg (2000). This theory integrates elements of the imagery hypothesis (which bears on strong top-down processes) and is reminiscent of Hoffman's statement that "pronounced linguistic expectations can generate perceptual outputs". Consistent with the perceptual expectations hypothesis are the findings reported by Haddock , Slade & Bentall (1995). They suggested to subjects that on listening to a word repeated over and over (e.g., the word "tress") they would hear new words. Indeed, the subjects reported hearing more transformations (e.g., stress, dress), but the subjects with hallucinations in addition reported hearing other words (e.g., caressed, Christmas).

An approach similar to the one by Grossberg (2000) has been described by Behrendt (1998), although he is less explicit in proposing a neural mechanism. Behrendt states that hallucinations could arise from "facilitated formation of cortical associations between representations of expectations and internal symbols" (p. 236). In this way, "mental factors of perception", rather than sensory information, take over to predominate the context and form of perception, which will in fact be a hallucination. Thus the normal balance between sensory and "mental" factors is distorted. (The "mental factors" of Behrendt refer to top-down mechanisms, whereas sensory factors refer to bottom-up mechanisms; for a more detailed description of theory and empirical evidence regarding top-down influences intrinsic in perception, see Kosslyn & Sussman [1995]).

Conclusion

Most cognitive theorists agree that hallucinations are misattributions of internally generated information to an external source. Different hypotheses have been developed, concerning the role of inner speech, speech perception, reality monitoring, and mental imagery. Probably, the most accurate summary of the current state of affairs was recently advanced by David (1999): "Auditory imagery – that is, a sensory component – is intuitively central to the experience of hallucinations, and recent fMRI studies support this. Either a distortion of the image itself (its prosody, pitch or timbre), its apparent coherence, or ego-alien content, or a defect in the self-monitoring (or a combination of all these) leads to a misattribution of the source. This mislabelling requires more precise cognitive dissection" (p. 101). One component that is not mentioned here by David is a possible perceptual deficit (although he discusses perceptual deficits earlier in his paper). McKay et al. (2000) have provided evidence for higher order perceptual deficits in hallucinating schizophrenic patients. In an attempt to further "cognitive dissection", we will take on the issue of an imbalance between imagery and perception in the next chapter.

References

Aleman, A. & De Haan, E.H.F. (1998). On redefining hallucination [letter]. *American Journal of Orthopsychiatry*, 68:656-658.

Aleman, A., Böcker, K.B.E., & De Haan, E.H.F. (1999). Disposition toward hallucination and subjective versus objective imagery in normal subjects. *Personality and Individual Differences*, 27:707-714.

Aleman, A., Nieuwenstein, M., Böcker, K.B.E., De Haan, E.H.F. (2000). Mental imagery and perception in hallucination-prone individuals. *Journal of Nervous and Mental Disease, 188,* 830-836.

Aleman, A., Nieuwenstein, M., Böcker, K.B.E., De Haan, E.H.F. (2001). Multidimensionality of hallucinatory predisposition: factor structure of the Launay-Slade Hallucination Scale in a normal sample. *Personality and Individual Differences, 30,* 287-292.

Al-Issa, I. (1995).The illusion of reality or the reality of illusion: hallucinations and culture. *British Journal of Psychiatry,166*, 368-373.

Baddeley, A.D. (1986). Working memory. Oxford: Oxford University Press.

Baddeley, A.D., & Hitch, G. (1974). Working memory. In G.H. Bower (Ed.), *The psychology of learning and motivation, vol. 8*. London: Academic press.

Barrett TR, Caylor MR (1998) Verbal hallucinations in normals, V: perceived reality characteristics. *Personality and Individual Differences, 25*, 209-221.

Barrett, T.R., & Etheridge, J.B. (1992). Verbal hallucinations in normals, I: people who hear 'voices'. *Applied Cognitive Psychology, 6*, 379-387.

Behrendt, R.-P. (1998). Underconstrained perception: a theoretical approach to the nature and function of verbal hallucinations. *Comprehensive Psychiatry, 39,* 236-248.

Bentall, R.P. (1990). The illusion of reality: a review and integration of psychological research on hallucinations. *Psychological Bulletin, 107*, 82-95.

Bentall, R.P., Baker, G., & Havers, S. (1991). Reality monitoring and psychotic hallucinations. *British Journal of Clinical Psychology, 30,* 213-222.

Bentall, R.P., & Slade, P.D. (1985). Reality testing and auditory hallucinations: a signal detecion analysis. *British Journal of Clinical Psychology, 24*, 213-222.

Böcker, K.B.E., Hijman, R., Kahn, R.S., & De Haan, E.H.F. (2000). Perception, mental imagery and reality discrimination in hallucinating and nonhallucinating schizophrenic patients. *British Journal of Clinical Psychology, 39*, 397-406.

Brasic, J.R. (1998). Hallucinations. *Perceptual and Motor Skills, 86*, 851-877.

Brébion, G., Amador, X., David, A., Malaspina, D., Sharif, Z., & Gorman, J.M. (2000). Positive symptomatology and source-monitoring failure in schizophrenia - an analysis of symptom-specific effects *Psychiatric Research, 95,* 119-131.

Coren S, Ward LM, Enns JT (1994). *Sensation and perception*. Fort Worth: Harcourt Brace Publishers.

David, A.S. (1999). Auditory hallucinations: phenomenology, neuropsychology and neuroimaging update. *Acta Psychiatrica Scandinavica, 99 (Suppl. 394),* 95-104.

David, A.S. & Lucas, P. (1993). Auditory-verbal hallucinations and the phonological loop: a cognitive neuropsychological study. *British Journal of Clinical Psychology, 32*, 431-441.

David, A.S., Woodruff, P.W.R., Howard, R. et al. (1996). Auditory hallucinations inhibit exogenous activation of auditory association cortex. *NeuroReport, 7*, 932-936.

Dierks, T., Linden, D.E., Jandl, M., et al. (1999). Activation of Heschl's gyrus during auditory hallucinations. *Neuron, 22,* 615-621.

Evans, C.L., McGuire, P.K., David, A.S., 2000. Is auditory imagery defective in patients with auditory hallucinations? *Psychological Medicine, 30*, 137-148.

ffytche, D.H., Howard, R.J., Brammer, M.J. et al. (1998). The anatomy of conscious vision: an fMRI study of visual hallucinations. *Nature Neuroscience, 1,* 738-742.

Frith, C.D. (1992). *The cognitive neuropsychology of schizophrenia.* Hove: Lawrence Erlbaum.

Frith, C.D., & Done, D.J. (1988). Towards a neuropsychology of schizophrenia. *British Journal of Psychiatry*, *153*, 437-443.

Galton, F. (1883). Inquiries into human faculty and its development. London: McMillan.

Green, M.F. & Kinsbourne, M. (1990). Subvocal activity and auditory hallucinations: clues for behavioral treatment. *Schizophrenia Bulletin, 16*, 617-625.

Grossberg, S. (1980). How does a brain build a cognitive code? *Psychological Review, 87*, 1-51.

Grossberg, S. (1999). How does the cerebral cortex work? Learning, attention, and grouping by the laminar circuits of the visual cortex. *Spatial Vision, 12*, 163-186.

Grossberg, S. (2000). How hallucinations may arise from brain mechanisms of learning, attention, and volition. *Journal of the International Neuropsychological Society, 6*, 583-592.

Haddock, G., Slade, P.D., & Bentall, R.P. (1995). Auditory hallucinations and the verbal transformation effect: the role of suggestions. *Personality and Individual Differences*, *19*, 301-306.

Haddock, G., Slade, P.D., Prasaad, R., Bentall, R.P. (1996). Functioning of the phonological loop in auditory hallucinations. *Personality and Individual Differences, 20,* 753-760.

Hoffman, R.E. (1986). Verbal hallucinations and language production processes in schizophrenia. *Behavioral and Brain Sciences, 9*, 503-548.

Hoffman, R.E., Rapaport, J., Mazure, C.E., Quinlan, D.M. (1999). Selective speech perception alterations in schizoprenic patients reporting hallucinated "voices". *American Journal of Psychiatry*, *156*, 393-399.

Horowitz, M.J. (1975). Hallucinations: an information processing approach. In R.K. Siegel & L.J. West (Eds.), *Hallucinations: Behavior, experience and theory* (pp. 163-196). New York: Wiley.

Howard, R., Williams, S., Bullmore, E., Brammer, M., Mellers, J., Woodruff, P. & David, A. (1995). Cortical response to exogenous visual stimulation during visual hallucinations. *Lancet, 345*, 70.

Johns, L.C., McGuire, P.K. (1999). Verbal self-monitoring and auditory hallucinations in schizophrenia. *Lancet, 353,* 469-470.

Johnson, M.K., & Raye, C.L. (1981). Reality monitoring. *Psychological Review, 88*, 67-85.

Johnson, M.K., Hashtroudi, S. & Lindsay, D.S. (1993). Source monitoring. *Psychological Bulletin, 114*, 3-28.

Junginger, J. & Frame, C.L. (1985). Self-report of the frequency and phenomenology of verbal hallucinations. *Journal of Mental and Nervous Disease, 173*, 149-155.

Keefe, R.S.E., Arnold, M.C., Bayen, U.J. & Harvey, P.D. (1999). Source monitoring deficits in patients with schizophrenia; a multinomial modelling analysis. *Psychological Medicine, 29,* 903-914.

Kosslyn, S.M. (1994). *Image and brain.* Cambridge (MA): MIT Press.

Kosslyn, S.M., Pascual-Leone, A., Felician, O., et al. (1999). The role of area 17 in visual imagery: convergent evidence from PET and rTMS. *Science, 284*, 167-170.

Kosslyn, S.M., & Sussman, L. (1995). Roles of imagery in perception: or, there is no such thing as immaculate perception. In MS Gazzaniga, ed: *The cognitive neurosciences* (pp. 1035-1041). Cambridge, MA: MIT Press.

Lennox, B.R., Bert, S., Park, G., Jones, P.B. & Morris, P.G. (1999). Spatial and temporal mapping of neural activity associated with auditory hallucinations. *Lancet, 353*, 644.

Leudar, I., Thomas, P. & Johnston, M. (1994). Self-monitoring in speech production: effects of verbal hallucinations and negative symptoms. *Psychological Medicine*, *24,* 749-761.

McGuire, P.K., Shah, G.M.S. & Murray, R.M. (1993). Increased blood flow in Broca's area during auditory hallucinations in schizophrenia. *Lancet, 342*, 703-706.

McGuire, P.K., Silbersweig, D.A., Wright, I., et al. (1995). Abnormal monitoring of inner speech: a physiological basis for auditory hallucinations. *Lancet, 346,* 596-600.

McGuire, P.K., Silbersweig, D.A., & Frith, C.D. (1996). Functional neuroanatomy of verbal self-monitoring. *Brain, 119,* 907-17.

McKay, C.M., Headlam D.M., & Copolov D.L. (2000). Central auditory processing in patients with auditory hallucinations. *American Journal of Psychiatry, 157*, 759-766.

Mehta, Z., Newcombe, F., & De Haan, E.H.F. (1992). Selective loss of imagery in a case of visual agnosia. *Neuropsychologia, 30*, 645-655.

Mintz, S., & Alpert, M. (1972). Imagery vividness, reality testing, and schizophrenic hallucinations. *Journal of Abnormal Psychology, 79,* 310-316.

Morrison, A.P., & Haddock (1997). Cognitive factors in source monitoring and auditory hallucinations. *Psychological Medicine, 27,* 669-679.

Morrison, A.P., Wells, A., & Nothard, S. (2000). Cognitive factors in predisposition to auditory and visual hallucinations. *British Journal of Clinical Psychology, 39,* 67-78.

Nayani, T.H. & David, A.S. (1996). The auditory hallucination: a phenomenological survey. *Psychological Medicine, 26*, 177-189.

Roman, R., & Landis, C. (1945). Hallucinations and mental illness. *Journal of Nervous and Mental Disease, 102,* 327-331.

Schneider, K. (1962). *Klinische Psychopathologie* (6e Auflage). Stuttgart: Georg Thieme.

Shergill, S.S., Brammer, M.J., Williams, S.C.R., Murray, R.M., & McGuire, P.K. (2000). Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. *Archives of General Psychiatry, 57,* 1033-1038.

Silbersweig, D.A., Stern, E., Frith, C., et al. (1995). A functional neuroanatomy of hallucinations in schizophrenia. *Nature, 378*, 176-179.

Slade, P.D., & Bentall, R.P. (1988). *Sensory deception; a scientific analysis of hallucination*. Baltimore: John Hopkins University Press.

Starker, S., & Jolin, A. (1982). Imagery and hallucinations in schizophrenic patients. *Journal of Nervous and Mental Disease, 170*, 448-451.

Suzucki, M., Yuasa, S., Minabe, Y. et al. (1993). Left superior temporal blood flow increases in schizophrenic and schizophreniform patients with auditory hallucinations: a longitudinal case study using ^{123}I-IMP SPET. *European Archives of Psychiatry and Clinical Neuroscience, 242,* 257-261.

Tien, A.Y. (1991). Distribution of hallucinations in the population. *Social Psychiatry and Psychiatric Epidemiology, 26*, 287-292.

Weiss, A.P., & Heckers, S. (1999). Neuroimaging of hallucinations: a review of the literature. *Psychiatry Research: Neuroimaging, 92,* 61-74.

Woodruff, P.W.R., Wright, I.C., Bullmore, E.T. et al. (1997). Auditory hallucinations and the temporal cortical response to speech in schizophrenia: a functional magnetic resonance imaging study. *American Journal of Psychiatry, 154,* 1676-1682.

Young, H.F., Bentall, R.P., Slade, P.D., & Dewey, M.E. (1986). Disposition towards hallucination, gender and IQ scores. *Personality and Individual Differences, 7,* 247-249.

Zatorre, R.J., Halpern, A.R., Perry, D.W., Meyer, E. & Evans, A.C. (1996). Hearing in the mind's ear: a PET investigation of musical imagery and perception. *Journal of Cognitive Neuroscience, 8*, 29-46.

Chapter 14

Imagery and perception in a continuously hallucinating patient

Summary

It has been hypothesized that hallucinations may be associated with vivid mental imagery or with deficient higher-order perception. In a neuropsychological case-study design, we studied a 41-year old patient (Mr. A.) with schizophrenia who experienced on-going auditory-verbal hallucinations. Performance was measured on four behavioral tasks of imagery and perception (two visual and two auditory) and compared with the performance of five patients without hallucinations. Performance on imagery conditions was compared relative to performance on the perception condition of each task. Relative to perception, Mr. A. showed substantial higher imagery scores on both auditory tasks, but not on the visual tasks. In contrast, the five comparison patients did not reveal such performance differences between the two modalities. The results support the hypothesis of an imbalance between imagery and perception specific to the modality of hallucination.

Aleman, A., Böcker, K.B.E., Hijman, R., Kahn, R.S., & de Haan, E.H.F. (submitted). Hallucinations in schizophrenia: distorted balance between imagery and perception? A cognitive neuropsychiatric approach.

Introduction

Hallucinations are a prominent and disturbing symptom of schizophrenia. For centuries, it has been hypothesized that hallucinations may arise from abnormally vivid mental imagery (Galton, 1883). Although the imagery hypothesis of hallucinations is usually taken to imply that hallucinating individuals will have more vivid imagery than non-hallucinating individuals, it has also been argued that people with hallucinations may suffer from an imagery deficit. For example, Horowitz (1975) hypothesized that hallucinating patients have less vivid mental images, which leads them to attribute occasional vivid images to an external source.

Studies investigating imagery in hallucinating and non-hallucinating patients do not provide consistent support for the hypothesis that imagery would be deficient or more vivid (reviewed by Bentall, 1990; cf. Evans et al. 2000). However, a shortcoming of these studies is that they did not assess imagery in relation to perception. This is important, as the absolute level of imagery vividness may not be the crucial issue, but rather the difference in vividness between imagery and perception, which determines the ease with which information of internal and external origin can be distinguished (Johnson & Raye, 1981). Recent theoretical accounts of hallucination (Grossberg, 2000; Behrendt, 1998) have suggested that a disordered balance between "mental" and "sensory" factors of perception could underlie hallucinations. Mental factors refer to top-down perceptual expectations (a form of mental imagery) and sensory factors refer to constraints imposed on perception by bottom-up sensory information. Specifically, "mental factors of perception", rather than sensory information, take over to predominate the context and form of perception, which will in fact be a hallucination. (Grossberg [2000] hypothesized that this occurs when a chronically hyperactive volitional signal is turned on, and he specified neuronal mechanisms that could be involved). In the present study we investigate whether a imbalance between performance on an imagery and a perception condition of the same task may be associated with hallucination. In the imagery condition, "mental" factors contribute importantly to performance, whereas in the perception condition, "sensory" factors play an important role in performing the task.

Another limitation of previous studies may be that imagery performance was not evaluated in different modalities, which could reveal relative, modality-specific alterations. Shallice et al. (1991) and David (1993) have argued that the neuropsychological case-study approach may be potentially fruitful in research on cognitive functions in schizophrenia. A limitation of studies with large groups of patients, may be that the heterogeneity of schizophrenia will lead to group means that do 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. In addition, with regard to hallucinations we hypothesized that the most pronounced effects may be observed when “the system is trapped in action”, i.e. studying patients with on-going hallucinations. It is hard to study such patients in a group design - most patients with hallucinations hallucinate for discrete periods and patients with ongoing hallucinations may be difficult to test due to concentration problems. In the present study, we applied a neuropsychological case-study design, in which we contrasted the performance of a patient with ongoing auditory-verbal hallucinations with the performance of 5 non-hallucinating patients on four tasks of mental imagery and perception (two in the auditory and two in the visual modality). David & Lucas (1993) applied the neuropsychological case study design to the study of continuous auditory-verbal hallucinations and demonstrated that these hallucinations do not call on the same verbal working memory resources as inner speech. Here, we focus on imagery and perception.

Method

Case study

Mr. A was a 41-year-old man with a DSM-IV diagnosis of schizophrenia, whose main complaint regarded continuous, medication-resistant auditory-verbal hallucinations. Severity of hallucination was rated ‘7’ on the hallucination-item of the PANSS (Positive and Negative Syndrome Scale). In addition, his score on the Topography of Voices Rating Scale (Hustig & Hafner, 1990) was 8 (extremes are 5 [very severe] – 25 [very mild]). Symptom ratings on the PANSS were 24 for the positive subscale, 26 for the negative subscale, and 48 for the general psychopathology subscale. Level of education was 11 years.

The phenomenology of Mr. A’s hallucinations was explored with the Cognitive Assessment Schedule (Chadwick & Birchwood, 1995), which concerns a structured interview to assess form and content of the voice; beliefs about the voices’ identity, meaning and power; patients’ evidence for their beliefs; and affective and behavioral responses. Mr. A heared one voice, in his ears (not in his head nor outside his head), and was not sure whether it concerned a male or female voice. The voice talks about him and also conversates with him. In addition, the voice can be commanding, and Mr. A. usually obeys this commands, "to relieve myself". The voice also insinuates and uses abusive language. There are almost no moments in which he doesn't hear the voice. Usually, his emotional reaction is one of distress, although it can also be flat, and incidentally angry when he is scolded. He is sure that the voice is very powerful and that he exerts no control whatsoever on it. He talks back (and sometimes screams) to the voice only when he is alone. He does not know who's voice he hears, but he is almost sure it must be a psychologist. According to the patient, the voice originates from small speakers that have been inserted by psychologists in his auditory organs. He does not know precisely why this has been done, but he suspects psychologists are interested in him because of his rare combination of a low level of education and nevertheless a high performance in chess.

Comparison patients

Five non-hallucinating, patients with schizophrenia who were participants in a larger study on hallucinations and cognitive functioning at our Department were included as comparison-subjects. Three of the patients had never hallucinated (which was confirmed by the consulting clinician), and the other two were hallucination-free for more than 3 months. All patients were male. DSM-IV diagnosis of schizophrenia was confirmed with the CASH interview (Andreasen, 1987). Mean age was 32 years (SD=8.6), and level of education was 12.4 years (SD=2.1). Symptom ratings on the PANSS were as follows: for the positive subscale, 12.6 (SD=1.5), for the negative subscale, 19.8 (SD=5.3), and for the general psychopathology subscale, 34.4 (SD=6.8).

Measures

Performance of Mr. A was compared to the 5 control patients on four tasks of mental imagery: two in the visual and two in the auditory modality (cf. Aleman et al., 2000). First, absolute perceptual thresholds were determined with the staircase method for both the auditory and visual modality, in order to exclude the possibility of gross hearing or vision impairment. For the auditory modality these thresholds were set for the loudness of tones in 74 dB(A) white noise, and for the visual modality the threshold was determined for the duration of dot presentation (1 pixel) on the centre of a computer screen. For all participants, these values were within the normal range.

Auditory and Visual Object imagery. The object imagery task concerns a quantitative comparison between imagery and perception of visual form characteristics of common objects (this task was adapted from Mehta et al. 1992) or sound characteristics of common sounds (auditory version). *Visual modality.* The task consists of 22 object names printed on cards and 22 triads of line drawings of common objects (Snodgrass and Vanderward, 1980). From the triads of line drawings, the item that is most deviant in terms of visual form characteristics has to be indicated. In the perceptual condition the line drawings are actually presented, whereas in the imagery condition the object names are read from cards. For example, in the perceptual condition pictures of the following three objects are presented: “pumpkin”, “lettuce” and “tomato”, whereas in the imagery condition only the names of these three objects were presented to the subject (figure 1). Thus, the imagery condition requires the participants to form mental images in order to be able to make a correct judgement (which in the example given would be “lettuce”). A difference-score was calculated by subtracting the correct responses in the imagery condition from the correct responses in the perceptual condition. *Auditory modality.* The auditory task was similar to the visual version in that a triad of common sounds was presented, and participants had to indicate the item that is most deviant in terms of acoustic characteristics. In the perceptual condition the sounds were actually presented (by the computer), whereas in the imagery condition the names of the sounds were read from cards. An example of a sound triad that was presented is “crying baby”, “laughing baby” and “meowing cat”, where “laughing baby” was regarded the deviant item.

Visual Letter Imagery. This task concerned an adaptation of the task described by Podgorny and Shepard (1978). The subject is asked whether an X-mark, presented in a 4x5 grid, falls on a capital letter. In the imagery condition, the letter is not actually presented in the grid, but must be imaged by the subject. For example, after a fixation point a lowercase letter ‘f’ is presented, followed by an empty grid with the X-mark at the lower right corner. The subject must decide whether the target would fall on an uppercase letter ‘F’ or not. In the perception condition, the letter actually appeared in the grid. Eight letters were randomly presented during the task: ‘c’, ‘f’, ‘h’, ‘j’, ‘l’, ‘p’, ‘s’, ‘u’. Each condition of the task consisted of 32 trials, 4 trials for each of the letters (two “on” and two “off” trials for each letter). We modified the task slightly, in that we allowed the X-mark to appear only in cells in which the chance that the X-mark would cover a letter was equal (thus, no X-marks appeared in the most left column, as most capital letters would cover these cells). Percentage correct responses was taken as dependent measure for both conditions (perception and imagery).

Auditory Musical imagery - . This task of musical imagery requires participants to mentally compare pitches of notes corresponding to song lyrics, and was adapted from Halpern (1988; experiment 2). Participants viewed the lyrics from the first line of a familiar Dutch song on a screen and were asked to decide whether, of two indicated lyrics (which were marked on both sides with asterisks and appeared in uppercase letters), the pitch of the second lyric was higher or lower than that corresponding to the first lyric. Lyric refers here to a monosyllabic word, or one syllable of a two-syllabic word. An English language example would be: "*OH* say can *YOU* see", taken from the American national anthem. In the perceptual condition, participants were actually presented with the song, which was played via a tape-recorder. The imagery condition was identical, with the exception that the song was not presented, and participants had to rely on their musical imagery in order to be able to perform the task correctly. They were not allowed to hum the melody. Again, percentage correct responses was taken as dependent measure for both conditions (perception and imagery).

Results

In order to examine possible differences between the performance of Mr. A and the control patients on the imagery measures, a z-score analysis was carried out on the imagery/perception difference scores. Significant differences emerged for both auditory tasks and for the visual letter imagery task (table 1). The interesting point is that the direction of the imagery/perception difference is opposite to the direction in the control group for both auditory measures only.

Table 1. Means for the continuously hallucinating patient Mr. A and the non-hallucinating control group (means with SDs) on measures of perception/imagery concordance (lower scores indicate larger concordance)

Imagery/perception measure		Mr. A	Non-hallucinating patients (N=5)	z-value
Object imagery	Visual	4	3.2 (2.9)	0.28
	Auditory	-2	2.6 (1.1)	-4.18***
Letter Imagery		19	4.4 (6.5)	2.24*
Musical imagery		-6	2.4 (3.4)	-2.47**

*p<0.05, **p<0.01, ***p<0.001

This difference in direction is more clearly illustrated in figure 1, that plots the performance of Mr A and the 5 controls on the auditory and the visual object imagery task (percentage correct responses). As is evident from the figure, Mr. A does not show the normal pattern of better perception performance relative to imagery performance on the auditory task (the modality of hallucination). In contrast, he does show this pattern on the visual task. Fig. 2 shows performance on the auditory musical imagery task and the visual letter imagery task. Again, Mr. A does not show the normal difference between imagery and perception on the auditory task, but does show this difference on the visual task.

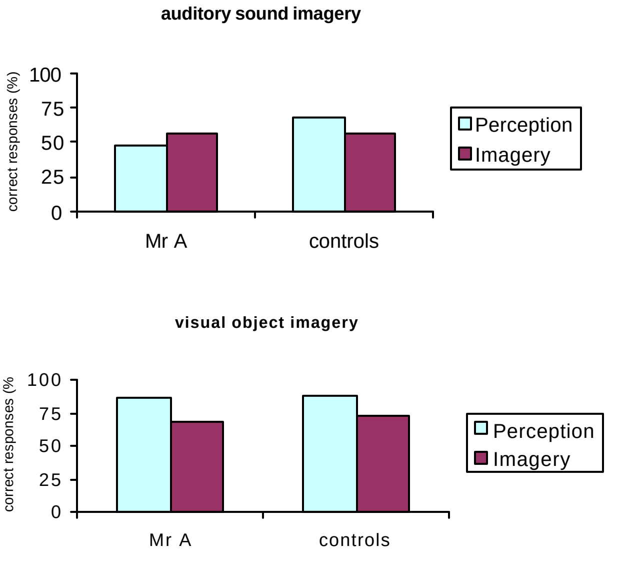

Fig. 1. Percentage correct responses on perception and imagery conditions of Auditory (A) and Visual Object Imagery (B) task for Mr. A and 5 non-hallucinating control patients

Discussion

Cognitive theories of hallucination in schizophrenia assume that an erroneous attribution is made of internally generated information to an external source (e.g., Bentall, 1990; David, 1999; Frith, 1992; Hoffman et al., 1999). Johnson & Raye

(1981; Johnson, Raye & Hashtroudi, 1993) have developed a theory of source discrimination and monitoring in which it is hypothesized that internally generated information (mental images) and information of external origin (percepts) are distinguished by the cognitive system by taking into account the proportion of sensory, contextual and semantic information, which is more detailed for percepts.

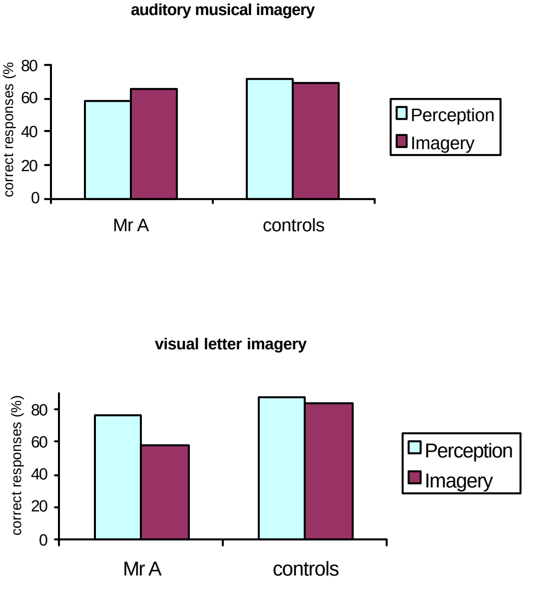

Fig. 2. Percentage correct responses on perception and imagery conditions of the Musical (A) and Letter Imagery (B) task for Mr. A and 5 non-hallucinating control patients

Evidence that mental images are less rich in perceptual details than percepts and that, as a consequence, images are more difficult to perform mental operations upon, was recently presented by Kosslyn et al. (1999). This implies that subjects will make more errors on an imagery condition of a cognitive task, compared to a perception condition of the same task. We recently reported that this indeed is the case for non-psychiatric college students (Aleman et al. 2000). However, in the present study we demonstrated that in a continuously hallucinating patient this balance (of more vivid perception relative to imagery) was reversed in the modality of hallucination (auditory), but not in another modality (visual).

Thus, the results of the present neuropsychological case-study suggest that auditory hallucinations may be associated with a modality-specific distortion in the balance between imagery and perception performance. Such a distortion may also be interpreted as a modality-specific increase in vividness of mental imagery relative to perception. In this way, our results are in accordance with Böcker et al. (2000), who observed more vivid auditory than visual imagery in auditory-verbal hallucinating patients. It could be argued, however, that the observed distortion in the balance between imagery and perception is mainly caused by higher-order perceptual dysfunction in hallucinating patients. This interpretation is supported by the recent study by McKay et al. (2000), in which a wide range of auditory perception tests were administered to hallucinating and nonhallucinating schizophrenic patients and to normal comparison subjects. Although all patients with schizophrenia appeared to perform worse on higher order perceptual tasks, this dysfunction was more pronounced for the hallucinating patients.

How a distortion in the balance of imagery and perception can lead to hallucinatory experiences can be best understood within the framework of Johnson & Raye's theory of reality monitoring (Johnson & Raye, 1981; Johnson, Raye & Hashtroudi, 1993). They hypothesize that sensory qualities of an experience help tag the event as having been perceived, whereas metacognitive processes associated with the activity of imagining would help tag the event as having been imagined. Increased sensory qualities of mental images, or decreased sensory qualities of percepts will then result in reality discrimination errors, in which internally generated information may mistakenly be attributed to an external source. In addition, metacognitive processes could also play an important mediating role. An internal attribution is based on reference to metacognitive processes, with the amount of effort involved in generation being a determining factor (Johnson & Raye, 1981). Perception may be as effortful as generating mental images for hallucinating subjects, which is evident from the relative low scores on perception conditions compared to imagery performance (and consistent with the findings by McKay et al., 2000). In contrast, in non-hallucinating individuals, mental imagery is clearly more effortful than perception. Thus, due to the smaller difference in effortful processing between imagery and perception, less information concerning the cognitive operations involved may be available to the hallucinating subjects, contributing to errors in source attribution. There is increasing evidence that reality monitoring is deficient in hallucinating patients (Bentall et al., 1991; Morisson & Haddock, 1997; Brébion et al., 2000). The present study may contribute in elucidating a potential underlying mechanism of such confusions, namely, a distortion in the balance between imagery and perception.

References

Aleman, A., Böcker, K.B.E. & De Haan, E.H.F. (1999). Disposition toward hallucination and subjective versus objective imagery in normal subjects. *Personality and Individual Differences* **27**, 707-714.

Aleman, A., Nieuwenstein, M., Böcker, K.B.E. & De Haan, E.H.F. (2000). Mental imagery and perception in hallucination-prone individuals. *Journal of Nervous and Mental Disease* **188,** 830-836.

Andreasen, N.C. (1987). *Comprehensive assessment of symptoms and history.* Iowa City, University of Iowa.

Behrendt, R.-P. (1998). Underconstrained perception: a theoretical approach to the nature and function of verbal hallucinations. *Comprehensive Psychiatry* **39**, 236-248.

Bentall, R.P. (1990). The illusion of reality: a review and integration of psychological research on hallucinations. *Psychological Bulletin* **107**, 82-95.

Bentall, R.P., Baker, G. & Havers, S. (1991). Reality monitoring and psychotic hallucinations. *British Journal of Clinical Psychology* **30**, 213-222.

Böcker, K.B.E., Hijman, R., Kahn, R.S. & De Haan, E.H.F. (2000) Perception, mental imagery and reality discrimination in hallucinating and nonhallucinating schizophrenic patients. *British Journal of Clinical Psychology* **39**, 397-406.

Brébion, G., Amador, X., David, A., Malaspina, D., Sharif, Z. & Gorman, J.M. (2000). Positive symptomatology and source-monitoring failure in schizophrenia - an analysis of symptom-specific effects. *Psychiatry Research* **95**, 119-131.

Chadwick, P.D. & Birchwood, M.J. (1995). The omnipotence of voices II: the Beliefs about Voices Questionnaire (BAVQ). *British Journal of Psychiatry* **166**, 773-776.

David, A.S. (1994). The neuropsychological origin of auditory hallucinations. In: A.S. David & J.C. Cutting (Eds), *The neuropsychology of schizophrenia.* Hove: Psychology Press.

David, A.S. & Lucas, P. (1993). Auditory-verbal hallucinations and the phonological loop: a cognitive neuropsychological study. *British Journal of Clinical Psychology* **32**, 431-441.

David, A.S. (1993). Cognitive neuropsychiatry? *Psychological Medicine* **23**, 1-5.

David, A.S. (1999). Auditory hallucinations: phenomenology, neuropsychology and neuroimaging update. *Acta Psychiatrica Scandinavica* **99 (Suppl. 394),** 95-104.

Evans, C.L., McGuire, P.K. & David, A.S., 2000. Is auditory imagery defective in patients with auditory hallucinations? *Psychological Medicine* **30**, 137-148.

Frith, C.D. & Done, D.J. (1988). Towards a neuropsychology of schizophrenia. *British Journal of Psychiatry* **153**, 437-443.

Galton, F. (1883). *Inquiries into human faculty and its development*. London: McMillan.

Grossberg, S. (2000). How hallucinations may arise from brain mechanisms of learning, attention, and volition. *Journal of the International Neuropsychological Society* **6,** 583-592.

Halpern, R. (1988). Mental scanning in auditory imagery for songs. *Journal of Experimental Psychology: Learning Memory and Cognition* **10**, 496-512.

Horowitz, M.J. (1975). Hallucinations: an information processing approach. In RK Siegel and LJ West (Eds) *Hallucinations: Behavior, experience and theory* (pp. 163-196). New York: Wiley.

Hustig, H.H. & Hafner, R.J. (1990). Persistent auditory hallucinations and their relationship to delusions of mood. Journal of Nervous and Mental Disease **178**, 264-267.

Johnson, M.K. & Raye, C.L. (1981). Reality monitoring. *Psychological Review* **88**, 67-85.

Johnson, M.K., Hashtroudi, S. & Lindsay, D.S. (1993). Source monitoring. *Psychological Bulletin* **114**, 3-28.

Kosslyn, S.M., Cave, C.B., Provost, D. & Von Gierke, S. (1988). Sequential processes in image generation. *Cognitive Psychology* **20**, 319-343.

Kosslyn, S.M., Sukel, K.E. & Bly, B.M. (1999). Squinting with the mind's eye: effects of stimulus resolution on imaginal and perceptual comparisons. *Memory & Cognition* **27**, 276-287.

McKay, C.M., Headlam D.M. & Copolov D.L., 2000. Central auditory processing in patients with auditory hallucinations. *American Journal of Psychiatry* **157**, 759-766.

Mehta, Z., Newcombe, F. & De Haan, E.H.F. (1992). Selective loss of imagery in a case of visual agnosia. *Neuropsychologia* **30**, 645-655.

Mintz, S. & Alpert, M. (1972). Imagery vividness, reality testing, and schizophrenic hallucinations. *Journal of Abnormal Psychology* **79**, 310-316.

Morrison, A.P. & Haddock, G. (1997). Cognitive factors in source monitoring and auditory hallucinations. *Psychological Medicine* **27**, 669-679.

Roman, R., Landis, C. (1945). Hallucinations and mental illness. *Journal of Nervous and Mental Disease* **102**, 327-331.

Shallice, T., Burgess, P.W. & Frith, C.D. (1991) Can the neuropsychological case-study approach be applied to schizophrenia? *Psychological Medicine* **21**, 661-673.

Slade, P.D. (1994). Models of hallucination: from theory to practice. In: A.S. David & J.C. Cutting (Eds), *The neuropsychology of schizophrenia.* Hove: Psychology Press.

Snodgrass, J.G. & Vanderward, M. (1980). A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity and visual complexity. *Journal of Experimental Psychology: Learning Memory and Cognition* **6**, 174-215.

Starker, S. & Jolin, A. (1982). Imagery and hallucinations in schizophrenic patients. *Journal of Nervous and Mental Disease* **170**, 448-451.

Chapter 15

Reality monitoring and mental imagery vividness

Summary

It is generally acknowledged that hallucinations in schizophrenia are a result of the erroneous attribution of internally generated information to an external source. Distortions in mental imagery vividness may underlie such confusions. We investigated performance of 43 patients with schizophrenia on multiple behavioral measures of auditory and visual mental imagery and perception, a measure of reality monitoring and a signal detection measure. Hallucinating patients were contrasted with non-hallucinating patients, after controlling for attentional factors that may influence task performance. We replicated earlier findings of significantly more source discrimination errors in hallucinating patients compared to non-hallucinating patients. No differences emerged on any of the mental imagery measures, nor on criterion bias in signal detection. Our results provide strong evidence that there is no trait-related distortion of mental imagery in patients with hallucinations.

Aleman, A., Böcker, K.B.E., Hijman, R., Kahn, R.S., & De Haan, E.H.F. (in preparation). Reality monitoring and imagery vividness in patients with and without hallucinations.

Introduction

An increasing number of recent studies report that hallucination-prone patients with schizophrenia have difficulties in discriminating between an internally generated, imagined event and an externally presented, real event (Bentall & Slade, 1985; Bentall et al., 1991; Morrison & Haddock, 1997; Brébion et al., 1998; Johns & McGuire, 1999; Böcker et al. 2000; Brébion et al., 2000; Franck et al. 2000). Such difficulties may arise from one of three possible mechanisms, or a combination of these (Böcker et al. 2000). The first possibility concerns deficits in perception: degraded percepts will more easily be confounded with mental images. Second, an increase in the "vividness" of mental images, in which images have more sensory characteristics than expected by the cognitive system, may lead to confusions between percepts and images. Finally, a bias in a meta-cognitive process involved in monitoring the source of information that is processed in our brains could account for the confusion. Specifically, it has been hypothesized that reality monitoring [1] biases, distinguishing between internally generated information and externally presented information, may underlie hallucinations in schizophrenia (Slade & Bentall, 1988).

Clearly, the recent research reporting biases in discriminating between imagined events and an externally presented events, is consistent with the third, "reality monitoring" hypothesis. This is not to say, however, that alterations in imagery or perception could not underlie such confusions. Research examining these hypotheses may more precisely delineate the cognitive mechanisms involved in hallucination. Regarding the perception hypothesis, Böcker et al. (2000) compared hallucinating versus non-hallucinating patients on measures of basic auditory and visual perception, specifically sensory acuity. No significant differences were observed. However, a recent study by McKay et al. (2000) also failed to find deficits in basic (low-level) perception associated with hallucinations, but did find higher order impairments. The authors administered a wide range of auditory perception tests to hallucinating and nonhallucinating schizophrenic patients and to normal comparison subjects. Although all patients

[1] A distinction has been made between the terms "reality monitoring" and "reality discrimination", where the latter refers to distinguishing "on-line" between real and imaginal events, whereas reality monitoring refers to *memories* of the (internal versus external) source of earlier presented information (Bentall, 1990). However, following recent authors (e.g. Brébion et al., 2000) we will use the terms interchangeably, as they concern the same psychological construct.

with schizophrenia appeared to perform worse on higher order perceptual tasks, this dysfunction was more pronounced for the hallucinating patients.

Most previous studies that investigated the imagery hypothesis of hallucinations (e.g., Roman & Landis, 1945; Mintz and Alpert, 1972; Starker & Jolin, 1982) did not include adequate behavioral measures of mental imagery, which may explain the inconsistent results. Two recent studies assessed the relation between mental imagery and hallucination with objective, behavioral measures (Evans et al., 2000; Böcker et al. 2000). Evans et al. (2000) only used auditory measures and failed to find differences between hallucinating and non-hallucinating patients. Böcker et al. (2000) assessed imagery and perception in the auditory and visual modalities. Consistent with Evans et al. (2000), no between-group differences were observed. However, after performing within-group comparisons, they observed more vivid auditory than visual imagery in hallucinating patients (that hallucinated in the auditory modality). This difference was not observed in the non-hallucinating group. Moreover, in a recent cognitive neuropsychiatric case-study (Aleman et al., submitted), we observed a modality-specific imbalance between imagery and perception in a patient with continuous auditory hallucinations, compared to five non-hallucinating patients. Specifically, whereas control subjects always perform better on a perception than on an imagery condition of the same task (the perception-superiority effect), this patient showed the reverse (imagery>perception) in the auditory, but not visual modality.

Our aim was twofold. First, to replicate the finding of reality monitoring errors in relation to hallucinations, and, second, to investigate whether differences in imagery vividness underlie such errors. Thus, the present study was designed as a thorough follow-up to the study by Böcker et al. (2000). Measures of imagery and perception were included, as well as measures of discrimination bias and reality monitoring. Specifically, the design was improved on five points with respect to earlier studies. First, a more comprehensive evaluation of imagery and perception was carried out by including more (behavioral) measures. Second, larger patient groups were studied. Third, patients with more severe hallucinations were included. Fourth, a subgroup of patients was included that had never hallucinated at all. Finally, we controlled statistically for non-specific attentional factors that contribute to cognitive test performance.

Method

Subjects

Forty-three patients with a clinical diagnosis of schizophrenia participated in the present study. They were recruited from the Schizophrenia Research Unit of the Department of Psychiatry, University Medical Center, and from a local Psychiatric Hospital (Willem Arntz Huis, H.C. Rümke Groep). DSM-IV diagnosis was established on the basis of the life-time version of the Comprehensive Assessment of Symptoms and History (CASH; Andreasen, 1987). With the exception of two patients, all were on neuroleptic treatment (Table 1). Clinical ratings were made from the Positive And Negative Symptom Scale (PANSS; Kay, Opler and Fiszbein, 1986), regarding the individual symptoms during the week preceding the interview. The interview, by the first author, who reached consensus with a second rater, took place on the first day of testing. Twenty patients had experienced hallucinations, ranging from a mild degree (once or twice, without behavioral consequences, score 3) to a very severe degree (hallucinations dominate thinking and behavior, causing verbal and behavioral reactions, score 7). Patients were included in the non-hallucinating group(N = 23) if they were hallucination-free for at least three months prior to testing (as indicated by self-report and confirmed by the consulting clinician). Eleven patients had never experienced hallucinations. Table 1 lists demographic and clinical characteristics of the patients included in the study.

Testing Materials

Reality monitoring, discrimination bias, and imagery/perception relations were tested by use of experimental psychological methods. To control for non-specific attentional factors, measures were included of attention and working memory, in the auditory and visual modality. These were the digit span forward and backward, from the Wechsler Adult Intelligence Scale (Wechsler, 1955), and the Visual Elevator test from the Everyday Attention Test (EAT; Robertson et al. 1996), respectively.

Reality monitoring and discrimination bias

Reality monitoring. This was an adaptation of the reality monitoring task described by Harvey (1985). During the learning-phase, one of the three most typical words (e.g., 'Gold') in one of twenty categories from Van Loon-Vervoorn and Pijpers-Kooiman (1988), was read aloud to the subjects. For a second word the category-name plus the first letter were presented (e.g. 'Metal-I....') with the assignment to image the first word which came to mind, as if actually spoken.

Table 1. Demographic and clinical characteristics of the studied sample

	Patients with hallucinations (N=20)	Patients without hallucinations (N=23)
Education[1]	12.9 (3.5)	13.5 (2.8)
Age[1]	32.2 (8.7)	29.5 (6.4)
Duration of illness[1]	10.1 (8.7)	4.4 (4.4)*
Number of hospitalisations	3.1 (2.1)	2.1 (1.3)
Hallucination rating (PANSS)	4.5 (1.1)	1 (0.0)***
Positive symptoms (PANSS)[2]	11.8 (4.3)	11.0 (4.5)
Negative symptoms (PANSS)	15.1 (6.1)	17.7 (6.5)
General psychopathology (PANSS)	31.0 (9.3)	31.5 (8.0)

[1]in years, [2]after subtraction of hallucination ratings
*p<0.05; ***p<0.001

In the test-phase the participants had to indicate verbally for each of 30 words whether it was perceived earlier ('Gold'), imaged earlier ('Iron') or whether it concerned a new word ('Copper'). This was done immediately after presentation of the words (immediate recognition) and again after 15 minutes (delayed recognition). Between both tests, another task was performed (the letter imagery task). Reality monitoring data were analyzed by calculating a source discrimination parameter, and two sensitivity parameters. The source discrimination parameter was the average conditional source identification measure (ACSIM), which, in contrast to more traditional measures, is independent of item recognition (Murnane & Bayen, 1996). In addition, we calculated recognition parameters D_1 and D_2 (Batchelder & Riefer, 1990), which refer to sensitivity for words that were heared (externally presented) and words that were imaged (internally generated), respectively.

Discrimination bias. The non-parametric measure for response bias (B) is regarded as an indicator of external attribution bias, an important factor in reality discrimination. A stronger external attribution bias leads to more false positives, i.e., more internal events being classified as external. It is determined in a signal-detection task.

The subjects were presented with 100 trials on which they were requested to indicate whether they perceived a particular word presented over a speaker at 60 to 65 dB(A) in 72 dB(A) white background noise. They verbally indicated this on a 5-point rating scale with the anchors being 'definitely yes', 'probably yes', 'don't know', 'probably not' or 'definitely not'. On 50% of the trials the word which was asked for had indeed been presented. Bentall and Slade (1985) found the response bias, which is inversely related to the external attribution bias, to be weaker in hallucinating subjects, who were more prone to acknowledge that they heard a stimulus in the noise.

The number of false alarms on the imagery-perception interaction tasks was also considered a measure of discrimination bias.

Relation mental imagery/perception

First, four tests will be described that concern concerned a *comparison* between imagery and perception. Subsequently, two measures will be described that are aimed at the *interaction* between imagery and perception (cf. Aleman et al. 2000; Böcker et al. 2000).

Imagery-perception comparison. The first two tasks (which we will call the visual and auditory *triad comparison* task) concerned a quantitative comparison between imagery and perception of visual form characteristics of common objects (this task was adapted from Mehta et al. 1992) or sound characteristics of common sounds (auditory version; Aleman et al., 2000). *Visual modality*. The task consists of 22 object names printed on cards and 22 triads of line drawings of common objects (Snodgrass and Vanderward, 1980). From the triads of line drawings, the item that is most deviant in terms of visual form characteristics has to be indicated. In the perceptual condition the line drawings are actually presented, whereas in the imagery condition the object names are read from cards. For example, in the perceptual condition pictures of the following three objects are presented: “pumpkin”, “lettuce” and “tomato”, whereas in the imagery condition only the names of these three objects were presented to the subject (figure 1). Thus, the imagery condition requires the participants to form mental images in order to be able to make a correct judgement (which in the example given would be “lettuce”). A difference-score was calculated by subtracting the percentage correct responses in the imagery condition from the percentage correct responses in the perceptual condition. *Auditory modality.* The auditory task was similar to the visual version in that a triad of common sounds was presented, and participants had to indicate the item that is most deviant in terms of acoustic characteristics. In the perceptual condition the sounds were actually presented (by the computer), whereas in the imagery condition the names of the sounds were read from cards. An example of a sound triad that was presented is “crying baby”, “laughing baby” and “meowing cat”, where “laughing baby” was regarded the deviant item.

The third task concerned *Letter imagery*. We adapted the letter imagery task used by Kosslyn et al. (1988). The subject is asked whether an X-mark, presented in a 4x5 grid, falls on a capital letter. In the imagery condition, the letter is not actually presented in the grid, but must be imaged by the subject. For example, after a fixation point a lowercase letter ‘f’ is presented, followed by an empty grid with the X-mark at the lower right corner. The subject must decide whether the target would fall on an uppercase letter ‘F’ or not. In the perception condition, the letter actually appeared in the grid (figure 2). Eight letters were randomly presented during the task: ‘c’, ‘f’, ‘h’, ‘j’, ‘l’, ‘p’, ‘s’, ‘u’. Each condition of the task consisted of 32 trials, 4 trials for each of the letters (two “on” and two “off” trials for each letter). We modified the task slightly, in that we allowed the X-mark to appear only in cells in which the chance that the X-mark would cover a letter was equal (thus, no X-marks appeared in the most left column, as most capital letters would cover these cells). The difference in percentage correct responses between the imagery and perception condition was the dependent measure.

The last imagery-perception comparison task was of *Musical imagery*. This task of requires participants to mentally compare pitches of notes corresponding to song lyrics, and was adapted from Halpern (1988; experiment 2). Participants viewed the lyrics from the first line of a familiar Dutch song on a screen and were asked to decide whether, of two indicated lyrics (which were marked on both sides with asterisks and appeared in uppercase letters), the pitch of the second lyric was higher or lower than that corresponding to the first lyric. Lyric refers here to a monosyllabic word, or one syllable of a two-syllabic word. An English language example would be: “*OH* say can *YOU* see”, taken from the American national anthem. Participants responded by means of a key press. In the perceptual condition, participants were actually presented with the song, which was played via a tape-recorder. The imagery condition was identical, with the exception that the song was not presented, and participants had to rely on their musical imagery in order to be able to perform the task correctly. Again, the difference in percentage correct responses between the imagery and perception condition was calculated.

Imagery-perception interaction. This test was based on the notion that stimuli which are presented at the level of the absolute perception threshold are detected more often when at the same time a person also images that stimulus. In the visual modality this has been reported for dots at locations covered by a concurrent image of a letter (Farah, 1989) and in the auditory modality for a tone while the subjects imaged a tone of the same frequency (Farah and Smith, 1983). At the first stage of this test absolute thresholds (for the duration of the target dot and the loudness of the two target tones in 74 dB(A) white noise, respectively) were determined by the staircase method. During the second stage two series of 32 trials were presented in each modality, while the subjects were imaging one of the two letters (capital T or H in a 5 * 5 square) or tones (440 or 1000 Hz). On 50% of the trials a target stimulus (dot or tone) was presented while the subjects were imaging. On each trial subjects indicated verbally whether or not they perceived a target stimulus. The difference score calculated from the number of stimuli detected when the image was similar (in location or pitch) to the target stimulus (25% of the trials), minus those detected when it was not (another 25% of the trials), is a measure for the *interaction* between imagery and perception. This difference is presumed to be larger in subjects with a more vivid imagery, which are the hallucinating patients according to our second hypothesis.

Procedure

The auditory and visual tests were administered in two sessions, on different days, with a maximum delay of one week. The order of the tests within one part was fixed, to minimize interference on the one hand and to create standard filled intervals on the other hand. A break was inserted halfway.

Experimental design and statistical analysis

This study focuses on the contrast between hallucinating and non-hallucinating patients. Comparing these two groups reveals the cognitive disturbances that probably contribute to the hallucinations. For direct comparisons between different imagery comparison tests the percentage correct responses was computed, because the measurement scales of the different tasks are not comparable. ANCOVA's were carried out on the data, with tests of attention/working memory as covariate. Two--tailed significance levels are reported, with exception of the reality monitoring task, for which the strong expectations of the direction of the effect (based on theory and empirical findings) allowed the use of one-tailed levels.

Results

Although the two groups did not differ significantly on digit span nor on Visual Elevator performance, these measures were included as covariate in the analyses, in order to control for the portion of variance in the cognitive measures that could be explained by attentional factors.

Reality monitoring and signal detection bias

For the reality monitoring task, a highly significant difference emerged between the hallucinating and non-hallucinating group on the delayed source discrimination measure $F(1, 36)=9.3$, $p<0.005$. For immediate source discrimination, this difference was also significant, $F(1,39)=2.9$, $p<0.05$. The groups did not differ on the recognition parameters D_1 and D_2. Thus, although patients with hallucinations made more source confusions, there was no differential sensitivity for self-generated or experimenter presented items. Table 2 lists the parameters for the source monitoring task.

Performance of hallucinating patients was indistinguishable from non-hallucinating patients on the non-parametric index of response bias in the detection task. That is, patients with hallucinations were not more willing to indicate they had heard a particular word in the white noise when that word was not actually present. Moreover, the groups did not differ in number of false alarms on the percepion interaction tasks.

Table 2. Reality monitoring parameters for the two groups

Parameter	Patients with hallucinations[1]	Patients without hallucinations[1]
Immediate ACSIM	0.93 (0.08)	0.97 (0.05)
Delayed ACSIM	0.85 (0.12)	0.90 (0.12)
Imm. D_1	0.61 (0.28)	0.55 (0.27)
Imm. D_2	0.90 (0.13)	0.87 (0.13)
Del. D_1	0.42 (0.34)	0.30 (0.38)
Del. D_2	0.91 (0.12)	0.68 (0.86)

[1]N for the different analyses: 20/22 for the immediate measures and 18/21 for the delayed measures

Imagery-perception comparisons

Table 3 shows means (and SDs) for the imagery-perception comparison measures. No between-group differences emerged from the MANCOVA on the four imagery-perception comparison measures ($F<1$, $p>0.20$). A 2 × 2 ANCOVA with modality as within-subjects factor with two levels (auditory, visual) also failed to show Group × Modality interactions. In addition, a subgroup analysis in which patients with hallucinations (N=17) were contrasted with patients that had never experienced hallucinations (N=9) neither revealed between-group differences.

Imagery-perception interactions

For the auditory imagery-perception interaction task we observed the predicted gain due to imagery. That is, stimuli that had been imaged were detected significantly better than stimuli that had not previously been imaged, $t=4.8$, $p<0.001$. However, there was no group difference in the effect of imagery on perception, $F(1,33)=2.01$, $p<0.20$.

For the visual imagery-perception interaction task, we failed to replicate the typical imagery gain (e.g., reported by Farah, 1989). This is essential to the validity of the task, as the task can not be said to measure imagery-perception interaction when no influence of imagery on perception is found. Therefore, we will not further discuss this task. (There were no group differences in performance on this task, $F<1$, $p>0.50$.)

Table 3. Means (and SDs) for perception minus imagery performance on the imagery-perception comparison tasks

Task	Patients with hallucinations[1]	Patients without hallucinations[1]
Auditory triad comparison	2.4 (3.1)	3.2 (2.2)
Visual triad comparison	2.8 (1.8)	2.2 (1.8)
Musical imagery	5.1 (10.4)	4.5 (8.7)
Letter imagery	9.8 (10.4)	13.0 (18.2)

[1]Due to practical problems not all tasks could be administered to some patients. Therefore the N was as follows: 20/23, 20/23, 18/19 and 17/18, respectively.

Discussion

The aim of the present study was twofold. First, to replicate the finding of reality monitoring errors in patients with hallucinations. Second, to test the "vivid mental imagery" hypothesis of hallucinations in schizophrenia, which states that mental images have more percept-like characteristics in hallucinating individuals. Our finding of source discrimination errors associated with hallucinations is consistent with a range of earlier studies on this subject (Bentall et al., 1991; Böcker et al. 2000; Morrison & Haddock, 1997; Brébion et al., 2000; Franck et al., 2000).

Although the finding of increased reality monitoring deficits in patients with hallucinations is usually taken to imply that biases in reality monitoring lead to hallucinations (Bentall, 1990), it has also been argued that reality monitoring errors are a consequence rather than a cause of psychotic experiences (Vinogradov et al., 1997; Hoffman et al., 2000). According to this account, patients develop an external attribution bias as an explanation for the overwhelming, emotional demanding and confusing abnormal perceptual/cognitive experiences of psychosis. Detailed longitudinal investigations in large patient groups are necessary to clarify the causal direction of reality monitoring errors in relation to hallucination.

Brébion et al. (1997 ; 2000) have pointed out that the term reality monitoring/discrimination can refer to different types of distinctions. For example, between actual events and non-events (i.e., perception vs. imagery) one one hand, and between self- and non-self-generated events on the other hand. In this study we found evidence that patients with hallucinations primarily differ from patients without hallucinations on the latter dimension (tapped by the reality monitoring task). In contrast, no differences were observed on discrimination bias in two signal detection tasks. Such discrimination biases (of the false alarm type) would reflect difficulties in distinguishing between actual and non-events. The lack of group differences on this measure is at odds with results reported by Bentall & Slade (1985) and Brébion et al. (1997), but is consistent with Böcker et al. (2000). The discrepancy may be explained by the fact that our task was identical to the one applied by Böcker et al. (2000), but differed from the tasks applied by Bentall & Slade (1985) and Brébion et al. (1997). More specifically, in the task of Bentall & Slade (1985) only one word was included, which could be present (in white noise) or absent (only white noise). In contrast, in our task a subject was asked to indicate whether a particular word was present in the noise (with different words being presented in the noise). Thus, the discrimination in our task was “same” versus “different”, whereas in Bentall & Slade’s task the discrimination concerned “present” or “absent”. Although both tasks measure the willingness of a subject to admit having heard a word that was not actually presented, Bentall & Slade’s task might more explicitly concern the distinction between material of internal and external origin.

The imagery hypothesis starts from the assumption that, in normal conditions, mental images are less vivid, i.e. have less sensory and contextual characteristics, than percepts. Kosslyn et al. (1999) and Aleman et al. (2000) recently provided evidence for this assumption in non-psychiatric samples. According to the theory of Johnson & Raye (1981) increased vividness of images will make them less distinctive from percepts, which may lead to reality monitoring errors. To test the imagery hypothesis, we investigated whether patients with hallucinations would show smaller differences in performance on imagery and perception conditions of the same task, after controlling for non-specific attentional variables.

For all four behavioral measures, no differences were observed between the hallucinating and non-hallucinating groups. This is consistent with our earlier findings in hallucination-prone individuals (Aleman et al., 2000). If cognitive alterations are associated with hallucinations as a trait (the disposition towards hallucination), our findings could be obscured by the fact that a number of patients in the non-hallucinating group had actually experienced hallucinations in the past (although this had to be more than three months before the study). Therefore, we conducted an analysis in which a subgroup of patients that had *never* hallucinated was contrasted with the hallucinating group. However, again no significant differences emerged on measures of imagery and perception. Neither were differences observed for imagery-perception interaction. The results corroborate earlier studies by Böcker et al. (2000) and Evans et al. (2000), who also failed to find between-group differences on multiple measures of imagery. However, Böcker et al. (2000) in addition observed more vivid auditory than visual imagery in hallucinating patients on an imagery-perception interaction task. We were not able to replicate this finding, which may be due to the fact that our visual imagery-perception interaction task failed to show the characteristic imagery-gain which is a prerequisite to the validity of the task. However, our other tasks did not show evidence of within-group modality differences.

In conclusion, the present study observed reality monitoring deficits in patients with hallucinations, but no abnormalities were found in imagery-perception relations. Thus, the present results strongly suggest that patients with hallucinations do not have a trait-like alteration of mental imagery that may eventually lead to the emergence of hallucinations. It could be hypothesized, however, that increased vividness of imagery is strictly confined to the hallucinatory state, i.e. occurs only during the actual experience of hallucinations. Indeed, evidence from a case-study of a continuous hallucinating patient suggests that transient, state-dependent alterations in vividness of imagery may play a role in hallucinations (Aleman et al., submitted; see chapter 14). We recommend future research to investigate this more extensively. In addition, research may concentrate on possible interactions between reality monitoring and abnormalities in perception (cf. McKay et al., 2000) or top-down perceptual expectations (cf. Grossberg, 2000).

References

Aleman A, Böcker KBE, De Haan EHF (1999) Disposition toward hallucination and subjective versus objective imagery in normal subjects. *Personality and Individual Differences* 27:707-714.

Aleman A, Hijman R, De Haan EHF, Kahn RS (1999) Memory impairment in schizophrenia: a meta-analysis. *American Journal Psychiatry* 156:1358-1366.

Aleman A, Nieuwenstein M, Böcker KBE, De Haan EHF. (2000). Mental imagery and perception in hallucination-prone individuals. *Journal of Nervous and Mental Disease* 188:830-836.

Batchelder, WH & Riefer, DM. (1990). Multinomial processing models of source monitoring. *Psychological Review, 97*, 548-564.

Bentall RP (1990) The illusion of reality: a review and integration of psychological research on hallucinations. *Psychological Bulletin* 107:82-95.

Bentall RP, Baker G, Havers S (1991) Reality monitoring and psychotic hallucinations. *British Journal of Clinical Psychology* 30:213-222.

Bentall RP, Slade PD (1985) Reliability of a scale measuring disposition towards hallucination: a brief report. *Personality and Individual Differences* 6:527-529.

Böcker, K.B.E., Hijman, R., Kahn, R.S., & De Haan, E.H.F. (2000) Perception, mental imagery and reality discrimination in hallucinating and nonhallucinating schizophrenic patients. *British Journal of Clinical Psychology, 39,* 397-406.

Brébion G, Amador X, David A, Malaspina D, Sharif Z, Gorman JM (2000) Positive symptomatology and source-monitoring failure in schizophrenia - an analysis of symptom-specific effects. *Psychiatry Research* 95: 119-131.

Brett EA, Starker S (1977) Auditory imagery and hallucinations. *Journal of Nervous and Mental Disease* 164:394-400.

Chadwick PD, Birchwood MJ (1995) The omnipotence of voices II: the Beliefs about Voices Questionnaire (BAVQ). *British Journal of Psychiatry* 166:773-776.

David AS (1994) The neuropsychological origin of auditory hallucinations. In: A.S. David & J.C. Cutting (Eds), *The neuropsychology of schizophrenia.* Hove: Psychology Press.

Evans CL, McGuire PK, David AS (2000) Is auditory imagery defective in patients with auditory hallucinations? *Psychological Medicine* 30:137-148.

Franck N, Rouby P, Daprati E, et al. (2000) Confusion between silent and overt reading in schizophrenia. *Schizophrenia Research* 41:357-364.

Frith CD, Done DJ (1988) Towards a neuropsychology of schizophrenia. *British Journal of Psychiatry* 153:437-443.

Grossberg S (2000) How hallucinations may arise from brain mechanisms of learning, attention, and volition. *Journal of the International Neuropsychological Society* 6:583-592.

Halpern R (1988) Mental scanning in auditory imagery for songs. *Journal of Experimental Psychology: Learning Memory and Cognition* 10:496-512.

Harvey PD (1985) Reality monitoring in mania and schizophrenia. The association of thought disorder and performance. *Journal of Nervous and Mental Disease* 173:67-73.

Hoffman RE, Rapaport J, Mazure CE, Quinlan DM (2000) Non-language cognitive deficits and hallucination in schizophrenia: Reply to Aleman and De Haan. *American Journal of Psychiatry* 157:487-488.

Horowitz MJ (1975) Hallucinations: an information processing approach. In RK Siegel and LJ West (Eds) *Hallucinations: Behavior, experience and theory* (pp. 163-196). New York: Wiley.

Johnson MK, Raye CL (1981) Reality monitoring. *Psychological Review* 88:67-85.

Johnson MK, Hashtroudi S & Lindsay DS (1993) Source monitoring. *Psychological Bulletin* 114:3-28.

Keefe RSE, Arnold MC, Bayen UJ, Harvey PD (1999) Source monitoring deficits in patients with schizophrenia; a multinomial modelling analysis. *Psychological Medicine* 29:903-914.

Kosslyn SM (1994) *Image and brain.* Cambridge, MA: The MIT Press.

Kosslyn SM, Cave CB, Provost D, Von Gierke S (1988) Sequential processes in image generation.

Cognitive Psychology 20:319-343.

Kosslyn SM, Sukel KE, Bly BM (1999) Squinting with the mind's eye: effects of stimulus resolution on imaginal and perceptual comparisons. *Memory & Cognition* 27:276-287.

McKay CM, Headlam DM, Copolov DL (2000) Central auditory processing in patients with auditory hallucinations. *American Journal of Psychiatry* 157:759-766.

Mehta Z, Newcombe F, De Haan EHF (1992) Selective loss of imagery in a case of visual agnosia. *Neuropsychologia* 30:645-655.

Mintz S, Alpert M (1972) Imagery vividness, reality testing, and schizophrenic hallucinations. *Journal of Abnormal Psychology* 79:310-316.

Morrison AP, Haddock G (1997) Cognitive factors in source monitoring and auditory hallucinations. *Psychological Medicine* 27:669-679.

Murnane, K & Bayen UJ (1996) An evaluation of empirical measures of source identification. *Memory & Cognition* 24:417-428.

Robertson IH, Ward T, Ridgeeway V, et al. (1996) The structure of normal human attention: the test of everyday attention. *Journal of the International Neuropsychological Society*, *2*, 525-534.

Roman R, Landis C (1945) Hallucinations and mental illness. *Journal of Nervous and Mental Disease* 102:327-331.

Seitz PFD, Molholm HB (1947) Relation of mental imagery to hallucinations. *Archives of Neurology and Psychiatry* 57:469-480.

Slade PD (1994) Models of hallucination: from theory to practice. In: A.S. David & J.C. Cutting (Eds), *The neuropsychology of schizophrenia.* Hove: Psychology Press.

Slade PD, Bentall RP (1988) *Sensory deception; a scientific analysis of hallucination*. Baltimore: John Hopkins University Press.

Snodgrass JG, Vanderward M (1980) A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity and visual complexity. *Journal of Experimental Psychology: Learning Memory and Cognition* 6:174-215.

Starker S, Jolin A (1982) Imagery and hallucinations in schizophrenic patients. *Journal of Nervous and Mental Disease* 170:448-451.

Chapter 16

Controversies and Discussions 4

Hallucinations and the cerebral hemispheres

Aleman, A. (in press). Hallucinations and the cerebral hemispheres. *Journal of Psychiatry & Neuroscience.*

In his thought-provoking commentary, Dr. Sher (*J Psychiatry Neurosci* 2000;25:239-240) draws attention to the recent suggestion by Olin (1999) that neuroimaging studies would confirm the hypothesis of hallucinations arising from a bicameral mind. More specifically, according to Olin two recent studies on the neuroanatomical basis of hallucinations in schizophrenia revive Julian Janes' theories, who in his 1976 book *The origin of consciousness in the breakdown of the bicameral mind* hypothesized that human beings had no consciousness until 1000 BC. Instead, their behavior was controlled by a "bicameral mind", with the left hemisphere as the site for speech, and hallucinations (voices of gods and demons) arising from the right hemisphere. However, of the two studies (Lennox et al. 1999; Dierks et al. 1999) cited by Olin, only one concluded that auditory hallucinations are associated with right hemisphere activation. This was the study by Lennox and colleagues which concerned one patient. The study by Dierks and co-workers concerned 3 patients, two of which showed predominantly left activation of the transverse temporal gyrus (these patients were right-handed), whereas the third showed right activation of this gyrus (this patient was left-handed). Dierks et al. indicate that "this result is suggestive of a particular role for the language-dominant hemisphere in the generation of auditory hallucinations" (p. 618), although they caution that the small sample size does not permit strong conclusions. Thus, the results of this particular study appear to be in *contradiction* with Janes' hypothesis of distinct roles of both hemispheres in language vs. hallucinations, rather than supporting it. In addition, a number of other neuroimaging studies concerning auditory hallucinations, which are not taken into account by Olin, did not reveal a special role for the right hemisphere in auditory hallucinations (Silbersweig et al. 1995; McGuire et al. 1993).

On the basis of the available evidence it must be concluded that the intriguing theories of Janes lack convincing support. Research on hallucinations should therefore focus on more "down-to-earth" hypotheses, for example, concerning cognitive processes like reality monitoring and mental imagery (e.g., Johns & McGuire, 1999).

References

Dierks, T., Linden, D.E., Jandl, M., et al. (1999). Activation of Heschl's gyrus during auditory hallucinations. *Neuron, 22,* 615-21.

Johns LC, McGuire PK. Verbal self-monitoring and auditory hallucinations in schizophrenia. *Lancet* 1999;353:469-470.

Lennox, B.R., Bert, S., Park, G., Jones, P.B., Morris, P.G. (1999). Spatial and temporal mapping of neural activity associated with auditory hallucinations. *Lancet, 353*, 644.

McGuire, P.K., Shah, G.M., & Murray, R.M. (1999). Increased blood flow in Broca's area during auditory hallucinations in schizophrenia. *Lancet, 342*, 703-706.

Olin, R. (1999). Auditory hallucinations and the bicameral mind. *Lancet, 354*, 166.

Silbersweig, D.A., Stern, E., Frith, C., et al. (1995). A functional neuroanatomy of hallucinations in schizophrenia. *Nature*, *378*, 176-179.

Chapter 17

Summary and conclusions

The research reported in the present thesis concerned the neurocognitive basis of hallucinations. Specifically, we focused on mental imagery, its neural correlates, and its relation to hallucinatory experiences in non-psychiatric participants and in participants with a diagnosis of schizophrenia. First, however, we reviewed cognitive dysfunction in schizophrenia in relation to symptom dimensions, to clarify the nature of general cognitive disability in schizophrenia.

Cognitive dysfunction in schizophrenia

Based on quantitative analyses and integration of the published evidence (*chapter 2*), we concluded that memory impairment in schizophrenia is of large magnitude, and not importantly affected by age, medication, duration of illness, patient status, severity of psychopathology or positive symptoms. Negative symptoms showed a small, but significant relation with memory impairment. Indeed, consensus is emerging that memory is a major domain of disability in schizophrenia, with implications for social and vocational functioning (Green & Nuechterlein, 1999). The meta-analysis was not able to address the question whether attentional dysfunction could underlie the memory impairment, as few studies have examined this in a design including a healthy control group. Recently, evidence has been presented that reduced speed of information processing may contribute substantially to memory dysfunction; even more so than deficits in selective attention (Brébion et al., 2000a; Krabbendam, 2000). No evidence for a relation between positive symptoms and memory impairment was observed in the meta-analysis. With regard to the mechanisms involved in hallucinations, this may imply that a non-specific failure in long-term or short-term memory factors can not account for hallucinations.

In *chapter 3*, meta-analyses of the relation between schizophrenia symptom dimensions and executive and attentional performance were presented. The weighted correlations across studies were only significant for negative and disorganisation dimensions. However, the correlations were small in magnitude. These typical weak associations were interpreted as evidence for a relative independence of executive and attentional functioning on the one hand and symptom dimensions on the other hand. Recent models of schizophrenia have also suggested that (clustered) psychiatric symptoms are to a large extent independent of cognitive deficits (Green & Nuechterlein, 1999). Positive symptoms (a category that includes hallucinations) did not show associations with traditional measures of cognitive dysfunction, which calls for a more detailed analysis of cognitive processes that might be involved in hallucinations.

After concluding that weak relations exist between schizophrenia syndromes and classical neuropsychological measures, we suggest the next step to be 1) investigate symptoms rather than syndromes, and 2) include very specific tests on the basis of theories regarding detailed cognitive mechanisms, rather than investigating broad constructs such as “attention” and “executive function”.

Hallucinatory experiences and mental imagery in non-psychiatric individuals

Investigating hallucinatory experiences and their cognitive basis in non-psychiatric individuals is a useful research strategy, as it avoids the confounding factors associated with psychopathology. A limitation might be that these hallucinatory experiences are less pronounced and do not interfere with normal functioning.

The structure of hallucinatory predisposition was investigated in a sample of 243 college students who completed the Launay-Slade Hallucination Scale (*chapter 5*). Factor analyses revealed three factors: (1) hallucinatory experiences, (2) perceived externality of thought, and (3) vivid daydreams. These results suggest that hallucinatory predisposition is a multi-dimensional construct. Future research may focus on the possibility of differential relations between these three factors and cognitive processes in patients with hallucinations. In addition, this study clearly shows that hallucinations may be seen as existing on a continuum with normal mental events (Slade & Bentall, 1988), given that daydream experiences were shown to correlate highly with the total LSHS score (which mainly consists of hallucination items).

Chapter 6 and *chapter 7* will be discussed together, as they were aimed at the same question: is hallucinatory predisposition associated with increased vividness of mental imagery? *Chapter 6* investigated the relation between subjective and objective indices of vividness of mental imagery and disposition towards hallucination in a sample of 74 non-selected college students. *Chapter 7* concerned a more detailed investigation, in which a high hallucination-prone group and a low hallucination-prone group were selected from a large sample. These two groups were then contrasted on six behavioral measures of imagery vividness. Both studies (chapters 6 and 7) converged in their results: subjects that were prone towards hallucination did not differ from the control subjects on the behavioral imagery measures. However, on introspective measures of imagery vividness (Marks, 1973; Richardson, 1969) hallucination-prone subjects rated their imagery as significantly more vivid than non-hallucination-prone subjects. Thus, these latter results are in accordance with the vivid imagery hypothesis. However, caution is needed, given the problems associated with introspection. Such problems include demand characteristics, individual differences in the conception of “vividness”, response tendency, and insight into one’s own psychological processes. Moreover, the experiences targeted by the LSHS and by such imagery questionnaires are highly similar phenomenologically. Slade & Bentall (1988) have indicated that explaining hallucinatory experiences with subjectively rated imagery vividness may border to circularity. Findings reported in this thesis clearly underline this warning.

In the second experiment (chapter 7) we observed larger correlations between imagery and perception in the hallucination-prone group compared to the control group. We think that this finding may support the plausibility of an interpretation in terms of processes that are involved in discriminating internal and external generated information, termed reality discrimination. The finding can be interpreted to imply that imagery and perception are more closely related in hallucination-prone subjects, and thus more difficult to distinguish from one another. Evidently, as this does not seem to be due to an increased vividness of mental images, it may originate from less distinctive meta-cognitive processes associated with internally versus externally generated information (cf. Bentall, 1990). Indeed, Rankin & O’Caroll (1995) observed reality monitoring biases in hallucination-prone college students compared to control students.

Mental imagery, hallucinations and the brain

According to Kosslyn (1994), imagery and perception basically share the same processing structures in the brain. Kosslyn’s theory of functional overlap of imagery and perception is highly relevant to the imagery hypothesis of hallucination, because if imagery and perception share the same processing systems, this enhances the plausibility that under certain circumstances an image can be mistaken for a percept. Up to now, studies on the functional neuroanatomy of auditory imagery have been limited to musical imagery (Zatorre et al. 1996; Halpern & Zatorre, 1999). It is suspected that other forms of auditory imagery will depend on the same auditory association areas as revealed by these two PET-studies. *Chapter 9* provides indirect support for this assumption. We hypothesized that music training may be associated with improved auditory imagery ability. Performance of musically trained subjects was compared with performance of musically naïve subjects on three measures, concerning musical imagery, non-musical auditory imagery, and a comparable measure of visual imagery, respectively. The musically trained group did not only perform better on the musical imagery task (as was expected) but also outperformed the musically naïve subjects on the non-musical auditory imagery task. In contrast, the two groups did not differ on the visual imagery task. We interpreted the results in light of the theoretical proposals about music processing and brain activity advanced by Rauscher and colleagues (e.g., Rauscher, Shaw & Ky, 1995). Interestingly, the notion that auditory imagery relies on auditory association areas in the temporal lobe, and the fact that neuroimaging studies of hallucinations show activity in these areas (chapter 13) is at least consistent with the hypothesis that imagery processes may play a role in the genesis of hallucinations.

Results of research on the functional neuroanatomy of visual mental imagery are mixed (for review, see Mellet et al., 1998; Behrmann, 2000). *Chapter 10* concerns a strong test of the hypothesis that visuospatial imagery (in contrast to merely depictive imagery, cf. Kosslyn et al., 1999) relies on the parietal cortex, not the visual cortex. Functional MRI and repetitive Transcranial Magnetic Stimulation (rTMS) were used to determine areas of activation, and whether such areas are crucially involved in the task performance. For each of the 5 subjects included in the fMRI study, activated voxels were observed in right posterior parietal, but not visual, cortex during visuospatial imagery (relative to a perception control condition with the same stimuli). In addition, rTMS (8 subjects) significantly delayed reaction times when applied over the P4 electrode scalp position (corresponding to posterior parietal cortex), but did not affect reaction times when applied over the occipital cortex. The results indicate that imagery does not necessarily rely on activation of sensory areas, but may share higher order brain areas with perception (cf. Trojano et al., 2000). With respect to hallucinations, most studies also fail to find activation of primary sensory cortex (e.g., Silbersweig et al., 1995; Shergill et al., 2000a; but see Dierks et al. 1999), whereas all studies report activation of modality-specific association areas (chapter 13).

Finally, the neuroanatomy of hallucinations was investigated with rTMS (*chapter 11*). Besides a fundamental hypothesis, i.e., whether the left temporal cortex is involved in auditory hallucinations, this study addressed a clinically relevant question: is rTMS effective in the treatment of medication-resistant hallucinations? Nine hallucinating patients with schizophrenia were stimulated 20 minutes daily over the left auditory cortex with TMS at 1Hz for ten treatment days. At baseline, after 5 days and after 10 days a standardized hallucination rating scale was completed. In addition, at baseline and after the treatment a wide range of verbal and nonverbal neuropsychological measures was administered. A statistically significant improvement was observed on the hallucination scale and on a measure of auditory imagery. No difference between pre- and post-treatment testing was observed on the other neuropsychological variables. The fact that rTMS over the temporal lobe affected auditory imagery is in accordance with our suggestion in chapter 10 that this cortical area is involved in auditory imagery processing. Complementing neuroimaging studies of hallucination, these preliminary findings for the first time show that left secondary auditory cortex may necessarily be involved in hallucinations (a number of previous PET and fMRI studies also found left temporal activation, but whereas these techniques reveal the cortical structures activated during hallucinations, they cannot establish whether this activation is essential to it). Although caution is needed because of the lack of a placebo-control, we tentatively conclude that TMS may have the potential to improve hallucination severity in patients with schizophrenia. In a placebo-controlled design, Hoffman et al. (2000a) recently reported that rTMS over the left temporo-parietal cortex was effective in reducing hallucination severity in patients with schizophrenia.

Cognitive basis of hallucinations in schizophrenia

Chapter 13 reviewed theory and findings with regard to hallucinations in schizophrenia. The phenomenology of hallucinations was discussed and it was concluded that, although there may be a large variability between patients in formal characteristics of hallucinations (frequency, location, clearness, loudness), most patients report high levels of conviction about the reality of the sensory stimuli, clarity of content, and lack of volitional control. In addition, for a majority of patients the contents of hallucinations are emotionally threatening. With regard to the neuroanatomy of auditory hallucinations it was concluded that, whereas a minority of studies report involvement of subcortical areas, language-production areas, and primary sensory cortex, all studies up to now report activity in the temporal lobe, more specifically in the middle or superior gyri. This implies a role of auditory-association areas, which may also include areas involved in language-perception (cf. the review by Weiss & Heckers, 1999). For visual hallucinations, activity has been reported in subcortical areas and in secondary visual areas.

Cognitive theorizing on hallucinations has taken different approaches in the past decades. Whereas a number of researchers focused on abnormalities in the production of inner speech, others have implied defective speech perception, and still others biases in the meta-cognitive skill of reality monitoring. Finally, the hypothesis that vivid mental imagery may underlie hallucinations (Galton, 1883) has recently been revived. Frith's verbal self-monitoring hypothesis (Frith, 1992), in which hallucinations are thought to arise from failures in the monitoring of own intentions during inner speech can be seen as an integration of the inner speech hypothesis and the reality monitoring hypothesis. It also overlaps to some extent with the speech-perception hypothesis, e.g., both approaches predict that hallucinations may be associated with errors in speech tracking. More recently, Grossberg (2000) proposed a mechanism by which "chronically hyperactive volitional signals" could lead to the generation of conscious sensory experiences by top-down sensory expectations that are not under volitional control. This approach can be seen as an integration of the imagery hypothesis (which bears upon strong top-down influences) and the speech perception account (which states that pronounced linguistic expectations can generate perceptual outputs), although it is not limited to auditory-verbal hallucinations (as is the case for the speech perception account).

Most empirical research has concentrated on the reality monitoring hypothesis and on the verbal self-monitoring/speech perception approach (cf. David, 1999). Findings have been reported that are consistent with these approaches (e.g., Morrison & Haddock, 1997; Johns & McGuire, 1999; Hoffman et al., 1999). However, there are a number of criticisms with regard to these hypotheses. First, it has been suggested that reality monitoring errors are a consequence rather than a cause of hallucinations (Hoffman et al., 2000). The persistent experience of hallucinations may condition patients to expect an external, non-self locus of control for particular thoughts. In addition, even though reality monitoring deficits are assumed to play a causal role, they may not provide a satisfactory account of hallucinations on their own, because reality monitoring deficits have also been associated with delusional thinking (Frith, 1987), thought disorder (Harvey, 1985) and have been reported in patients who are not characterized by positive symptoms (Keefe et al., 1999; Vinogradov et al., 1997). Thus, an additional alteration may be necessary for hallucinations to arise. With regard to the verbal self-monitoring hypothesis, an important study failed to observe such deficits in patients with hallucinations (Leudar et al., 1994).

Very relevant points of concern have been raised by Behrendt (1998): "One could, however, doubt whether thoughts, inner speech, verbal images, or memories transform into external experiences just by virtue of their misattribution to an external origin. A difficult question to answer is how these mental events acquire acoustic qualities that are characteristic for verbal hallucinations (tone, loudness, etc.). Moreover, theories have to account for the fact that verbal hallucinations resemble voices of particular people and not just the hallucinator's voice, as would be expected from an alienation of thoughts or inner voice. Furthermore, one needs to explain how mental events, in becoming verbal hallucinations, could acquire a grammatical structure that is typical for hallucinations in schizophrenia. Hallucinatory voices tend to appear in the grammatical form of a third person discussing or commenting about the patient. Self-generated mental events do not normally obey grammatical laws of interpersonal communication." (p. 238). Clearly, an approach that focuses on mental imagery may overcome the limitations that are listed here. For example, the hypothesis that, in hallucinations, vivid mental images are mistaken for percepts does not neglect the fact that mental events acquire sensory properties. In addition, whereas inner speech, in contrast to verbal hallucinations, is usually not in the third person grammatical form, auditory-verbal imagery may well occur in second or third person grammatical forms. We therefore conducted a thorough investigation of imagery vividness (with the use of behavioral measures) in patients with and without hallucinations.

In a cognitive neuropsychiatric case-study design, we investigated whether the normal balance between imagery and perception performance would be distorted in the modality of hallucination in a patient with continuous auditory hallucinations, Mr. A. (*chapter 14*). In normal conditions, when performance on an imagery and a perception condition of the same task is compared, subjects show better performance in the perception condition (the perception-superiority effect). In contrast to five comparison patients without hallucinations, who showed the normal perception-superiority effect, Mr. A had higher imagery scores, relative to perception, on auditory tasks. This was not the case for visual tasks (for these tasks he showed the normal perception superiority, which we expected, as he hallucinated in the auditory, not visual, modality). Expanding on theoretical suggestions from Böcker et al. (2000) and from our earlier work (chapter 7) we propose that an *imbalance* between imagery and perception might be a potential underlying mechanism in reality monitoring errors. Indeed, this new approach, that stresses the balance between imagery and perception, moves on from the traditional hypotheses of either defective imagery (Evans et al., 2000), vivid imagery (Mintz & Alpert, 1972), or defective perception (cf. Böcker et al. 2000; McKay, Headlam & Copolov, 2000). These earlier hypotheses are all stated in rather absolute terms, whereas the "balance-hypothesis" concerns relative relations, which may have more explanatory power in the light of Johnson & Raye's model of reality monitoring (1981). According to Johnson and Raye (1981) percepts, which originate from externally presented stimuli, are characterized by more detailed sensory, contextual and semantic information than internally generated images. Confusions between percepts and images may arise when mental images become more rich in perceptual detail, or when percepts become less rich. Clearly, it is the relative relation between images and percepts that matters here, not the absolute level.

Chapter 15 investigated imagery/perception relations in a group study. Measures included multiple behavioral tasks of auditory and visual mental imagery and perception, a measure of reality monitoring and a signal detection measure. Hallucinating patients were contrasted with non-hallucinating patients, after controlling for attentional factors that may influence task performance. Consistent with a body of previous research, hallucinating patients made significantly more errors in source discrimination than non-hallucinating patients (Bentall et al., 1991; Morrison & Haddock, 1997; Johns & McGuire, 1999; Böcker et al. 2000; Brébion et al., 2000b; Franck et al. 2000). However, no differences emerged on any of the mental imagery measures. The results corroborate earlier studies by Böcker et al. (2000) and Evans et al. (2000), who also failed to find between-group differences on multiple measures of imagery. The fact that our study included more measures, larger patient groups, patients with more severe hallucinations, a subgroup of patients that had never hallucinated at all, and finally, controlled statistically for non-specific attentional factors, allows us to conclude with more confidence that patients with hallucinations do not have more vivid imagery relative to perception than patients without hallucinations. Thus, there is no trait-like alteration in mental imagery that eventually leads to hallucinations.

Within the framework provided by Johnson & Raye (1981), two possibilities remain to be investigated more thoroughly: (1) It could be hypothesized that increased vividness of imagery is strictly confined to the hallucinatory state, i.e. occurs only during the actual experience of hallucinations. Our case-study provides some evidence for this hypothesis. (2) According to Johnson & Raye (1981; Johnson et al., 1993), reality discrimination difficulties can arise in one of two ways: the images and percepts are less distinctive with regard to their sensory characteristics, or they are less distinctive with regard to the meta-cognitive processes associated with each (e.g., generating mental images requires more cognitive effort). The second possibility has received little attention hitherto, in relation to hallucinations. Indeed, the research of Heilbrun (1980) merits extension: he reported that patients with hallucinations are less familiar with the properties of their own thinking than non-hallucinating patients, which would make hallucinating patients more likely to mislabel the source of their thoughts.

Final Comments

The enigma of hallucination has not been solved yet. Notwithstanding, the studies described in this thesis have the potential of furthering our knowledge of the cognitive and neuroanatomical basis of hallucinations. We demonstrated that a symptom-oriented, cognitive neuropsychiatry approach may contribute significantly to the research into hallucinations. Specifically, our data suggest that a state-dependent imbalance between imagery and perception may play a role in the confusion between internally generated and externally presented stimuli. Such an imbalance may be strictly limited to periods in which hallucinations are actually experienced, as we observed an imbalance between imagery and perception only in a continuous hallucinating patient, not in patients that hallucinated during the week prior to testing. Indeed, the findings in normal and psychiatric samples strongly suggest that there is no stable, trait-like alteration in mental imagery that eventually leads to hallucinations. In our research, we focused on universal cognitive mechanisms that might underlie the phenomenon of hallucination. It would be interesting for future research to take into account the contents of hallucination, and relate this, for example, to experimental psychological measures of emotion-processing.

It was concluded that the temporal cortex plays an important role in auditory hallucinations, and secondary visual areas in visual hallucinations. This is consistent with the hypothesis of a state-dependent alteration of imagery processes, as mental images have been shown to be processed in such modality-specific association areas. Future functional neuroimaging studies must focus on these regions and their connectivity by investigating group-differences associated with hallucinations during different cognitive tasks (involving reality monitoring, mental imagery/perception comparisons, etc.). Two important neurophysiological aspects were not addressed in our research, and deserve further investigation (cf. Asaad & Shapiro, 1986): the relation between the neurophysiology of dreams and that of hallucinations, and neurotransmitter systems involved in hallucinations (e.g., postsynaptic catecholamine, indoleamine, or a neuroregulatory imbalance among normally interacting neurotransmitter systems).

With respect to clinical practice, our findings have a number of implications. First, memory impairment is extensive in many patients with schizophrenia, which will affect daily functioning and the type of therapies that are indicated (for example, certain insight-related therapies might be too demanding). Second, although not acknowledged by a substantial number of clinicians, hallucinations are not necessarily pathological (cf. Honig et al., 1998). For purposes of diagnosis, it may not be the presence or absence of hallucinatory experiences that matters, but rather whether such hallucinations are experienced as unpleasant, emotionally demanding or interfere with normal functioning. Third, there is increasing scientific basis for developing cognitive behavioral therapies aimed at improving reality monitoring skills. Indeed, such therapies are being developed, and the positive results of the first evaluation studies indicate that they will become an important treatment strategy in the near future (for reviews, see Haddock et al., 1998; Shergill, Murray & McGuire, 1998). Moreover, our research demonstrated that sensory factors may contribute to the mechanism of hallucinations. Therefore, it may be worth the effort to focus cognitive behavior therapy not only on content-related factors, but also on distinguishing between differential sensory qualities of internally generated and externally presented perceptual material. Finally, rTMS may be a new tool in the treatment of medication-resistant hallucinations, although more research is needed to establish its efficacy, moderating factors (e.g., atypical medication), and possible contra-indications.

References

Asaad, G., Shapiro, B. (1986). Hallucinations: theoretical and clinical overview. *American Journal of Psychiatry*, 143, 1088-1097.

Behrendt, R.-P. (1998). Underconstrained perception: a theoretical approach to the nature and function of verbal hallucinations. *Comprehensive Psychiatry, 39,* 236-248.,

Behrmann, M. (2000). The mind's eye mapped onto the brain's matter. *Current Directions in Psychological Science, 9*, 50-54.

Bentall, R.P. (1990). The illusion of reality: a review and integration of psychological research on hallucinations. *Psychological Bulletin, 107*, 82-95.

Bentall, R.P., Baker, G., & Havers, S. (1991). Reality monitoring and psychotic hallucinations. *British Journal of Clinical Psychology, 30,* 213-222.

Böcker, K.B.E., Hijman, R., Kahn, R.S., & De Haan, E.H.F. (2000). Perception, mental imagery and reality discrimination in hallucinating and nonhallucinating schizophrenic patients. *British Journal of Clinical Psychology, 39,* 397-406.

Brébion, G., Smith M.J., Gorman J.M., Malaspina D., Sharif Z., & Amador, X. (2000a). Memory and schizophrenia: differential link of processing speed and selective attention with two levels of encoding. *Psychiatry Research, 34,* 121-7

Brébion, G., Amador, X., David, A., Malaspina, D., Sharif, Z., & Gorman, J.M. (2000b). Positive symptomatology and source-monitoring failure in schizophrenia - an analysis of symptom-specific effects *Psychiatric Research, 95,* 119-131.

David, A.S. (1999). Auditory hallucinations: phenomenology, neuropsychology and neuroimaging update. *Acta Psychiatrica Scandinavica, 99 (Suppl. 394),* 95-104.

Dierks, T., Linden, D.E., Jandl, M., et al. (1999). Activation of Heschl's gyrus during auditory hallucinations. *Neuron, 22,* 615-621.

Evans, C.L., McGuire, P.K., David, A.S., 2000. Is auditory imagery defective in patients with auditory hallucinations? *Psychological Medicine, 30,* 137-148.

Franck, N., Rouby, P., Daprati, E., et al. (2000). Confusion between silent and overt reading in schizophrenia. *Schizophrenia Research, 41,* 357-364.

Frith, C.D. (1987). The positive and negative symptoms of schizophrenia reflect impairments in the perception and initiation of actions. *Psychological Medicine, 17,* 631-648.

Frith, C.D. (1992). *The cognitive neuropsychology of schizophrenia.* Hove: Lawrence Erlbaum.

Galton, F. (1883). *Inquiries into human faculty and its development*. London: McMillan.

Green, M.F. & Nuechterlein, K.H. (1999). Should schizophrenia be treated as a neurocognitive disorder? *Schizophrenia Bulletin, 25,* 309-319.

Grossberg, S. (2000). How hallucinations may arise from brain mechanisms of learning, attention, and volition. *Journal of the International Neuropsychological Society, 6,* 583-592.

Haddock, G., Tarrier, N., Spaulding, W., et al. (1998). Individual cognitive-behavior therapy in the treatment of hallucinations and delusions: a review. *Clinical Psychology Review, 18,* 821-838.

Halpern, A.R., Zatorre, R.J., When that tune runs through your head: a PET investigation of auditory imagery for familiar melodies. *Cerebral Cortex*, 1999, 9, 697-704.

Harvey, P.D. (1985). Reality monitoring in mania and schizophrenia. The association of thought disorder and performance. *Journal of Nervous and Mental Disease, 173,* 67-73.

Heilbrun, A.B. (1980). Impaired recognition of self-expressed thought in patients with auditory hallucinations. *Journal of Abnormal Psychology, 89,* 728-736.

Hoffman, R.E., Rapaport, J., Mazure, C.E., Quinlan, D.M. (1999). Selective speech perception alterations in schizoprenic patients reporting hallucinated "voices". *American Journal of Psychiatry, 156,* 393-399.

Hoffman, R.E., Boutros, N.N., Hu, S., Berman, R.M., Krystal, J.H., & Charney, D.S. (2000a). Transcranial magnetic stimulation and auditory hallucinations in schizophrenia. *Lancet, 355,* 1073-1075.

Hoffman, R.E., Rapaport, J., Mazure, C.E., Quinlan, D.M. (2000b). Non-language cognitive deficits and hallucination in schizophrenia: Reply to Aleman and De Haan. *American Journal of Psychiatry, 157***,** 487-488.

Honig, A., Romme, M.A.J., Ensink, B.J., Escher, S.D., Pennings, M.H.A., & deVries, M.W. (1998). Auditory hallucinations: A comparison between patients and nonpatients. *Journal of Nervous and Mental Disease, 186,* 646-651.

Johns, L.C., McGuire, P.K. (1999). Verbal self-monitoring and auditory hallucinations in schizophrenia. *Lancet, 353,* 469-470.

Johnson, M.K., & Raye, C.L. (1981). Reality monitoring. *Psychological Review, 88,* 67-85.

Johnson, M.K., Hashtroudi, S. & Lindsay, D.S. (1993). Source monitoring. *Psychological Bulletin, 114*, 3-28.

Keefe, R.S.E., Arnold, M.C., Bayen, U.J. & Harvey, P.D. (1999). Source monitoring deficits in patients with schizophrenia; a multinomial modelling analysis. *Psychological Medicine, 29,* 903-914.

Kosslyn, S.M. (1994). *Image and brain.* Cambridge, MA: MIT Press.

Kosslyn, S.M., Pascual-Leone, A., Felician, O., et al. (1999). The role of area 17 in visual imagery: convergent evidence from PET and rTMS. *Science, 284,* 167-170.

Krabbendam, L. (2000). *Cognitive functions in schizophrenia.* (Doctoral thesis). Maastricht: Neuropsych Publishers.

Leudar, I., Thomas, P. & Johnston, M. (1994). Self-monitoring in speech production: effects of verbal hallucinations and negative symptoms. *Psychological Medicine, 24,* 749-761.

Marks, D.F. (1973). Visual imagery differences in the recall of pictures. *British Journal of Psychology, 64,* 17-24.

McKay, C.M., Headlam D.M., & Copolov D.L. (2000). Central auditory processing in patients with auditory hallucinations. *American Journal of Psychiatry, 157*, 759-766.

Mellet, E., Petit, L., Mazoyer, B., Denis, M., & Tzourio, N. (1998). Reopening the mental imagery debate: lessons from functional anatomy. *NeuroImage, 8,* 129-139.

Mintz, S., & Alpert, M. (1972). Imagery vividness, reality testing, and schizophrenic hallucinations. *Journal of Abnormal Psychology, 79,* 310-316.

Morrison, A.P., & Haddock, G. (1997). Cognitive factors in source monitoring and auditory hallucinations. *Psychological Medicine, 27,* 669-679.

Rankin, P.M., O'Carroll, P.J. (1995). Reality discrimination, reality monitoring and disposition towards hallucination. *British Journal of Clinical Psychology, 34,* 517-528.

Rauscher, F.H., Shaw, G.L., & Ky, K.N. (1995).Listening to Mozart enhances spatial-temporal reasoning: towards a neurophysiological basis. *Neuroscience Letters*, 185, 44-47.

Richardson, A. (1969). *Mental imagery.* New York: Springer.

Shergill, S.S., Murray, R.M., & McGuire, P.K. (1998). Auditory hallucinations: a review of psychological treatments. *Schizophrenia Research, 32,* 137-150.

Shergill, S.S., Brammer, M.J., Williams, S.C.R., Murray, R.M., & McGuire, P.K. (2000). Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. *Archives of General Psychiatry, 57,* 1033-1038.

Silbersweig, D.A., Stern, E., Frith, C., et al. (1995). A functional neuroanatomy of hallucinations in schizophrenia. *Nature, 378*, 176-179.

Slade, P.D., & Bentall, R.P. (1988). *Sensory deception; a scientific analysis of hallucination*. Baltimore: John Hopkins University Press.

Trojano, L., Grossi, D., Linden, D.E.J., et al. (2000). Matching two imagined clocks: The functional anatomy of spatial analysis in the absence of visual stimulation. *Cerebral Cortex, 10,* 473-481.

Vinogradov, S., Willis-Shore, J., Poole, J.H. et al. (1997). Clinical and neuro-cognitive aspects of source monitoring errors in schizophrenia. *American Journal of Psychiatry, 154,* 1530-1537.

Weiss, A.P., & Heckers, S. (1999). Neuroimaging of hallucinations: a review of the literature. *Psychiatry Research: Neuroimaging, 92,* 61-74.

Zatorre, R.J., Halpern, A.R., Perry, D.W., Meyer, E. & Evans, A.C. (1996). Hearing in the mind's ear: a PET investigation of musical imagery and perception. *Journal of Cognitive Neuroscience, 8*, 29-46.

Samenvatting

Hallucinaties zijn een merkwaardig psychologisch verschijnsel. Het betreft een vorm van sensorisch bedrog, die bij patiënten met schizofrenie het dagelijks functioneren belemmert en de kwaliteit van leven negatief beïnvloedt. Het brein neemt iets waar: een geluid, een stem, een beeld. Maar in werkelijkheid is er niets. Hoe is dat mogelijk? Hoewel er geen afdoende psychologische verklaring is voor het optreden van hallucinaties, zijn onderzoekers het er over eens dat er sprake is van het foutief toewijzen van intern gegeneerde informatie aan een externe bron. Het doel van het in dit proefschrift beschreven onderzoek is om meer inzicht te verkrijgen in de mogelijke cognitieve en neurobiologische mechanismen die hiertoe kunnen leiden.

Het onderzoek is verricht vanuit de cognitief-neuropsychiatrische benadering, waarbij er van uit gegaan wordt dat hallucinaties in isolatie bestudeerd kunnen worden. De voornaamste hypothese die onderzocht werd stelt dat (1) hallucinaties op een continuum van psychologische processen liggen, die loopt van subjectieve ervaringen bij mensen uit de gezonde populatie tot de ervaringen die patiënten met schizofrenie rapporteren, en (2) dat hallucinaties secundair zijn aan gestoorde cognitieve verwerkingsprocessen. Dergelijke cognitieve stoornissen kunnen gerelateerd worden aan specifieke hersengebieden die in verband gebracht worden met schizofrenie. Meer in het bijzonder werd de hypothese getoetst dat een abnormale mentale verbeelding cruciaal is bij de foutieve toekenning van intern gegenereerde ervaringen naar een externe bron.

Eerst werden cognitieve stoornissen die voorkomen bij patiënten met schizofrenie in het algemeen door middel van kwantitatief literatuuronderzoek samengevat. Vervolgens werden hallucinatoire ervaringen onderzocht bij mensen zonder psychiatrische afwijking en werd de relatie tussen dergelijke ervaringen en de levendigheid van de mentale verbeelding gemeten. Daarna werd ingegaan op de neurale basis van mentale verbeelding en van hallucinaties. Tenslotte werd onderzocht of patiënten met hallucinaties verschillen van patiënten zonder hallucinaties op diverse maten voor waarneming, mentale verbeelding en het vermogen tot brondiscriminatie.

Er spelen een aantal controversen in het cognitieve schizofrenie onderzoek, die betrekking hebben op methodologische en conceptuele vragen. Aan het eind van elke sectie van het proefschrift wordt dit geïllustreerd door een kritische evaluatie van een controversieel punt, behorend tot het onderwerp van de sectie. Dit zijn de hoofdstukken 4, 8, 12 en 16.

Cognitieve functiestoornissen bij schizofrenie

In *hoofdstuk 2* wordt op basis van een kwantitatieve integratie van gepubliceerde studies (meta-analyse) geconcludeerd dat er bij schizofrenie sprake is van een aanzienlijke stoornis in diverse geheugenfuncties. Deze geheugenstoornissen worden niet noemenswaardig beïnvloed door leeftijd, medicatie, lengte van de ziekte, of de patiënt wel of niet opgenomen is of ernst van de symptomen. In tegenstelling tot negatieve symptomen lieten positieve symptomen geen verband zien met de ernst van de geheugenstoornis. Dit betekent dat hallucinaties en wanen niet verklaard kunnen worden door non-specifieke geheugenstoornissen. *Hoofdstuk 3* betrof een meta-analyse naar verbanden tussen symptoom dimensies van schizofrenie en het concentratie- en denkvermogen (volgehouden aandacht en mentale flexibiliteit). De resultaten lieten verbanden zien tussen negatieve symptomen en beide domeinen van neuropsychologisch functioneren. Disorganisatie symptomen waren alleen gerelateerd aan mentale flexibiliteit. Hierbij was het steeds zo dat hoe ernstiger de symptomen, hoe slechter de prestatie op de neuropsychologische taken was. De correlaties waren echter steeds klein. Positieve symptomen lieten geen verband zien met verminderd functioneren in de twee onderzochte cognitieve domeinen. Geconcludeerd werd dat symptoom dimensies grotendeels onafhankelijk zijn van stoornissen in de klassieke neuropsychologische functiedomeinen, in overeenstemming met een recent model. Een volgende stap is om het onderzoek te richten op individuele symptomen en op gedetailleerde subprocessen die aan het licht gebracht zijn door de experimentele psychologie.

Hallucinatoire ervaringen en mentale verbeelding

In *hoofstuk 5* werd de factorstructuur van de Launay Slade Hallucinatie Schaal (LSHS) onderzocht, de meest gebruikte schaal om de dispositie tot hallucinatoire ervaringen te meten. De schaal werd afgenomen bij 243 studenten, waarvan ongeveer 5% bij vragen naar hallucinatoire ervaringen "zeker van toepassing" antwoordde, en 25% "waarschijnlijk van toepassing". Voorts bleken er drie dimensies te onderscheiden van de LSHS, die we aanduidden met "hallucinatoire ervaringen", "externe attributie van gedachten", en "levendige dagdromen". De resultaten ondersteunen de hypothese dat hallucinatoire ervaringen een continuüm vormen met normale psychologische processen.

Zowel *hoofdstuk 6* als *hoofdstuk 7* betreffen de vraag: is dispositie tot hallucinaties gerelateerd aan een sterkere levendigheid van het mentale verbeeldingsvermogen? In hoofdstuk 6 werd dit met een subjectieve en een objectieve taak voor levendigheid van de mentale verbeelding gemeten bij 74 studenten. Hoofdstuk 7 beschrijft een uitvoeriger onderzoek waarin een groep personen die hoog scoorde op gevoeligheid voor hallucinatie vergeleken werd met een groep die daar laag op scoorde (deze groepen waren geselecteerd uit een grote steekproef). Bij beide groepen werden zes gedragsmatige taken voor perceptie en mentale verbeelding afgenomen en een drietal introspectieve taken. Beide studies (hoofdstukken 6 en 7) lieten dezelfde resultaten zien: personen met een geneigdheid tot hallucineren verschilden niet van personen zonder deze geneigdheid op gedragsmatige taken van levendigheid van mentale verbeelding. Op de subjectieve (introspectieve) maten verschilden beide groepen echter wel - de groep met hallucinatoire ervaringen had een levendiger verbeelding. Aangezien de betreffende subjectieve verbeeldingslijsten en de gebruikte hallucinatielijst fenomenologisch verwante verschijnselen in kaart brengen, is dit wellicht niet zo verwonderlijk. Onderzoek met objectieve, gedragsmatige taken bij patiënten (met ernstiger en frequenter hallucinaties dan deze groepen) is noodzakelijk als uiteindelijke toets van de "mentale verbeeldingshypothese" van hallucinaties.

Mentale verbeelding, hallucinaties en het brein

Kosslyns theory van gedeelde processen bij perceptie en mentale verbeelding is relevant voor onderzoek naar de "mentale verbeel-dingshypothese" van hallucinaties. Wanneer perceptie en verbeelding dezelfde hersenstructuren activeren, verhoogt dit de plausibiliteit van de hypothese dat onder bepaalde omstandigheden hallucinaties kunnen ontstaan doordat perceptie en verbeelding niet goed van elkaar onderscheiden worden. Onderzoek met beeldvorming van hersenactiviteit heeft zich tot nu toe beperkt tot muzikale verbeelding en perceptie. Gedacht wordt dat dezelfde hersengebieden betrokken zijn bij andere vormen van auditieve verbeelding. In *hoofdstuk 9* wordt hier indirecte ondersteuning voor gegeven. Muzikaal getrainde proefpersonen werden vergeleken met proefpersonen zonder muzikale training op drie taken voor mentale verbeelding: een muzikale taak, een andere (niet-muzikale) auditieve taak en een vergelijkbare visuele taak. Onze voorspelling was dat de muzikaal getrainde groep niet alleen op de muzikale verbeeldingstaak beter zou presteren dan de controlegroep, maar ook op de niet-muzikale auditieve verbeeldingstaak (als deze inderdaad op dezelfde hersengebieden een beroep zou doen). De groepen zouden dan echter niet moeten verschillen op de visuele verbeeldingstaak (waar immers andere hersengebieden bij betrokken zijn). De resultaten waren conform deze voorspelling.

In een directer onderzoek werd in *hoofdstuk 10* de functionele neuro-anatomie van visuele mentale verbeelding onderzocht met behulp van functionele magnetische resonantie beeldvorming (fMRI) en repetitieve transcraniële magnetische stimulatie (rTMS). Hierbij werd geen activatie van de primaire schors gevonden, zoals voorspeld door sommige theorieën, maar wel betrokkenheid van de posterieure pariëtale schors. Dit werd door beide methoden bevestigd. Met betrekking tot hersenactiviteit tijdens hallucinaties vinden de meeste studies eveneens geen activiteit in primaire sensorische gebieden en wel in modaliteit-specifieke associatie cortex. *Hoofdstuk 11* onderzocht de effectiviteit van TMS over de linker auditieve cortex op het verminderen van hallucinaties. Deze studie kan daarmee tevens uitspraken doen over de neuro-anatomie van hallucinaties. Negen hallucinerende patiënten werden gedurende 10 dagen met TMS behandeld, 20 minuten per dag. Metingen voor en na de behandeling lieten een significante vermindering van de auditieve hallucinaties zien. Ook was er verbetering op een maat voor auditieve verbeelding. Hoewel voorzichtigheid geboden is, gezien het ontbreken van een placebo-controle, laten de resultaten zien dat TMS mogelijk ingezet kan worden als behandeling van medicatie-resistente hallucinaties. Overigens liet een recente placebo-gecontroleerde studie van TMS bij hallucinaties eveneens positieve resultaten zien.

Cognitieve basis van hallucinaties bij schizofrenie

Hoofdstuk 13 gaf een overzicht van theorie en empirische bevindingen met betrekking tot hallucinaties bij schizofrenie. Eerst werd de fenomenologie besproken. Hallucinaties kunnen in elke modaliteit voorkomen. Zo zijn er auditieve, visuele, tactiele, smaak- en geurhallucinaties. Bij schizofrenie zijn auditieve hallucinaties het meest frequent – zo'n 65% van de patiënten heeft er op enig moment van de ziekte last van (Slade & Bentall, 1988). Visuele hallucinaties komen minder voor, bij een kleine 20% van de patiënten. Minder dan 5% van de patiënten heeft hallucinaties in de overige modaliteiten. De meeste patiënten ervaren hallucinaties als onprettig en emotioneel bedreigend. Studies naar hersenactiviteit tijdens hallucinaties laten de betrokkenheid van subcorticale gebieden zien en met name van secundaire auditieve gebieden in de temporale schors (mediale en superieure gyrus), zowel in de rechter- als linkerhemisfeer. Ook bij visuele hallucinaties wordt voornamelijk activiteit gerapporteerd in de secundaire visuele gebieden. Cognitieve theorievorming werd uitvoerig beschreven. Deze theorievorming heeft zich gericht op taalverwerkingsprocessen, brondiscriminatie en mentale verbeelding. Sommige benaderingen betreffen een integratie van dergelijke hypotheses, een voorbeeld is de "verbal self-monitoring" theorie van Frith. Weinig studies hebben de balans tussen perceptie en verbeelding onderzocht.

In *hoofdstuk 14* werd een cognitief-neuropsychiatrische studie beschreven die expliciet met dit doel opgezet was, namelijk om te onderzoeken of een continu hallucinerende patiënt (auditieve hallucinaties) een disbalans tussen perceptie en mentale verbeelding zou laten zien, in vergelijking met patiënten zonder hallucinaties. Onder normale condities scoren mensen altijd hoger op een perceptie variant van een taak dan op een verbeeldings-variant (waarbij de proefpersoon hetzelfde moet doen, maar dan op basis van zijn verbeelding in plaats van op basis van aangeboden stimuli). Bij de continu hallucinerende patiënt vonden we echter het tegenovergestelde op twee auditieve taken, hij scoorde hier hoger op de verbeeldingsconditie dan op de perceptieconditie. Zoals voorspeld was dit echter niet het geval voor twee visuele taken, de modaliteit waarin hij niet hallucineerde. *Hoofdstuk 15* betrof een uitgebreider onderzoek onder 43 patiënten met schizofrenie. Hierbij werd een groep patiënten met hallucinaties vergeleken met een groep patiënten zonder hallucinaties op taken voor perceptie, verbeelding en brondiscriminatie. Patiënten werden in de hallucinerende groep ingedeeld als zij in de week voorafgaand aan het onderzoek hallucinaties hadden ervaren. Deze groep verschilde niet van de controlegroep (zonder hallucinaties) op maten voor de balans tussen perceptie en verbeelding. Wel was er een significant verschil tussen beide groepen op een maat voor brondiscriminatie: patiënten met hallucinaties hadden meer moeite om interne en externe bronnen van informatie uit elkaar te houden.

Conclusie

In *hoofdstuk 17* werden de belangrijkste bevindingen samengevat en de implicaties besproken voor de theorievorming, toekomstig onderzoek en de klinische praktijk. We vonden ondersteuning voor de notie dat hallucinatoire ervaringen een continuüm vormen met normale psychologische processen. Met betrekking tot de betrokken cognitieve mechanismen suggereren onze resultaten dat een toestandsafhankelijke disbalans tussen perceptie en mentale verbeelding verantwoordelijk zou kunnen zijn voor de verwarring tussen informatie van interne versus externe origine, die karakteristiek is voor hallucinaties. Resultaten van functionele neurobeeldvormingsstudies zijn consistent met deze these. De gedragsmatige bevindingen in gezonde en psychiatrische groepen lieten echter zien dat er geen sprake is van een stabiele dispositie tot levendige mentale verbeelding die eventueel zou leiden tot de ervaring van hallucinaties.

Er zijn een aantal implicaties van het beschreven onderzoek voor de klinische praktijk. Eén daarvan is dat rekening gehouden moet worden met de geheugenstoornissen die veel patiënten met schizofrenie hebben (bepaalde therapieën die een sterk beroep doen op deze functies zijn daardoor ongeschikt). Voorts zijn hallucinatoire ervaringen niet per definitie pathologisch, wat niet door alle clinici onderkend wordt. Voor diagnostische doeleinden is wellicht de aard van de hallucinaties en de subjectieve waardering ervan belangrijker dan louter de vraag of deze al dan niet aanwezig zijn. Er is in toenemende mate wetenschappelijke ondersteuning voor de effectiviteit van cognitieve gedragstherapie in de behandeling van hallucinaties. Aangezien ons onderzoek laat zien dat sensorische factoren een rol kunnen spelen bij het ontstaan van hallucinaties verdient het aanbeveling dat deze therapieën zich, naast inhoudsgerelateerde factoren, richten op het leren onderscheiden tussen de differentiële sensorische eigenschappen van intern gegenereerde en extern gepresenteerde perceptuele informatie. Tenslotte blijkt uit ons onderzoek dat rTMS mogelijk een nieuwe behandelingsmethode biedt voor medicatie-resistente hallucinaties.

Publications

Aleman, A., & De Haan, E.H.F. (1998). On redefining hallucination. *American Journal of Orthopsychiatry, 68*, 656-658.

Aleman, A., Verhaar, H.J.J., De Haan, E.H.F., De Vries, W.R., Samson, M.M., Drent, M.L., Van der Veen, E.A. & Koppeschaar, H.P.F. (1999). Insulin-like growth factor-1 and cognitive function in healthy older men. *Journal of Clinical Endocrinology and Metabolism, 84,* 471-475.

Aleman, A., Böcker, K.B.E. & De Haan, E.H.F. (1999). Disposition towards hallucination and subjective versus objective vividness of imagery in normal subjects. *Personality and Individual Differences, 27,* 707-714.

Aleman, A., Hijman, R., De Haan, E.H.F., & Kahn, R.S. (1999). Memory impairment in schizophrenia: a meta-analysis. *American Journal of Psychiatry, 156,* 1358-1366.

Aleman, A., d' Alfonso, A.A.L., Postma, A. & De Haan, E.H.F. (1999). Involvement of primary visual cortex in visual mental imagery: a transcranial magnetic stimulation study. *Neuroscience Research Communications, 25,* 25-31.

Aleman A, Nieuwenstein M, Böcker KBE, De Haan EHF. (1999) Temporal stability of the Launay-Slade Hallucination Scale for high and low scoring normal subjects. *Psychological Reports, 85,* 1101-1104.

Aleman, A., De Vries, W.R., De Haan, E.H.F., Verhaar, H.J.J., Samson, M.M., Koppeschaar, H.P.F. (2000). Age-sensitive cognitive function, growth hormone, and insulin-like growth factor-1 plasma levels in healthy older men. *Neuropsychobiology, 41,* 73-78.

Aleman, A., De Haan, E.H.F., Verhaar, H.J.J., Samson, M.M., De Vries, W.R., & Koppeschaar, H.P.F. (2000). Relation between cognitive and physical function in healthy older men: a role for aerobic power? *Journal of the American Geriatrics Society, 48,*104-105.

Aleman, A. & De Haan, E.H.F. (2000). Non-language cognitive deficits and hallucination in schizophrenia. *American Journal of Psychiatry, 157,* 487.

Aleman, A. & De Haan E.H.F. (2000). Antipsychotics and working memory in schizophrenia. *Science, (July 7, 2000) 289,* 56-57.

Aleman, A., Nieuwenstein, M., Böcker, K.B.E., & De Haan, E.H.F. (2000). Music training and mental imagery ability. *Neuropsychologia, 38,* 1664-1668.

Aleman, A., Nieuwenstein, M., Böcker, K.B.E., & De Haan, E.H.F. (2000). Mental imagery and perception in hallucination-prone individuals. *Journal of Nervous and Mental Disease, 188,* 830-836.

Aleman, A., Nieuwenstein, M., Böcker, K.B.E., De Haan, E.H.F. (2001). Multi-dimensionality of hallucinatory predisposition: factor structure of the Launay-Slade Hallucination Scale in a normal sample. *Personality and Individual Differences, 30,* 287-292.

Aleman, A., Verhaar, H.J.J., De Haan, E.H.F., De Vries, W.R., Samson, M.M., Bol, E., & Koppeschaar, H.P.F. (2001). Relationship between circulating levels of sex hormones and insulin-like growth factor-1, and fluid intelligence in older men. *Experimental Aging Research*, in press.

Aleman, A. (2001). Hallucinations and the cerebral hemispheres. *Journal of Psychiatry & Neuroscience*, in press.

Rispens, J., Aleman, A. & Goudena, P.P. (1997). Prevention of child sexual abuse victimization: a meta-analysis of school programs. *Child Abuse & Neglect, 21*, 975-987.

Kessels, R.P.C., Aleman, A., Verhagen, W.I.M., & Van Luijtelaar, E.L.J.M. (2000). Cognitive functioning after whiplash injury: a meta-analysis. *Journal of the International Neuropsychological Society, 6*, 271-278.

Van Dam, P.S., Aleman, A., De Vries, W.R., Deijen, J.B., Van der Veen, E.A., De Haan, E.H.F., & Koppeschaar, H.P.F. (2000). Growth hormone, insulin-like growth factor-1 and cognitive functions in adults. *Growth Hormone and IGF Research, 10 (suppl. B)*, 69-73.

Verhaar, H.J.J., Samson, M.M., Aleman, A., De Vries, W.R. , De Vreede, P.L., Koppeschaar, H.P.F. (2000). Relationship between indices of muscle function and circulating anabolic hormones in healthy elderly men. *Aging Male, 3*, 75-80.

De Haan, E.H.F., Appels, B., Aleman, A., & Postma, A. (2000). Inter- and intramodal encoding of auditory and visual presented material: effects on memory performance. *Psychological Record, 50,* 577-586.

Van Zandvoort, M.J.E., Aleman, A., Kapelle, J., & De Haan, E.H.F. (2000). Cognitive functioning before and after a single lacunar infarct. *Cerebrovascular Diseases, 10,* 478-479.

Sommer, I.E., Aleman, A., Ramsey, N.F., Bouma, A., & Kahn, R.S. (2001). Handedness, laterality and asymmetry in schizophrenia: a review and meta-analysis. *British Journal of Psychiatry*, in press.

Aleman, A. (1996). PET-beeldvorming van cognitieve functies. *Nederlands Tijdschrift voor de Psychologie, 51*, 145-153.

Aleman, A. & De Haan, E.H.F. (1999). Clozapine en cognitief functioneren. *Tijdschrift voor Psychiatrie*, *41*, 37-43.

Aleman, A., Nieuwenstein, M., Böcker, K.B.E., & De Haan, E.H.F. (1999). Hallucinatoire ervaringen bij gezonde personen uit de normale populatie: factorstructuur van de Launay-Slade Hallucinatie schaal. *Nederlands Tijdschrift voor de Psychologie, 54*, 241-246.

Aleman, A. & De Haan, E.H.F. (1999). Nieuwe antipsychotica verbeteren het cognitief functioneren bij schizofrenie. *Nederlands Tijdschrift voor Geneeskunde, 143,* 2336.

Aleman, A. (2000). Hallucinaties bij schizofrenie: hoe het brein zichzelf misleidt. *De Psycholoog, 35*, 154-159.

Aleman, A. & Tuijl, C.A. van (2000). Meta-analyse, heterogeniteit en de effecten van voorschoolse interventieprogramma's: een kritische beschouwing. *Pedagogiek, 20,* 162-166.

Kessels, R.P.C. & Aleman, A. (2000). Cognitieve stoornissen bij patienten met het whiplashsyndroom. *Gedrag & Gezondheid, 28,* 229-234.

Manuscripts under review, or in revision

Aleman, A. & Kahn, R.S. Effect of the atypical antipsychotic risperidone on hostility and aggression in schizophrenia: a meta-analysis of controlled trials. *Manuscript in revision.*

Aleman, A., Böcker, K.B.E., & De Haan, E.H.F. Self-report and behavioral indices of auditory imagery vividness: relation with hallucinatory predisposition. *Manuscript in revision.*

Nieuwenstein, M.R., Aleman, A., & De Haan, E.H.F. Relationship between schizophrenia syndromes and neurocognitive functioning: a meta-analysis of CPT and WCST studies. *Manuscript in revision.*

D'Alfonso, A.A.L., Aleman, A., Kessels, R.P.C., Schouten, E.A., Postma, A., Van der Linden, J.A., Cahn, W., Greene, Y., De Haan, E.H.F., & Kahn, R.S. TMS over the left auditory cortex in schizophrenia: effects on hallucinations and neurocognition. *Manuscript in revision.*

Rutten, G-J., Aleman, A., Sitskoorn, M., Dautzenberg, G., & Ramsey, N.F. Activation of striate cortex in the absence of visual stimulation: an fMRI study of synesthesia. *Manuscript in revision.*

Aleman, A., Ramsey, N.F., Van Honk, J., Kessels, R.P.C., Hoogduin, J., Schutter, D.L.G., Postma, A., Kahn, R.S., & De Haan, E.H.F. Parietal cortex mediates visuospatial imagery: evidence from fMRI and rTMS. *Manuscript submitted for publication.*

Aleman, A. & De Haan, E.H.F. Do people with better mental imagery ability make more reality monitoring errors? *Manuscript submitted for publication.*

Aleman, A., Böcker, K.B.E., Hijman, R., Kahn, R.S., & De Haan, E.H.F. Hallucinations in schizophrenia: imbalance between imagery and perception? A cognitive neuropsychiatric study. *Manuscript submitted for publication.*

Aleman, A. & De Haan, E.H.F. Hallucinations in schizophrenia: a review of neurocognitive theory and findings. *Manuscript submitted for publication.*

Van Tuijl, C., Aleman, A., Siebes, RC. What do we know about efficacy of preschool intervention? A critical review and meta-analysis. *Manuscript submitted for publication.*

Kessels, R.P.C., Van Honk, J., Aleman, A., d'Alfonso, A., Schutter, D.J.L.G., Postma, A., & De Haan, E.H.F. Transcranial magnetic stimulation in inducing cognitive effects: online versus offline stimulation. *Manuscript submitted for publication.*

Abstracts

Aleman, A., Verhaar, H.J.J., De Haan, E.H.F., Samson, M.M., De Vries, W.R., & Koppeschaar, H.P.F. (1998). Growth hormone and cognitive function in healthy older men. *Growth Hormone and IGF Research, 8*, 329.

Aleman, A., Verhaar, H.J.J., De Haan, E.H.F., Samson, M.M., De Vries, W.R., & Koppeschaar, H.P.F. (1998). Serum IGF-1 and DHEAS: markers of cognitive aging? *Proceedings of the 5th International Pituitary Congress*, Naples, Florida, June 28-30 1998.

Aleman A, d'Alfonso AAL, Postma A, De Haan EHF (1999). TMS at the occipital cortex interferes with visual mental imagery processing. *Journal of Cognitive Neuroscience, 11 (Suppl.),* 90.

Aleman, A., Nieuwenstein, M., Böcker, K.B.E., De Haan, E.H.F. (1999). Do subjective and objective measures of imagery vividness measure the same thing? In Richardson J.T.E. (ed.), *Proceedings of the Seventh European Workshop on Imagery and Cognition*, p. 11. Windsor: Brunel University Press.

Aleman, A., D'Alfonso, A.A.L., Jongen, A., Postma, A., & De Haan, E.H.F. (2000). Single-pulse TMS at the Oz electrode position and at the parieto-occipital cortex during a visual imagery task. *Journal of Psychophysiology*, *Suppl. 1:* S34.

Aleman, A., Böcker, K.B.E., Hijman, R., Kahn, R.S., & De Haan, E.H.F. (2000). Modality-specific vividness of mental imagery in a hallucinating patient with schizophrenia. *Journal of the International Neuropsychological Society*, *6*, 401.

Aleman, A., Böcker, K.B.E., Hijman, R., Kahn, R.S., & De Haan, E.H.F. (2001). Reality monitoring and mental imagery in patients with and without hallucinations. *Psychopharmacology*, in press.

Aleman, A., Böcker, K.B.E., Hijman, R., Kahn, R.S., & De Haan, E.H.F. (2001). Hallucinations in schizophrenia: distortions in mental imagery or reality monitoring failures? *Schizophrenia Research*, in press.

Van Zandvoort, M.J.E., Aleman, A., Kapelle, L.J., & De Haan, E.H.F. (2000). Cognitive functioning before and after a lacunar infarct. *Journal of the International Neuropsychological Society, 6*, 403.

D'Alfonso, A.A.L., Aleman, A., Kessels, R.P.C., Schouten, E.A., Postma, A., Van der Linden, J.A., Cahn, W., Greene, Y., De Haan, E.H.F., Kahn, R.S. (2000, May). The effects of rTMS at the left auditory cortex on hallucinations and neurocognition in schizophrenia. *Paper presented at the 3rd annual meeting of the International Society for Transcranial Magnetic Stimulation (ISTS), Chicago, IL*.

Krabbendam, L. & Aleman, A. (2001). Efficacy of cognitive rehabilitation in schizophrenia: a meta-analysis of controlled studies. *Psychopharmacology*, in press.

Dankwoord

Bij het uitvoeren van het in dit proefschrift beschreven onderzoek heb ik de afgelopen jaren hulp en steun ondervonden van veel mensen, die ik hartelijk wil bedanken.

Op de eerste plaats professor Edward de Haan. Je hebt het project van a tot z gesuperviseerd en ik ben je zeer erkentelijk voor je goede begeleiding. Door jouw open en ontspannen stijl van leidinggeven, samen met je nadruk op zelfstandigheid en academische vrijheid, heb ik mijn werk in een bijzonder stimulerende onderzoeksomgeving kunnen doen. Professor René Kahn wil ik bedanken voor de begeleiding vanuit het Universitair Medisch Centrum, en voor de mogelijkheid om onderzoek te doen met patiënten en gebruik te maken van de UMC-faciliteiten. Het was een leuke ervaring om een steentje bij te mogen dragen aan het internationaal toonaangevende schizofrenie-onderzoeksprogramma van het UMC.

Koen Böcker heeft vooral het eerste deel van het project intensief begeleid. Koen, ik heb veel gehad aan je praktische aanwijzingen om door de "opstartproblemen" heen te komen. Ook je commentaar op eerdere versies van hoofdstukken van het proefschrift heb ik als waardevol ervaren. Ron Hijman maakte me wegwijs in het (toen nog) AZU, leerde me “PANSSen”, en vervulde een sleutelrol bij het werven van patiënten voor deelname aan het onderzoek.

I am grateful to professor Anthony David for reading the final thesis. Eveneens leden van de leescommissie, dank ik professor Jan Rispens en professor Jelle Jolles voor het doornemen van het definitieve manuscript.

Nick Ramsey ben ik dank verschuldigd voor de mogelijkheid om onderzoek te doen met functionele magnetische resonantie beeldvorming en Hans Hoogduin niet minder voor de uren die hij opofferde om mij de beginselen van deze kunst aan te leren.

Mijn collega's Roy Kessels, Alfredo d’Alfonso, Mark Nieuwenstein, Jack van Honk, Dennis Schutter en Albert Postma hebben allen inhoudelijk aan een of meer hoofdstukken bijgedragen. Roy, jou wil ik in het bijzonder bedanken voor je collegiale hulp bij de vele aspecten van manuscript preparatie. Andere collega's waar ik steeds op kon rekenen: Martine van Zandvoort, Claudy Oomen, professor Frans Verstraten, Rob Markus en Michel Schmitt. Van de fMRI-groep: Geert-Jan Rutten, Iris Sommer, Martijn Jansma en René Mandl.

Maureen Postma, bedankt voor je inspanningen om de financiële aspecten van het project in goede banen te leiden.

Een speciaal woord van dank komt de deelnemers aan de onderzoeken toe. En ook de diverse behandelaars die patiënten vroegen of ze mee wilden doen aan mijn onderzoeken. In het bijzonder wil ik Wiepke Cahn en Esther Caspers bedanken voor het coördineren hiervan in het UMC, en René Keet en professor Willem Nolen voor hun hulp in het Willem Arntz Ziekenhuis (H.C. Rümke groep). Marieke Kooman, Anke Jongen, Rachel Brans, Jaap Nagtegaal en Mascha van 't Wout dank ik voor hun hulp bij het testen van patiënten.

Veel administratieve bijstand kreeg ik van Ans Hörchner, Ria Konter en Veronica Maassen (secretariaat Psychonomie) en van Susan van Hemert en Emmy Drost (Psychiatrie). David van de Vliet hielp bij computerproblemen.

Mijn broers dank ik voor hun bereidheid om paranimf te willen zijn, en mijn schoonouders, Beppe en Oma voor hun betrokkenheid en steun.

Daar aangekomen waar dankbaarheid niet meer in woorden uit te drukken is, toch maar een enkele aanduiding.

Mijn ouders hebben me altijd aangemoedigd en gesteund in school en studie, en creëerden de randvoorwaarden om mijn mogelijkheden te ontplooien.

Finnie, jij leefde mee door dik en dun. Jouw liefde was onmisbaar.

Alline maakte de tekening op de voorkant en zorgde ervoor dat ik ook de Nederlandse literatuur bijhield, met name van auteurs met hoge impactscores (A.M.G. Schmidt, Dagmar Stam, e.a.). Martijn, jouw nieuwsgierigheid en exploratiedrang zijn een dagelijkse inspiratiebron voor een wetenschapper.

Uiteindelijk komt God, die alles maakte, onderhoudt en regeert, de dank toe. Hem zij alle lof en eer!

Curriculum vitae

André Aleman werd geboren op 20 juni 1975 in Leiden. In 1993 behaalde hij het Atheneum diploma aan de Pieter Zandt Scholengemeenschap te Kampen. Een jaar later behaalde hij de propedeuse Psychologie en de propedeuse Pedagogiek aan de Universiteit Utrecht. Hij vervolgde zijn psychologiestudie in twee richtingen: neuropsychologie en fysiologische psychologie. In 1997 voltooide hij zijn klinische stage in het algemeen psychiatrisch ziekenhuis "Veldwijk" te Ermelo. In hetzelfde jaar studeerde hij af in beide genoemde richtingen. In 1998 begon hij als onderzoeker-in-opleiding aan de capaciteitsgroep Psychonomie van de Universiteit Utrecht (in samenwerking met de afdeling Psychiatrie van het Universitair Medisch Centrum) met het vierjarig project *Hallucinaties: cognitieve functiestoornissen en fysiologische basis.*