Language lateralization in schizophrenia

Taal lateralisatie bij schizofrenie

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de
Universiteit van Utrecht op gezag van de
Rector Magnificus, Prof. Dr. W.H. Gispen
Ingevolge het besluit van het College voor Promoties
In het openbaar te verdedigen op
Dinsdag 27 januari 2004 des middags te 12.45 uur

Door

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Geboren op 31 augustus 1970 te Roermond

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The studies described in this thesis were performed at the Department of Psychiatry, Universitary Medical Center Utrecht

Printing of this thesis was financially supported by: Eli Lilly Nederland b.v., Pfizer b.v., Janssen-Cilag b.v., GlaxoSmithKline en AstraZenica

ISBN: 90-9017730-2

Printed in the Netherlands by: Ridderprint Offsetdrukkerij B.V.
Design and lay-out: Multimedia, Grafische Studio, UMC Utrecht

“The truth is discovered by scepticism and disbelief”

Nietzsche

CONTENTS

Aims and outline

"The ancient man, who had no concept of self-fulfilment, was virtually autonomous. He heard voices inside his head and called them gods. These gods told him what to do and how to act. Their minds were divided into two parts: an executive part called 'god' and a follower part called 'man'. When writing and other complex language activity started weakening the authority of the auditory hallucinations, this 'bicameral mind' slowly broke down. The voices of the gods fell silent, and what we call consciousness was born." (Jaynes 1976)

At the time Jaynes formulated his ideas about cerebral lateralization of language, it was not possible to study the representation of cerebral functions in vivo. Twenty years later, when the studies described in this thesis were performed, an elegant, non-invasive technique; functional magnetic resonance imaging (fMRI), had become available to study cerebral functions in healthy and diseased subjects. In this thesis, fMRI was applied to study the representation of language functions in patients with schizophrenia.

Schizophrenia is a complex syndrome, incorporating a wide range of symptoms that may occur in individual patients at certain stages of the disease. Schizophrenia is also a severe psychiatric disorder, which generally has major impact on affected subjects. Most patients are not able to maintain a paid job, and approximately half of them are unable to live independently (Green 1996). Considering the severe, debilitating course, one would expect to find major brain abnormalities in schizophrenia. The paradox of schizophrenia is that on post-mortem investigation the brains of individual patients can generally not be distinguished from healthy brains (Harrison 1999). When groups of patients are compared to control groups in Magnetic Resonance Imaging (MRI) or post-mortem studies, some abnormalities, such as enlarged ventricles, may become apparent. Still, for all reported brain abnormalities a large overlap between healthy and affected subjects exists (Harrison 1999). Given this relative absence of clear structural pathology in the schizophrenic brain, one would expect that functional MRI may shed more light on the brain processes underlying the symptoms of schizophrenia, as assessment of actual brain functioning represents a closer correlate of abnormal behaviour.

The symptoms of schizophrenia can largely be divided into positive and negative symptoms. In short, the positive symptoms are the signs of psychosis, and the negative symptoms represent the defect syndrome. Functional MRI studies may focus on cerebral correlates of both positive and negative symptoms and various imaging groups have done so. To my opinion, fMRI is more apt to study positive symptoms, since it is difficult to interpret cerebral activity of a function that is decreased or absent. If a patient is not able to perform a function as well as a control subject, fMRI is likely to reveal decreased cerebral activity in the patient as compared to the control. However, it remains unclear whether decreased cerebral activity results from decreased performance or vice versa. Therefore, we decided to focus on the psychotic symptoms. Hallucinations are among the most intriguing and characteristic symptoms of schizophrenic psychosis. In 65% hallucinations are auditory verbal in nature, i.e. "hearing voices" (Slade and Bentall 1988). Thus, a frequent positive symptom of schizophrenia concerns language activity. Other prominent positive symptoms in schizophrenia, such as thought insertion and formal thought disorder can also be considered to be a disorder of language functioning. Language is one of the few cognitive functions of which the cerebral anatomy is relatively well known. This is an important advantage when a function is studied with fMRI.

There are three main theories that try to explain auditory verbal hallucinations in schizophrenia. First, the mental imagery hypothesis states that pronounced linguistic expectations can generate a perceptual experience (David 1999). In other words, hallucinations are thought to arise from abnormally vivid mental imagery.

A second model was proposed by Frith (1992). According to this theory, hallucinations arise from a failure in the self monitoring of own intentions during inner speech. In healthy subjects, language reception areas are inhibited to respond to language that is derived from covert inner speech. This inhibitory system may be malfunctioning in schizophrenia. Thirdly, Nasrallah (1985) proposed that verbal hallucinations and other language-related positive symptoms arise from inappropriate language activity of the non-dominant hemisphere. This was partly based on reports of more bilateral language lateralization in schizophrenia (Chaugule and Master 1981). The malfunctioning inhibition system proposed by Frith may coexist with the increased right hemispheric language activity proposed by Nasrallah. Considering these three models of hallucinations, we choose to focus on the theory of Nasrallah, since it proposes a central role for language processing in the aetiology of hallucinations. This central position appears to be justified since the great majority of hallucinations in schizophrenia are auditory verbal in nature. Furthermore, it is a very testable model, especially when fMRI can be applied.

One way to test the hallucination model would be to make functional scans of schizophrenia patients at the time they are actually experiencing auditory hallucinations. However, this is a very demanding design. It requires a group of subjects that experience clear-cut periods of hallucinations alternated with periods without hallucinations, all during the time span of a scanning session. These patients have to be able to indicate exactly when the hallucinations are present and when not. It would also demand a long scanning period, with a complex fMRI protocol. At the time that I started my PhD work, such a protocol was considered unrealistic. Besides, several other groups had already succeeded to obtain scans of schizophrenia patients during auditory verbal hallucinations. A meta-analysis of these studies is provided in chapter 12.
For this thesis, another approach was chosen. Functional MRI scans were obtained from patients and control subjects during the performance of language tasks, yielding a language activation map. From these language activation maps, the degree of lateralization can directly be measured.
If Nasrallah's hypothesis on the basis of language-related psychotic symptoms is right, we would expect a more bilateral language representation pattern in patients as compared to controls. Results of the language activation scans in schizophrenia patients and controls are described in chapter 9 and 10. If decreased lateralization were indeed a characteristic of schizophrenia patients, it would be informative to know if the lower degree of language lateralization is a genetic predisposition to schizophrenia (i.e. whether it constitutes a risk factor for the disease) or if it is merely a result of chronic illness and its treatment. This can be tested by applying the same language activation protocol to monozygotic twin pairs that are discordant for schizophrenia. This is described in chapter 11.

Before starting these studies, several issues needed to be clarified. A problem that is frequently observed in schizophrenia research is that the exact characteristics of certain cerebral processes are not well defined in healthy subjects. In some areas, schizophrenia research develops faster than research on the healthy human brain. This was also the case with language lateralization. The first issue to be clarified in healthy subjects concerned sex differences in language lateralization. It is a popular belief that women have a more bilateral pattern of language representation than men and, indeed, there is some evidence for this idea (reviewed by McGlone 1980). A possible sex difference in language lateralization is of special concern to this thesis, given the remarkable sex differences in the onset, symptomatology and prognosis of schizophrenia (DeLisi et al. 1989). In chapter 4, available studies on sex differences in healthy subjects are reviewed in a meta-analysis.

Another area of dispute is language lateralization in monozygotic twin pairs (Boklage 1977). To clarify this issue, language lateralization was studied in a sample of healthy monozygotic twin pairs (chapter 5). Finally, little is known about the pharmacological background of language lateralization. Some suggestion is made that dopamine may be involved (Glick and Shapiro 1984), which would be relevant to the study of language lateralization in schizophrenia. A possible correlation between cerebral dopamine neuro-transmission and language lateralization in healthy subjects is studied in chapter 6.

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Part 1 Language lateralization in the healthy brain

CHAPTER 1

Cerebral language lateralization

INTRODUCTION

The two hemispheres of the human brain are not equal, neither in shape nor in function. In this thesis, the term "asymmetry" refers to anatomical differences between the hemispheres. It is also used for differences in chemistry between the hemispheres. Specialisation of the hemispheres in certain functions is called lateralization. Apart from the direction of lateralization (i.e. left or right), a degree of lateralization can also be defined. A high degree of lateralization indicates that a function is mediated almost exclusively by one hemisphere; a low degree of lateralization means that a function is represented more bilaterally.
Cerebral lateralization was first observed for language. In 1861 Paul Broca noted on post-mortem brains of aphasic patients that: "…the lesion is in all cases situated in the posterior portion of the third frontal convolution and a thing most remarkable is that in all of these patients the lesion is on the left side." Broca went on to consider the relationship between motor and language lateralization in suggesting that both were attributable to the inborn superiority of the left hemisphere. Since then, the hemisphere specialised for language is called the "dominant" hemisphere. Though the concept originally associated with this term underestimates the role of the right hemisphere, the term "cerebral dominance" is still widely used. Much later, in the second half of the twentieth century, cerebral lateralization was also demonstrated for a variety of other cognitive functions, such as mental rotation (Sheperd 1970), pitch discrimination (Zatorre et al. 1992), face recognition (Kelley et al. 1998) and emotional appraisal (Bottini et al. 1994). In humans, the left hemisphere is generally dominant for language and arithmetic calculations, while the right hemisphere is dominant for spatial processing, and discrimination of non-speech sounds (Hugdahl and Davids 2003).

Different methods to measure language lateralization

Cerebral lateralization for language has been studied extensively, with the first reports dating from the second half of the 19th century. In general, four different types of studies on language lateralization can be distinguished based on their method of assessment. The first type establishes a link between language functions and brain organization by associating disrupted function of a brain area with a change in linguistic behavior, usually a deficit. Historically, patients with unilateral brain damage are studied for loss of function (Broca 1861). In the late fifties, Juhn Wada assessed cerebral dominance by infusing a short acting barbiturate (sodium-amytal) into the internal carotid artery to switch off one hemisphere and assess the remaining language functions (Wada 1960). This test is still widely used to assess cerebral dominance prior to neurosurgery. Another example of this type of studies is the use of intra-operative electrical stimulation to assess the exact location of critical language areas (Penfield 1959; Ojemann 1991).

A second type of study that is frequently used to estimate the direction and degree of language lateralization is the measurement of perceptual asymmetry. In dichotic listening tests and tachistoscopic tests a stimulus is perceived with only one sensory field, one ear or one visual half field respectively. Healthy subjects perceive language stimuli more quickly and more accurately from the ear or eye contralateral to the dominant hemisphere. The difference in performance between stimuli presented contralateral or ipsilateral to the dominant hemisphere is used to estimate the degree of language lateralization.

The third type of studies record physiological measures of brain activation while subjects are engaged in a language task. These studies include data obtained with Event Related Potentials (ERP), such as the N100 paradigm and with functional brain imaging methods, such as Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), functional Magnetic Resonance Imaging (fMRI) and in recent years Magnetic Encephalo Graphy (MEG). Finally, asymmetry of language-related structures may be used to reflect language dominance. More specifically, the asymmetry of the planum temporale may be used as an index of cerebral dominance

Findings with these four types of studies have yielded partly overlapping results. The main findings will be discussed in the following sections.

Information from lesion studies

Paul Broca (1861) first noted that lesions of the left hemisphere lead to aphasia. Other syndromes that typically follow left hemisphere lesions are alexia and acalculia. Broca also noticed a relation between language dominance and handedness. The classical rule then settled that the dominant hemisphere is contralateral to the writing hand. Approximately one century later, Penfield found evidence against this rule of contralaterality by applying the intra-operative electrode technique. He noticed that left-handers had aphasia after left hemisphere surgery just as often (72%) as right-handers

(73%) (Penfield 1972). Studies of aphasic stroke patients confirmed that the lesion most often involved the left hemisphere, both in right- and left-handers (McManus 1985). However, the difference between both handedness groups becomes clear after lesions of the right hemisphere. Right-handers hardly ever become aphasic after right hemisphere damage (2%), whereas left-handers develop aphasia in 20 to 30% after right hemisphere lesions (McManus 1985). Another remarkable difference is that aphasia in left-handers recovers more quickly than in right-handers (Subirana 1958). Even right-handers with left-handed relatives recover earlier than right-handers with only right-handed family (Luria 1947). It is possible that the quicker recovery after lesion of the left cerebral language areas in the left-handed patients is associated with a higher language potential of the contralateral homologue areas in the right hemisphere (Kinsbourne 1971).

After right hemisphere damage, many patients have difficulties in understanding metaphors and detecting absurd or humorous content (Winner and Gardner 1977). Right hemisphere damaged patients may also produce sentences with unlikely meanings (Cavalli 1981) and show deficits in the affective and connotative aspects of language (Ross and Mesulam 1979).

Although lesion studies have provided valuable information on the deficits that occur after damage of one hemisphere, it remains unknown which functions would be affected in individual patients after lesion of the other hemisphere. Yet, this information is necessary to distinguish between unilateral and bilateral language representation. Furthermore, the exact location and extend of the lesion is of great importance to the remaining function. It is often not possible to determine whether the remaining language function originates from the unaffected hemisphere or from intact areas within the damaged hemisphere.

Information from Wada-tests

Information on both hemispheres can be obtained with the Wada test, which is generally considered to be the most reliable test to determine language dominance (Binder et al. 1996). In this procedure, a catheter is introduced into the femoral artery and pushed up onto the bifurcation of the carotid artery. When the tip of the catheter is at the entrance of the internal carotid artery, the barbiturate is infused. The patient remains conscious but specific functions of that hemisphere are temporarily switched off. By applying neuropsychological tests, exact function loss is noted. However, the test battery has to be concise, since, the infused hemisphere regains its normal function again after five to 20 minutes. The same procedure is then carried out at the other side. Wada (1960) reported that when the dominant hemisphere is inactivated, patients are still able to comprehend spoken commands, to produce automatic speech (emotional outcries and swearing) and to sing. Severe disturbances are observed in object naming, responding to specific questions and word recall. Wada tests of right-handers revealed 4% right sided language dominance and virtually no bilateral dominance. Left-handers showed 70% left cerebral dominance, 15% right cerebral dominance and bilateral language representation in the remaining 15% (Rasmussen 1977). However, the Wada procedure is highly invasive and therefore only used as a pre-operative tool in patients with cerebral pathology, most frequently epilepsy or tumours. In these patients, a long standing history of brain pathology may have altered their pattern of language representation. The right hemisphere may have taken over some language functions of the lesioned left hemisphere. Patients with cerebral pathology of childhood onset are most prone to have such a reorganisation of language functions. Therefore, results from Wada test studies may not be applicable to predict language lateralization in healthy subjects, since they may overestimate the occurrence of right and bilateral language dominance.

Information from perceptual asymmetry studies

Most right-handers show a right ear advantage (REA) for dichotically presented verbal stimuli (Kimura 1967) and a left ear advantage (LEA) for melodies (King and Kimura 1972), musical chords, clicks and environmental sounds such as telephone ringing and traffic noise (Knox and Kimura 1970). Perceptual asymmetry for non-speech sounds is generally smaller and less consistent than for verbal stimuli. Between 75 and 85% of normal right-handed subjects show a REA in verbal dichotic listening tasks (Hugdahl 2002).

Four verbal tasks are used frequently to estimate language lateralization: the triad task, the dichotic word task, the consonant-vowel task and the fused word task. In the triad task, three pairs of digits (or other words) are presented simultaneously to the two ears and the subject has to recall all digits heard with each ear. The subject has to repeat as many digits as possible, in any order. In the dichotic word task, only two words are presented, one to each ear. For the triad task and the word task subjects have to respond to all stimuli on either ear. Subjects with high performance may answer 100% correct on several items of these tasks, in which case no

perceptual asymmetry is measured for these items. These ceiling effects in subjects with high performance may become problematic when patient groups are compared to a healthy control group, since these tasks will tend to decrease asymmetry in the control group. In the consonant-vowel task syllables of two letters (most often "ba, da, ga, pa") are presented to each ear. And finally, in the fused or rhyme word task, two words are offered at either ear that differ only in the first letter. For the consonant-vowel and the fused-word task, subjects are asked to respond only to the most clearly perceived item, thereby avoiding the problem of ceiling effects. From the percentage of items reported from the right and from the left ear, a lateralization index is calculated. Indices of the four different tasks show low inter-task correlations (Teng 1981). The consonant-vowel task yields highest lateralization indices (Hugdahl 2002).
From five large dichotic listening studies (Orsini et al. 1985, Searleman et al. 1980, Lake et al. 1976, McKeever et al. 1984 and McKeever et al. 1986), three studies (Orsini et al. 1985, McKeever et al. 1984, McKeever et al. 1986) found a significantly lower REA in left-handers. Right-handers with left-handed relatives were also found to have a lower REA (Hugdahl 2002).

Perceptual asymmetry measurement offers a cheap, non-invasive way to assess language lateralization, but has the disadvantage of a large error of measurement variance compared to the variance in true lateralization differences (Segalowitz 1980). Several studies compared cerebral dominance assessed with dichotic listening tasks to Wada test results (Strauss et al. 1986, Strauss et al. 1988, Geffen et al. 1981, Zatorre et al. 1989). Three of four studies found reasonably good correlations for persons with left cerebral dominance (85%-96% agreement), but rather poor correlations for right- or bilateral dominant subjects (around 50%). This indicates that perceptual asymmetry studies may not yield a reliable reflection of individual language lateralization.

Information obtained with functional imaging techniques
Functional imaging techniques can measure (a reflection of) regional cerebral metabolism when the subject is engaged in a language task, yielding a language activation map. PET data on language dominance showed a high correspondence with Wada test results (Desmond et al. 1995). For language dominance measured with fMRI, Binder et al. (1996) reported 100% agreement between fMRI findings and the results of Wada tests in 22 sub-

jects of variable cerebral dominance. Rutten et al. (2002) reported 91% agreement between fMRI and Wada test results for left dominant patients, 75% for subjects with bilateral language representation and 67% for patients with right cerebral dominance. In this study, agreement with Wada test results was optimal when a combination of three language tasks was applied (see chapter 3). This implies that functional imaging can provide a correct reflection of cerebral dominance, although it may not be accurate enough to replace the Wada test for presurgical assessment of cerebral dominance.

Functional imaging studies confirmed that in the vast majority of both right and left-handed subjects the left cerebral hemisphere is dominant for language (Pujol et al. 2001). Figure 1 shows the findings of Pujol et al. (2001) who measured language lateralization with fMRI in 100 healthy subjects (50 right-handers and 50 left-handers). In both right and left-handers left cerebral dominance appears to be the norm, with a larger standard deviation in left-handers than in right-handers. Strong right cerebral dominance is

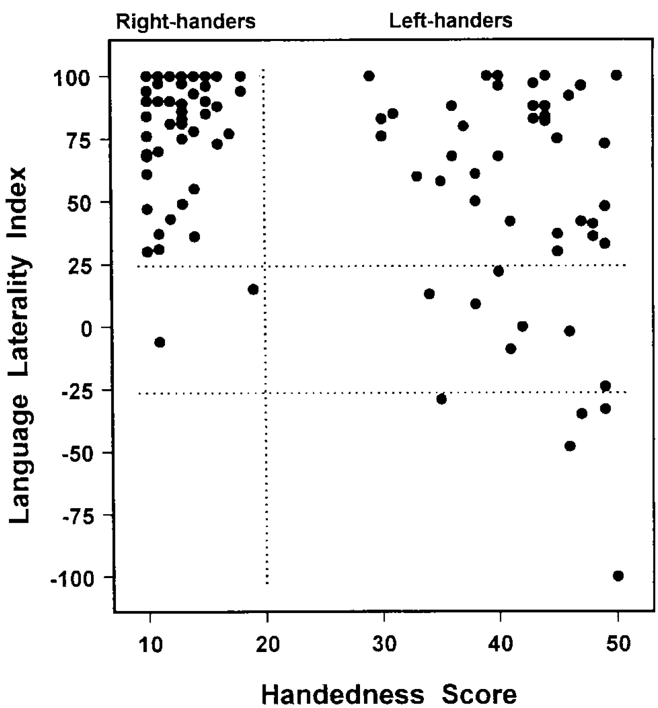

Figure 1.
Language laterization index in 100 healthy subjects. From Pujol et al. (2001)

hardly ever encountered in healthy subjects, even in left-handers, with the possible exception of certain left-handed monozygotic twins (see chapter 5).

In addition to the direction of language lateralization (i.e. left or right) functional imaging techniques have provided information on the degree of lateralization. However, the degree of language lateralization in healthy right-handed volunteers may vary considerably between functional imaging studies. Several research groups report language activity exclusively in the left hemisphere (Petersen et al. 1989, Desmond et al. 1995, Binder et al. 1996), whereas others report more bilateral language activation (Latchaw et al. 1995, Shaywitz et al. 1995). For example, Latchaw et al. (1995) reported on 14 right-handed subjects from whom two had language activation in the right hemisphere almost equal to that in the left, and one subject had right-sided activation 75% greater than that of the left hemisphere. This variation across functional imaging studies is largely due to differences in the language tasks used. The earlier functional imaging studies mostly applied single word tasks, such as the semantic decision task (Desmond et al. 1995), the verb generation task (Binder et al. 1996; Petersen et al. 1993), the letter fluency task (Latchaw et al. 1995) and the rhyme word task (Shaywitz et al. 1995). Semantic decision tasks generally yield a much lower degree of language lateralization than word generation tasks (such as verb generation and letter fluency), but have the advantage of an easy performance measurement (see chapter 3). More recent imaging studies have also studies the activation patterns obtained with more complex language tasks, such as sentence comprehension (Friederich et al. 2003) and story listening (Kansaku et al. 2000). Sentences or stories also generate more bilateral activation than the word production tasks.

An important contribution of functional imaging studies is the information on the role of the right hemisphere in several aspects of language. Right sided language activation is reported for pitch discrimination of speech (Zattore et al. 1992) and for the understanding of figurative language aspects such as emotional colour, humour and metaphors (Bottini et al. 1994). Possibly, normal language processing takes place in the right and left hemisphere simultaneously; while the left hemisphere makes a rapid selection of a single meaning, the right hemisphere maintains a wider set of meanings, permitting verbal input to be interpreted within the overall context of the discourse (Chiarello et al. 990).

Anatomical asymmetry

Post mortem studies found anatomical asymmetry in the frontal lobe, which is generally somewhat larger on the right side, and in the occipital lobe, which is greater on the left in most subjects (LeMay 1977). Other asymmetries are found in the thalamus which is larger on the left in most right-handers, and the pyramidal tracts, from which the left is generally larger and decussates first. Heschl's gyrus (the primary auditory cortex) is usually larger in the right hemisphere and frequently there are two gyri on this side and only one on the left (Chi 1977). Largest differences between the right and left hemisphere are found in the temporo-parietal region, particularly the planum temporale (upper surface of the temporal lobe), which is part of Wernicke's area. At the surface of the brain, planum temporale asymmetry is reflected in a longer and less steep Sylvian fissure at the dominant side. A summary of asymmetrical aspects of the human brain is provided in table 1.

In 70% of adult human brains, the left planum temporale is about 40% larger than the right (LeMay et al. 1972). The right planum temporale is larger in only 8%, whereas 22% of human brains have symmetrical plana. MRI studies found that that left-handed subjects, as a group, had smaller asymmetry of the planum temporale than right-handers (Steinmetz et al. 1991). Right-handers with left-handed relatives also had lower asymmetry than right-handers with only right-handed relatives (Steinmetz et al. 1991). Strongly left-handed subjects with first degree left-handed relatives had smallest asymmetry of the planum, close to zero (Steinmetz et al. 1991). Interestingly, the left planum temporale is not larger in asymmetrical brains than in symmetrical brains, but that the right planum is smaller (Galaburda et al. 1978). Symmetrical brains have two large plana, whereas asymmetrical brains have only one large planum. Thus, anatomical asymmetry appears to be accomplished by selective inhibition of the outgrowth of the non-dominant temporal language areas.

Asymmetry of the planum temporale is also found in neonatal (Witelson and Pallie 1973) and foetal brains (Wada et al. 1975), which indicates that the larger left planum is probably genetically determined. A correlation is reported between the direction of asymmetry of the planum temporale on MRI scans and language dominance as assessed with the Wada test (Foundas et al. 1994), which suggests that the above mentioned asymmetry can be considered to reflect functional language lateralization. The asymmetry of the planum temporale induces another asymmetrical aspect of the

brain: asymmetry of the Sylvian fissure, which is longer and less steep at the side of the larger planum.
Asymmetry of the frontal language areas has been studied less extensively than asymmetry of the temporal areas. Wada et al. (1975) found a smaller surface area of the triangular and opercular part of the inferior frontal gyrus (Broca's area) in the left hemisphere than in the right, in both adults and infants. However, the external surface represents only a part of the total convolutional area. When the entire region, including the cortex buried in the sulci is measured, the left frontal language area is reported to be significantly larger than its contralateral homologue in 75% of subjects (Falzi et al. 1982).

Table 1 Anatomical asymmetry of cerebral structures

Anatomical region	**Asymmetry**
Frontal lobe	larger on the right
Occipital lobe	larger on the left
Heschl's gyrus	larger on the right
Pyramidal tracts	left larger and decussates first
Thalamus	larger on the left
Planum temporale	larger on the left
Sylvian fissure	longer and less steep on the left
Broca's area (inferior frontal)	larger on the left
Occipital horn lateral ventricle	larger on the left
Temporal horn lateral ventricle	larger on the right

Factors that influence language lateralization

Handedness

Language lateralization is related to handedness, although this correlation is rather weak (see figure 1). Approximately 90% of subjects use the right hand for skilled unimanual tasks (Annet 1972).This percentage is roughly similar in all populations that have been studied (Corballis 1991), though left-handedness may have a slightly lower incidence in some Asian countries (for example in China, Shang-Ming et al. 1985).
The majority of right-handed persons tend to be consistent in the use of the right hand for all unimanual tasks (i.e. they are strongly right-handed).

In contrast, only one in ten non-right-handers is strongly left-handed (Annett 1995). Hence, the term non-right-handedness correctly describes the continuous group of left-handed and ambidextrous subjects. However, for the readability of this thesis, the correct term is not always used.
In parallel to the findings on asymmetry of the planum temporale, the preference to use the right hand in right-handed subjects results from a remarkable weakness and clumsiness of the left hand, rather than from excellence of the right hand (Annett 1992). In contrast, left-handers are generally quite skilled with both hands. It thus appears that the factor that induces human right-handedness is an inhibiting influence on the right hemisphere, rather than a positive effect on the left hemisphere.

The origin of handedness is not known, but several arguments suggest that handedness is a genetic trait. Firstly, left handedness tends to run in families (Bryden 1975). Adoption studies further show that handedness of a child is strongly related to handedness of the biological parents, while handedness of the adoption parents is of little influence (Hicks and Kinsbourne 1976). Annett 's (1995) theory on handedness states that right handedness is secondary to a dominant allele, the "right shift factor". In her theory, there is no allele for left-handedness. This genetic model can be compared to a road with a T-junction. The right shift factor acts as a traffic sign to direct towards right-handedness. In the absence of this factor, as in the homozygote recessive genotype, handedness is determined by chance, resulting in 50% right-handedness and 50% left-handedness. Indeed, children from two left-handed parents, who are supposed to be of the homozygote recessive genotype, are only in 50% of cases left-handed themselves (Annett 1974).
An argument against Annett's theory is the low concordance for handedness in monozygotic twins, which hardly exceeds that of dizygotic twins (McManus 1980). However, monozygotic twinning may sometimes occur at a time when the embryo has already developed left-right asymmetry. After splitting of this embryo, further development of left-right asymmetry may be disrupted in one twin. The resulting twin pair may then be very different for laterality-dependent traits such as handedness and cerebral dominance. Therefore, handedness in twins may not be a fair test for genetic models (see chapter 5).
At the "nurture side", Bakan (1973) proposed that all left-handedness and all anomalous language lateralization is a result of brain injury, however

subtle ("pathologic left-handedness"). Although there is evidence that pre- and perinatal brain injury may indeed affects manifested handedness, this theory can not explain the familial occurrence of left-handedness.

Gender

Gender may be related to handedness, asymmetry and lateralization, though the relation is still disputed. Females are found to be left-handed in only 6%, compared to 10% left-handedness in men (Oldfield 1971). On the other hand, women were reported to have more symmetrical plana temporale than men (Good et al. 2001). In a study on aphasia, men showed more severe impairment in verbal intelligence after left hemisphere injury than women (McGlone 1980). However, this gender difference could not be replicated in a meta-analysis (Inglis and Lawson 1982). Several functional imaging studies also found higher language lateralization in men as compared to women (Shaywitz et al. 1995; Kansaku et al. 2000). However, three large studies (Frost et al. 1999; Knecht et al. 2001; Pujol et al. 2001), found no gender difference in language lateralization. We may resume that the literature findings on sex differences in asymmetry and language lateralization are as yet inconclusive. This topic is further studied in chapter 4.

The role of sex hormones

The mammalian brain is capable of developing in either masculine or feminine direction, regardless of genetic factors. The direction taken depends on the gonadal hormone environment during critical periods early in life (Hines 1982). Testosterone can be metabolised to oestradiol, which is thought to be responsible for the foetal brain to develop in a male direction (Hines 1982). Diethylstilboestrol (DES) is an artificial hormone that has been administered to pregnant women to prevent miscarriages. DES can also be converted to oestradiol and it has strong masculinising effects on the female prenatal brain (Hines 1982). Some, but not all studies found higher REA on a verbal dichotic task and more pronounced right-handedness in women with prenatal DES exposure than in their unexposed sisters (Smith and Hines 2000). Females with high prenatal testosterone levels due to congenital adrenal hyperplasia were found to be more often left-handed than unaffected females (Nass 1987), a finding that is inconsistent with the results of the DES studies. Grimshaw and Bryden (1995) measured testosterone in amniotic fluid obtained in the second trimester of 96 pregnancies. Low prenatal testosterone levels related to low degrees of language lateralization, as measured with dichotic listening, and more left-handedness at age 10, in both boys and girls. This implies that lower prenatal testosterone levels can results in lower degrees of motor and language lateralization. Consequently, one would also expect decreased lateralization in patients with the complete androgen insensitivity syndrome, who have no effective testosterone signaling. However, the percentage left-handedness in this patient group is normal (Imperato-McGinley 1991). Witelson (1991) proposed that low pre and perinatal testosterone levels lead to little axon elimination in the corpus callosum, resulting in a low degree of lateralization. Indeed, in experimental animals alterations of neonatal testosterone levels lead to changes in callosal width (Fitch 1990), but there are no equivalent findings in humans.

Post-natal hormone levels may also influence language lateralization in adults. Some, but not all studies found a correlation between lower free testosterone and left-handedness in adult men (reviewed by Forget and Cohen 1994). In adult women, language lateralization is more pronounced in the post menstrual phase, when estrogen levels are low (Altemus et al. 1989). Treatment of transsexuals with cross-gender hormones provides another opportunity to study the effects of sex steroids on the adult brain. Genetically male transsexuals, who had received female steroid treatment, had a lower degree of language lateralization than normal men (Cohen and Forget 1995). Genetically female transsexuals are found to have higher degrees of language lateralization after treatment with testosterone than normal women (van Goozen et al. 1995). Taken together, some indication exists that testosterone increases language lateralization both prenatal and during adult life. However, studies are scarce and results are inconsistent.

Differences in cognitive strategy

The two hemispheres may not be specialised so much in a particular type of stimulus (e.g. verbal or spatial), but rather in a specific type of processing (Sergent 1981). The left hemisphere is considered to be analytic, detailed and logic, the right hemisphere is holistic, global and synthetic. The right hemisphere is best suited to handle novel information while the left tends to be more adept with familiar material (Goldberg 1990). Both hemispheres are capable of most functions and differ only in the relative efficacy of processing. If more emphasis is put on one particular way of language processing, the pattern of language lateralization may change accordingly.

For example, in pre-school children language is processed more bilaterally than in older children (Springer and Deutsch 1998a). In written language, grammar and form are important aspects, with a relative decrease in the global and emotional content as compared to spoken language. This is probably the reason why language processing becomes more restricted to the left hemisphere when children are taught the correct use of grammar and spelling (Springer and Deutsch 1998a). Interestingly, illiterate adults are reported to develop aphasia following left hemisphere damage less frequently than literates, while the opposite is true after lesion of the right hemisphere (Lecours et al. 1987, Lecourse et al. 1988). This implies that cerebral representation of language is more bilateral in illiterates than it is in school educated subjects. Several other factors, such as the emotional content of language, familiarity of the subject with the text and the mode of presentation (auditory or visual language) can also lead to variation in the degree of lateralization.

The influence of different languages on lateralization

Luria (1965) reported that languages without direct correspondence between the sound and the symbol (English for example) depend more on left hemisphere processing than languages that do have this correspondence (Russian for example). Bilingual Indian school children showed more right hemisphere activation on EEG registration, when listening to a story in Hopi, then when listening to the same story in English (Rogers et al. 1977). In addition, a higher incidence of crossed aphasia (aphasia after right hemisphere lesions in right-handers) is found in multilinguals (14%) as compared to subjects who speak just one language (2%) (Fabbro 2001). This suggests a more bilateral lateralization pattern for the second and third language as compared to the first language. However, with intra-operative stimulation, no difference was found in cerebral dominance between bilinguals and unilinguals, nor between first and second languages (Ojemann 1978).

Language lateralization may also be influenced by the way a language is learned. Formal language acquisition, which uses grammatical rules and a meta-linguistic awareness of the structure of a language, may rely more on the left hemisphere, whereas informal learning, which is more naturalistic and meaningful, involves more right hemisphere processing. Indeed, more left hemisphere involvement is found in English students who learned Spanish in a deductive teaching method than in English students who learned Spanish in an informal manner (Springer and Deutsch 1998b).

Possible cerebral mechanisms that maintain language lateralization

Callosal homotopic inhibition

The corpus callosum carries connections to homologue cortical areas. The corpus callosum of an adult human brain is composed of more than 200 million fibres (Innocenti 1986). This number is more than enough for every cortical collumna to have one afferent and one efferent fibre to and from its contralateral homologue (Cook 1984). At the neurophysiological level, almost all callosal fibres are excitatory (Innocenti 1994). However, their functional effects may be either excitatory or inhibitory, depending on the nature of the interneurons. Stimulation of the cortex or of the callosal fibres directly results in a brief excitation of the contralateral homologue area followed by a prolonged inhibition (reviewed by Doty 1973). This inhibitory effect may prevent unnecessary duplication of brain activity and thus accomplish cerebral lateralization of functions. The hemisphere most specialised (i.e. dominant) for a function may suppress this function in the other hemisphere. Support for this theory is found in observations of language improvement after surgical removal of a damaged, malfunctioning hemisphere (Smith et al. 1966). The malfunctioning hemisphere is thought to continue its suppression on the unaffected hemisphere and removal of the damaged hemisphere, will unleash contralateral language potentials.

Cook (1984) proposed the "callosal homotopic inhibition" theory for cerebral lateralization. In this theory, an activated area in one hemisphere is thought to suppress activity in exactly the same contralateral area. Together with this inhibition, surrounding areas at the contralateral side are facilitated, resulting in a photographic negative of the activation pattern at the contralateral side. In the case of language, the left hemisphere is thought to inhibit the contralateral area corresponding to the literal meaning while enhancing contextual meaning in the right hemisphere. The right hemisphere then provides a contextual framework in which the left performs its focal analysis.

If callosal inhibition is to play an important role in language lateralization, subjects with congenital callosal agenesis should be expected to have low degrees of language lateralization, since direct inhibition from the contralateral hemisphere is lacking. However, dichotic listening studies on subjects with callosal agenesis (congenital absence of the corpus callosum) reported language lateralization within the normal range (Lassonde 2002), which implies that callosal homotopic inhibition is not the only mechanism that underlies cerebral lateralization.

The role of the thalamus in lateralization.

The focusing of attention is assumed to be accomplished by the selective activation of a subset of cortical neurons by a subcortical excitatory mechanism, most likely the thalamus. Several arguments suggest that the thalamus selectively activates the cortical area that is most specialised for a function and at the same time inhibits other, non-dominant areas. Firstly, in post mortem brains the left planum temporale was found to be larger only when there also was a larger left thalamus (Eidelberg and Galaburda 1982). Secondly, lesions of the left thalamus, especially of the ventrolateral and pulvinar nuclei are known to cause language deficits consisting of paucity of spontaneous speech, perseverations, dysnomia and neologisms with intact comprehension and repetition (Crosson 1999). Thirdly, during intra-operative electrical stimulation of the dominant thalamus half, performance on verbal dichotic listening tests was enhanced and the REA increased (Mateer 1983). And finally, in Parkinson patients treated with stereotactic thalamotomy, language lateralization increases during direct electrical stimulation of the left ventrolateral thalamus and subsequently decreases after thermocoagulative destruction of this nucleus (Hugdahl and Wester 2000). These effects are absent when stimulation and coagulation is applied to the right ventrolateral thalamus (Hugdahl and Wester 2000).

In non-right handers, thalamo-cortical connections may be more bilateral, resulting in more diffuse activation of the cerebrum. In right-handers without familial left-handedness, gradual recovery from aphasia is thought to reflect the establishment of new connections between the dominant thalamus and the right hemisphere, as it becomes responsible for aphasic speech (Kinsbourne 1971). Perceptual asymmetry studies in aphasia patients found a correlation between the gradual progress to a LEA and recovery of language functions (Johnson 1977). Left-handers and right-handers with left-handed family, who may have more bilateral thalamo-cortical connections, will more readily switch to the other hemisphere for language. This could explain the quicker recovery of aphasia in these groups.

The thalamic model of language lateralization has not been tested thoroughly, and should at this time be considered hypothetically.

Chemical asymmetry

Asymmetries in several neurotransmitter concentrations have been demonstrated in the human brain. Amaducci et al. (1981) found greater choline acetyltransferase activity in the left planum temporale as compared to the contralateral homologue. Norepinephrine concentration was reported to be higher in the left than the right thalamus (Oke et al. 1978) and dopamine levels were reported to be higher in the left than in the right amygdala (Reynolds et al. 1983).

In rats, the dopamine concentration is found to be higher in the striatum contralateral to the rat's preferred paw for lever pressing (Zimmerberg et al. 1974). After unilateral amphetamine administration, rats were observed to rotate towards the lowest dopamine side (Glick 1974). Amphetamine, through its action on dopamine, may affect a fundamental mechanism that regulates paw preference and rotational preference.

In humans, Wilson et al (1984) observed that neuroleptic-induced dyskinesias are generally lateralised. Given the antidopaminergic properties of neuroleptic drugs, this implicates an asymmetry in basal ganglia dopamine in the human brain as well. Furthermore, patients with hemi-Parkinson's disease who have exaggerated asymmetry of striatal dopaminergic activity were also shown to rotate asymmetrically: predominantly away from the hemisphere with the higher dopamine levels (Bracha et al. 1987). Only one post-mortem study (Glick et al. 1982) focused on left-right differences of neurotransmitter concentrations within the basal ganglia of the human brain. Asymmetry was found for several neurotransmitters in various structures. Most pronounced asymmetry was found in the globus pallidus, with the left structure having significantly higher levels of dopamine than its right-sided homologue. These findings imply that motor dominance may be related to higher levels of dopamine in the striatum of the dominant hemisphere. Possibly, dopaminergic asymmetry may be a mediating factor for language dominance as well.

Ontogeny of handedness and cerebral lateralization

Handedness in humans and "pawedness" in animals, becomes visible in the performance of precise unimanual tasks. These fine motor tasks are not easily studied in all animals. Nevertheless, several animal species that have been studied, such as rats, mice and apes consistently preferred to use one paw (either the left or the right) for precision tasks (Corballis 1991). Therefore, handedness may not be an exclusively human phenomenon.

However, the unequal distribution between left and right-handedness probably is unique for humans. Most animal populations showed an even distribution between right and left paw preference (Corballis 1991). In contrast, human populations appear to have been predominantly right-handed for at least 5000 years, as indicated in the examination of tools and art work of different geographical regions (Corballis 1991). However, left-handedness has persisted in a small, but stable, minority in prehistoric and historic times (Annett 1995).
Because of the association with language, cerebral lateralization has been considered to be specific for humans. However, cerebral lateralization of other functions, such as vision, singing and spatial orientation, have been demonstrated in the brains of apes, in rats, in birds and even in fish (Corballis 1991). In fact, cerebral lateralization appears to be a rather general property of the vertebrate brain. In humans, language lateralization probably has a long evolutionary history, since asymmetry of the Sylvian fissure favouring the left hemisphere has been identified in the endocasts of the skulls of Neanderthal men and of the Peking man (Corballis 1991).

Is aberrant cerebral dominance disadvantageous?

It is not clear whether a different cerebral organisation for language (i.e. right or bilateral cerebral dominance) causes differences in cognitive functions, special talents or specific disadvantages. A commonly held belief is that left-handers are more artistic than right-handers. Most famous examples are Leonardo daVinci and Michelangelo. Indeed, non-right-handed persons are found to be overrepresented among artists (Mebert and Michel 1980) and also among architects (Peterson and Lansky 1974). In addition, some studies reported that left-handers are more talented for music (Mebert and Michel 1980). It is possible that a more bilateral cerebral activation pattern results in a less standardised, more creative way of thinking. However, reported differences are subtle and could not always be replicated (reviewed by Mebert and Michiel 1980). Neuropsychological aspects of left-handers have been studied extensively (for an overview see Herron 1980). A large study on cognitive functioning of right-handers and non-right-handers failed to find significant differences (Hicks 1978). Despite their higher frequency of bilateral and right cerebral dominance, non-right-handers appear to perform within normal limits on all tests of cognitive abilities (Herron 1980). However, within the group of non-right handers the strongly left-handed subjects score equal or slightly better than right-handers, while the ambidextrous subjects score significantly worse (Annett 1995). In the UK National Child Development cohort, a large population-based prospective study, children with more equal hand skills were found to be disadvantaged on cognitive abilities relative to children with more asymmetric hand skills (Crow 1996).

In conclusion, there are no major cognitive advantages or disadvantages associated with non-right-handedness, but a low degree of motor dominance (whether right or left) may be disadvantageous as compared to strong motor dominance.

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Part 1 Language lateralization in the healthy brain

CHAPTER 2

Lateralization and evolution

Behavioural Brain Sciences 2003 26(2) 239 - 240

ABSTRACT

In this chapter, a model is proposed in which unilateral development of Broca's and Wernicke's area in the human brain results from one or more uniquely human "language genes". These language genes are hypothesized to have an expression pattern that is generally restricted to the left hemisphere. Bilateral or right-sided cerebral dominance for language can be understood as an aberrant expression pattern of the hypothesized language genes which causes the language areas to develop normally, but at a different location.

Corballis (2003) proposed a theory to explain why human handedness is related to cerebral language lateralization. Based on several intriguing findings in monkeys, apes, hominids and humans he hypothesized that human speech and right hand preference has evolved from gestures, which is the basis of communication in monkeys and apes.
Evidence for this theory is derived from the function of the inferior frontal area in monkey and man. The mirror-neurons, located in the monkey's homologue of Broca's area and its contralateral homotope, can initiate a grasping movement, but these neurons can also recognize the same movement performed by another animal. These cells may have provided the essential neurological basis on which language developed. The dual function of these mirror-neurons guarantees the necessary parity between speaker and listener, which requires the two parties to have a common understanding of the communicative elements. This parity is essential to account for the human ability to perceive the invariant articulatory units, despite of the great variability in the acoustic signal (i.e. pitch, loudness, velocity, and emotional color). This dual function of the neurological substrate for language (production and recognition) is the core premise of one of the most influential theories on language: "the motor theory of speech perception" (Liberman and Whalen 2000). This theory assumes that the basic phonetic elements of speech are not the sounds, but the articulatory gestures necessary to generate these sounds. This assumption is supported by the finding of functional imaging studies that listening to speech activates the frontal areas of the brain (the "motor-lobe") much more than the temporal areas (the "sound-lobe") (Bookheimer 2002). Thus, part of the frontal neurons that represented the production and perception of gestures in monkeys may gradually have acquired more facial mimic and eventually speech.

However, basic language functions in human are generally lateralized to the left hemisphere, while the monkey's mirror-neurons appear to be bilaterally similar. Whatever evolutionary mutation took place, it appears to have particularly affected the left hemisphere.
An explanation for this "unilateral evolution" could be found in an evolutionary principle in molecular genetics. At the molecular genetic level, an evolutional change often starts with the duplication of a gene (Cooper 1999). One gene copy maintains to function as before, thereby preventing loss of a vital protein, while the redundant copy is free to mutate into a potentially useful variant. The latter gene copy may accumulate formerly

lethal mutations and in some instances acquires a hitherto non-existing function.
Evolution of the human brain may have progressed parallel to this molecular principle. The left cerebral hemisphere could be viewed as the redundant copy, the one that gradually adopted a new function: language, while the right hemisphere warranted the continuation of conventional attainments: the production and perception of automatic emotional utterances.
The monkey's vocal productions are characterized as automatic, emotional utterances without semantic or syntactic content (Corballis 2003). This description bears close resemblance to the speech of aphasia patients who suffered severe left hemispheric stroke. These patients can hardly produce any intentional speech, but can sometimes produce unexpected automatic speech (frequently curses) in emotional situations. As in the monkey, this speech is not under voluntary control and most likely originates from the right hemisphere, since it is lost after a second infarction at the right side (Kinsbourne 1971). It could thus be hypothesized that the verbal capacity of the human right hemisphere is the homologue of the monkey's vocal system.

Evolution of language areas, in one hemisphere only, could result from a gene (or a cascade of genes), most likely a transcription factor, which has an expression pattern restricted to the left hemisphere. Such unilateral expression patterns have previously been discovered for transcription factors that induce asymmetric development of the heart and great vessels (Levin and Mercola 1998). Parallel to asymmetry of the heart, asymmetry of the brain may also result from an asymmetric expression pattern of certain gene products (discussed in chapter 5).

Presently, only one gene has been identified to have a major role in human language: the transcription factor FOXP2 (Enard et al. 2002). However, the importance and the uniqueness of this gene for human language capacity have yet to be established.
If we accept that FOXP2 or other language-related genes enable the brain for language functions, then the human variance in language lateralization could be explained as a genetic polymorphism that affects not the function, but only the expression pattern of such a language gene. Aberrant expression patterns of the hypothesized language gene would cause the language areas to develop normally, but at a different location (i.e. bilateral or in the right hemisphere).

According to our view, motor dominance is not likely to result from the same gene (s) as language dominance, since 70% of the left-handed subjects have left cerebral dominance (Knecht et al. 2000). However, genetic and environmental factors that disrupt the unilateral left sided expression pattern of the language gene(s) may also disrupt unilateral expression of gene(s) that support the development of manual dexterity. This could explain why deviant language lateralization is more common, but not standard in subjects with deviant motor dominance.

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CHAPTER 3

The fMRI method to measure language lateralization

Neuroimage. 2001 Apr;13(4):719-33.

ABSTRACT

Recent advances in functional neuroimaging techniques have prompted an increase in the number of studies investigating lateralization of language functions. One of the problems in relating findings of various studies to one another is the diversity of reported results. This may be due to differences in the tasks that are used to stimulate language processing regions and in the control tasks, as well as differences in the way imaging data are analyzed, in particular the threshold for significance of signal change. We present a simple method to assess language lateralization that allows for some variation of tasks and statistical thresholding, but at the same time yields reliable and reproducible results. Images acquired during a set of word comprehension and production tasks are analyzed conjointly. As opposed to the use of any one particular task, this combined task analysis (CTA) approach is geared towards identifying language regions that are involved in generic language functions rather than regions that are involved in functions that are specific to single tasks. In two experiments CTA is compared to single task analysis in healthy right-handed males. In a third experiment left-handed males were examined. Results indicate that CTA: 1) improves detection of language-related brain activity in individual subjects, and 2) yields a high language laterality index (LI) in right-handed males with a small variance across subjects. The high LI matches the strong left-hemisphere dominance for language that is typical for these subjects as reported in neuropsychological and clinical tests in other studies.
In the left-handed subjects dominance was found either in the left (n=4) or right (n=1) hemisphere, or was absent (n=3). The LI derived from CTA is more consistent across statistical thresholds for significance of signal change in fMRI analysis than individual task analysis. Also, the CTA results are very similar to those obtained with conjunction analysis of the same data.

INTRODUCTION

Processing of language is one of the few cognitive domains that is clearly mediated by predominantly unilateral brain structures. In most healthy individuals, language functions involved in production and phonological and semantic processing are mediated predominantly by regions in the left, hence 'dominant', hemisphere (Binder 1997; Fiez 1997). Reliable assessment of hemispheric dominance for language is typically required for neuro-surgery of brain structures in or near the language regions (Binder et al. 1996a; Binder et al. 1997). In recent years, laterality of language functions has become subject of interest in psychiatry, as various disorders appear to be associated with reduced laterality, such as autism (Hier et al. 1979), dyslexia (Dalby et al. 1977), attention deficit hyperactivity disorder (Gazzaniga 1973) and schizophrenia (Bruder et al. 1995). With the advent of in vivo neuroimaging techniques, in particular functional Magnetic Resonance Imaging (fMRI), it has become possible to measure laterality of language functions in the brain non-invasively (Jonides et al. 1998; Paulesu et al. 1993; Petersen et al. 1989; Rueckert et al. 1994; Small et al. 1998). An important issue of concern however, is the reliability of imaging-derived measures of laterality (laterality index, LI) in individual subjects. fMRI measurements are quite variable across subjects, as well as within subjects when tested for a second time (e.g. Ramsey et al. 1996), in terms of which brain regions are activated and in terms of magnitude (i.e. degree of signal change) and extent (i.e. size of activated regions) of activation. Measurements of neuroimaging-derived LI also vary considerably across studies. For instance, LI ranges from 0.15 (Benson et al. 1999) to 0.83 (Lee et al. 1999) on a scale of –1 to +1 for healthy right-handed subjects performing one or another word generation task (Binder et al. 1995; Pujol et al. 1999; Springer et al. 1999; Xiong et al. 1998a).

In contrast, clinical studies on language processing indicate that lateralization of language functions is very consistent across individual subjects. Clinical indication that language processing is lateralized, is obtained in several ways: by assessing effects of brain lesions, and by inactivating one hemisphere at a time by means of intracarotid amobarbital infusion (the Wada test). Damage to the left lateral inferior frontal cortex (mainly Broca's area but also extending beyond) (Broca 1861), or to the left parieto-temporal cortex (including Wernicke's area)(Wernicke 1874), typically results in one of several types of aphasia (Alexander et al. 1989; Alexander and Schmitt 1980; Costello and Warrington 1989; Damasio 1981; Geschwind 1970; Geschwind et al. 1979; Kertesz et al. 1979; Rasmussen and Milner 1977), whereas damage to the right-hemisphere homologues of these areas rarely results in such language deficits (Geschwind 1970). For clinical purposes laterality is assessed by means of the Wada test (Wada and Rasmussen 1960). Wada testing in patients who are considered for surgical treatment of epilepsy has shown that inactivation of the left hemisphere results in loss of language production and comprehension (Loring et al. 1990; Rasmussen and Milner 1977) in most right-handed patients. According to Wada studies, the left hemisphere is dominant in most right-handed as well as left-handed patients (>76 % and >70 % respectively) (Binder et al. 1996b; Kurthen et al. 1994; Woods et al. 1988; Wyllie et al. 1990). Some caution should be practiced with extrapolation of these numbers to healthy subjects, as in patients with temporal lobe pathology language processes may have become restructured over time. Nevertheless, lesion and Wada studies indicate that the vast majority of right-handed, and to a lesser extent left-handed, subjects are left-hemisphere dominant for language. Another clinical procedure that is used in epilepsy surgery is electrocortical stimulation mapping (ESM), which is applied during surgery (or before by means of implanted stimulation grids, e.g. (Schäffler et al. 1996)) on the dominant hemisphere. This procedure identifies regions that are critical for language processing (Ojemann 1991) by inactivating specific cortical areas during speech production and/or comprehension, and has confirmed the existence of the classical critical language regions first reported by Broca and Wernicke. These regions are typically located in the same hemisphere (Ojemann et al. 1989; Schäffler et al. 1996), and are regarded as essential for comprehension and production of language. Thus, whereas language laterality appears to be a clear-cut phenomenon clinically, fMRI studies produce variable results. Variability may be the result of several factors, including type of language task and control task (Binder 1997), volume of braintissue that is imaged and/or included in analysis (ranging from a few slices to whole brain), and the algorithms and thresholds used in image analysis.

Comparison of functional neuroimaging with ESM in the same patients typically indicates that neuroimaging identifies more language regions than ESM, suggesting that functional imaging identifies additional regions that participate in the network(s) that subserve language processing but are not critical (Bookheimer et al. 1997; Fitzgerald et al. 1997).The contribution of these additional regions may be highly specific for the task, or may be non-specific (such as attention or interfacing with long-term memory) and therefore potentially less lateralized (Binder 1997; Knecht et al. 1996). One way to deal with this issue in functional imaging is to use multiple tasks with different characteristics, and to then focus on regions that are active in all tasks. In this so-called ''conjunction analysis" (Price et al. 1997; Price and Friston 1997) the function of interest is ideally the only one that is invoked by all tasks. The analysis then aims at selectively detecting activity that is common to all tasks. In principle one should then be more focussed on the regions that are indispensable for language comprehension and production. In a recent study where fMRI of language processing was compared with ESM, we noted that a good match between language foci was obtained only in voxels that were activated in more than one language task (Rutten et al. 1999). This agrees with the notion of conjunction in that language structures that are active in multiple tasks may correspond to the critical structures observed in clinical studies (Papathanassiou et al. 2000; Price and Friston 1997), and accordingly may provide a more reliable index of laterality than one based on a single task.

In this paper we take this notion further, introducing a method that involves conjoint analysis of scan data across different language tasks (combined task analysis, CTA). Tasks were selected that had been shown to effectively predict outcome of the Wada test in epileptic patients, i.e. semantic decision and word generation. These tasks require intact word comprehension for correct performance, and to some degree word production depending on the specific instructions given to the subjects. Three tasks were selected for the current study, to address functions underlying word comprehension and word production, i.e. semantic decision (Binder et al. 1996b; Binder 1997; Desmond et al. 1995), verb generation (Benson et al. 1999; Pardo and Fox 1993), and antonym generation. The latter was included because recent studies suggest that the processes involved in the generation of nouns and of verbs (Damasio and Tranel 1993) may not overlap completely. The three tasks were expected to invoke activity in the cortical regions that play an important role in language, the so-called "transmodal epicenters" (Mesulam 1998; Papathanassiou et al. 2000) in or near the areas of Broca and Wernicke. Other candidates for epicenters have also been proposed, such as the anterior inferior temporal gyrus (Papathanassiou et al. 2000; Schäffler et al. 1996). The classic regions are essential for both comprehension and production, although Broca's area may be more involved in the latter (Ojemann 1983; Schäffler et al. 1996). We did not include an object naming task, which has also been used frequently in imaging studies (Bookheimer et al. 1997; Hunter et al. 1999), because some studies including one of ours (Rutten et al, 2002) indicate that it does not yield strong laterality measures (Benson et al. 1999). Verbal fluency tasks (Hertz-Pannier et al. 1997; Lehericy et al. 2000; Zerrin Yetkin et al. 1998) carry the disadvantage that performance cannot be adequately monitored in an MRI scanner.

Compared to individual task analysis, CTA was expected to yield a better index of language laterality based on the notion that 1) different language tasks activate different networks of brain structures (Binder 1997; Damasio and Tranel 1993; Ojemann 1991), 2) these networks share several (common) brain structures, and 3) common structures may correspond to the language-critical regions observed with ESM (Ojemann 1991; Rutten et al. 1999). By combining several tasks, the analysis is expected to favor detection of those regions that are active in all tasks, over those that are not. This approach is conceptually similar to conjunction analysis introduced by Price et al. (1997), but the implementation is different. Instead of testing for consistency of activation across tasks after performing subtraction analyses within task-control pairs and subsequently masking-out voxels where interaction between tasks exceeds a preset threshold, the test for consistent activity is in our study incorporated in one single factor in the multiple regression factor matrix, resulting in a more direct analytical procedure. Both methods are compared in one of the experiments.

The issue of fMRI-based laterality assessment within individual subjects is addressed with a focus on the following methodological factors: the potential advantage of using and analyzing multiple language tasks conjointly, differences between several widely used language tasks, and the effect of threshold-level for significance of fMRI signal change. As there is no simple solution to the problem of comparing reliability of different fMRI protocols, we followed an indirect strategy. Firstly, to test for optimal detection of left-hemisphere dominance, part of the study focused on healthy right-handed males, assuming that they all exhibit strong left-hemisphere dominance for language (Lee et al. 1999; Woods et al. 1988). Secondly, the chance of failing to detect activity in language regions in individual subjects was measured, since such failure does not allow for measurement of laterality. Thirdly, sensitivity of the laterality variable to the level of statistical thresholding was examined, as an index of robustness across analytical approaches. Fourthly, degree of laterality, and its variability across subjects was assessed. Assuming that all right-handed subjects were strongly lateralized to the left, a maximum laterality index close to 1.0 (see methods section for calculation) was expected, with minimal variability. Also, the relationship between the tasks was examined to determine consistency of the laterality index. As most right-handed subjects are expected to show strong left-hemisphere dominance, the range of values was expected to be too small for a correlation analysis. To increase this range, an additional group of left-handed subjects was tested, in whom laterality is reportedly diminished or even in the opposite direction (Annett 1976; Annett 1998; Pujol et al. 1999; Tzourio et al. 1998b; van der Kallen et al. 1998).

MATERIALS AND METHODS

Three experiments were conducted. In experiment 1, three widely used single-word processing tasks were used which involve semantic processing and word production, i.e. a verb-generation (VERB) task (Xiong et al. 1998b), a categorical semantic decision (CAT) task (Kapur et al. 1994), and an antonym-generation (ANT) task (Benson et al. 1996), in a group of healthy right-handed males. The group of subjects was extended with eight left-handed healthy males in experiment 2, for comparison of LI, and for correlation analyses across tasks and regions. We noted that the brain activity maps associated with the CAT task, the only task that allowed for measurement of performance in the scanner, were of a poor quality both in terms of levels of activity and of degree of lateralization. With the purpose of forcing phonological and lexical processing of each word and thus increasing language-related brain activity, a novel task was made where the words were spelled backwards (see ''language tasks''). In experiment 3 this task was tested, again with healthy right-handed males, together with the VERB task, and CTA was performed.

Subjects.

For experiments 1 and 2, eight healthy right-handed male subjects (age 25, sd 5 years), and eight healthy left-handed males (age 23, sd 5 years) were included respectively. The mean handedness index as calculated from the Edinburgh Handedness Inventory (Oldfield 1971) was 0.98 (sd 0.04) for the right-handers and –0.88 (sd 0.35) for the left-handers. The high standard deviation for left-handers was due to one subject with an index of –0.04. The others were strongly left-handed (index < -0.92). In experiment 3, a new group of eight healthy right-handed males, aged 24 (sd 5 years), participated. Subjects were not taking any medication or street drugs, and alcohol consumption did not exceed 15 drinks per week. Subjects were students, with Dutch as primary language. After oral and written explanation of all procedures, the subjects signed an informed consent, approved by the ethical committee.

Language tasks

In experiment 1 and 2, the ANT, VERB and CAT tasks were used. Words for all three tasks were presented visually, one every three seconds, and consisted of four to eight characters. For all tasks subjects were instructed to repeat the presented word as well as the generated word (VERB and ANT) silently, i.e. without overt articulation, to prevent head motion. In the ANT task the subject had to think of a word that was the opposite of the presented word. In the VERB task the subject had to generate an appropriate verb for the presented concrete noun. In the control condition for these tasks a small fixation dot was presented in the middle of the screen. For the CAT task, the subject had to decide if the concrete noun presented on the screen was an animal. Affirmative responses were given by pushing an air-mediated button and performance was recorded with a computer. The control task included the same number of button press responses, which were cued with a small dot on the screen with random intervals. Subjects responded with the dominant hand (right hand in experiment 1, left hand in experiment 2). Error rate on the CAT task, including misses and intrusions, was 3% (sd 2%) for right-handed subjects and 4% (sd 4%) for left-handers.
To avoid the risk of inadvertently eliminating language-related brain activity (Binder 1997), we did not use characters from the alphabet during any of the control periods. The three tasks were similar in that processes involved in word comprehension were activated (i.e. orthographic and implicit phonological processing, lemma and conceptual access), and those involved in word production. The CAT differed from the other tasks in that category information was mapped onto the response hand, and that a response had to be made. VERB and ANT differed in the type of association to be made.

Thus the common processes were word comprehension and production. The latter two in particular have been shown to be highly lateralized in Wada test studies.

In experiment 3, the VERB task was used and a novel task. In this task, referred to as the ''BACK'' task, the same words as in the CAT task were used (with different volunteers), and the instruction was the same (push the button if the word represents an animal), but the difference was that the words were presented in reverse spelling (e.g. ''ekans'' for snake). None of these words had a meaning when read front-to-back. This was explained to the subjects beforehand and they practiced on a few of these words. We expected that phonological processing would be enhanced, as recognition of the word form was impossible with the letters spelled backwards. Again, the control task involved an equal number of button press responses cued with a dot, and performance was recorded. Due to technical problems the performance data was lost for 1 subject. For the remaining seven, error rate on the BACK task was 9 % (sd 7 %), i.e. 14 % of the animal words were missed, and responses were given on 4 % of the non-animal words (intrusions) This increase in error rate compared to the CAT task indicates that the BACK task was more difficult. The VERB task was selected from experiment 1 on the basis of the finding that group-mean activity in the left-hemisphere language regions was significant at the high Tcrit only in this individual task (see fig.1C), combined with a significant LI.

Scanning protocol

Each task was performed during ten periods of 29 seconds, alternated with rest periods of 29 seconds. During each period, four fMRI volumes were acquired. Functional scans initiated and terminated seven seconds later than the task to compensate for the delay of the vascular response. Activity was measured with a Philips ACS-NT Gyroscan 1.5 Tesla clinical scanner with PT1000 gradients (10 mT/m) and a standard quadrature headcoil, using the navigated BOLD-sensitive 3D PRESTO fMRI sequence (Ramsey et al. 1998; Van Gelderen et al. 1995). The 3D PRESTO scan technique differs from Echo Planar Imaging in that artifacts resulting from inflowing and draining blood are strongly reduced due to continuous excitation of the whole volume and to the use of strong 'crusher' gradients (Duyn et al. 1995) respectively. With this technique a close match between site of fMRI signal change and site of critical neuronal function, measured with ESM, has been shown (Rutten et al. 1999). Sequence characteristics are: TE/TR 37/26 ms, flip angle 9 degrees, FOV 225x180x70, matrix 64x52x22, slice thickness 3.51 mm, scan time 7.25 s. Spatial resolution after reconstruction was approximately 4 mm isotropic, at an isotropic voxel size of 3.51 mm. The functional volume was oriented such that the anterior and posterior language regions were included in all subjects. Functional maps were superimposed on a registered anatomical volume, to determine location of brain activity. The anatomical image was acquired for each subject at the end of the session using 3D-FFE (TE/TR 4.6/30, flip angle 30 degrees, FOV 256x256x100, slice thickness 1.2 mm). Stimuli were presented by means of a PC, a video projector positioned outside the scanner room and a through-projection screen at the scanner bed that was viewed via a mirror fixed to the headcoil. The head was supported by foam padding.

Analyses

Data were processed off-line on an HPTM workstation using PV-waveTM processing software, separately for each subject. The inferior two slices were not analyzed, because signal intensity in these slices was lower than that in the rest of the volume. All scans were registered to the last volume of the last block to correct for head movements (for details see Ramsey et al. 2002). Brain activity was analyzed for each individual subject, by means of a multiple regression algorithm (Worsley and Friston 1995). This analysis was done for each task separately, i.e. ANT, CAT and VERB in experiments 1 and 2, and VERB and BACK in experiment 3. An additional analysis was performed on the total set of data for the individual tasks combined (combined task analysis: CTA), by applying multiple regression to the whole set as if one single task was used (see introduction for rationale). Thus in experiments 1 and 2 the CTA contained the data from ANT, CAT and VERB, and for experiment 3 the CTA contained the data from VERB and BACK. Each regression analysis contained one experimental factor consisting of value 1 for every scan acquired during execution of the language task(s), and value 0 for those acquired during the rest or control condition (BoxCar). Three additional factors modeled scanner noise and linear signal drift (i.e. one for drift across all scans, one for drift in each contiguous scan series (i.e. 80 scans) and one for drift within each condition. Scans were normalized to mean MRI signal intensity of the whole scanned volume prior to regression analysis.

To estimate how the CTA is affected when activity in a particular voxel occurs in only 2 or 3 out of three tasks, we calculated the correlation between the CTA input function (i.e. a factor with value 1 for the active epochs of all three tasks, and value 0 for the passive epochs) and simulated datasets. The latter were constructed by assigning a value 1 to active states of 1, 2 or 3 tasks, and a value 0 to the active epochs of the remaining task(s) and to all passive epochs, and then adding random values to each datapoint, with a normal distribution and a standard deviation of 1/CNR, where CNR is a constant representing the contrast-to-noise ratio. The CNR is the ratio of percent signal change due to activation to standard deviation of fMRI signal over time (scans). Correlation values were then calculated and averaged over 1000 simulated datasets, for each of several CNR values. Analysis of simulated datasets indicated that when activity in a voxel occurs in only 2 or 1 out of 3 tasks, correlation with the input function declines by approximately 30 % and 58 % respectively, relative to activity in all 3 tasks (at contrast to noise ratios ranging from 0.5 to 4.0). These numbers hardly change, even when CNR is set at a hypothetical 10.0 (numbers are 29 % and 56 % respectively). A realistic CNR value with PRESTO was previously shown to be 2 for activity in the primary motor cortex (Ramsey et al. 1998). At this CNR value, current analysis of simulated datasets indicated that activity in 1, 2 or 3 tasks would result in a correlation, with the CTA input factor, of 0.27, 0.48 and 0.71 respectively. Even when activity was twice as high (i.e. CNR of 4) in the case of one task, correlation remained low (0.37). This indicates that the CTA approach strongly favors activity that occurs in all tasks as compared to activity that occurs in only 1 or 2 tasks. To further examine whether the CTA analysis was sensitive to activity in less than 3 tasks, we also applied conjunction analysis to the CTA dataset from experiment 1. The latter differs in that each of the six conditions, i.e. rest and active conditions for each individual task, is modeled separately. The main effect map is then obtained by contrasting the three regression coefficients of the active conditions to the three coefficients of the rest conditions, for each voxel. Interaction between the tasks are measured by contrasting coefficients of 2 tasks at a time, resulting in three interaction effects (ANT versus CAT, ANT versus VERB and CAT versus VERB). Voxels which displayed any interaction, at a liberal threshold of t=3.0, were then removed from the main effect map. For each subject the final map was compared to that of the CTA analysis.

For each image analysis, Bonferroni correction was used to correct for the total number of comparisons (i.e. number of voxels in the whole brain), resulting in a critical t-threshold (Tcrit) of $t > 4.5$, at $p<0.05$ (one-sided) (Ramsey et al. 1998). It should be noted that this threshold may appear to be high for imaging experiments, but it is in our view mathematically the correct threshold for a corresponding p-value of 0.05 if the images are not smoothed (Van Gelderen et al. 1995). Some correlation does exist in space as a result of signal fluctuations caused by physiological processes, but this cannot be determined accurately. Smoothing is not applied in this study, as in our experience language-mediating structures tend to be small (Rutten et al. 1999). In order to assess the sensitivity of analyses to the choice of this Tcrit, the same procedure was followed for all subjects with a Tcrit of 3.0, which is roughly comparable to the threshold that is used in the widely used SPM analysis program (Friston et al. 1995a) on smoothed images when activity is expected a priori. Thus, for each subject several brain activity maps were obtained, one for each task (ANT, CAT, VERB, CTA in experiments 1 and 2; BACK, VERB, CTA in experiment 3) and Tcrit (4.5 and 3.0).

Individual laterality indexes (LI's) were obtained by comparing the number of active voxels (i.e. voxels exceeding the Tcrit) within specified regions of the brain (volumes of interest, VOI's), between the left and right hemisphere. To reduce contribution of non-specific brain activity, only language regions were included in the analyses.
The regions were manually delineated, blind to the activity maps, using the mapping system introduced by Brodmann (Brodmann 1909) as described in the atlas of Duvernoy (1991), and consisted of the areas that mediate language processing. We defined one VOI in each hemisphere, being the combination of anterior language regions corresponding to Brodmann areas (BA) 44 and 45, and posterior regions consisting of BA 21, 22, 41 and 42 (middle and superior temporal gyrus), BA 40 (supramarginal gyrus) and BA 39 (angular gyrus).These regions cover the areas of Broca and Wernicke (left VOI) and the contralateral homologues (right VOI). Care was taken not to include BA 9 and 46, as these regions mediate working memory rather than language-specific functions (Courtney et al. 1998; Mellers et al. 1995). As the scan volume did not include the anterior and inferior temporal cortices, these were not included in the analysis. Initially separate VOI's were made for the anterior and the posterior language regions, but as we found no significant effect of this factor in any of the analyses, these

regions were combined into one. The relative contribution of anterior and posterior regions is tested in experiment 1. For each subject, task and Tcrit, the LI was calculated as follows : LI = nVx in left VOI minus nVx in right VOI, divided by total nVx in left and right VOI's, where nVx is the number of voxels that exceed the Tcrit.

For all subjects of this study, the scan data were analyzed in the same way. The experiments differed only with regard to subject handedness (right-handed in experiment 1 versus left-handed in experiment 2), and in set of language tasks (VERB, ANT and CAT in experiment 1 versus VERB and BACK in experiment 3).
Correlations for laterality indices between tasks (each individual task versus CTA) were investigated in all subjects from experiments 1 and 2 taken together.

RESULTS

Experiment 1

Activity

Before performing parametric statistical analyses on the numbers of active voxels in the VOI's, each VOI and taskset was checked for normal distribution of the data across subjects by means of Kolmogorov-Smirnov tests. None of the left hemisphere regions, but some of the right hemisphere data, failed the criterion for normal distribution. Some caution should however be practiced with this small number of subjects. At the Bonferroni-corrected level of $p<0.05$, i.e. a Tcrit of 4.5, all subjects exhibited activity in the language regions (left and right VOI combined) in the CTA analysis. In the individual tasks however, not all subjects did (see Table 1). As can be seen in fig.1A, when analyzing numbers of active voxels group-wise, significant activation (one-sided t-test against value zero at $p<0.05$) occurred in the left VOI only in the CAT, VERB and CTA sets. Failure to reach significance for the ANT task was probably due to one subject with an exceptionally high number of active voxels (without this subject the test was significant). Group-averaged activity in the right hemisphere VOI occurred only in the CTA set. The three individual-task sets were compared to each other by means of a General Linear Model analysis for repeated measurements (SPSS version 9), with task and hemisphere as within-subject factors. There were no significant differences between the tasksets, neither a main effect of taskset nor interactions involving this factor. Overall, the effect of hemisphere was significant (multivariate test $F(1,7)=8.4$, $p<0.05$).

The CTA maps were compared to the conjunction maps, of which the interaction effects were thresholded at 3.0, and the main effects at 4.5 (after removal of voxels which exhibited an interaction effect). Firstly, the voxels obtained with CTA (at the high Tcrit) were tested for presence of interaction effects as obtained with the conjunction analysis. Secondly, the CTA maps were compared to the conjunction maps in terms of numbers of active voxels in language regions. Thirdly the LI was compared. No interaction effects were present in any of the CTA map voxels in the language regions, which supports the notion that CTA is not sensitive to activity in less than the three tasks. The conjunction analysis yielded somewhat higher numbers of active voxels in the left hemisphere (on average 3 voxels), which is most likely due to a somewhat better fit in the regression model when conditions are modeled separately. The LI values were marginally higher (a mean LI increase of 0.05) as a result.

In the lower threshold analysis, i.e. a Tcrit of 3.0, all subjects exhibited activation in all four sets. In the group-wise analyses activation was found in both left and right VOI in almost all sets (fig.1B), as was expected at this low threshold. Similar to the high-threshold analysis, no significant task effects were found in the GLM analysis, but the overall hemisphere effect was significant (multivariate test $F(1,7)=19.4$, $p<0.01$). The same GLM

Table 1. Absence of significant language activity in individual subjects

task	Experiment 1	Experiment 2	task	Experiment 3
ANT	2	5		
CAT	4	4	BACK	1
VERB	3	4	VERB	2
CTA	0	2	CTA	0

Numbers of subjects that do not show significant activation in any of the language regions (left and right hemisphere combined), above a T-threshold of 4.5. Numbers are shown for each experiment (see methods for details) and task. Eight subjects in each experiment. Abbreviations : ANT antonym generation, VERB verb generation, CAT categorical semantic decision, BACK categorical decision task with words spelled in reverse, CTA combined task analysis.

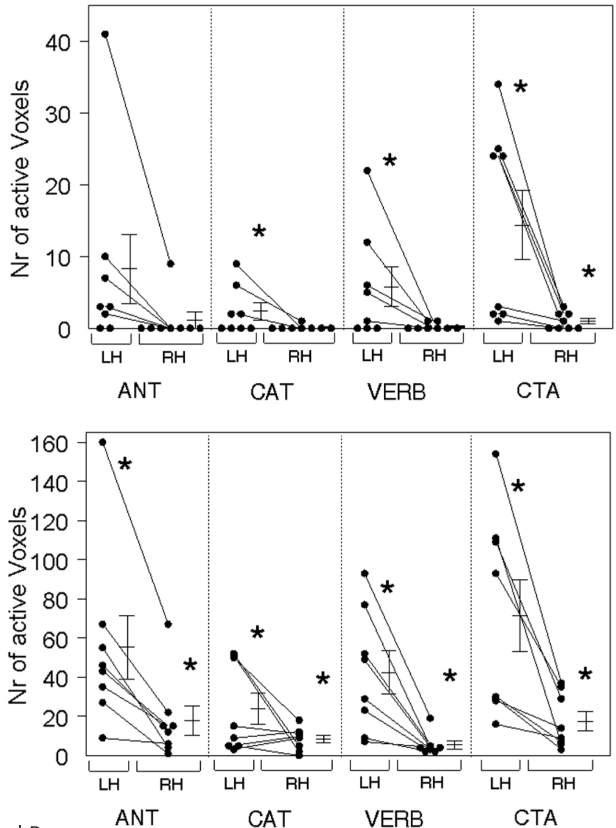

Figure 1A. and B.
Language-related brain activity for three individually analyzed tasks and the combined analysis in 8 right-handed subjects (experiment 1), in language regions in left and right hemisphere, for a high and low threshold for significant activation. Result for individual subjects are plotted, and group-mean values are presented in the graphs. Dots represent individual values, i.e. numbers of voxels exceeding significance threshold. Group-mean values are shown with standard deviation. Results are shown for the high threshold (Tcrit=4.5, figure A), and for the low threshold (figure B). Abbreviations : ANT antonym generation, VERB verb generation CAT categorical semantic decision, CTA combined task analysis, LH left hemisphere, RH right hemisphere.
Significance of number of voxels relative to zero (t-test one-sided) : * $p<0.05$.

analyses were applied with anterior and posterior regions separated (as an additional factor), to assess possible differences in anterior-posterior ratios between tasks. No effect was found involving this factor. Depending on task and Tcrit, activity in posterior regions (i.e. Wernicke and parieto-temporal cortex) was between 56 % and 65 % of total activity in the VOI's, indicating similarity of anterior-posterior ratios.

Laterality index

When no activity occurs in any of the language regions, a LI can not be determined mathematically. However, in order to maintain those subjects in further analysis, for those subjects the LI was set to zero in the tasks where no activation was detected. This occurred only when a Tcrit of 4.5 was used (see previous paragraph).

In the high threshold analyses, the mean LI exceeded 0.4 in all the analyses (Fig. 2). When testing group-mean LI against a value of zero, it was significant in all sets and VOI's (indicated with asterixes). As can be seen in fig. 2, the CTA analysis yielded the highest degree of laterality (LI=0.88). Interestingly, the standard deviation was by far the smallest in the LI of the CTA task, which reflects a high correspondence of this LI between the subjects. Comparing the three individual tasks by means of GLM for repeated measures with task as within-subject factor was not meaningful, as only 3 subject showed activity on all three individual tasks.

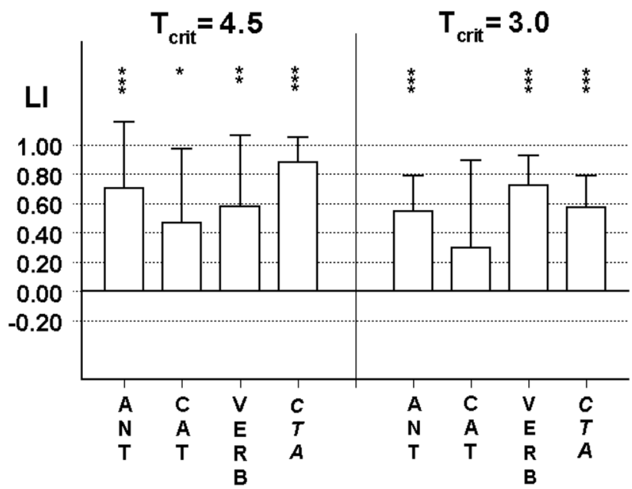

Figure 2
Laterality index presented per task and threshold level, averaged within the group of 8 right-handed subjects for experiment 1. Abbreviations: ANT antonym generation, VERB verb generation, CAT categorical semantic decision, CTA combined task analysis, LI laterality index.
Significance of LI relative to LI=0 (t-test one-sided) : * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

In the low threshold analyses, the LI's were very similar to those derived from the high threshold sets (Fig.2), although the LI's of the CAT task were reduced and became more variable. When contrasting the three individual tasks by means of GLM analysis (with task as repeated measure) a weak effect was found ($F(2,14)=4.69$, $p=0.058$, epsilon-corrected). Subsequent pairwise comparisons of tasks indicated that VERB yielded the highest LI, followed by ANT and then CAT. Overall, the LI's at the 3.0 threshold tended to be lower than those in the 4.5 threshold (difference not significant). This was expected as with the low threshold the number of 'false positives', i.e. voxels that exceed it merely by chance, increases irrespective of region or hemisphere. These voxels expectedly add, in approximately equal numbers, into both hemispheres, thereby diluting the contribution of true active voxels and causing the LI to move towards zero.

Experiment 2

Activity

The eight left-handed subjects performed the same tasks, but exhibited less activity in language regions than the right-handed subjects. This difference was not significant, but it may explain the larger number of subjects that did not activate above the high threshold (Table 1). At the low threshold, all but one subject showed activity in language regions.

To determine whether the difference in total activity between subjects was consistent across tasks, correlations between individual tasks were calculated. Combining subjects from experiment 1 and 2, at the low threshold, only ANT and CAT were correlated ($r=0.68$, $p=0.004$). Other combinations of tasks were not ($r<0.3$, $p>0.28$). The same effects were found when only right-handed subjects were analyzed, and when the high threshold data were used. This shows that different subjects displayed high activity in different tasks. Interestingly, each task correlated significantly with the CTA (16 subjects at low threshold, $r>0.58$, $p<0.05$).

Laterality index

Figure 3 shows the LI for the CTA analysis at the high and low threshold. The left-handed subjects displayed a wider range, with half the group being left-lateralized and half either non- or right lateralized, in contrast with right-handed subjects who were all clearly lateralized to the left. The difference between left-and right handed subjects was significant only at the high

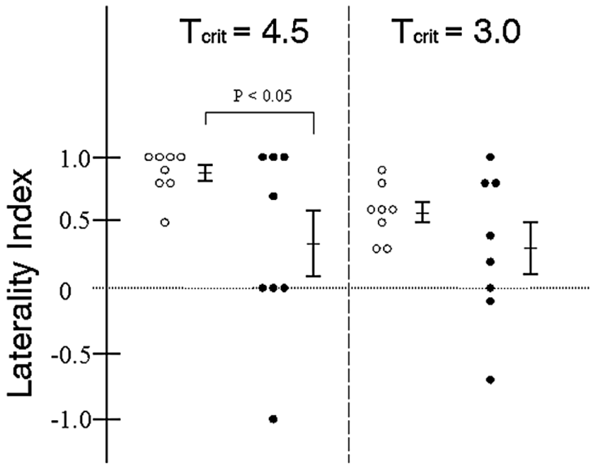

Figure 3
Comparison of laterality index between right-handed (open symbols) and left-handed (closed symbols) subjects from experiments 1 and 2, for a high and low Tcrit. Laterality index is based on the CTA datasets. Group-average values are shown with standard deviations.

threshold ($t(14)=2.02$, $p=0.037$). The difference diminished with the lower threshold, as was expected (all LI values move towards zero with the increase of false positive voxels).

Consistency (across tasks) of the laterality indices was examined by correlation analyses on the low-threshold data of all 16 subjects of experiments 1 and 2. The high-threshold results would have been more appropriate given the result of experiment 1, but there were too many missing LI values in the left-handers to make analyses meaningful (see Table 1). Each task was compared to the LI of the CTA. Correlation values were : 0.90 for ANT ($p<0.001$), 0.62 for CAT ($p<0.01$) and 0.88 for VERB ($p<0.001$), indicating a high correspondence across tasks, particularly for ANT and VERB. Between individual tasks, only VERB and ANT correlated well (rho=0.89, $p<0.001$). CAT was only weakly correlated with VERB (rho=0.43, n.s.) and ANT (rho=0.46, n.s.).

Consistency of the LI across the two threshold levels was examined in the total of 16 subjects, for each taskset. Tests for significance were one-sided as only positive correlations were expected. For the individual tasks the correlation ranged from 0.3 to 0.47, but none were significant. In the CTA taskset however, the LI was highly correlated across thresholds (rho=0.93, p<0.001). The correlation effects did not change when tested non-parametrically, and remained significant when correcting for the four comparisons. When correlations were recalculated with exclusion of cases where LI had been substituted with value zero (due to absence of activity in the high Tcrit, see Table 1), again only the CTA showed significant correlation. The clear distinction between the individual tasksets and the CTA set indicates that the LI derived from the latter is considerably less sensitive to level of thresholding. With regard to effect of performance on the CAT task, we found no effect on any of the brain activity or LI measures.

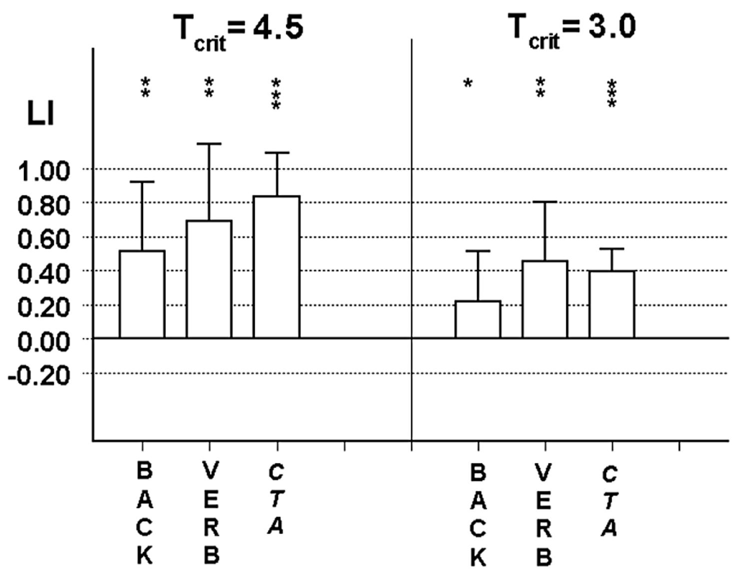

Figure 4
Laterality index presented per task and threshold level, averaged within the group of 8 right-handed subjects for experiment 3. Abbreviations: VERB verb generation, BACK backward-read categorical semantic decision, CTA combined task analysis, LI laterality index.
Significance of LI relative to LI=0 (t-test one-sided) : * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Experiment 3

Activity

Similar to experiment 1, the data were normally distributed in all VOI's except for some of the right hemisphere data. At the Tcrit of 4.5, all subjects exhibited activity in the VOI's in the CTA analysis. In the individual tasks however, not all subjects did (Table 1). In the lower threshold analysis (Tcrit = 3.0) all subjects exhibited activation in all three sets, i.e. VERB, BACK and CTA.

Laterality index

With the high threshold, the mean LI exceeded 0.5 in all the analyses (Fig. 4). When testing group-mean LI against a value of zero, it was significant in all sets. As can be seen in fig. 4, the VERB as well as the CTA analysis yielded almost the same results as the VERB and CTA analyses in experiment 1. Again, the CTA results were the best in terms of numbers of subjects with significant activity (Table 1), degree of laterality and standard deviation of LI. The BACK task analysis reflects a weak lateralization of brain activity in comparison with the other two sets, in spite of the relatively low numbers of subjects that fail to activate above threshold (Table 1). When comparing BACK and VERB (excluding subjects without activity in either) , the difference was significant $(F1,5)=8.0$, $p=0.037$). In comparison with the CAT task from experiment 1, the BACK task was slightly more successfull in activating language regions above the high threshold (Table 1).

In the low threshold analyses, the LI's were lower than those with the high threshold criterion (fig. 4),as would be expected (see experiment 1). Similar to the CAT task in experiment 1, the BACK task was associated with a low degree of laterality. When comparing BACK and VERB, the difference was not significant $(F1,7)=1.6$, $p=0.25$). VERB and BACK were not correlated, but VERB and CTA were ($rho=0.86$, $p<0.01$).The LI for the VERB task was compared to the LI for the same task in experiment 1, by means of a t-test. The reduction of laterality relative to experiment 1 (see figs 2B and 3B) was almost significant ($p=0.08$). Thus, with application of the low threshold, the results were less reproducible than with the high threshold. This may be due to the inclusion of 'false positive' voxels.

The range of performance on the BACK task across subjects (5-23 % errors) allowed for a meaningful correlation analysis with imaging data. This showed that it was not related to LI, as it did not correlate with any of the LI values, at either high or low Tcrit ($p>0.2$). It did however correlate with total activity, i.e. number of significant voxels for all tasks and Tcrit levels ($rho>0.77$, $p<0.05$), indicating that extent of activity increased with better performance across subjects.

DISCUSSION

One of the main objectives of the study was to determine whether assessment of a laterality index for language-processing in individual subjects would benefit from a multiple-task procedure. Combined task analysis (CTA) produced better results than analysis of each individual task in terms of: 1) robustness of detection of language-related brain activity, 2) the degree of laterality derived from individual brain activity maps, 3) small variability of laterality across subjects and 4) consistency of laterality across levels of threshold for significance of brain activity. The results indicate that CTA is a powerful method for laterality assessment in individual subjects.

In comparing the individual tasks to one another, the verb (VERB) and antonym generation (ANT) tasks tended to yield higher degrees of laterality than the two semantic decision tasks (CAT and BACK), in spite of the fact that subjects were instructed to vocalize the presented words silently in all tasks. A similar result has been reported by others (Benson et al. 1999; Lehericy et al. 2000). The finding of reduced LI persisted even when a low threshold for significant activation was applied, indicating that during semantic decision both hemispheres may be engaged. One explanation for the difference between production and decision tasks in our study is that phonological processing, which appears to be mediated by left prefrontal regions (Fiez 1997), contributes significantly to the laterality index in the production tasks. The decision tasks do not require word production other than a ''yes" or ''no" response. Another explanation may be that the control task for the decision tasks was not optimal, as it may not have minimized inadvertent language processing. Binder for instance reports clear laterality with a semantic decision task which is contrasted with an auditory (tone) decision task that reduces unintended language processing (Binder 1997).

For a CTA procedure to be effective in identifying language regions that are not specific for any particular task, the tasks should address different networks. The VERB and ANT tasks are similar in appearance and in the types of functions that are addressed, but the specific networks appear to be different (Damasio and Tranel 1993; Spitzer et al. 1995). The semantic decision tasks differ from the production tasks in that the meaning of the presented words is judged on categorical grounds, and retrieval and generation of new words is not required. The CAT task proved to be relatively ineffective in producing brain activity, and was therefore replaced by the BACK task, which was designed to enhance language processing by emphasizing (implicit) phonological processing of the presented word. Indeed the BACK task appeared to increase the number of subjects that activated above threshold (Table 1). The degree of laterality was however not affected by the modification, suggesting that both tasks still engage the same network, and supporting the notion that semantic decision is in itself not the best choice for assessing language lateralization. Of course the BACK task contains additional cognitive components, i.e. constructing the word letter by letter in reading the reverse-spelled word from back to front, which may introduce non-language-related processing. However, from the results it appears that this does not affect the CTA outcome, which illustrates that CTA is relatively insensitive to such confounding factors in task design (unless the factors are equally present in all tasks). An interesting finding was that performance on the BACK task was associated with extent of activity (total number of active voxels in all language regions in both hemispheres). This study does not indicate whether bad performance is the result of low levels of language-related brain activity, or whether both are the consequence of not being fully focused on the task. Importantly, performance did not relate to LI values, which suggests that although effort may affect brain activity maps, it does not seem to affect assessment of LI.

The VERB generation task was tested in two experiments. The results were very similar at the high threshold, but not at the low threshold. This finding suggests that reproducibility benefits from using stringent statistical thresholding for brain activation, where in principle only those regions are detected that are strongly involved in performing the task. The disadvantage is, however, that brain activation did not exceed the threshold in all subjects. Further analyses could elucidate the relationship between reproducibility and thresholding, but this was not done in the current study as reproducibility was not the main objective.

The rationale for CTA was that it would be sensitive to brain activity that is common to the different tasks, and that the obtained brain activity maps would represent an overlap of the different networks that are specific for the different tasks. As such, the CTA analysis is expected to be more selective for brain structures that are indispensable for (semantic) language processing than the individual tasks. In addition, a CTA analysis should increase the statistical power for detection of activity in those structures by including the total number of scans summed over tasks. In the current study we could not separate the two effects directly. However, the fact that LI for the different individual tasks was not consistent within subjects indicates that even if each task was administered for a longer period, thereby obtaining more scans to increase power, different tasks would produce different LI values for any particular subject. The LI obtained from the CTA was correlated with each individual task LI, indicated that it represented a weighted mean LI.

If CTA is effective in selectively identifying the essential language regions, i.e. the ''epicenters'' or the classical regions of Broca and Wernicke, then it should yield a high degree of laterality in healthy right-handed male individuals because those regions are typically located in the left hemisphere (as observed in lesion and surgical studies). The present results support these expectations: in contrast to the individual tasks, activity in the language regions was found in all subjects at a high threshold, the mean LI was the highest in both the experiments with right-handed subjects, and the variability across subjects was small compared to the individual tasks. Whether the activity maps selectively represent indispensable regions remains to be determined, perhaps by investigating patients who are subjected to the Wada test. An important advantage of the CTA analysis is the consistency of individual subject LI's across levels of thresholding, indicated by high correlations in the present study. The CTA approach is therefore a more robust method of assessing hemispheric dominance for language in individual subjects than the individual task approach.

The CTA approach is conceptually similar to the conjunction analysis designed by Price and colleagues (Price et al. 1997;Price and Friston 1997), but it differs in several respects. Firstly, only one factor is constructed for the ''main effect" of language processing, whereas in conjunction analysis each task is modeled with a separate factors. The main effect is then obtained by testing a linear contrast of the individual regression coefficients (Friston et al. 1995b). Secondly, potential differences in activity between tasks, i.e. ''interaction effects" within voxels, are explicitly removed from the final statistical maps in SPM 96/97, which was not done in the current study. Instead, CTA relies on the differential sensitivity for activation in some versus all tasks, as we showed with analysis of simulated datasets. Conjunction analysis is a more sophisticated method of searching for voxels that are active in all tasks, but there also interactions may still play a role if they remain below a set threshold for significance. One argument for excluding voxels with an interaction effect from the final statistical maps is that one task where activity is very strong, may contribute to a main effect in the absence of activity in the other task(s). We show that even when activity in one particular task is twice the normally observed magnitude of activity, the contribution of this to the regression coefficient obtained with CTA (when there is no activation in the other tasks) is quite limited. This is further supported by the fact that, when comparing CTA to conjunction analysis in experiment 1, no interactions were found in any of the CTA voxels. We did observe that conjunction analysis was slightly more sensitive to activation, which we attribute to better modeling in the regression analysis. The fact that we did not find interaction effects in the voxels identified with CTA suggests that interaction between tasks need not be explicitly tested with CTA. This does require further testing with different types of tasks (with known interactions).

In spite of the relatively small numbers of subjects, the difference in LI between left- and right-handed subjects (at the CTA / high threshold analysis) is convincing: whereas all right-handed subjects of experiments 1 and 3 exceeded a LI of 0.3, half the left-handed subjects were either non-lateralized or lateralized to the right hemisphere. This supports the observations of Annett (1976; 1998a) in neurological patients, that left-handers are much more likely to be either non- or right-lateralized. Our finding is also in agreement with a study by Tzourio et al (1998b) who observed a relatively high incidence of non-left lateralization in left-handers, using a story-listening task, as well as with other imaging studies using a word generation task (Pujol et al. 1999; van der Kallen et al. 1998).

The tasks all involved word production and semantic processing, albeit to different degrees. In addition some phonological processing may have occurred during silent vocalization of the presented and the generated words. Semantic processing has been attributed to the regions of Wernicke and Broca, both of which were included in the present VOI's. Recent studies have indicated that in the inferior frontal cortex semantic processing may be distinct from phonological processing, i.e. located in BA 47/45 as opposed to BA 44/45 (Fiez 1997; Poldrack et al. 1999). Regardless of the exact functional topography however, ESM studies have shown that language comprehension (Schäffler et al. 1996) as well as production (Ojemann et al. 1989; Schäffler et al. 1996) can be affected by inactivation of both posterior and anterior language regions. With the tasks used in the current study we found no significant difference in activity in frontal and posterior temporal language regions nor in degree of laterality. This is in agreement with other reports (Damasio 1992; Ojemann 1983; Schäffler et al. 1996) which indicate that function of anterior and posterior language regions is coupled and is similarly lateralized within individual subjects.

The tasks were not tightly controlled with closely-matched control tasks. As a result it cannot be ruled out that non-language activity contributed to the activity maps, most notably language-related attention but also orthographic processing and visual processing. This confound of the study may explain the presence of activity in the right hemisphere (as detected with CTA at the high threshold) in half of the right-handed subjects (fig 1A). Activity in the regions typically associated with working memory and attention, i.e. dorsolateral prefrontal cortex and anterior cingulate cortex, did not contribute to the results, as these regions were not included in the VOI's. Right hemisphere language-related activity has been observed by other groups also (eg (Papathanassiou et al. 2000 with conjunction of two tasks), and is thought to represent for instance language-specific attentional processing (Papathanassiou et al. 2000), and prosody (Damasio 1992). As Wada tests have shown that in most subjects inactivation of the right hemisphere has no clear effects on language processing, it seems that CTA is not fully successful in separating ''essential'' from ''involved but not essential'' language regions. However, for LI assessment in this study, the contribution of right hemisphere activity was marginal, as it occurred in only half of the subjects, and constituted on average no more than 6% of activity in all language regions.

Several issues were not addressed in the study. For one, it is not clear how other language tasks, for instance sentence processing or comprehensive reading, would affect the results of CTA. Engagement of frontal and parieto-temporal regions depends on whether the task involves production, syntax, semantics, phonology, or other functions (Binder 1997), so it is conceivable that particular tasks activate frontal but not temporal regions and vice versa. In this study the tasks were selected for their ability to engage both regions (Fiez 1997). Another issue is that of statistical thresholding for significance of signal change (Tcrit). Thresholding affects the size of areas of activity. Low thresholds will identify not only task-related voxels, but also voxels where signal change exceeds the threshold by mere chance (false positives), whereas high thresholds will identify only the strongest signal changes (Worsley 1994). As a result the boundary of truly activated regions cannot be determined reliably by fMRI. Conversely, the proportion of false to true positives in a region deemed active with fMRI can not be quantified accurately at all levels of Tcrit. It is therefore not possible to determine which threshold would yield the closest match of brain activity maps to the pattern of task-related neuronal activity. An advantage of applying a Tcrit that is based on Bonferroni correction is that the confounding presence of false positive voxels in the brain activity maps is virtually absent, and that the probability that the significant regions are truly associated with the task, is very high (Worsley 1994). One should however keep in mind that the accuracy of localization in fMRI depends on the used techniques (i.e. pulse sequence). Some are more sensitive to inflowing blood and/or to draining veins than others, and as a result are more prone to signal changes located up- or downstream from the site of neuronal activity (Duyn et al. 1994; Duyn et al. 1995). The PRESTO technique minimizes sensitivity to these sources of signal change (Grandin et al. 1997), at the price however of an increase in signal instability (Duyn et al. 1995).

Functional brain maps are typically smoothed to improve overlap of language regions across subjects, and to improve detection of language-related signal change. The latter argument may not be true for language processing regions, as there is evidence that these are typically small, i.e. as small as several millimeters in diameter (Ojemann et al. 1989; Rutten et al. 1999), and dispersed across the parieto-temporal cortex (Ojemann 1991). Smoothing of images improves detection power if the active region is considerably larger than the size of the measured units (voxels), but effectively decreases power if active regions are small, as appears to be the case in critical language regions. Individual assessment of laterality is more appropriate than group-wise assessment for use not only in neurosurgery, to reliably predict the consequences of tissue removal in individual epileptic patients considered for surgery, but also in studies on psychiatric syndromes. This is particularly the case when one is interested in correlations between laterality on the one hand, and clinical and cognitive variables on the other.

The current study supports the notion that laterality may be better assessed by means of a CTA design than a single task design. Although this approach conceptually implies that the obtained brain activity maps represent regions that are critical for language processing, this notion was not tested appropriately. This would require a comparison of these maps with results obtained with a more invasive technique such as intra-operative electrical stimulation mapping where the cortical surface is mapped in awake patients (Ojemann et al. 1989; Rutten et al. 1999). The current results could serve as a guide for such a study. Several groups have however focused on the issue of distinguishing critical from non-critical language-processing regions by means of neuroimaging. Price and colleagues have shown that neuroimaging can complement information about the role of specific brain regions derived from brain lesioned subjects (Price et al. 1999). They showed that left inferior frontal cortex was not necessary for normal performance on a semantic similarity judgement task, although it was typically involved in healthy subjects.

For less critical purposes, such as studies on psychiatric syndromes, and neurological (e.g. dementia) and language (e.g. aphasia, dyslexia) disorders, the implication of the current findings is that acquisition of short time series, i.e. few fMRI scans, and the use of only one language task may result in poorly reproducible laterality indices, and in limited power to distinguish between groups with different degrees of hemispheric lateralization.

In the present study the measurement of lateralization of language functions by means of fMRI was investigated. The goal was to find an optimal strategy for assessing hemispheric dominance for language functions with fMRI. The main conclusions are that: 1) combining tasks in one analysis improves detection of language-related brain activity in individual subjects; 2) combining tasks yields the strongest laterality index in right-handed males; 3) Laterality index is consistent (within subjects) across word generation tasks; 4) use of a high threshold yields a high degree of laterality in right-handed males; 5) use of a low threshold for voxel-wise significance improves detection of language-related brain activity in individual subjects but at the same time yields a reduced degree of laterality compared to that obtained with a high threshold; 6) use of a high threshold for voxel-wise significance enables distinction between groups of left-handed and right-handed subjects better than a low threshold, suggesting that a high threshold may be better in general for comparisons of hemispheric dominance for language between groups.

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Part 1 Language lateralization in the healthy brain

CHAPTER 4

Sex differences in language lateralization, a meta-analysis

Submitted

ABSTRACT

Sex differences in cognition are consistently reported, with men excelling in most visuo-spatial tasks and women in certain verbal tasks. It has been hypothesized that this sex difference in cognition results form a more bilateral pattern of language representation in women than in men. This bilateral pattern of language representation in women is thought to interfere with visuo-spatial functions in the right hemisphere.

To test whether language representation is indeed more bilateral in the female than in the male brain, meta-analysis was performed on studies that assessed language activity with functional imaging in healthy men and women. Effect sizes were weighted for sample size and the meta-analytic method was applied to obtain a combined effect size.

Fourteen studies were included, providing data on 377 men and 442 women. Meta-analysis yielded a Mean Weighted Effect d of 0.21, 95% Confidence Interval: -0.05 to 0.48, indicating no significant difference in language lateralization between men and women. Thus, the assumption that there is a difference in language lateralization between men and women is not supported. This implies that differences in language lateralization are probably not the cause of sex differences in cognitive performance, and the neuronal basis for these cognitive sex differences as yet remains elusive.

INTRODUCTION

Sex differences in cognitive performance are consistently reported, with men excelling in mental rotation and spatial perception and women performing better on verbal memory tasks, verbal fluency tasks and in speed of articulation (Linn and Petersen 1985; Kimura 2000). Furthermore, language and reading disorders are reported to occur approximately two times more often in boys than in girls (Flannery and Lieberman 2000). Since the sex difference in the risk for language disorders may be associated with the sex difference in cognitive skills, it would be both of scientific and clinical importance to obtain insight into the mechanism that underlies these sex differences in cognitive functions.

The cerebral substrate of the sex differences in cognition is not known. It has been hypothesized that language functions are represented more bilaterally in the female brain as compared to the male brain (McGlone 1980; Gur et al. 2000; Dorion et al. 2000). Women might thus use both hemispheres for language functions, while males use the dominant hemisphere only. A more bilateral pattern of language representation is thought to result in better verbal skills, while visuo-spatial processing would be inferior in subjects with bilateral language representation (Levy 1969). Thus, the female deficit in spatial performance is hypothesized to result from competition between verbal and spatial functions in the right hemisphere.
The theory that sex differences in cognition arise from more bilateral representation of language functions in females than in males is supported by two findings. Firstly, female stroke patients have been reported to exhibit verbal impairment less frequently after lesions of the left hemisphere than male patients (McGlone 1980). Secondly, structural MRI studies demonstrated that asymmetry of the planum temporale (the upper surface of the temporal lobe largely overlapping with Wernicke's area) is less pronounced in females than in males (Kulynych et al. 1994; Foundas et al. 2002). However, both observations only provide indirect support for decreased functional lateralization in the female brain. At present, functional imaging techniques have become available that can directly visualize cortical language representation in the human brain. Several functional imaging groups have reported data on sex differences in cortical language representation, but the results are inconsistent. In order to test whether language representation is indeed more bilateral in the female than in the male brain, a meta-analysis

was performed on studies that assessed language activity with functional imaging techniques in healthy men and women.

METHOD

Search Strategy and Selection Criteria

Studies were identified in Medline and PsychLit using combinations of the following search terms: sex, gender, language, words, dominance, lateralization, fMRI, PET. Additional references were retrieved from selected articles. Only English publications from international journals were selected. In addition, the last five volumes of three journals (Brain, NeuroImage and Human Brain Mapping) were searched manually to check for other suitable studies.
The identified studies had to meet the following criteria:
1. Language activation assessed bilaterally with an established functional imaging technique, such as Positron Emission Tomography (PET), functional Magnetic Resonance Imaging (fMRI), or functional Transcranial Doppler Ultrasound.
2. Activation assessed during the performance of a language task involving phonological and/or semantic processing of words, pseudo-words, sentences or stories. These tasks should generally yield a left-lateralized activation pattern in healthy volunteers.
3. Data available from healthy women and men who were well matched for handedness
4. Sufficient statistical data reported for males and females separately (means and standard deviations of the activation in each hemisphere), or exact F or T-values of the appropriate tests.

Analysis

For each study Cohen's d, the difference between the mean of the experimental group and the mean of the comparison group, divided by the pooled standard deviation (Shadish and Haddock 1994) was calculated. In this case, the mean lateralization index for women was subtracted from the mean lateralization index for men, divided by the pooled standard deviation of both. When means and standard deviations were not given, d-values were computed from exact p-values, t-values or F-values (cf. Lipsey and Wilson 2001).

After computing effect sizes for each study, the meta-analytic method was applied in order to obtain a combined effect size (Rosenthal 1991), which indicated the magnitude of the association across all studies. Effect sizes were weighted for sample size, in order to correct for upwardly biased estimation of the effect in small sample sizes. In addition, a homogeneity statistic (Qw) was calculated, to assess the heterogeneity of results across studies (Rosenthal 1991). When significant, this Qw-statistic indicated that the observed variance in study effect sizes is significantly greater than would be expected by chance if all studies had shared a common population effect size. Since several studies could not be included in the meta-analysis, a vote-count analysis was also carried out, in which each study was given a weight, based on its sample size. The total weight of all studies that reported a sex difference in language lateralization was compared to the total weight of all studies that reported no sex difference. All studies were included in this vote-count analysis to obtain a general picture of all published evidence. In studies that applied two or three language tasks, scan data of all tasks were used (i.e. these subjects were counted twice or thrice)

RESULTS

Twenty-four studies had been selected that had measured language lateralization with functional imaging techniques in healthy men and women and reported on a possible sex difference. Characteristics and main findings of these 24 included studies are provided in table 1.

From these studies, fourteen studies could be included in the meta-analysis, providing data on 377 men and 442 women. Figure 1 shows the individual weighted effect size of each study. The meta-analysis yielded the following results: Mean Weighted Effect: d= 0.21, 95% Confidence Interval: -0.05 to 0.48, indicating no significant difference in language lateralization between men and women. The homogeneity index Qw was 31.8, p=0.003, indicating significant heterogeneity among the studies.

All twenty-four studies were included in the vote-count analysis, providing data on 619 men and 743 women. From the 24 studies, 15 studies reported to have found no sex difference in language lateralization. Nine studies did report to find a sex difference, for at least one language task. Remarkably, the presence or absence of a sex difference reported by the authors did not always reflect the effect size that resulted from the meta-

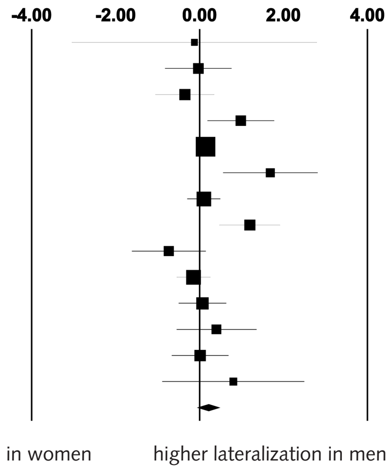
Tabel 1. Functional imaging studies (fMRI, fTCD or PET) on sex differences in language lateralization

Study	Number of healthy subjects	Language task	sex differences reported	Effect size or reason for exclusion
Binder 1995	2 men, 3 women	Semantic decision	No	Included, d=-0.17
Buckner 1995	12 men, 20 women	Stem completion	No	Excluded, insufficient data
		Verb generation	No	
Shaywitz 1995	19 men, 19 women	Rhym judgement	Yes	Included, d=1,22
		Semantic decision	No	
Pugh 1996	19 men, 19 women	Rhym judgement	Yes	Excluded, same subjects and scans as Shaywitz 1999
		Semantic decision	No	
Jaeger 1998	9 men, 8 women	Past tense generation	Yes	Excluded: insufficient data
		Verb generation	No	
Vd Kallen 1998	10 men, 10 women	Verbal fluency	No	Included, d=0,42
Schlosser 1998	6 men, 6 women	Verbal fluency	Yes	Excluded, insufficient data
Xiong 1998	5 men, 4 women	Verb generation	No	Included , d=0.9
Springer 1999	52 men, 48 women	Semantic decision	No	Included, d=-0.15
Frost 1999	50 men, 50 women	Semantic decision	No	Excluded, same subjects and scans as Springer 1999
Pujol 1999	50 men, 50 women	Verbal fluency	No	Included, d=0.1
Vingerhoets 1999	38 men, 52 women	Several verbal tasks	No	Excluded: no separate data for spatial and verbal tasks
Gur 2000	14 men, 13 women	Semantic decision	Yes	Included, d=0.03
Kansaku 2000	16 men, 14 women	Story listening	Yes	Included, d=1.01
Knecht 2000a	77 men, 111 women	Verbal fluency	No	Excluded, subjects overlap with Knecht 2000b
Knecht 2000b	128 men, 198 women	Verbal fluency	No	Included, d=0.14
Phillips 2000	10 men, 10 women	Story listening	Yes	Included, d=1.76
Vikingstad 2000	17 men, 19 women	Verb generation	Yes	Included, d=0.01
		Picture naming	Yes	
Billingsley 2001	6 men, 5 women	Rhyme task	No	Excluded: insufficient data
		Semantic decision	No	
Sommer 2003	12 men, 12 women	Verb generation	No	Included, d=-0.76
		Semantic decision	No	
Baxter 2002	9 men, 10 women	Semantic decision	Yes	Excluded: insufficient data
Hund-Georgiadis 2002	18 men, 16 women	Semantic decision	No	Included, d=-0.36
Rossell 2002	6 men, 6 women	Target detection of words	Yes	Excluded: hemifield projection of stimuli
Szaflarski 2002	24 men, 26 women	Semantic decision	No	Included, d=0.07
Sommer 2004	10 men, 14 women	Verb generation	No	Excluded: insufficient data
		Semantic decision	No	

Figure 1. Direction and weight (=size of the squares of rack studie)

Citation	Effect	NTotal
Binder 1995	-.124	5
Gur 2000	-.029	27
Hund-Georgiadis 2002	-.351	34
Kansaku 2000	.983	30
Knecht 2000	.140	326
Phillips 2000	1.686	20
Pujol 1999	.099	100
Shaywitz 1995	1.194	38
Sommer 2001	-.734	24
Springer 1999	-.149	100
Szaflarski 2002	.069	50
Van de Kallen 1998	.402	20
Vikingstad 2000	.010	36
Xiong 1998	.800	9
Combined (14)	**.214**	**819**

Random



analytic calculations. The vote-count revealed a score of 1137 for studies that found no sex difference, compared to 285 for studies that did find a sex difference. This implies that the studies that did report a sex difference generally had a much smaller sample size than the studies that reported no difference between the sexes.

DISCUSSION

In this study, data on language lateralization of healthy men and women from 14 functional imaging studies were combined in a meta-analysis. The difference in language lateralization between men and women was not significant. The vote-count analysis showed that the majority of studies reported no difference in lateralization between the sexes. The studies that did report a sex difference were generally relatively small, which may reflect a publication bias in favour of studies with positive findings. The results of this meta-analysis imply that the sex difference in language lateralization is very small or non-existent.

Functional imaging studies on sex differences in lateralization have not been reviewed previously with a meta-analytic technique. However, sex differences in language lateralization have been estimated with other methods, such as clinical studies on patients with unilateral brain lesions and

experiments in which dichotic listening tests are applied to measure perceptual asymmetry.
McGlone (1980) first reported a higher incidence of aphasia in 23 men as compared to 20 women after unilateral lesions of the left hemisphere. Kimura (1983) replicated McGlone's finding of a higher incidence of aphasia in men after left hemisphere injury in a sample of 144 men and 92 women. However, if this sex difference in the incidence of aphasia would results from a more bilateral pattern of language representation in women than in men, the incidence of aphasia after right hemisphere injury would be expected to be higher in women than in men. This prediction was not met, since the incidence of aphasia was similar (2% for men and 1% for women) in a group of 134 men and a group of 100 women with lesions of the right hemisphere (Kimura 1983). However, Kimura (1983) found that aphasia in women was more common after anterior lesions than after posterior lesions within the left hemisphere, whereas in men, aphasia was more common after lesions of the posterior language areas (Kimura 1983). Because anterior lesions occur less frequently than lesions of the posterior language areas, this offers an alternative explanation for the lower incidence of aphasia in women after left sided lesions. In contrast to McGlone's and Kimura's findings, Kertesz and Sheppard (1981) reported that 78 right-handed females who had suffered left hemispheric stroke performed slightly worse on the Western Aphasia Battery (WAB) than 114 males with similar lesions. No difference in score on the WAB between men and women was found after right hemisphere stroke.
Thus, a sex difference after left hemisphere lesions has not been consistently reported and differences in aphasia after right hemisphere lesions have never been demonstrated. Furthermore, the possible sex difference in the incidence of aphasia after left hemisphere lesions may rather result from intrahemispheric differences in the representation of language functions than from differences in the degree of lateralization.

Another test of sex differences in cerebral dominance for language is provided by experimental studies using dichotic listening techniques. Sex differences in dichotic listening tests have been reported by several relatively small studies (Lake and Bryden 1976; Voyer 1996; Coney 2002), but not by others (Witelson 1976). Furthermore, two large dichotic listening studies reported no gender difference in language lateralization. Hiscock and MacKay (1985) administered verbal dichotic listening tests to 477 right-handed volunteers in five consecutive experiments. None of the five analyses yielded a significant sex difference. Similarly, Hugdahl (2003) found no sex difference in a database of 1018 healthy subjects performing a verbal dichotic listening test. Thus, the results from dichotic listening studies are inconsistent. Since two large studies found no sex difference in language laterization, the sex difference, if present, is supposedly subtle. These findings are in line with the result of this meta-analysis.

In contrast to the findings on functional language lateralization, studies that measure anatomical size of the planum temporale do provide evidence for a gender difference in asymmetry. Structural MRI studies found a larger left planum temporale in men as compared to women (Kulynych et al. 1994; Foundas et al. 2002). A large voxel based analysis on MRI scans of 465 healthy adults reported increased asymmetry of the planum temporale in men as compared to women, which was caused by smaller left plani in women (Good et al. 2001)
It is not clear whether increased asymmetry of the planum temporale in men, as compared to women, reflects a higher degree of functional language lateralization in men. Two studies investigated the correlation between asymmetry of the planum temporale and cerebral dominance for language. Foundas et al. (1994) reported that asymmetry of the planum temporale correlated to cerebral dominance assessed with the Wada test in 11 subjects, while Tzourio et al. (1998) found no correlation between the same measurements in 14 subjects. The latter study did find a correlation between cerebral dominance and the size of the left planum. Thus, asymmetry of the planum temporale may not be an accurate predictor of functional language representation.

This study has several limitations. Firstly, a relatively large number of studies could not be included in the meta-analysis since they provided only qualitative information or insufficient statistical data about sex differences in lateralization. However, the sample size of the meta-analysis is still relatively large and the result of the vote-count analysis is congruent with the finding of the meta-analysis. Another limitation is that we analysed all language activation tasks that are generally lateralized to the left hemisphere, without dividing them into specific categories. Shaywitz et al. (1995) stated that only tasks requiring phonologically processing yield more bilateral language lateralization in women, while semantically processed task yield no sex difference in lateralization. Alternatively, Kansaku and Kitazawa (2001) suggested that only tasks that present real words in stead of non-words elicit a sex difference. There are many possible subdivisions that could be made on basis of task characteristics, such as visual or auditory presentation, single word stimuli or stories, phonological or semantic processing, productive or receptive tasks and abstract or concrete words, to name but a few. All these divisions appear to be equally valid candidates that may differently affect the degree of lateralization in the two sexes. However, all these separate tests would decrease the sample size and thus decrease the power of the meta-analysis. Furthermore, too many additional tests would increase the chance of a false positive finding. Therefore, we preferred to analyse the whole sample of all left-lateralized language activation tasks.

In summary, this meta-analysis found no sex difference in functional language lateralization. Thus, the hypothesis that language functions are represented more bilateral in women than in men is not supported. This suggests that language lateralization is unlikely to underlie sex differences in cognition and their biological basis as yet remains elusive. Future research may be aimed at other cerebral systems that could underlie sex differences in cognition.

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CHAPTER 5

Language lateralization in monozygotic twin pairs

Lancet 1999 Oct 23;354(9188):1445-6
Brain 2002 Dec;125(Pt 12):2710-8

ABSTRACT

An unexpectedly high percentage of monozygotic twin pairs is discordant for handedness. Some of these twins show mirror-imaging of several ectodermally derived features. Both features of discordant left-right asymmetry may be caused by relatively late monozygotic twinning, when the original embryo has already lost its bilateral symmetry. Language lateralization is related to handedness and may therefore also be altered during embryological asymmetry development in some monozygotic twins.

In this study, language lateralization was measured with functional MRI in 12 monozygotic twin pairs who were concordant for handedness and in 13 monozygotic twin pairs discordant for handedness. Lateralization indices were calculated from individual language activation patterns. Correlations were calculated to test intra-pair resemblance for language lateralization.

The intra-pair correlation for language lateralization was significant in the handedness concordant group, but not in the handedness discordant group. In the handedness discordant group, five twin pairs were also discordant for cerebral dominance. The other twin pairs of discordant handedness exhibited remarkable similarity in language lateralization.

The high intra-pair correlation for language lateralization in the handedness concordant twins suggests a genetic basis for language lateralization. However, in monozygotic twin pairs of discordant handedness, discordance for language dominance occurs in a significant number of twins. Discordant language dominance may be caused by a relatively late time of splitting of the original embryo, which disrupts the normal development of left-right asymmetry.

INTRODUCTION

Though symmetry across the anterior-posterior axis is the basic structure for animal and human life, many structures in the human body show left-right asymmetry. Even bilaterally paired organs, such as the lungs, kidneys and the testes show consistent left-right asymmetry in anatomy or function (Fujinaga 1997). Left-right asymmetries of the internal (mesodermally derived) organs are generally extremely stable, though inversions of some, or all, internal organs do occur (Fujinaga 1997). Complete reversal of visceral left-right asymmetry, situs inversus, is a very rare finding (approximately 1:10,000), but lesser degrees of disturbed visceral situs, isomerism, are more frequent (Fujinaga 1997). Isomerism may be expressed as poly or asplenia, as congenital heart disease or ectopic vein malformation (Burn 1991; Fujinaga 1997).

The cerebral hemispheres can be considered a paired organ as well. Unlike the mesodermally derived organs, the ectodermally derived cerebral hemispheres show a normal variation in asymmetry (Geschwind et al. 1979). Cerebral asymmetry is most pronounced for language function, for which the left hemisphere is generally dominant (Geschwind et al. 1979; Knecht et al. 2000a). Handedness is correlated with language dominance, in that left-handed persons are more likely to divert from standard left cerebral dominance (Pujol et al. 1999; Knecht et al. 2000a). While there are relatively few large scale studies on language dominance, handedness has been studied extensively (Herron 1980). Despite the abundance of studies, controversy remains about the origin of left-handedness. Several arguments favour a genetic mechanism. Firstly, studies in singletons show that left handedness tends to run in families; children of left-handed parents are three to ten times more likely to be left-handed than children from two right-handed parents (Coren 1992; McManus and Bryden 1992). Adoption studies further show that handedness of a child is strongly related to handedness of the biological parents, while handedness of their adoption parents is of little influence (Hicks and Kinsbourne 1976; Carter-Saltzman 1980). McManus (1985) introduced a genetic model for handedness, which poses that handedness is determined by one gene with two alleles: “D” for dextral and “C” for chance. The DD genotype always leads to right-handedness, but the CC genotype provides no direction to handedness, which then develops in a random fashion (i.e. left-handedness in 50% and right-handedness in 50%). The intermediate genotype, CD is an additive type, which gives rise

to right-handedness is a certain percentage (some 75%) of cases. Indeed, children from two left-handed parents, who are likely to be of the CC genotype, are only in 50% of cases left-handed themselves (Annett 1974).
Twin studies partly support a genetic basis for handedness. Several large twin studies on handedness did not find increased concordance in monozygotic twin pairs as compared to dizygotic pairs (McManus 1980; Derom et al. 1996; Orlebeke et al. 1996; Ross et al. 1999), although a large meta-analysis on 9,969 twin pairs from 28 studies found slightly but significantly higher concordance for handedness in monozygotic than in dizygotic twin pairs (Sicotte et al. 1999). This discrepancy between family and twin studies may indicate the presence of another, non-genetic factor in determining handedness in twins (Derom et al. 1996; Sicotte, et al. 1999).
In contrast to the abundance of studies on handedness in twins, only two studies assessed cerebral dominance for language in twins (Springer and Searleman 1978; Jancke and Steinmetz 1994). Both studies reported no significant intra-pair resemblance in monozygotic twin pairs on the dichotic listening paradigm (Springer and Searleman 1978; Jancke and Steinmetz 1994), suggesting non-genetic influences on cerebral dominance for language.
An obvious explanation for the low concordance for handedness and language lateralization in twin pairs is that twin birth is more complicated and more frequently preterm than singleton birth, which could cause "pathologic left-handedness", i.e. left-handedness as a result of left hemispheric brain injury, and deviant language dominance (Annett 1974; Annett and Ockwell 1980; van den Daele 1974). However, this can not be the only explanation, since brain lesions resulting from perinatal asphyxia are almost completely confined to the second born twin (Bulmer 1970; Arnold et al. 1987; Prins 1994), but left-handedness in twins is not more frequent in second born than in first born twins (Nachshon and Denno 1986; Nachshon and Denno 1987; Orlebeke et al. 1996; Christian et al. 1979). Another possible explanation for the low concordance for language dominance in monozygotic twin pairs is that the twinning process itself can sometimes disrupt normal asymmetry development of the embryo (Boklage 1987; Levin 1999; Sommer et al. 1999). This process may increase discordance for language lateralization and handedness only in monozygotic twin pairs, thereby lowering the difference in concordance between monozygotic and dizygotic twin pairs.
In chicken, mouse and frog a cascade of genes has been discovered that regulates left-right orientation at a very early stage (Levin and Mercola

1998a). Without asymmetric expression of these genes left-right asymmetry develops in a random fashion (Levin 1998). A similar genetic cascade probably determines asymmetry development in the human embryo as well (Levin and Mercola 1998b; Schneider and Brueckner 2000).

The time of splitting of a human embryo into monozygotic twin pairs is variable. Based on anatomy of the placenta, monozygotic twins can be divided into two groups: approximately one third of monozygotic twins are dichorionic and two thirds are monochorionic (Bryan 1992). The twinning process of dichorionic monozygotic twins probably occurs before blastocyst formation, whereas monochorionic twin pairs split after formation of the chorion, at least four days after fertilisation (Bulmer 1970; Derom et al. 1995). Of the monochorionic twins, only about four percent is monoamniotic (Bulmer 1970). These monoamniotic twins are thought to arise still later, at least eight days after fertilisation (Bryan 1992; Derom et al. 1995). Inactivation of one X chromosome in female embryos is closely associated in time with monozygotic twinning, and occurs when the embryo consists of approximately 20 cells (Puck et al. 1998). By studying similarity of X inactivation patterns in female monozygotic twin pairs, these time periods for twinning into dichorionic (Monteiro et al. 1998), monochorionic (Monteiro et al. 1998) and monoamniotic (Chinis et al. 1999) twins have been confirmed.

When monozygotic twinning occurs relatively late, as in monochorionic twins, the cascade of asymmetrically expressed genes regulating left-right asymmetry may already have been initiated. Splitting of this asymmetric embryo may leave one side with inappropriate information on left-right orientation. In the individual that develops from this side, left-right asymmetry may become deviant, which would increase the discordance rate for asymmetrical traits, such as handedness and cerebral dominance, in monozygotic twin pairs.

Monochorionic monozygotic twins, who result from a late twinning process, would be especially prone to this process. Two studies assessed concordance for handedness in monochorionic and dichorionic monozygotic twin pairs. Derom et al. (1996) studied handedness in 750 monozygotic twins and found no difference in handedness concordance between monochorionic and dichorionic monozygotic twin pairs. However, the failure to find a difference could be an artifact. In this study, handedness was scored as "unknown" in cases of ambidexterity. In the monochorionic monozygotic twins there were 19 cases of unknown handedness, against only 4 in the dichorionic monozygotic twins. If discordance for handedness had been defined as ambidexterity and left-handedness (non-right-handedness) in one twin and right-handedness in the co-twin, then the prevalence of handedness discordance would have been significantly higher in monochorionic than in dichorionic twins. Carlier et al. (1995) reported on 4 handedness discordant twin pairs in 20 monochorionic monozygotic twin pairs, against 2 in 20 dichorionic monozygotic twin pairs.

Since handedness is related to cerebral language representation, discordance in monozygotic twin pairs may also be expected for cerebral dominance. In this study language lateralization is assessed in monozygotic twin pairs. By assessing functional language lateralization patterns in monozygotic twin pairs, we tried to differentiate between genetically defined discordant handedness (as a result of the CC or CD genotype) and discordant handedness as a component of disrupted embryological development of laterality.

MATERIALS AND METHODS

Subjects

Twelve monozygotic twin pairs were included who were concordant for handedness (both right-handed). Another 13 monozygotic twin pairs were included who were discordant for handedness (one right-handed, one left-handed). Twelve twin pairs were male and 13 were female. Monozygosity was confirmed by genotyping. Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). Familial left-handedness was defined as one or more first-degree relatives, apart from the left-handed twin, that are left-handed. Three handedness concordant twin pairs and five handedness discordant twin pairs had familial left-handedness.

To decrease the chance of including a subject with “pathological left-handedness” (Coren, 1994) the following exclusion-criteria were used: born before the 35th week of pregnancy, birth-weight under 2 kg and paediatric admission due to perinatal complications.

Information on chorion type could be retrieved for 20 twin-pairs. From these, 13 twin pairs (five handedness concordant and eight handedness discordant pairs) were monochorionic and seven twin pairs (four handedness concordant and three handedness discordant pairs) were dichorionic.

After complete description of the study to the subjects, written informed consent was obtained, according to the declaration of Helsinki (1991) and approved by the Ethical Committee of our hospital.

Scanning protocol

The fMRI technique, the language activation tasks and the statistical analysis of the individual scans are described in detail by Ramsey et al. (2001).
Briefly, functional scans were acquired with a Philips ACS-NT 1.5 Tesla clinical scanner, using the blood oxygen level dependent (BOLD) sensitive, navigated 3D PRESTO pulse sequence (Ramsey et al. 1998), with the following parameter settings: TE/TR 35/24 ms, flip angle 9°, FOV 180x225 x91 mm, matrix 52x64x26, voxel size 3.51 mm isotropic, scan time per fMRI volume 2.4s. Following the fMRI procedure an anatomical scan was acquired (3d-FFE, TE/TR 4.6/30 ms, flip angle 30°, FOV 256x256x180 mm, matrix 128x128x150, slice thickness 1.2mm).

Language tasks

Two word tasks were used: a verb-generation task and a semantic decision task. For both tasks, words were presented visually, one every three seconds. Silent vocalisation was used to avoid head motion. All tasks were presented during ten blocks of 30 seconds each, alternated with periods of 30 seconds baseline conditions. For the semantic decision task, answers were given by pushing an air-mediated button and recorded by a computer.

Analyses

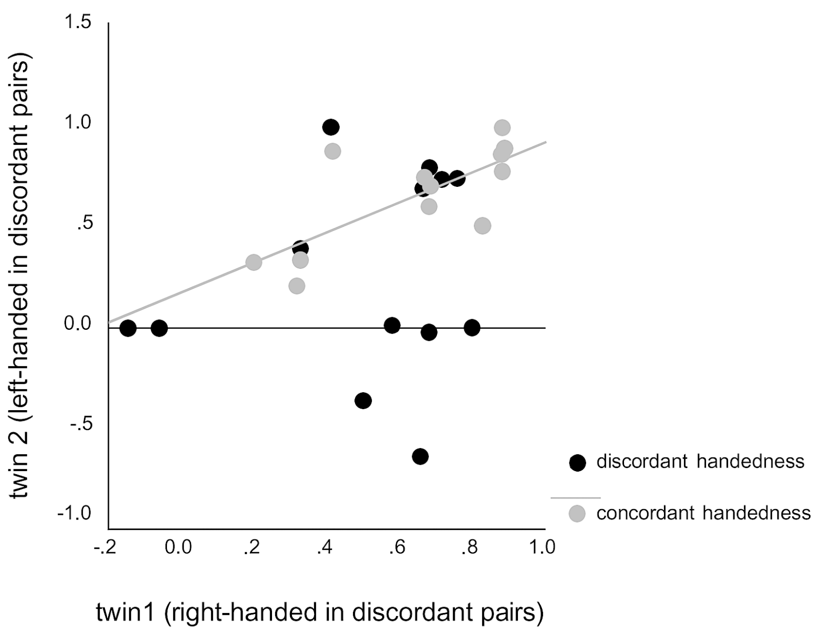
Functional images were analysed for each subject separately, on a voxel by voxel basis using multiple regression analysis (Worsley and Friston 1995). Voxels were considered 'active' if the task-related t-value exceeded 4.0 (corresponding to $p<0.05$ Bonferroni-corrected for the total number of voxels in all volumes of interest). Brain activity maps were obtained by analyzing the fMRI scans acquired during the two tasks together. Advantages of this combined task analysis are discussed by Ramsey et al. (2001).
Five volumes of interest (VOI) were delineated manually in each hemisphere of all anatomical scans, blind to statistical results. The VOI's comprised Broca's area and its contralateral homologue (Brodmann area (BA) 44 and 45), middle temporal gyrus (BA 21), superior temporal gyrus (BA 22, 38, 41, 42 and 52), supramarginal gyrus (BA 40) and angular gyrus (BA 39). Activation maps were superimposed on the anatomical scan.

A lateralization index was calculated for each subject using the formula: lateralization index = number of active voxels in all VOI's of the left hemisphere - number of active voxels in all VOI's of the right hemisphere / sum of activated voxels in all VOI's of both hemispheres.
Correlations were calculated between LI of the first and the second twin of a pair for the concordant and the discordant group in order to test intra-pair resemblance.

RESULTS

All subjects performed well on the semantic decision task (less than 10% mistakes). Significant activation of the language areas could be demonstrated in all subjects.
The mean lateralization index of the handedness concordant twins (n=24) was 0.62 (s.d. 0.32) and the mean lateralization index of the handedness

Figure 1
Language lateralization in handedness concordant monozygotic twins (grey) and handedness discordant monozygotic twins (black)



discordant group (n=26) was 0.38 (s.d. 0.43), the difference was significant (t=-2.3, p<0.05).

Within the handedness discordant group, the mean lateralization index of the right-handed subjects was 0.48 (s.d. 0.3), that of the left-handed subjects was 0.27 (s.d. 0.51); this difference was not significant (t=1.7, p=0.1).

The correlation between the lateralization index of the first and the second twin of a pair was significant in the handedness concordant group: rho=0.74, p<0.01 (plotted in figure 1).

The correlation between the lateralization index of the twins in the handedness discordant pairs was not significant rho=0.18, n.s (figure 1).

Lateralization indices and demographic data of the twin pairs are given in table 1 and 2.

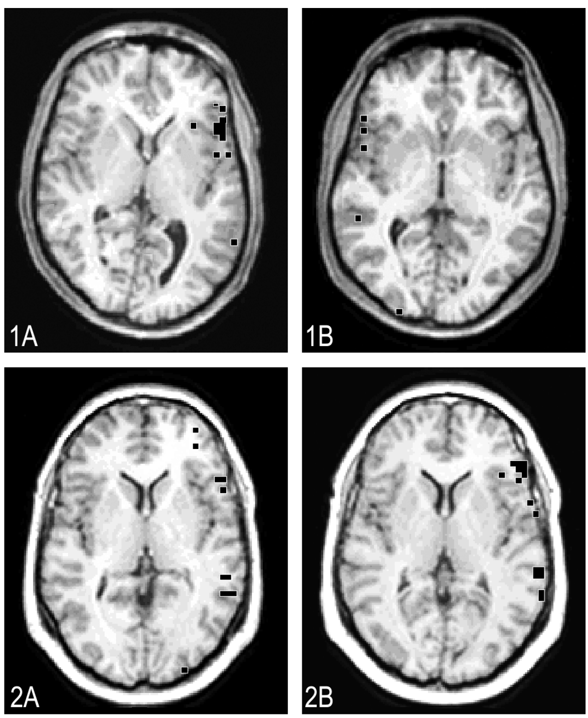


Figure 2,
Transaxial slices through Broca's and Wernicke's area of the 3D statistical brain activity maps. The black voxels indicate language-related activity. Shown are results for one monozygotic twin pair with discordant cerebral language dominance (1A: right-handed twin, 1B: left-handed co-twin) and for one monozygotic twin pair with similar cerebral dominance (2A: right-handed twin, 2B: left-handed co-twin).

Table I. Summary of findings in handedness concordant twins

Twin no.	LI first RH twin	LI second RH twin	Intra-pair difference	Familial LH	gender	Chorion
1	0.68	0.61	0.07	Yes	F	No information
2	0.33	0.34	0.01	No	F	Monochorionic
3	0.88	0.79	0.09	No	M	Dichorionic
4	0.88	1	0.12	No	F	Monochorionic
5	0.83	0.51	0.32	No	M	Monochorionic
6	0.68	0.71	0.03	No	F	Dichorionic
7	0.89	0.89	0	No	F	Monochorionic
8	0.42	0.88	0.46	No	F	No information
9	0.88	0.87	0.01	No	F	Monochorionic
10	0.67	0.75	0.08	No	M	Dichorionic
11	0.2	0.33	0.13	Yes	M	No information
12	0.82	0.9	0.08	Yes	M	Dichorionic

LI = language lateralization index, RH = right-handed, familial LH = one or more left-handed first-degree relatives, M=male, F=female

Table 2. Summary of findings in handedness discordant twins

Twin no.	LI RH twin	LI LH twin	Intra-pair difference	Familial LH	gender	Chorion
1	0.33	0.39	0.06	Yes	M	Monochorionic
2	0.72	0.74	0.02	Yes	M	Dichorionic
3	0.76	0.74	0.02	Yes	M	Monochorionic
4	0.8	0	0.8	No	F	No information
5	0.58	0.01	0.57	No	F	Monochorionic
6	0.68	-0.02	0.7	No	M	Monochorionic
7	-0.06	0	0.06	Yes	F	No information
8	0.67	0.7	0.03	Yes	F	Dichorionic
9	0.5	-0.36	0.86	No	M	Monochorionic
10	-0.15	0	0.15	No	M	Monochorionic
11	0.41	1	0.59	No	M	Monochorionic
12	0.68	0.8	0.12	No	M	Dichorionic
13	0.66	-0.64	1.3	No	F	Monochorionic

LI = language lateralization index, RH = right-handed, LH = left-handed, familial LH = one or more left-handed first-degree relatives apart from the left-handed twin, M=male, F=female

Examples of language activation patterns of a handedness discordant twin pair with discordant lateralization and a handedness discordant twin pair with similar language lateralization are shown in figure 2.

DISCUSSION

Language lateralization was studied in 12 monozygotic twin pairs of concordant handedness and 13 pairs of discordant handedness. In the handedness concordant twins, the intra-pair correlation was 0.74, which is high if we take into account that the reproducibility of this language activation method yields a test-retest correlation of 0.79 (Rutten et al. 2001). The high intra-pair resemblance in the handedness concordant twins suggests a genetic component for language lateralization. In the handedness discordant twin pairs, some pairs had high resemblance for language lateralization, while other pairs showed opposite patterns of lateralization.

Though this is the first study to assess language lateralization in monozygotic twins with fMRI, language lateralization was previously estimated in monozygotic twins with the dichotic listening paradigm. Springer and Searleman (1978) applied this technique to examine a large sample of 75 monozygotic twin pairs, of which 19 pairs were discordant for handedness. However, the data were only analysed group-wise, which prevents the distinction between twin pairs with similar and pairs with discordant perceptual asymmetry. Jancke and Steinmetz (1994) also applied the dichotic listening paradigm to study language lateralization in 20 monozygotic twin pairs, from which 10 were handedness discordant. Based on the low intra pair correlation of the whole group, Jancke and Steinmetz concluded that language lateralization is non-genetic in origin. A non-genetic origin of language lateralization would indeed explain their findings. However, language lateralization is correlated to handedness, which is known to be strongly determined by handedness of the biological parents, but not by handedness of adoption parents (Hicks and Kinsbourne 1976; Carter-Saltzman 1980). It therefore appears likely that language lateralization will also be genetic in origin. To our knowledge, only one study has directly addressed language lateralization in families and found more similar language lateralization among family members (Bryden 1975).

In the 20 monozygotic twin pairs from the Jancke and Steinmetz study (1994) asymmetry of the planum temporale was also assessed with structural MRI (Steinmetz et al. 1995). Though intra pair correlations for the degree of planum temporale asymmetry were low, the individual data showed similar asymmetry in some and discordant asymmetry in other twin pairs. The authors concluded that cerebral asymmetry is likely to be genetic, but its expression could be disrupted in some monozygotic twin pairs. Recently, Geschwind et al. (2002) assessed anatomical asymmetry of the frontal and temporal lobes in 72 monozygotic and 67 dizygotic twin pairs. They found strong intra-pair correlations in monozygotic twins who were concordant for right-handedness, but loss of intra-pair correlations in monozygotic twins of discordant handedness. Interestingly, dizygotic twin pairs of discordant handedness showed no decrease in intra-pair correlations as compared to handedness concordant dizygotic twins. However, it is not clear if the findings of Geschwind et al. can be compared to the results of the present study since they observed a significant right-ward asymmetry of the temporal and frontal lobe in the sample as a whole, and in the right-handed twins. Their asymmetry indices can therefore not be the anatomical substrate of left cerebral dominance for language.

Discordance for handedness in monozygotic twin pairs can be explained by the genetic model of McManus (1985): if the twins are of genotype CC they would have a 50% chance of becoming discordant for handedness (and 25% chance for the CD genotype). However, for language lateralization this model can not accommodate our data. Genetic models predict that monozygotic twin pairs, who have identical genes, would have similar chances of developing left, right, or bilateral dominance for language (McManus 1985). This was not the case in the 13 handedness discordant twin pairs of this study: 11 of 13 right-handed twins had left cerebral dominance for language, against 6 of the 13 left-handed co-twins. We further noted that the discordant twin pairs with similar lateralization indices had familiar left-handedness. In a post-hoc t-test on the twin pairs of discordant handedness, pairs with familial left-handedness turned out to have significantly lower absolute intra-pair differences in lateralization than pairs without familial left-handedness ($t=3.4$, $p<0.05$). Thus, twin pairs with familiar left-handedness, i.e. who probably are of DC or CC genotype, may both express the same genetically defined pattern of language lateralization. Furthermore, four of the five twin pairs that were discordant for both handedness and language dominance were known to be monochorionic (infor-

mation lacking from the fifth twin pair), which implies that the split into monozygotic twins occurred at a relatively late stage of embryological development, at least four days after fertilisation (Bulmer 1970).
We postulate that in these monozygotic twin pairs the splitting of the original embryo into two genetically identical twins took place at a stage when the original embryo had already lost its bilateral symmetry. In that case, the split may have disrupted the genetically defined pattern of language lateralization in one of the twins.
Though there is little knowledge on asymmetry development in the human embryo, recent animal research yielded several new insights in this field. In non-human vertebrates, the first occurrence of left-right asymmetry is the asymmetric expression of a cascade of patterning genes (Schneider and Brueckner 2000). In chicken, for example, several patterning genes such as Chicken Activin Receptor IIa (cAct-RIIa), Sonic hedgehog (Shh) and chicken Nodal-Related 1 (cNR-1) are expressed asymmetrically in embryos before the first signs of morphological asymmetry become apparent. CAct-RIIa is initially expressed more strongly on the right side of the primitive streak and then exclusively in the right half of Hensen's node (the chicken homologue of the primitive node), in ectoderm only (Levin 1998). This asymmetric expression occurs approximately 18 hours after conception when the primitive streak begins to develop. At stage five, approximately 20 hours after conception, when the head process develops, cAct-RIIa expression in ectoderm becomes symmetrically. Expression of other patterning genes, such as Shh and cNR-1, appears to be induced by the cAct-RIIa concentration, hence initiating a cascade of asymmetrically expressed genes. Shh is initially expressed symmetrically, but its expression becomes restricted to the left when cAct-RIIa is expressed at the right side of Hensen's node, also exclusively in ectoderm (Levin and Mercola 1998a). The gradient thus provided by these asymmetrically expressed genes probably regulates embryological development of left-right asymmetry, since manipulation of the asymmetric expression of Shh results in asymmetry development in a random direction (50% normal, 50% inverted)(Levin 1998). The elements of this genetic cascade are well conserved among vertebrates (Levin and Mercola 1998b) and homologue genes have been identified in human for most of these factors (Schneider and Brueckner 2000). It could thus be assumed that similar patterning genes are expressed asymmetrically during early human embryogenesis. In human, Shh, mapped to 7q36, encodes a signal that is instrumental in patterning many structures of the early embryo (Placzek

1995). Shh is necessary for the early subdivisions in the human neural plate (Kobayashi et al. 2002) and patterns the dorsoventral axis of the nervous system in combination with other factors (Robertson et al. 2001). If Shh is also expressed asymmetrically at some point during human embryogenesis, this factor could be responsible for the asymmetrical organisation of the cerebral hemispheres.

Splitting into monochorionic twins has been estimated to occur at the blasocyst stage, when the inner cell mass consists of approximately 128-256 cells (Monteiro et al. 1998) and even later for monoamniotic monochorionic twins (Chinis et al. 1999). At the time of splitting into monochorionic diamniotic twins, the anterior-posterior axis is already defined (Gardner 2001). The layout of the anterior-posterior axis and other early patterning of the embryo is largely defined by homeobox genes, from which the transcripts can be detected in the very first days after conception (Gardner 2001). In the light of these recent observations, the concept that the monozygotic twinning process itself is related to the development of congenital malformations seems plausible. Splitting of the embryo can lead to unequal distribution of such homeobox-derived proteins (Flannery 1987). Maldistribution of these essential controlling compounds could then upset the regulatory balance between these proteins and the DNA in individual cells, which can result in failure to begin or end a particular developmental task. Indeed, several studies consistently found more congenital malformations, such as macrocephaly, encephalocele, cleft lip and palate, tracheoesophagal fistula, malrotation of the alimentary tract and congenital heart disease in monozygotic twins than in singletons (reviewed by Luke and Keith 1990). Many of these malformations can be regarded as disturbances of left-right asymmetry or as a failure of the two bilateral halves to fuse in the midline (midline defects). Interestingly, among monozygotic twins, the monoamniotic twins, who have the latest separation, showed the highest frequency of these congenital malformations (Luke and Keith 1990; Boklage 1990).

It is not known how spontaneous splitting into monochorionic twins takes place in human (Steinman 2001; Luke and Keith 1990). Reorganisation into two co-dominant growth axes (i.e. anterior-posterior axes) has been proposed (Steinman 2001). The Fused gene, which was later renamed Axin, plays a critical role in the initial establishment of the embryonic anterior-posterior axis (Gardner 2001). In mice with two mutant alleles of this gene duplication of the anterior-posterior axis and subsequent splitting into monochorionic twins has been observed (Gluecksohn-Schoenheimer 1949). However, it remains uncertain if this mechanism also underlies spontaneous monochorionic monozygotic twinning events.

The most extreme case of late monozygotic twinning results in incomplete separation of the twins. When conjoined human twins have distinct hearts, the right-sided twin commonly has dextrocardia (Levin et al. 1996). In non-conjoined monozygotic twins, situs inversus is rare, but probably more frequent than in singletons (Torgersen 1950). Several congenital heart malformations such as tetralogy of Fallot, hypoplastic left heart and anomalous great vessel implantation can be viewed as milder laterality disturbances (Burn and Corney 1984). These malformations are significantly more frequent among monozygotic twins, typically affecting only one of the pair (Burn 1991).

The heart differentiates from the mesoderm, which develops in a later embryological stage, when monozygotic twinning only rarely occurs (Bulmer 1970). This could explain why disturbances of visceral laterality are rare, even in monozygotic twins. The ectoderm develops earlier and indeed mirror-imaging of ectodermal features, such as location of hair whorl and tooth eruption pattern are frequently present in monozygotic twin pairs (Farber 1981). Results from our study suggest that laterality disturbances of the cerebral hemispheres, ectodermally derived organs as well, may also be rather common in monozygotic twins.

If the monozygotic twinning process can indeed alter the embryonic development of left-right asymmetry, this could also have implications for singletons. Ultrasound studies have shown that at least 70% of twin pregnancies diagnosed before the 10th week miscarry or convert to a singleton in early pregnancy (Hall and Lopez-Rangel 1996). This implies that left-handedness and right cerebral dominance in some subjects born as singletons may also be the result of a late monozygotic twinning process from which only one twin survived.

In summary, language lateralization appears to have a genetic component, given the similarity in most monozygotic twin pairs of this sample. Discordance for handedness and language lateralization in some monozygotic twin pairs may result from disruption of normal ectodermal asymmetry development by the twinning process itself. Though the concept of laterality disturbance in human monozygotic twins is difficult to prove, it is obvious that monozygotic twinning is a very different process than dizygotic twinning, and more susceptible to malformations (Luke and Keith 1990). This phenomenon may complicate the interpretation of twin studies on laterality-dependent traits, but could provide a window into human embryological development of left-right asymmetry.

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Part 1 Language lateralization in the healthy brain

CHAPTER 6

Pharmacological aspects of language lateralization

Submitted

ABSTRACT

Differences in cerebral dopamine concentration have been found to affect the degree of cerebral dominance for motor control in animals. In humans, cerebral dopamine neurotransmission is correlated to motor dominance. Since language dominance is related to motor dominance, alteration in dopamine concentration might also affect cerebral dominance for language. To test this hypothesis, language activation was measured twice with functional magnetic resonance imaging in ten healthy right-handed men in a double blind crossover design two hours after amphetamine or placebo administration. Language-related activation increased significantly in task-related areas, but the individual lateralization index was not affected in the amphetamine condition as compared to placebo.
This suggests that alterations in the dopaminergic neurotransmission do not affect language dominance.

INTRODUCTION

A large number of functional and neuro-anatomical studies have demonstrated that the human brain is lateralized (Hugdahl and Davidson 2003). One hemisphere, usually the left, is dominant over the other in the control of language and handedness (Hugdahl and Davidson 2003). Despite the extensive documentation of cerebral lateralization, the neurochemical basis for dominance in the human brain remains elusive (Hugdahl and Davidson 2003). In contrast, substantial evidence shows that the rat brain displays multiple chemical asymmetries, some of which correlate with functional asymmetries (Glick et al. 1984).

Although rodents do not show the population bias towards right-handedness as found in human populations, they do show individual forelimb preferences. This preference is closely related to the directional preference of the animal for turning, circling and running in a specific direction in a T-maze (Glick et al. 1979; Zimmerberg et al. 1974). The neurological basis for the rat's forelimb preference is thought to reflect both chemical and pharmacological asymmetries of the nigro-striatal system. In the rat striatum an asymmetric distribution of presynaptic D3-dopamine receptors is found, with higher concentrations in the striatum contralateral to the preferred side (Glick and Shapiro 1984). The concentrations of dopamine in the two striata normally differs by about 15% (Zimmerberg et al. 1974) and this asymmetry could be increased to approximately 25% following administration of dextroamphetamine (Glick et al. 1974). Furthermore, the directional preference for turning behavior can be enhanced by administration of amphetamine or cocaine, substances that increase cerebral dopamine turnover (Glick et al. 1984; Glick et al. 1988). The efficacy of cocaine and amphetamine in stimulating turning to the preferred side suggests that these drugs affect a fundamental mechanism involved in the regulation of brain asymmetry.

In humans, Wilson et al (1984) observed that neuroleptic-induced dyskinesias are generally lateralized. Given the antidopaminergic properties of neuroleptic drugs, this implicates an asymmetry in dopamine receptor density of the basal ganglia in the human brain as well. Furthermore, patients with hemi-Parkinson's disease who have exaggerated asymmetrical striatal dopaminergic activity were also shown to rotate asymmetrically: predominantly opposite to the hemisphere with the higher dopamine levels (Bracha et al. 1987). Human post-mortem studies on chemical asymmetries reported conflicting results (Rossor et al. 1980; Glick et al. 1982), but quite pronounced asymmetry was reported for the globus pallidus, with the left structure having significantly higher levels of dopamine than its right-sided homologue (Glick et al. 1982). Given that 90% of humans are right-handed (Annett 1972), most of the subjects of this study presumably had been right-handed and the dopamine concentrations were thus higher contralateral to the dominant hand. In addition, volumetric studies of human brains reported that the left globus pallidus is also significantly larger than its non-dominant homologue (Kooistra and Heilman 1988; Orthner and Sendler 1975). A large Single Photon Emission Computed Tomography (SPECT) study found significant left greater than right asymmetry in the concentration of dopamine transporters (DATs) in the striatum and putamen of 126 healthy volunteers (van Dyck et al. 2002). In addition, a Positron Emission Tomography (PET) study of 20 healthy volunteers found that the degree of motor lateralization, as measured with the Purdue pegboard test, correlated positively with the left-right asymmetry in fluorodopa uptake in the putamen (de la Fuente-Fernandez et al. 2000). These findings suggests that asymmetry of dopaminergic metabolism in the putamen could also play a role in the determination of human handedness. Since motor dominance is related to language dominance (Hugdahl and Davidson 2003), dopaminergic neurotransmission may play a role in language lateralization as well. To investigate this hypothesized relationship, the present study examined the effects of amphetamine administration on language activation.

METHODS

Subjects

Ten healthy right-handed male volunteers were included in the study (mean age 21, s.d. 4). Handedness was assessed with the Edinburgh Handedness Inventory (Oldfield 1971). Only physically healthy subjects without a personal or family history of psychiatric illness (including drug or alcohol abuse) were included. The study was approved by the Human Ethics Board of the University Medical Center Utrecht. After oral and written explanation of the study, all subjects gave written informed consent in accord with the Helsinki Declaration of 1975 before enrolment in the study. Subsequently, they were interviewed using the Comprehensive Assessment of Symptoms and History (CASH) and History Schedule for Affective Disorder and Schizophrenia Lifetime version (SADS-L)(Andreasen et al. 1992) to ascertain absence of psychiatric illnesses. In addition, they filled out a medical checklist and underwent a full physical examination, including an electrocardiogram and routine laboratory tests. Subjects were asked to refrain from using caffeine, nicotine, over-the-counter-drugs and alcohol 24 hours before and after the administration of the medication. Subjects were fasting three hours before and after the administration of the medication, to minimize differences in blood uptake of amphetamine caused by differences in content of the digestive tract. On arrival, urine screening was performed to exclude the use of opiates, cocaine, amphetamines and cannabis. None of the subjects included had positive urine tests.

Procedure

The experiment had a double blind, placebo-controlled, crossover design. All subjects received both placebo and amphetamine on two separate occasions, one week apart.

Opaque gelatin capsules were manufactured that contained 2.5 mg of dextro-amphetamine or no active component (placebo). For every 10 kg bodyweight the subjects ingested one capsule, corresponding to 20 mg of dextro-amphetamine for a median body weight of 80 kg. The moderate dose of 20 mg dextro-amphetamine was chosen because this produces reliable increases on a variety of subjective psychostimulant measures, without causing troublesome side effects (Wachtel and de Wit 1999).

Heart rate and blood pressure were measured at baseline and every 30 minutes after ingestion of the medication to monitor the subjects.

After assessment of baseline physiological measures, the subject was given active or placebo medication. Two hours after administration of the medication the subject was scanned with fMRI technique. Timing of administration of amphetamine was based on pharmacokinetic data indicating that plasma levels of amphetamine peak two to three hours after oral administration (Wachtel and de Wit 1999).

Blood samples were drawn once, at the beginning of each fMRI session, and plasma dextro-amphetamine levels were measured using liquid chromatography, with a sensitivity of 10 ng/ml.

Scans

Functional scans were acquired with a Philips ACS-NT 1.5 Tesla clinical scanner, using the blood oxygen level dependent (BOLD) sensitive, navigated 3D PRESTO pulse sequence (Ramsey et al. 1998) with the following parameter settings: TE/TR 35/24 ms, flip angle 9°, FOV 180x225x91 mm, matrix 52x64x26, voxel size 3.51 mm isotropic, scan time per fMRI volume 2.4 s. Following the fMRI procedure, an anatomical scan was acquired (3d-FFE, TE/TR 4.6/30 ms, flip angle 30°, FOV 256x256x180 mm, matrix 128x128x150, slice thickness 1.2mm).

Activation tasks

Tasks and scan technique have been described in detail by Ramsey et al. (2001). Briefly, two word tasks were used: a paced verb-generation task and a semantic decision task. For the verb-generation task a noun appeared on the screen every 3.6 seconds. The subject was instructed to generate a verb that is appropriate for that noun. To avoid head motion, silent vocalization was used. During the baseline condition of the verb generation task subjects were instructed to fixate on a number of squares projected on the screen at the same frequency as the words.

For the semantic decision task, the subject had to decide if the concrete noun presented on the screen is an animal. Affirmative responses were given by pushing an air-mediated button with the right hand. The control task included the same number of button press responses, which were cued with a fixed number of asterisks that appeared with random intervals. Performance was recorded with a computer. Both tasks were performed during 10 periods of 29 seconds, alternated with 29 seconds of baseline conditions. Tasks were projected in a fixed order starting with the verb generation task.

Combined task analysis

Brain activity maps were obtained by analyzing the fMRI scans acquired during both tasks conjointly. We have previously shown that such an analysis improves reliability of the subsequently computed laterality index, as compared to that obtained with individual task analyses (Ramsey et al. 2001). The rationale for combined analysis, which is closely related to the "conjunction analysis"(Price and Friston 1997), is that it improves sensitivity for brain activity that is present in both tasks, while reducing contribution of activity that is specific for individual language tasks. Brain activity maps obtained with different language tasks have been shown to vary considerably (Curtis et al. 1999), resulting in large intra-individual variation. An additional advantage of combined task analysis is the greater latitude for the baseline tasks, since it is not necessary to control for all components that are not shared (Price and Friston 1997).

fMRI Analyses

The outer two slices (most dorsal and most ventral) of the transaxial fMRI volumes were not analyzed, since registration causes signal fluctuations at the edges of the volume. Functional scans started and ended seven seconds later than the task to compensate for the delay of the vascular response. All scans, including the anatomical scan, were registered to the last volume of the last block to correct for head movements and translated and rotated to the standard brain from the Montreal Neurological Institute (Collins et al. 1994) without scaling. Functional images were analyzed on a voxel by voxel basis using multiple regression analysis (Worsley and Friston 1995) with one factor coding for activation (task versus rest), and three for signal drift (due to scanner hardware). The regression coefficient for activation was converted to a t-value for each voxel, yielding a t-map. Significant activation was then determined in each voxel by applying a threshold of 3.0.

Ten volumes of interest (VOI) were manually delineated on the structural MRI scan of each subject, blind to the statistical results. Manual delineation was performed in sagittal orientation using the DISPLAY tool from the Montreal Neurological Institute (MNI).

For manual delineation, the following landmarks were used: lateral fissure, its ramus anterior and ramus ascendens and the sulcus temporalis superior. The VOI's selection was based on the activation pattern of healthy subjects scanned with this protocol in an earlier study (Ramsey et al. 2001), and comprised Brodmann area (BA) 44 and 45 (Broca's area and its contralateral homologue), middle temporal gyrus (BA 21), superior temporal gyrus (BA 22, 38, 41, 42 and 52), supramarginal gyrus (BA 40) and angular gyrus (BA 39). Together, these VOI's encompassed the main areas where language processing of visually presented words is thought to be mediated. In each VOI the number of activated voxels was determined.

In addition to the individual analysis, the functional data were also analyzed group-wise to check for any task-related activation outside the VOI's. For this purpose, group-wise t-maps were calculated using the individual contrast maps by testing the values in each voxels against zero using a pooled variance calculated over all included voxels. This was done after scaling the t-maps of each subject to the standard MNI brain, and smoothing with a gaussfilter, resulting in a full width at half the maximum of 9mm. Voxels showing a t-value above the threshold of 3.0 in the amphetamine versus placebo condition were considered to show language-related activation.

Statistical Analyses

Systolic blood pressure, measured every 30 minutes after ingestion of the medication, was tested in a General Linear Model (GLM) for the factors time and medication (amphetamine or placebo). In addition, performance on the semantic decision task was compared between the active and the placebo condition with a paired samples Student's t-test.
Furthermore, the number of activated voxels in the VOI's was analyzed by a repeated measurement GLM, with factors VOI, hemisphere (left, right) and medication (placebo, amphetamine). Paired samples Student's t-tests were used for further exploration of significant effects. Finally, for all subjects a lateralization index was calculated for the amphetamine and for the placebo condition, defined as the difference in number of active voxels in the left versus the right hemisphere (within the VOI's) divided by the total sum of activated voxels in the VOI's of both hemispheres. Lateralization indices were compared between the placebo and the amphetamine condition with a paired samples Student's t-test.

RESULTS

Physiological parameters

Mean systolic blood pressure showed a significant main effect for medication ($F(1,7)=12.6$, $p=0.024$), with higher mean values in the amphetamine condition. There was no main effect for time ($F(1,7)=1.1$, n.s.), but a significant medication by time interaction was found ($F(2,7)=3.0$, $p=0.02$) (figure 1).

Plasma levels of amphetamine

Amphetamine was detected in the blood of all subjects two hours after administration of the medication (mean blood level 23.2 ng/ml, s.d. 6.0).

Task performance

No significant difference was found between the amphetamine (mean: 3, s.d. 5) and placebo (mean 4, s.d. 4) condition in the number of errors on the semantic decision task.

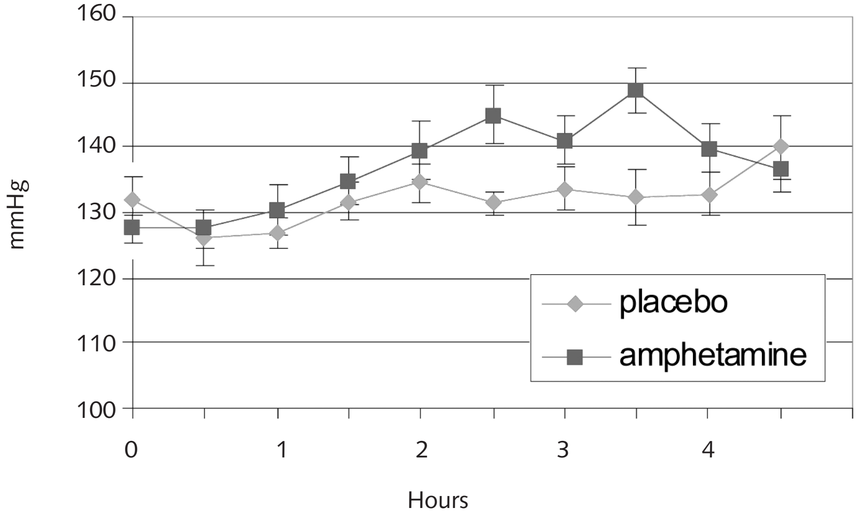

Figure 1
Mean systolic blood pressure and the standard deviation of the subjects with placebo (grey) and amphetamine (black) measured directly before administration of the medication (t=0), and then every 30 minutes.

Brain activation pattern

The GLM revealed a main effect for VOI (F(6,4)=68.6, p=0.0001), for hemisphere (F(9,1)=38.1, p=0.0001), for treatment (F(9,1)=6.2, p=0.034), and a hemisphere by treatment interaction (F(6,4)=5.0, p=0.05). No other significant effects were found.

Further analysis using paired sample t-tests revealed significant higher activation in the left hemisphere during the amphetamine conditions than in the placebo condition (t= 3.2, p=0.01). Activation in the right hemisphere was not significantly different between the placebo and the amphetamine condition. Activation was significantly higher during the amphetamine condition as compared to the placebo condition in three VOI's: Broca's area (t=2.9, p=0.02), the right hemispheric homologue of Broca's area (t=3.0, p=0.01) and the left supramarginal gyrus (t=3.9, p=0.004)(figure 2).

No significant difference was found between lateralization indices in the placebo and in the amphetamine condition (0.50, s.d. 0.24 and 0.46, s.d. 0.16, respectively; t=0.53, p=0.61) (figure 3).

Group-wise analysis revealed no additional activation outside the VOI's in the amphetamine versus the placebo condition.

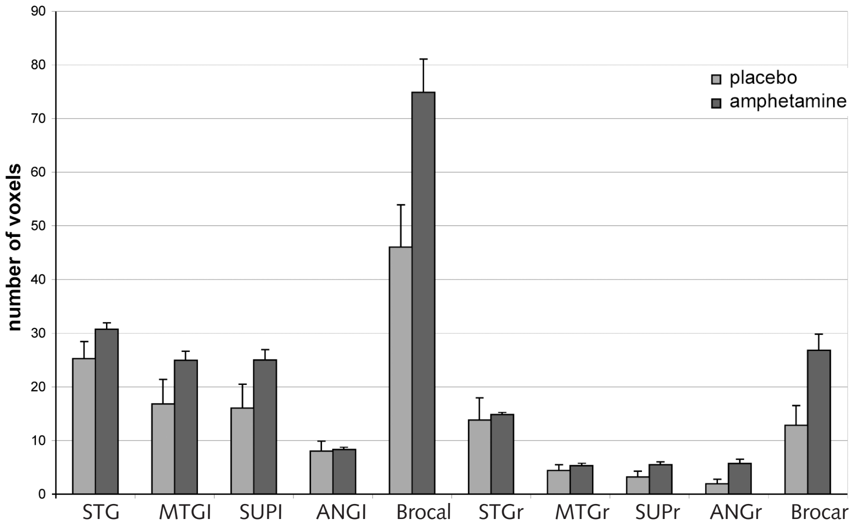

Figure 2
Mean number of activated voxels per volume of interest and the standard error of the mean. grey= placebo, black= amphetamine .Volumes of interest are on the X-axis: STG left= superior temporal gyrus left, MTG left= middle temporal gyrus left, SUP left= supramarginal gyrus left, ANG left= angular gyrus left, BROCA left= Broca's area, STG right= superior temporal gyrus right, MTG right= middle temporal gyrus right, SUP right= supramarginal gyrus right, ANG right= angular gyrus right, BROCA right= contralateral homologue of Broca's area

DISCUSSION

To our knowledge, this is the first study in which the effects of amphetamine on language activation was investigated with fMRI. Our results showed that amphetamine generally increased language-related activity, most pronounced in Broca's area, in the right-sided homologue of Broca's area and in the left supramarginal gyrus. Though the treatment by hemisphere interaction was also borderline significant, amphetamine had no effect on language dominance as expressed in a lateralization index. It appears that amphetamine increases task-related activation in proportion to the extent of activation in the placebo condition. Our language tasks generate a highly asymmetrical activation pattern, with the bulk of activated voxels in the VOI's of the left hemisphere. In the amphetamine condition, the left hemisphere thus shows a higher absolute increase in activation than the right hemisphere, which is reflected in the significant hemisphere by medication interaction. However, the relative activation of the left hemi-

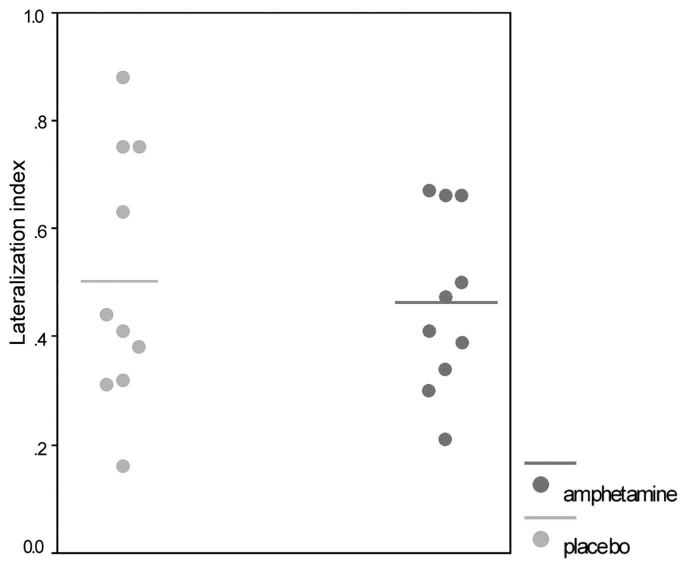

Figure 3
The individual lateralization indices of the ten subjects with placebo (grey) and with amphetamine (black).

sphere, as compared to that of the right, does not change. This stability in the relation between language activation in the two hemispheres is reflected in the failure to find a difference in the lateralization index between the two conditions.
Furthermore, amphetamine did not produce an fMRI signal in any new region outside the VOI's that was not also activated during the placebo condition.

Amphetamine increased language-related activation, but produced no signal change in cortical areas other than those that were already activated during the placebo condition. It thus appears that the effect of amphetamine is to increase activation in task-related areas. Several other functional imaging studies assessed the effects of amphetamine on cognitive tasks by way of fMRI. Uftring et al. (2001) studied the effects of amphetamine with fMRI during a tone detection task and during a motor task in ten healthy volunteers. They administered 20 mg of dextro-amphetamine, which is similar to the dose of the present study. Similar to our results, amphetamine increased the number of activated voxels in task-related areas, which were the left

and right primary auditory cortices during the tone detection task and the sensori-motor cortex during the motor task. The number of activated voxels in other cortical areas was not affected by amphetamine.
Howard et al. (1996) studied functional activation in three healthy subjects during story listening and while being stimulated with flashing lights. In contrast to Uftring et al. (2001), the three subjects from Howard et al. (1996) showed slightly lower activation of the auditory cortex during story listening in the amphetamine condition as compared to placebo. They also found lower activation in the visual cortex with amphetamine during the flashing lights. The discrepancy between Howard et al. (1996) findings and the results from Uftring et al. (2001) and our study may reflect the lower dose of d-amphetamine in the Howard et al. (1996) study (10mg) and their small sample size (three), which permitted no statistical testing. Mattay et al. (2000) studied the effects of 0.25 mg/kg amphetamine (similar to the present study) on the brain activation pattern during a working memory task. They found that amphetamine increased performance in subjects who had low working memory capacity in the placebo condition but worsened performance in subjects with high capacity in the placebo condition. Signal intensity in the right prefrontal area correlated inversely to the task performance in the amphetamine condition. These studies, together with the present study, support the notion that amphetamine increases activity in task-related areas without affecting other areas.

The mechanism by which amphetamine may lead to this increased activity in task-related cortical areas is not clear. It may reflect a generally increased readiness of the cortical neurons specialized for a certain function to be activated. Certainly, the increased activation following amphetamine challenge is not restricted to cortical areas that have a high density of dopaminergic receptors, such as the dorsolateral prefrontal areas (Goldman-Rakic et al. 2000). Therefore, the effects of amphetamine on cortical activation are not likely to be a result of direct stimulation of cortical dopamine receptors. Rather, the increase in cortical activation may be secondary to an activating influence of amphetamine on subcortical structures. Since amphetamine increases not only the metabolism of dopamine, but also that of norepinephrine and serotonin, increased tone of these monoamines may also have an overall alerting effect on the cortex, in decreasing the threshold of the cortical neurons to respond. Furthermore, amphetamine is known to have a vasoconstrictive effect (Angrist et al. 2001), which could also alter the cerebral blood flow pattern. However, the increased activity in the present study was found after subtracting the scans during baseline conditions to scans during task conditions. More general effects of amphetamine on cerebral circulation would thus be lost in this subtraction.

A second finding of this study is that the individual degree of language lateralization is not affected by oral administration of amphetamine. In animals, motor lateralization could be altered by administration of amphetamine, which is thought to reflect asymmetric dopaminergic neurotransmission in the striatum (Glick and Shapiro 1984). In humans, the level of dopamine in the striatum and pallidum is reported to be asymmetrical, in favor of the dominant hemisphere (van Dyck et al. 2002). This asymmetry is correlated to the degree of handedness (de la Fuente-Fernandez et al. 2000). Since language is related to handedness, it might be affected by changes in the dopaminergic metabolism as well. However, the present results show that human language dominance is not increased by manipulation of the dopaminergic neurotransmission. The difference between the findings for lateralization of movement and for lateralization of language may be related to the differences in the cortical structures that serve these functions. Movements are directed from motor neurons in the precentral gyrus. These motor neurons are present and functional in both hemispheres. In contrast, Broca's and Wernicke's area (the cortical structures that serve language functions) may be capable for language functions only in the dominant hemisphere. Indeed, most right-handed subjects are not able to speak or to read when the left hemisphere is anaesthetized during the Wada procedure (Rasmussen and Milner 1976). This implies that the right hemisphere generally contains no cortical areas that can serve basic language functions. It thus appears that the homologue areas of Broca and Wernicke of the non-dominant hemisphere can not be induced to take over basic language functions by altering the dopaminergic metabolism because these areas are not functionally capable for these functions. Probably, the individual degree of language lateralization is a rather static characteristic of the brain.

The present study has several limitations. Most importantly, the number of subjects included in the study is relatively small. However, it is doubtful whether a larger sample size would have resulted in an effect of amphetamine on language lateralization, since the lateralization index failed to show

even a slight trend in either direction. The groupwise analysis, which showed no additional activation outside the VOI's in the amphetamine condition compared to placebo is most sensitive to a lack of power. If the sample size would have been larger, the results of the groupanalaysis might have been different.
Furthermore, the dose of amphetamine could have been too low to achieve an effect on language dominance. However, this is quite unlikely, since a significant increase in activation was detected in several VOI's. Besides, other studies found changes in cerebral activation with the same dose of amphetamine (Uftring et al. 2001; Mattay et al. 2000). Finally, amphetamine stimulates neurotransmission of several monoamines (Parada et al. 1988). This prevents the differentiation between dopaminergic effects and the effects of increased concentrations of other monoamines. The reason that we selected amphetamine despite this disadvantage is that animal studies reported changes in functional cerebral asymmetry after amphetamine stimulation (Glick et al. 1988).

In summary, the hypothesis that language dominance in human can be affected by manipulation of dopaminergic neurotransmission was not supported. This might suggest that language lateralization is a rather stabile brain characteristic.

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Part 2 Language lateralization in schizophrenia

CHAPTER 7

Schizophrenia (introduction)

HISTORY

Schizophrenia is a long-recognised disorder which probably has the most fascinating complex of symptoms in medicine. The pathophysiological theories and therapeutic interventions for schizophrenia have varied greatly over the past century and parallel the history of psychiatry itself. The clinical symptoms of schizophrenia have already been described at the end of the 19th century (Kraepelin 1896). Emil Kraepelin named the disorder "dementia preacox" and accurately described most symptoms currently known to encompass the schizophrenic syndrome. He distinguished this disorder from manic-depressive disorder, in which patients regain normal function between the periods of illness. Kraepelin described patients with dementia praecox as having delusions and hallucinations, paired with a progressive deterioration. His colleague Alzheimer started neuropathological studies into its biological basis, before he moved to a more fruitful research area (Harrison 1999).
The term "schizophrenia" was introduced by Eugene Bleuler in 1920, who tried to emphasise that cognitive deterioration, implicated in the term "dementia preacox", was not the necessary outcome of the syndrome. With the new term "schizophrenia": split mind, Bleuler tried to signify the separation between the emotional part of the mind, which he thought was most affected by the disorder and the relatively unimpaired cognitive functions. Bleuler characterized schizophrenia patients with the four A's: affective disturbances, autism, ambivalence and associational looseness (Stotz-Ingenlath 2000). In the United States, Bleuler's broader criteria for schizophrenia were followed, which could also include patients that would currently be diagnosed as having a bipolar disorder with psychotic features or a borderline personality disorder. The concept took hold that schizophrenia was the natural result of a unique life history of physical, social and psychological events. Therefore, every patient demanded intense individual study to unravel the essential ingredients of his or her particular illness. No standard theoretical explanation was accepted. Later, modified psychoanalytic principles were applied to study schizophrenia. Observable behaviour played little role, but instead "inferred intense anxiety" was thought to be the basis of the disorder. Sullivan (1933) wrote: "The schizophrenic suffers from an almost unceasing fear of becoming an exceedingly unpleasant form of nothingness by a collapse of the self".
The European concept of schizophrenia in the first half of the 20th century, which emphasised the description of Kreapelin, paid greater attention to

observable phenomena and to prognosis. In this spirit, Kurt Schneider formulated the "first rank symptoms" (later called the Schneiderian symptoms) that were considered to be pathognomonic for schizophrenia (Schneider 1959). They included hallucinatory symptoms, such as hearing thoughts being spoken aloud, voices commenting on the patient's activities and voices speaking about the patient in the third person. In the delusional domain, the first rank symptoms included highly personalised meanings to normal happenings. The third main abnormality was believed to be the deficit of ego boundary, reflected in belief in alien control of feelings, impulses and actions.

Later, in the sixties, the family approach movement gathered momentum in psychiatry. In this view, a person with a psychiatric disorder was regarded as an indicator of family psychopathology, which demanded investigation and treatment of the whole family (Howells 1991). It was believed that schizophrenia arose from mothers who did not accept their feelings of anxiety and hostility towards their child and expressed these feelings in overt, but insincere, loving behaviour. This contradicting verbal and non-verbal communication, when not intervened by a strong insightful father, was believed to lead to confusion and ultimately psychosis of the child. As an extension of the family approach, the so called "anti-psychiatrists" saw schizophrenia as a normal reaction to a sick social environment. In their view, it was the psychiatric setting itself that leads the patient to display psychotic symptoms. In later years Ron and Harvey (1990) wrote that "to have forgotten that schizophrenia is a brain disease will go down as one of the greatest aberrations of twentieth century medicine".

At the same time, major progress was made in pharmacological therapy of schizophrenia. In the late 1950s Delay and Deniker introduced the first antipsychotic drug, chlorpromazine, for the treatment of schizophrenia (Delay et al. 1965). Based on the specific actions of these new drugs, the hypothesis was developed by Arvid Carlsson and co-workers, that the principal mode of action of neuroleptic drugs was the interference with synaptic transmission of dopamine in the brain (Carlsson et al. 1958). These findings led to the hypothesis that schizophrenia results from an overactivity of the dopamine neurotransmitter system.

After extensive biological research on schizophrenia in the last twenty years, the dopamine hypothesis is presently still the best-founded etiological hypothesis (Kapur 2003).

EPIDEMIOLOGY

Schizophrenia is a relatively common disorder, with a lifetime prevalence of 1-1.5 % (Jablensky 1995). The gender distribution was formerly thought to be even, but the prevalence was recently shown to be significantly higher in men (Aleman et al. 2003).
The onset of schizophrenia is in early adulthood for men, with peak ages between 20 and 25, whereas the peakages for women are significantly later, between 20 and 35 years of age (Castle et al. 2000). Symptom profiles also differ between the sexes, with men having more negative symptoms and women having more paranoid psychotic symptoms and more affective symptoms. Male patients are reported to have poorer premorbid social competence. Female patients generally respond better to treatment and finally, outcome is also better in female than in male patients (Castle et al. 2000).

SYMPTOMATOLOGY

The phenomenology of schizophrenia can be divided into positive and negative symptoms (Crow 1980). The positive symptoms are the psychotic symptoms: hallucinations, delusions, catatonic behaviour and thought disorder. In 65% of cases, the hallucinations consist of auditory verbal hallucinations, i.e. “voices” (Slade and Bentall 1988). The positive symptoms often have a fluctuating course, with periods of florid psychosis alternating with periods of remission. Negative symptoms reflect the absence or diminution of normal functions and include lack of initiative, lack of energy, social withdrawal, emotional flattening and poverty of speech. The negative symptoms are generally more chronic in nature. They generally show no improvement with medication and persist after remission of the psychosis.

COGNITION

Cognitive dysfunctions are by some authors regarded to be the core abnormality in schizophrenia (Frith 1992, Weinberger et al. 1986). In the healthy brain, the majority of incoming perceptual information or motor output is processed automatically, by using cognitive schemes that were learned in earlier situations. Patients with schizophrenia are thought be unable to make sufficient use of these cognitive schemes to organize the perceived information and to plan motor acts. Instead, the information that is normally processed automatically now has to be handled consciously, which places extra load on working memory and attention (Hijman et al. 1995). Conscious attention is normally reserved for new, unexpected, or possibly dangerous situations. Therefore, conscious attention and special meaning are tightly related to each other. When trivial perceptions are processed with attention (since the normal automatic route cannot be used), this perceptual information will give the impression of having a special, possibly threatening, meaning. The result is that many coincidal facts are perceived as being highly relevant or dangerous, which can easily give rise to a delusional idea or a dysperception (Green 1996)

AETIOLOGY

Despite the early recognition of the disorder, insight into the pathophysiology of schizophrenia has progressed slowly. At present, there is no overall model that can explain all aspects of the disorder and has consistent empirical support. However, several findings that may play a role in the aetiology of schizophrenia have quite consistently been reported. In the following sections, the models that try to relate these findings to an etiological theory are discussed.

Dopamine hypothesis

The dopamine hypothesis of schizophrenia posits that schizophrenia is associated with an overactivity of the dopamine synapses in the brain. Although there is little consistent evidence directly demonstrating such an overactivity (Kapur 2003), there is wide circumstantial support for this hypothesis. Firstly, all antipsychotic drugs, effectively block dopamine D2 receptors. Secondly, drugs that raise dopamine concentrations in the brain, such as amphetamine and apomorphine can precipitate or exacerbate psychosis in schizophrenic patients (Janowsky et al. 1977; Snyder 1973). However, most post-mortem studies reported normal dopamine levels in several brain structures of unmedicated schizophrenia patients (reviewed by Arbuthnott and Murray 1975). Some PET studies have shown that there is an increased level of (dopamine)-D2 receptors in the striatum of schizophrenia patients

(Wong et al. 1986; Seeman et al. 1987), but other studies could not replicate this finding (Farde et al. 1990).
Dopamine is involved in cerebral processes that regulate reinforcement of a stimulus. An increase in dopamine neurotransmission during stimulus perception can yield a feeling of reward, but it can also precipitate a negative emotion (Salamone et al. 1997). Dopamine release is thought to have an important function in transforming neutral stimuli into stimuli with a positive or negative significance (Kapur 2003). These "dopamine-labelled" stimuli will be signified as important and the subject will pay attention to them. During psychosis, the dopamine neurotransmission is disturbed, which leads to inadequate dopamine-labelling and the attribution of importance to random, trivial elements of one's experiences. Irrelevant stimuli may become labelled as having great positive or negative emotional valence. In order to explain all these strange important stimuli, the subject may create a delusion: a cognitive effort to make sense of these abnormal experiences (Kapur 2003). In support of this theory, schizophrenia patients have been observed to show increased synaptic dopamine release after the presentation of neutral stimuli as compared to non-psychotic subjects (Abi-Dargham et al. 1998).

Environmental and genetic aetiological factors

Schizophrenia is observed in all populations and in all socio-economic strata (Jablensky 1995). However, the prevalence is not evenly distributed among different areas. The risk to develop schizophrenia is increased in subjects who were born in big cities, and decreased in subjects from rural areas (Marcelis et al. 1998; Mortensen et al. 1999). Urban residency during upbringing also increases the risk for schizophrenia, independent of the place of birth (Pedersen and Mortensen 2001). Furthermore, several studies reported significantly increased risks for schizophrenia among immigrant as compared to native inhabitants (Selten and Cantor-Graae 2004). The increased risk seems to be dependent on contextual factors, because the increase in risk varied greatly among various ethnic groups. The stress of a change in cultural setting and the experience of being different from the majority may increase the risk to develop schizophrenia in these groups (Selten and Cantor-Graae 2004). Another consistent finding is that subjects with schizophrenia have a 5-8% higher risk of birth in winter time or early spring as compared to healthy subjects, both in northern and southern hemispheres (Torrey et al. 1997). This finding suggests a role for a seasonspecific environmental factor, such as a viral infection, or the treatment of these infections, or a dietary component (more saturated fatty acid in wintertime). Obstetric complications have been reported to have a modest, but significant effect on the risk of schizophrenia (Cannon et al. 2002). Finally, the use of cannabis is associated with an increased risk to develop schizophrenia, both in retrospective and prospective studies (Bersani et al 2002). It remains uncertain, however, whether the association represents a causal mechanism.

On the other hand, ample evidence exists for a genetic component in schizophrenia. Relatives of schizophrenia patients have a higher risk to develop the disorder than subjects without affected family members. The risk for a family member to become schizophrenic can be deducted from the degree to which genes are shared with the proband, ranging from approximately 2-5% in second degree relatives to 35-50% in monozygotic co-twins of a schizophrenic patient (Tsuang 2000). Dizygotic twins of schizophrenia patients have a risk of 10-15% to develop schizophrenia, a risk that is quite similar to the risk for non-twin brothers or sisters of schizophrenia patients. From a large sample of 224 twin pairs with schizophrenia, Cardno et al. (1999) estimated the heritability for schizophrenia to be between 82 and 85%.
In addition, adoption studies clearly demonstrate that the risk for schizophrenia is largely determined by the health status of the biological parents and not by the adoptive care takers (Cardno et al. 2002). Thus, the genetic component for schizophrenia is presently well documented to be large.

Neurodevelopmental versus neurodegenerative model

The neurodevelopmental hypothesis of schizophrenia posits that genetic and/or environmental events occur in the critical early periods of development of the central nervous system that negatively affect patterning and differentiation of the brain. Evidence for this hypothesis is derived from several research fields. First, cytoarchitectonic studies suggest that displaced migration in the embryonic brain leads to inappropriate connectivity (reviewed by Weinberger 1996). Second, models of neonatally lesioned animals showed a delay in the manifestation of abnormal behaviour and in related dopaminergic hyperresponsiveness until early adulthood (Lipska et al. 1993). This finding suggests that early abnormalities in neuronal connectivity of the human brain may also remain “dormant” until the second or third trimester. Third, morphological studies have consistently reported ventricular enlargement and cortical volume loss in schizophrenia (Cannon et al. 1989). These abnormalities have also been demonstrated in adolescents who are at a high risk of developing schizophrenia (Cannon et al. 1993), suggesting that the brain pathology antedates the clinical onset of the disease. Fourth, several studies reported that head circumference at birth is already reduced in babies who develop schizophrenia in adult life (reviewed by McNeil et al. 2000). Fifth, there are slight behavioural abnormalities, such as eye tracking deficits and impaired fine motor control in children who later develop schizophrenia (Holzman et al. 1988; Green 1998). As a group, children who later develop the disorder are less socially confident (Goldberg et al. 2001), have a lower IQ (Chua and Murray 1996) and develop motor and language skills at a later time that their peers (Crow 1996). A sixth, and last, important finding in support of a neurodevelopmental origin is the relative absence of a gliotic response in the schizophrenic brain (reviewed by Harrison 1999). The foetal brain is believed to be able to generate a gliotic response by the end of the second trimester (Harrison 1999). Hence, the absence of gliosis implies that the disease process started in the first or second trimester of foetal development.

On the other hand, there are certain other findings in schizophrenia that are not congruent with the concept of a neurodevelopmental disorder. Structural MRI studies of schizophrenia patients detected an increase in extraventricular cerebro-spinal fluid (Harrison 1999), which is not likely to result from a neurodevelopmental origin. Brain growth in the first five years of life determines growth of the intracranial cavity and intracranial space is fixed after closure of the skull sutures. Therefore, loss of brain tissue in the pre or perinatal period would produce a smaller cranial space and possibly an increase in ventricular size, but not an increase in extraventricular cerebro-spinal fluid. Other findings also contradict a purely neurodevelopmental hypothesis. Repeated structural MRI scans in schizophrenia patients have revealed evidence of progressive changes, especially in the inferior gyri of the frontal lobes (Cahn et al. 2002) in the early phase of the disease. The presence of these progressive decreases in brain tissue may argue for a late, or at least an ongoing pathophysiological process in schizophrenia.
In summary, there are many findings that suggest a neurodevelopmental factor in the aetiology of schizophrenia. Some insult, be it genetic or environmental in nature, is expected to affect the brain in the early prenatal period. However, there is also evidence that a neurodevelopmental insult is

not the only determinant of the schizophrenia syndrome. An aetiology involving a "two-hit" model has been suggested (Church et al. 2002; Manschreck et al. 2000), in which the first "hit" consists of the genetic vulnerability and possible adverse events in the early prenatal period and the second "hit" is caused by the physical changes resulting form rising hormone levels in puberty and the increasing cognitive demands of adulthood.

Hypofrontality

Several negative symptoms of schizophrenia, such as loss of interest, alogia, lack of initiative and poor social skills are also found in neurological patients with frontal lobe lesions. This similarity has stimulated research on the function of the frontal lobes in schizophrenia. Therefore, the initial studies applying functional brain imaging techniques during cognitive tasks mainly focused on frontal dysfunction. During tasks that should activate the frontal cortex, such as the Wisconsin Cart Sorting Test, the Tower of London and word generation tasks, cerebral activity was generally lower in schizophrenia patients than in controls (Weinberger et al. 1986; Andreasen et al. 1997). However, this finding of "hypofrontality", as it is called, turned out to reflect the lower performance of patients on these difficult tasks. When the control group is matched for performance, hypofrontality in schizophrenia disappeared (Frith et al. 1995). For comparison, with functional imaging we could measure that a walking subject has lower metabolism of his leg muscles than a person who is running. However, this would not justify the conclusion that the walker is unable to run because the metabolism in the muscles of his legs is too low.

However, with a more sophisticated design, frontal activity in schizophrenia did show some modest abnormality. Jansma et al. (2000) applied the Sternberg task to test working memory function in schizophrenia. When healthy volunteers rehearse this task, their performance increases, while their frontal brain activity decreases. The decline in brain activity probably indicates automatic processing of the memory task and may reflect reduced need for conscious control. In patients with schizophrenia, rehearsing of the task also lead to increased performance, but brain activity remained high (Jansma et al. 2000). Thus, even when performance is similar for patients and controls, patients appear to have reduced physiological benefit from practice. This benefit is essential because it reduces the claim on the central processing capacity.

Schizophrenia as a disturbance of lateralization

In a study on post-mortem brains, Crow et al. (1989) found that the normal asymmetry of the language areas was decreased in schizophrenia. He proposed that schizophrenia could arise from a failure of the brain to develop cerebral lateralization. Positive symptoms, such as verbal hallucinations and thought disorder, may arise from inappropriate language activity of the non-dominant hemisphere (Nasrallah 1985). Verbal thoughts originating from the non-dominant hemisphere may not be recognised as self-generated language. If it is not recognised as one's own thoughts, the subject consequently concludes that they must have an external origin, leading to the experience of verbal hallucinations. This theory is consistent with previous observations of verbal hallucinations to be accompanied by sub-vocalisations (articulations without overt speech) (Gould 1950). These sub-vocalisations corresponded to the subjective loudness of the hallucinations (Inouye and Shimizu 1970). According to this theory, schizophrenia patients would thus be expected to have relatively high language activity in the right cerebral hemisphere. Studies that have tested this hypothesis have been meta-analysed in chapter 8.

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Part 2 Language lateralization in schizophrenia

CHAPTER 8

Cerebral lateralization in schizophrenia, a review of the literature

British Journal of Psychiatry. 2001 Apr;178: 344-51.

ABSTRACT

Cerebral lateralization appears to be decreased in schizophrenia. Results of studies investigating this, however, are equivocal. In this study we aimed to quantitatively review the literature on decreased lateralization in schizophrenia. Meta-analyses were conducted on 19 studies on handedness, 10 dichotic listening studies and 39 studies investigating anatomical asymmetry in schizophrenia.

The prevalence of non-right-handedness was significantly higher in schizophrenic patients as compared to healthy controls, and also as compared to psychiatric controls. The analysis of dichotic listening studies revealed no significant difference in lateralization in schizophrenia. However, when analysis was restricted to studies using consonant-vowel or fused word tasks, significantly decreased lateralization in schizophrenia emerged. Asymmetry of the planum temporale and the Sylvian fissure was significantly decreased in schizophrenia, while asymmetry of the temporal horn of the lateral ventricle was not. We concluded that strong evidence is provided for decreased cerebral lateralization in schizophrenia.

INTRODUCTION

Right handedness, left cerebral dominance for language and normal cerebral asymmetry are considered to be secondary to a dominant allele, the "right shift factor" (Annett 1998).
In schizophrenia, several studies reported an excess of non-right-handedness (Shan-Ming et al. 1985), decreased language lateralization on the dichotic listening paradigm (Bruder et al. 1999) and decreased (Petty et al. 1995) or reversed (Barta et al. 1997) anatomical asymmetry. It has been postulated that the genetic mechanism underlying normal left hemispheric dominance is altered in schizophrenia (Crow et al. 1989). Were this to be true, the discovery of the "right shift factor" may also identify a locus where genetic aberrations predispose for schizophrenia (Crow 1999). However, literature on decreased cerebral dominance in schizophrenia is equivocal. The aim of the present study was therefore to quantitatively review studies on handedness, language lateralization on the dichotic listening paradigm and anatomical asymmetry in schizophrenia.

METHOD

Literature search

Studies were retrieved that dealt with lateralization in schizophrenia, published between January 1980 (introduction of DSM-III) and December 1999. Only English publications from international journals and book chapters were selected.

Inclusion

The included studies had to meet the following criteria:
1. Patients had a diagnosis of schizophrenia, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III, DSM-IIIR, DSM-IV, Research Diagnostic Criteria (RDC), International Classification of Disease (ICD)-9 or ICD-10. Studies on patients with schizophrenia-spectrum disorder (schizoaffective and schizophreniform disorder or schizotypal personality disorder) were not included.
2. Studies had compared schizophrenic patients to healthy controls that were not at increased risk for schizophrenia or psychosis. For an additional

analysis on hand preference, we also included studies using non-schizophrenic psychiatric and neurological patients as control groups.
3. Studies reported data on handedness, language lateralization as measured with the dichotic listening paradigm, or anatomical asymmetry of the planum temporale, Sylvian fissure, temporal horn of the lateral ventricle or superior temporal gyrus.
4. Studies had reported sufficient statistical information, i.e. frequencies, means and standard deviations, exact F or t values, or exact p values.

Analyses

After computing effect sizes for each study (Hedges et al. 1985), meta-analytic methods were applied in order to obtain a combined effect size, which indicated the magnitude of the association across all studies (cf. Aleman et al. 1999). In addition, Stouffer's Z, weighted for sample size, provided an indication of the significance of the difference between the patient and the comparison group. Finally, a homogeneity statistic (Q) was calculated, to assess heterogeneity of results across studies (Shadish et al. 1994). If heterogeneity reached significance, further analyses may be carried out to examine potential moderators on the effect size. In order to investigate such potential moderators, correlations (Pearson coefficients, two-tailed) were calculated between the effect size of the studies and available variables.

Handedness

Prevalences of mixed- and left-handedness were grouped together as "non-right-handedness". For each study, odds ratios were calculated from the prevalence of non-right-handedness in schizophrenic or pre-schizophrenic subjects and in the comparison subjects. Odds ratios were combined by applying the method of logarithmic odds ratio meta-analysis (Shadish et al.1994).

Dichotic listening studies

Effect sizes (Hedges et al. 1985) were calculated from the "right ear advantages" (score right ear- score left ear) of patients and controls, from the "laterality index" (score right ear- score left ear, divided by score right ear + score left ear) or from F-values.

Anatomical asymmetry

Only two studies on brain torque (Guerguerian et al. 1998; Luchins et al. 1981) reported means and standard deviations of an asymmetry index for patients and controls, while others gave frequencies of abnormal frontal and occipital asymmetry. On these studies, meta-analysis was performed using the "difference rate" i.e. the difference between the proportion of individuals with absent or reversed asymmetry in the patient group and in the control group.

For the meta-analyses on asymmetry of planum temporale, Sylvian fissure, temporal horn of the lateral ventricle and superior temporal gyrus, effect sizes were computed from the mean size (and standard deviation) of left and right structures. The measurements concerned absolute structure sizes, not corrected for total brain volume, and total structure sizes (not only grey matter volumes). When studies gave separate data for men and women, these were included as two independent effect-sizes, thereby increasing the total number of effect sizes "K".

Each study was used for three meta-analyses. In the first meta-analysis asymmetry of the structure was calculated for the control subjects. In the second meta-analysis asymmetry was calculated for the patients. The third meta-analysis was conducted on the difference of the two d-values of each group and compared asymmetry in patients to that in controls. In this way, differences in overall brain size between patients and controls could not influence the outcome, as every structure was compared to its contralateral homologue first, after which the resulting standardised asymmetry indices were compared between the groups. Differences in measurement technique between the studies were largely controlled for as well, as the statistic results from within-study comparisons.

When studies that measured the superior temporal gyrus provided separate data on anterior, middle and posterior segments, these were pooled.

All studies had included predominantly right-handed subjects, except for Holinger et al. (1999), who measured superior temporal gyral volumes in left-handed schizophrenic patients and left-handed controls. To increase homogeneity among studies, this study was excluded in the meta-analysis, but included for the calculation of a possible correlation between handedness distribution and asymmetry.

RESULTS

Handedness

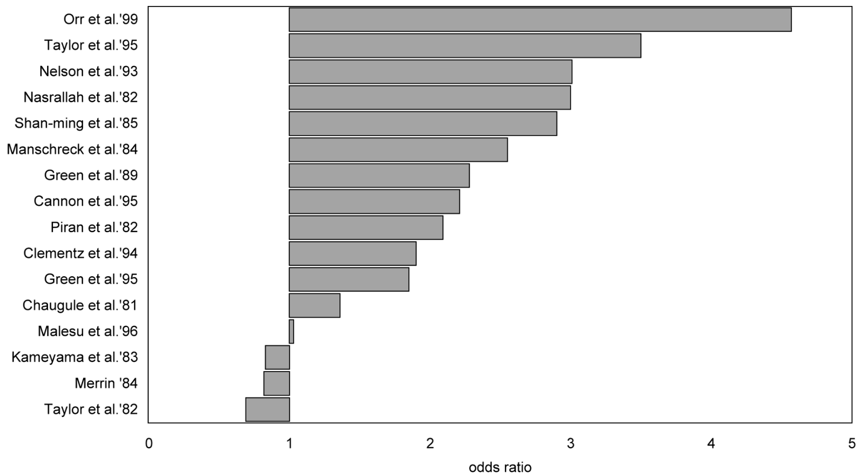
Sixteen cross-sectional studies that assessed handedness in schizophrenic and healthy subjects were included (Cannon et al. 1995; Chaugule et al. 1981; Clementz et al. 1994; Green et al. 1989; Green et al. 1995; Kameyama et al. 1983; Malesu et al. 1996; Manschreck et al. 1984; Merrin 1985; Nelson et al. 1993; O'Callaghan et al. 1995; Orr et al. 1999; Piran, et al. 1982; Shan-Ming et al. 1985; Taylor et al. 1995; Taylor et al. 1980).

Table 1. Summary of meta-analyses of difference in cerebral dominance between schizophrenic patients and comparison subjects.

Index	K	N	D	OR	DR	95% CI	Z (p)	Q (p)
Handedness								
Schiz. patients vs healthy controls	16	5467		1.61		1.41-1.83	3.69(0.0002)	23.6(0.13)
Schiz. patients vs psychiatric controls	9	1492		1.54		1.28-1.84	2.36(0.009)	11.46(0.2)
Prospective	3	55579		1.48		1.23-1.79	2.07(0.02)	2.24(0.31)
Dichotic listening								
All verbal tasks	10	434	-0.19			-0.6-0.2	-0.92(0.18)	29.2(0.001)
Only CVC and fused-words	6	267	-0.48			-0.83-0.14	12.74(0.003)	8.9(0.11)
Anatomical asymmetry								
Frontal torque	3	383			0.24	0.15-0.34	5.11(0.05)	8.4(0.05)
Occipital torque	5	579			0.22	0.12-0.28	7.59(0.01)	87.55(0.003)
Planum temporale	11	368	-0.51			-1.04-0.02	-1.87(0.03)	54.5(0.0005)
Sylvian fissure	3	185	-0.62			-1.04-0.2	-2.87(0.002)	11.1(0.03)
Temporal horn lateral ventricle	12	629	-0.11			-0.61-0.4	-0.41(0.34)	106.83 (0.0001)
Superior temporal gyrus	17	1020	0.21			-0.08-0.51	1.41(0.08)	93.3(0.0001)
Posterior segment STG	5	238	0.7			0.41-1	6.3(0.0001)	5.42(0.37)

K=number of effect-sizes, N=number of subjects, D= mean weighted effect size, OR= Mean Weighted Odds Ratio, DR= mean weigthed difference rate, 95%CI= 95% Confidence Interval, Z(p)= Stouffer's Z and significance of effect size, Q=Within –category homogeneity statistic

Figure 1.
Odds ratios of non-right-handedness in schizophrenia



Meta-analysis on these studies showed that the prevalence of non-right-handedness was significantly higher in schizophrenic patients than in healthy subjects (table 1). The magnitude of the odds ratios of each study is shown in figure 1.

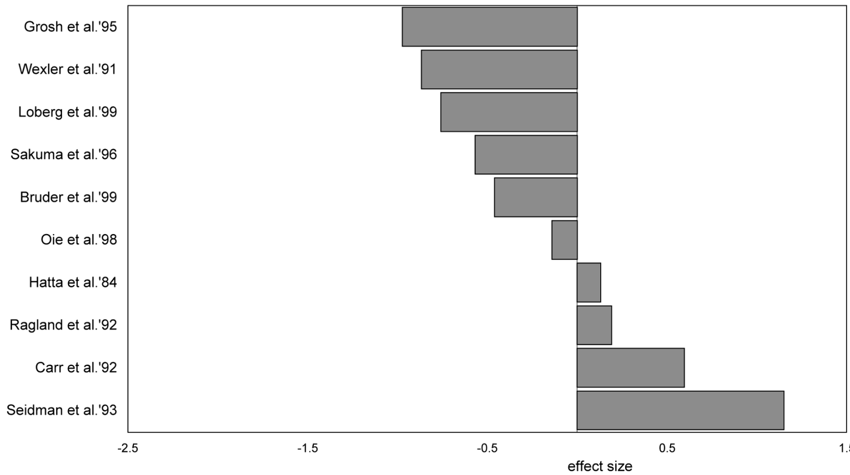
Three prospective follow-up studies measured hand preference in children of large birth cohorts, who were screened for schizophrenia in adult life (Cannon et al. 1997; Crow et al. 1996; David et al. 1995). From these, only one study (Crow et al. 1996) provided quantitative indices on the degree of handedness. In the meta-analysis of these studies, pre-schizophrenic subjects were significantly more often non-right-handed than the general population (table 1).

Additional analysis was performed on 9 studies where the comparison group consisted of non-schizophrenic psychiatric or neurological patients (Clementz et al. 1994; Chaugule et al.1981; Malesu et al. 1996; Manschreck et al. 1984; Merrin 1985; Orr et al. 1999; Piran et al. 1982; Shan-Ming et al. 1985; Taylor et al. 1995). The results indicated that the prevalence of non-right-handedness was significantly higher in schizophrenic subjects than in other psychiatric and neurological patients (table 1).

Dichotic listening studies

Meta-analysis was conducted on 10 dichotic listening studies that compared schizophrenic patients to healthy controls (Bruder et al. 1999; Carr et al.

Figure 2
Effect sizes of dichotic listening studies in schizophrenic (patients-controls)



1992; Grosh et al. 1995; Hatta et al. 1984; Loberg et al. 1999; Oie et al. 1998; Ragland et al. 1992; Sakuma et al. 1996; Seidman et al. 1993; Wexler et al. 1991). The right ear advantage was not significantly decreased in schizophrenia, with significant heterogeneity among studies (table 1). The magnitude of the effect size of each study is visualised in figure 2.
A possible cause for the inhomogeneity in these studies may be the difference in verbal tasks the studies used to elicit a right ear advantage. Four different tasks were used: the triad task, the fused-word task, the consonant-vowel task and the word-monitoring task. The fused-word and the consonant-vowel task are considered to reflect cerebral dominance most accurately (see discussion). When only studies that used the fused-word and the consonant-vowel task were included, the right ear advantage was significantly lower in schizophrenia and studies were no longer heterogeneous (table 1).

Anatomical asymmetry

Brain torque

Meta-analyses were conducted on the frequency of abnormal asymmetry of the frontal (Andreasen et al. 1982; Falkai et al. 1995b; Jernigan et al. 1982) and the occipital lobe (Andreasen et al. 1982; Falkai et al. 1995b; Jernigan et al. 1982; Luchins et al. 1986; Luchins et al. 1983). The results showed that the frequency of abnormal asymmetry was significantly higher in schizophrenia for both the frontal and the occipital lobe, but studies were heterogeneous (table 1). The small number of studies allowed no further investigation of potential moderators.

Planum temporale

Meta-analysis was performed on ten studies that measured the planum temporale in schizophrenia (Barta et al. 1997; Falkai et al. 1995a; Frangou et al. 1997; Jacobsen et al. 1996; Kleinschmidt et al. 1994; Kulynych et al. 1995; Kwon et al. 1999; Petty et al. 1995; Rossi et al. 1994; Rossi, et al. 1992). In the meta-analysis, significant asymmetry favouring the left hemisphere was found for the healthy subjects, but not for the patients (table 2). Studies were homogeneous for the comparison subjects, but heterogeneous for the patients, indicating that difference in measurement technique is not a factor. Possible moderators may be found in characteristics of the patient samples. Only three variables were reported frequently enough to calculate correlations, but no significant result emerged: gender distribution: n=10, r=-0.25, n.s. handedness distribution: n=9, r=0.38, n.s. duration of illness: n=6, r=-0.29, n.s.

In the meta-analysis directly comparing patients and controls, asymmetry of the planum temporale was significantly reduced in patients (table 1). The magnitude of the difference in effect sizes of asymmetry between patients and controls is shown in figure 3.

Figure 3
Difference in asymmetry (patients-controls) of the planum temporale

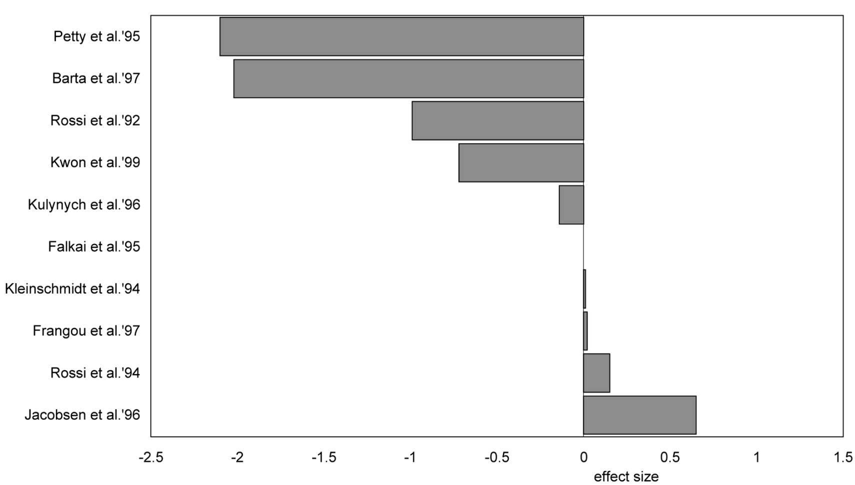


Table 2. Summary of meta-analyses of difference in size between left and right hemispheric structures in controls and patients.

Index	K	N	D	95% CI	Z (p)	Q (p)
Healthy controls						
Planum temporale	11	187	0.7	0.49-0.91	6.5(0.00001)	4.3(0.89)
Sylvian fissure	3	100	0.87	0.43-1.32	3.86(0.00006)	9.85(0.04)
Temporal horn lateral ventricle	12	303	-0.25	-0.41—0.09	-3.05(0.001)	9.32(0.59)
Superior temporal gyrus	17	399	-0.47	-1.1-0.14	-1.5(0.07)	140.23(0.0001)
Posterior segment STG	5	130	-0.2	-0.44-0.05	-1.58(0.06)	1.5(0.9)
Schizophrenic patients						
Planum temporale	11	181	0.18	-0.33-0.69	0.7(0.24)	48.7(0.001)
Sylvian fissure	3	97	0.31	-1.04-0.2	2.87(0.002)	4.72(0.32)
Temporal horn lateral ventricle	12	324	-0.42	-0.88—0.04	-1.81(0.04)	92.5(0.00001)
Superior temporal gyrus	17	469	-0.73	-1.2—0.25	-2.95(0.0016)	151.7(0.0001)
Posterior segment STG	5	108	-0.9	-1.17—0.62	-6.23(0.00001)	4.85(0.43)

K=number of effect-sizes, N=number of subjects, D= mean weighted effect size, 95%CI= 95% Confidence Interval, Z(p)= Stouffer's Z and significance of effect size, Q=Within –category homogeneity statistic

Sylvian fissure

In the meta-analysis on studies on asymmetry of the Sylvian fissure (Bartley et al. 1993; Falkai et al. 1992; Hoff et al. 1992), both controls and patients showed significant asymmetry favouring the left hemisphere (table 2), but studies were heterogeneous for both groups. The small number of studies allowed no further investigation of potential moderators.

When asymmetry of the Sylvian fissure was directly compared between schizophrenic and healthy subjects, patients showed significantly decreased asymmetry (table 1).

Temporal horn of the lateral ventricle

Eight studies on asymmetry of the temporal horn of the lateral ventricle were included (Becker et al. 1996; Bogerts et al. 1990; Dauphinais et al. 1990; DeLisi et al. 1991; Flaum, et al. 1995; Marsh et al. 1997; Pearlson et al. 1997; Zipursky et al. 1994). In healthy as well as in schizophrenic subjects, rightward asymmetry was found (table 2). Studies were homogeneous for

the analysis of control subjects, but heterogeneous in the patients' analysis (table 2). Correlations between asymmetry in patients and possible moderators were not significant gender distribution: n=8, r=-0.44, n.s., handedness distribution n=5, r=0.27, n.s. duration of illness n=6, r=-0.7, n.s.
In the meta-analysis directly comparing patients and controls, asymmetry of the temporal horn was not significantly different between schizophrenic and healthy subjects (table 1).

Superior temporal gyrus
Meta-analysis was performed on 15 studies measuring superior temporal gyrus in schizophrenic subjects and healthy controls (Barta et al. 1990; Bryant et al. 1999; Flaum et al. 1995; Frangou et al. 1997; Havermans et al. 1999; Highley et al. 1999; Hirayasu et al. 1998; Jacobsen et al. 1998; Kulynych et al. 1996; Marsh et al. 1997; Menon et al. 1995; Pearlson et al. 1997b; Reite et al. 1997; Vita et al. 1995; Zipursky et al. 1994).
The results showed that the superior temporal gyrus was larger in the right hemisphere in schizophrenic subjects, while controls showed a trend towards asymmetry in the same direction (table 2). Studies were heterogeneous for both groups and thus differences in measurement technique may have acted as moderators. The only study on post-mortem brains (Highley et al. 1999) found larger volumes of the superior temporal gyrus in the left hemisphere in controls, while 13 of 14 MRI studies found larger volumes in the right hemisphere in controls. However, when the post-mortem study was excluded from analysis, heterogeneity among studies remained high. Correlations between the effect size of asymmetry in controls and other potential moderators were not significant (slice and gap thickness: n=15, r=-0.039, n.s., sample size: n=15, r=-0.22, n.s., gender distribution: n=15, r=-0.29, n.s., handedness distribution: n=15, r=0.32, n.s.). Correlations between potential moderators and the effect size of asymmetry in patients were not significant either (slice and gap thickness: n=15, r=0.15, n.s., sample size: n=15, r=-0.18, n.s., gender distribution: n=15, r=-0.29, n.s., handedness distribution: n=15, r=-0.29, n.s., duration of illness; n=5, r=-0.51, n.s.).
In the meta-analysis directly comparing patients and controls, the schizophrenic patients tended to have increased asymmetry of the superior temporal gyrus favouring the right hemisphere, but statistical significance was not reached (table 1).

Posterior segment of the superior temporal gyrus

A separate analysis on 5 studies (Hirayasu et al. 1998; Jacobsen et al. 1998; Kulynych et al. 1996; Menon et al. 1995; Pearlson et al. 1997b) was performed to assess asymmetry of the posterior segment of the superior temporal gyrus. Rightward asymmetry was found for the patients, while the controls showed a trend towards asymmetry in the same direction (table 2). In the meta-analysis directly comparing patients and controls, rightward asymmetry of the posterior segment of the superior temporal gyrus was significantly larger in patients (table 1).

DISCUSSION

The purpose of this study was to summarise present literature on cerebral dominance in schizophrenia quantitatively. The resulting analyses showed that functional asymmetry is decreased in schizophrenia, which was reflected in an increased prevalence of non-right-handedness and decreased language lateralization in dichotic listening studies that applied the fused-word or consonant-vowel task. Decreased structural asymmetry in schizophrenia was found for brain torque, planum temporale and Sylvian fissure, but not for the temporal horn of the lateral ventricle.

Hand preference

In the meta-analysis on handedness in cross-sectional studies, schizophrenic subjects were more frequently non-right-handed than healthy persons. However, these studies mainly included hospitalised schizophrenic patients, thus tending to overrepresent severe cases. Prospective cohort studies do not have this limitation, since they are population-based. In the meta-analysis on three prospective cohort studies, the prevalence of non-right-handedness in subjects that later developed schizophrenia was significantly increased.

However, many diseases that involve subtle brain damage may be accompanied by increased prevalence of non-right-handedness (Satz et al. 1999). To investigate the specificity of increased non-right-handedness in schizophrenia, an additional analysis was conducted comparing schizophrenic patients to non-schizophrenic psychiatric and neurological patients. In that analysis non-right-handedness was still significantly increased in schizophrenia, suggesting that aspecific cerebral lesion can not explain the increased prevalence of non-right-handedness in schizophrenia. Thus, a more fundamental, possibly genetic mechanism may be involved. Interestingly, several studies report increased non-right-handedness in healthy relatives of schizophrenic patients (Chapman et al. 1987; Hallett et al. 1986; Orr et al. 1999), suggesting a genetic cause for decreased cerebral dominance in schizophrenia (Crow et al. 1989).

Dichotic listening studies

In the analysis of dichotic listening studies, the right ear advantage was not significantly decreased in schizophrenia, while heterogeneity among studies was high. This may be attributable to the difference in verbal tasks used to elicit a right ear advantage. For the triad task and the word-monitoring task subjects have to respond to all stimuli on either ear. Schizophrenic subjects generally have a lower performance on these tasks than healthy subjects (Sakuma et al. 1996; Seidman et al. 1993; Car et al. 1992; Hatta et al. 1984). On several items of these tasks, controls may answer 100% correct, in which case no perceptual asymmetry is measured. These ceiling effects in the control, but not in the schizophrenic group, may cause relatively low ear asymmetry in the control group. For the consonant-vowel and the fused-word task, subjects were asked to respond only to the most clearly perceived item, thereby avoiding the problem of ceiling effects. When only studies that applied the consonant-vowel or fused-word task were included, schizophrenic patients showed a significantly decreased right ear advantage and heterogeneity disappeared. A decreased right ear advantage was also reported in healthy parents (Grosh et al. 1995) and children (Hallett et al. 1986) of schizophrenic patients, supporting the hypothesised genetic origin of decreased lateralization in schizophrenia.

Anatomical asymmetry

In the meta-analysis of anatomical studies, the direction of brain torque was more frequently inverted, while planum temporale and Sylvian fissure showed reduced asymmetry in schizophrenia. The decreased temporo-parietal asymmetries probably reflect decreased language dominance, since planum temporale and Sylvian fissure asymmetries are related to cerebral dominance (Gerschlager et al. 1998). Shapleske et al. (1999) published an extensive review on planum temporale that also contained a meta-analysis on planum temporale in schizophrenia. This study, using more stringent inclusion criteria and including several recently published studies, confirms

Shapleske's finding of decreased asymmetry of the planum temporale in schizophrenia.

Crow et al. (1989) reported that the temporal horn of the lateral ventricle was larger in the right hemisphere in the normal control group of their post-mortem study, probably caused by the more extended language-related cortex at the dominant side. The present results from the meta-analysis on healthy subjects confirm this finding. However, while Crow reported reduced asymmetry of the temporal horn in schizophrenia, the present meta-analysis found no significantly decreased asymmetry in schizophrenia. Asymmetry of the superior temporal gyrus is also frequently used as an indication of language lateralization (Pearlson et al. 1997b; Highley et al. 1999; Holinger et al. 1999; Levitan et al. 1999). However, direction and magnitude of asymmetry of this structure is not well established in healthy subjects. In this meta-analysis controls showed a trend towards asymmetry favouring the right hemisphere, while the superior temporal gyrus was found to be greater on the right in patients. The trend towards rightward asymmetry in healthy subjects is surprising since it partly overlaps with Wernicke's area. However, the superior temporal gyrus also incorporates primary and secondary auditory cortex that generally show rightward asymmetry, reflecting right hemispheric dominance for non-verbal sounds (Zattore et al.1992). The posterior segment of the superior temporal gyrus might be a better candidate to reflect cerebral dominance for language, since it mainly consists of language-related heteromodal cortex (Pearlson 1997a). However, in the current meta-analysis, this segment also showed a trend towards asymmetry favouring the right hemisphere in healthy subjects. Therefore, neither the superior temporal gyrus, nor its posterior segment appears suited for the assessment of cerebral dominance for language.

Limitations

The presented paper included only studies on language lateralisation that used the dichotic listening paradigm. We were unable to retrieve enough visual half-field studies using language stimuli to allow for meta-analysis. A second limitation of the study is our choice to include only studies on patients with strict diagnosis of schizophrenia, excluding studies that used the broad DSM-II criteria for schizophrenia and studies that used patients with schizophrenia-spectrum disorders. Another reason that several studies could not be included was the absence of healthy control groups. By applying these strict inclusion criteria, the total number of studies was lower, but the contrast between the experimental and the comparison group was maximal.

Clinical implications

The reported excess of non-right-handedness and decreased right ear advantage in healthy relatives of schizophrenic patients suggest a genetic cause underlying the decreased cerebral lateralization in schizophrenia. If this were true, a deviation of the genetic mechanism underlying cerebral dominance, the hypothesised "right shift factor" may cause a vulnerability for schizophrenia (Crow 1999; Annett 1999). This implies that the search for genes predisposing for schizophrenia may focus on loci that have a role in the establishment of cerebral dominance. In addition, indicators of decreased cerebral dominance in individuals, such as non-right-handedness, decreased right ear advantage on the dichotic listening paradigm or decreased asymmetry of the planum temporale may help to identify subjects at increased risk for schizophrenia.

In sum, when literature on handedness, dichotic listening studies and asymmetry of language-related structures is reviewed quantitatively, compelling evidence emerged for decreased cerebral dominance in schizophrenia.

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Part 2 Language lateralization in schizophrenia

CHAPTER 9

Language lateralization in men with schizophrenia

Schizophrenia Research 2001 Oct 1;52(1-2):57-67

ABSTRACT

Anatomical studies have shown that cerebral asymmetry is reduced in schizophrenia. Functional asymmetry appears to be reduced also, as was shown with dichotic listening studies. These studies, however, have not revealed whether reduced lateralization is the result of decreased language activity of the left hemisphere or whether it is the consequence of increased language-related activity in the right hemisphere. To elucidate this, we examined hemispheric dominance for language processing by means of functional MRI. Twelve schizophrenic patients and twelve healthy controls were scanned while they were engaged in a verb-generation and a semantic decision task. Activation was measured bilaterally in the frontal, temporal and temporo-parietal language areas, and a laterality index was derived from activity in these regions of interest in the left and the right hemisphere. Clinical symptoms were rated at time of scanning. The results indicate that language processing is less lateralized in patients than in controls (a mean laterality index of 0.35 versus 0.63 respectively. Analysis of variance of the extent of activity, i.e. numbers of active voxels, revealed a significant hemisphere by group interaction, which was probably due to increased activation in the right hemisphere of the patients. We found no
evidence of reduced activity in the left hemisphere. Further analysis of clinical symptoms rated prior to scanning revealed that decreased language lateralization was associated with more severe hallucinations. We postulate that decreased language lateralization in schizophrenia may result from failure to inhibit the right hemisphere.

INTRODUCTION

In healthy individuals the brain exhibits asymmetric organization of anatomy and of function. One of the most robust findings is hemispheric dominance for processing of language, in that the brain regions that are critical for language comprehension and production are typically located in the left hemisphere (Galaburda and Geschwind 1981). With the recent advent of in vivo functional neuroimaging techniques it has become clear that lateralization is a graded variable in healthy subjects, ranging from strong leftward lateralization (in most subjects) to bilateral processing, and in rare cases to rightward lateralization (Springer et al. 1999).

Based on studies investigating handedness and cerebral anatomical features, the degree of language lateralization is reportedly decreased in schizophrenia. Handedness is associated with language lateralization, in that left-handed subjects more frequently deviate from strong left cerebral dominance (Annett 1970). Schizophrenic patients are more often left- or mixed-handed as compared to healthy subjects and also as compared to non-schizophrenic psychiatric patients (Sommer et al. 2001). Furthermore, a causal relation between schizophrenia and decreased cerebral lateralization is suggested by the prospective study of Crow et al. (1996) who found that children of mixed hand preference more often developed schizophrenia in later life.

Cerebral dominance for language can be estimated by measurement of structural asymmetry of certain anatomical areas. Structural asymmetry can be found in the frontal lobe, which is generally larger on the right, and the occipital lobe, which is greater on the left in most subjects. These two asymmetrical features give the brain a twisted appearance called "brain torque". Several studies reported that the direction of brain torque is more often inverted in schizophrenia (Falkai et al. 1995a; Lee et al. 1985; Luchins et al. 1981; Luchins et al. 1986), but other studies could not replicate this (Andreasen et al. 1982; Guerguerian et al. 1998; Jernigan et al. 1982; Luchins et al. 1983). More specific anatomical asymmetry is found in the temporo-parietal region, particularly in the planum temporale, which is part of Wernicke's area (Shapleske et al.1999). At the surface of the brain, asymmetry of the planum is reflected in a longer and less steep Sylvian fissure at the side of the largest planum (Galaburda and Geschwind 1981). Asymmetry of the planum temporale is associated with handedness {according to Steinmetz et al. 1989), 67% of right-handed subjects have the typical asymmetry described above versus 22% of non-right-handers}, and with language dominance as assessed with the Wada test (Gerschlager et al.1998). These reports indicate that asymmetry of the planum temporale and Sylvian fissure is an indirect measure of language dominance. Studies on this measure in schizophrenia have produced equivocal results in that some (Barta et al. 1997; DeLisi et al 1994; Falkai et al. 1992; Falkai et al. 1995b; Hoff et al. 1992; Kwon et al. 1999; Petty et al. 1995; Rossi et al. 1992), but not others (Bartley et al. 1993; Frangou et al. 1997; Jacobsen et al.1998; Kleinschmidt et al.1994; Kulynych et al. 1995; Rossi et al. 1994) have found reduced or even inverted asymmetry. Asymmetry of the superior temporal gyrus has also been argued to be a measure of language dominance (Highley et al.1999; Holinger et al.1999), but meta-analysis of the healthy control groups in studies on schizophrenia did not support this (Sommer et al. 2001).

Language lateralization can be measured more directly with dichotic listening tests, visual half-field paradigms, event-related potentials and functional imaging. Dichotic listening tests are the most commonly used technique to investigate language lateralization. In a typical dichotic listening test, two different stimuli are presented simultaneously, but separately, to the right and left ear. Verbal stimuli are normally perceived better with the right ear, a phenomenon called the right ear advantage (REA) (Hughdahl 1988). For this effect various verbal tasks can be used. The so-called fused-word and the consonant-vowel task are considered to reflect cerebral dominance most accurately (Wexler and Halwes 1983). When these two tasks are used, 82% of right-handed subjects and 64% of non-right-handed subjects display REA, which corresponds to neurological data on language dominance distribution (Hughdahl 1988). The so-called triad task and the word-monitoring task are less effective, presumably due to ceiling effects in healthy subjects with good performance resulting in relatively low values of REA. Several studies measured the REA in schizophrenia, using the consonant-vowel task (Bruder et al. 1995; Bruder et al. 1999; Loberg et al.1999; Oie et al.1998), the fused-word task (Grosh et al.1995; Ragland et al.1992; Wexler et al.1991), the triad task (Gruzelier and Hamond 1980; Sakuma et al.1996; Seidman et al.1993) and the word-monitoring task (Carr et al.1992; Hatta et al. 1984). Overall, the results of these studies are equivocal, but when only those studies are considered that used the consonant-vowel or the fused-word task, the REA is generally significantly reduced in schizophrenic patients (Sommer et al. 2001). On the basis of these dichotic listening studies, it was concluded that in schizophrenic patients the left hemisphere is dysfunctional, rendering it incapable of assuming a dominant role in language (Bruder et al. 1999; Loberg et al. 1999; Ragland et al. 1992). However, as dichotic listening measures do not reflect brain activity directly, they cannot provide evidence for left hemispherical dysfunction. Reduced REA may also be the consequence of enhanced contribution of brain structures in the right hemisphere. Such a unilaterally increased activity may underlie certain schizophrenic symptoms (Nasrallah 1985).

The purpose of the present study is to compare the degree of language lateralization between schizophrenic and healthy subjects. The advantage of functional neuroimaging is that it allows for measurement of levels of language-related brain activity, and as such can differentiate between decreased activity of the left and increased activity of the right hemisphere as a source of abnormal lateralization. Schizophrenic patients and control subjects participated in a functional Magnetic Resonance Imaging (fMRI) experiment with two language tasks. Language-related brain activity was measured in the frontal, temporal and temporo-parietal areas of both hemispheres. For each individual, a lateralization index was calculated based on activity levels in left and right hemisphere, and this index was compared across groups. Finally we tested the hypothesis that decreased language lateralization is associated with increased severity of hallucinations.

METHODS AND MATERIALS

Subjects

Twelve male schizophrenic patients aged 27 (S.D. 6) were included in the study. All were diagnosed on the basis of DSM-IV as determined by an independent psychiatrist using the Comprehensive Assessment of Symptoms and History (CASH) and History Schedule for Affective Disorder and Schizophrenia Lifetime version (SADSL)(Andreasen et al. 1992). Patients with diagnosis of drug dependence or drug use in the three months prior to entry were excluded.

Since we were interested in a possible correlation between hallucinations and lateralization, patients were selected who were actively psychotic, in spite of optimal pharmacotherapy. Auditory hallucinations were a prominent symptom in the clinical picture of all patients. To increase group homogeneity, only patients on clozapine were selected, with the mean dose being 355 mg (S.D. 69 mg)/day. They had received clozapine for a mean duration of 1.6 years (S.D. 1 year). Mean age at onset of illness was 21 years (S.D. 3). The Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) was used for symptom assessment immediately prior to the scan session. Ratings were carried out by a medical doctor and a second rater who had been trained for the interview and scores were determined by means of consensus. Presence and severity of positive and negative symptoms over the last two weeks were scored. The score on item three was used to express severity of hallucinations. In this item, presence and degree of hallucinations are rated on a scale ranging from 1 ("absent") to 7 ("extremely severe").

The control group consisted of 12 healthy men aged 28 (S.D. 5). Subjects with medical or neurological illness were excluded. Subjects met Research Diagnostic Criteria for "never mentally ill" according to the CASH and SADS-L interview. The section "substance abuse" from the CASH was used to determine whether subjects met the DSM-IV criteria for substance dependence, in which case they were excluded.

Parental educational levels were measured by the total number of years of education. No significant differences in parental educational level were found between patients and controls [11 years (S.D. 4) for the fathers of the patients and 9 years (S.D. 3) for their mothers; 11 years (S.D. 3) for the fathers of the controls and 8 years (S.D. 2) for their mothers].

All subjects were right-handed as assessed with the Edinburgh Handedness Inventory (Oldfield 1971). The primary language of all subjects was Dutch.

After complete description of the study to the subjects, written informed consent was obtained.

Task

Two word tasks were used: the verb-generation task (Warburton et al. 1996) and a new word processing task, the reverse-read task (Ramsey et al. 2003). For the verb-generation task a noun appeared on the screen every 3.6 seconds. The subject was instructed to vocalize the presented word silently and then generate and silently vocalize a verb that was appropriate for that word. To avoid head motion, silent vocalization was used.

For the reverse-read task, the subject had to read words that were spelled from right to left (not in mirror-image print). These words also appeared once every 3.6 seconds. The reversed spelling of the words is thought to avoid direct orthographical word recognition and to put more emphasis on phonological decoding. The subject was instructed to vocalize the word silently and push a button if the word was an animal. Performance was recorded by computer for the reverse-read task. Both tasks were performed during 10 periods of 29 seconds, alternated with 29 seconds rest. During the rest condition, subjects were instructed to keep their eyes open while fixating on a small dot in the center of the screen. Patients were asked to report hallucinations if they occurred during the scan by depressing the scanner alarmbutton.

Scans

Functional scans were acquired with a Philips ACS-NT 1.5 Tesla clinical scanner, using the blood oxygen level dependent (BOLD) sensitive, navigated 3D PRESTO pulse sequence (Ramsey et al. 1998; van Gelder et al. 1995), with the following parameter settings: TE/TR 35/24 ms, flip angle 9°, FOV 225 x180x77 mm, matrix 64x52x26, voxelsize 3.51 mm isotropic, scan time per fMRI volume 2.4s. Following the fMRI procedure an anatomical scan was acquired (3d-FFE, TE/TR 4.6/30 ms, flip angle 30°, FOV 256x256x180 mm, matrix 128x128x150, slice thickness 1.2mm).

FMRI Analyses

For each subject the fMRI data were processed off-line on an HPTM workstation using PV-waveTM processing software. The outer two slices (most dorsal and most ventral) of the transaxial fMRI volumes were not analyzed, since registration causes signal fluctuations at the edges of the volume. Functional scans started and ended seven seconds later than the task to compensate for the delay of the vascular response. All scans, including the subjects' anatomical volume, were registered to the last volume of the last block to correct for head movements (Ramsey et al. 1998).

Brain activity maps were obtained by analyzing the fMRI scans acquired during both tasks conjointly. We have previously shown that such an analysis improves reliability of the subsequently computed laterality index, as compared to that obtained with individual task analyses (Ramsey et al. 2000; Rutten et al. 2000; Ramsey et al. 2001). The rationale for conjoint analysis, which is essentially the same as ''conjunction analysis" as described by Price and Friston (1997), is that it improves sensitivity for brain activity that is present in both tasks, while reducing contribution of activity that is specific for individual language tasks. Brain activity maps obtained with different individual tasks have been shown to vary considerably (Curtis et al.1999), resulting in different values of laterality within subjects (Lehericy et al.

2000; Benson et al.1996). The shared components of the verb-generation and the reverse-read task are reading of the stimulus word, interpreting its semantic content and retrieving a verbal answer, while nonspecific components such as planning of motor output are unshared. An additional advantage of conjoint analysis is the increase in statistical power, compared to separate analyses. It also provides greater latitude for the baseline tasks because it is not necessary to control for all unshared components (Price and Friston 1997).

Functional images were analyzed on a voxel by voxel basis using multiple regression analysis (Worsley and Friston 1995) with one factor coding for activity (task versus rest), and three for signal drift (due to scanner hardware). The regression coefficient for activity was converted to a t-value for each voxel, yielding a t-map. Significant activity was then determined in each voxel by applying a threshold. The threshold corresponded to a p-value of 0.05, Bonferroni-corrected for the total number of voxels in the fMRI scan volume, and amounted to a t-value of approximately 4.5 (depending on the number of voxels for each individual). Six volumes of interest (VOI) were manually delineated bilaterally, on the structural MRI of each brain, blind to statistical results. Manual delineation was performed in sagittal orientation using the following landmarks: lateral fissure, its ramus anterior and ramus ascendens and the sulcus temporalis superior. The VOI's comprised Brodmann area (BA) 44 and 45 (Broca's area and its contralateral homologue), dorsolateral prefrontal cortex (BA 9 and 46), middle temporal gyrus (BA 21), superior temporal gyrus (BA 22, 38, 41, 42 and 52), supramarginal gyrus (BA 40) and angular gyrus (BA 39). Together, these VOI's encompassed the main areas where language processing is thought to be mediated.

In each VOI the number of active voxels was determined. For subsequent analyses the VOI's were combined, yielding one measure of language-related activity for each hemisphere.

Laterality was compared by means of analysis of variance (patients versus controls) with repeated measures (left versus right hemisphere) on the number of active voxels, investigating main effects for hemisphere, for diagnosis and a hemisphere-by-diagnosis interaction. A logarithmic transformation was applied to the numbers of voxels for this analysis.

A lateralization index was calculated also, to facilitate comparison with other studies (conform Binder et al. 1996). Lateralization index was defined as the difference in number of active voxels in the left versus the right hemisphere (within the VOI's) divided by the total sum of activated voxels in both hemispheres. For the patient group, a correlation between the lateralization index and the score on the hallucination-item of the PANSS was calculated and tested for significance.

RESULTS

The mean total PANSS score at the time of scanning was 60 (S.D. 12.5). The mean total score on the items on positive symptoms was 15 (S.D. 4), and the mean total score on the items on negative symptoms was 13 (S.D. 3.7). The scale of the PANSS ranges from 0 to 112, with a maximum score of 49 for the items on positive and on negative symptoms. Only one patient experienced two brief episodes of hallucinations during the scan. Since this occurred in two of the 20 rest periods and the duration was short as compared to the test protocol, it is unlikely that these hallucinations influenced the activation pattern.

Table 1. Mean activation (number of active voxels) and standard deviations in each volume of interest (VOI) for patients and controls.

Volume of Interest (Brodmann areas)	**mean activation (S.D.) patients**	**mean activation (S.D.) controls**
Dorsolateral prefrontal cortex left (46, 9)	11.2 (10.8)	17.1 (11.2)
Broca's area left (44, 45)	20.4 (21.3)	14.4 (9.2)
Angular gyrus left (39)	7.1 (8.4)	8.0 (6.7)
Supramarginal gyrus left (40)	3.6 (4.9)	4.3 (5.4)
Superior temporal gyrus left (22, 38, 41, 42, 52)	12.0 (13.9)	6.9 (11.6)
Middle temporal gyrus left (21)	3.3 (4.4)	3.3 (3.5)
Dorsolateral prefrontal cortex right (46, 9)	5.7 (6.8)	2.8 (4.2)
Right homologue of Broca's area (44, 45)	12.3 (12.4)	5.1 (5.1)
Angular gyrus right (39)	2.7 (3.3)	0.8 (0.9)
Supramarginal gyrus right (40)	3.3 (2.7)	1.2 (1.3)
Superior temporal gyrus right (22, 38, 41, 42, 52)	3.2 (4.4)	1.3 (2.3)
Middle temporal gyrus right (21)	0.8 (1.5)	0.4 (0.8)

Performance on the reverse-read task was reduced in the patient group: mean of 21 errors (S.D. 10) on 128 trials, versus 8 (S.D. 4) for the controls ($t(22)=4.44$, $p<0.001$).
Mean activation in the VOI's of each hemisphere is provided for both groups (table 1). Analysis of variance (with factors hemisphere and diagnosis) revealed a significant main effect for hemisphere ($F(1,22)=86.9$, $p<0.001$), no main effect for group ($F(1,22)=0.57$, n.s.) and a significant hemisphere by group interaction ($F(1,22)=11.2$, $p<0.01$). This was due to increased activation in the right hemisphere of the patients relative to the controls (post-hoc t-test: $p<0.05$), while activation in the left hemisphere was not different between the two groups.
The mean lateralization index was 0.35 (S.D. 0.27) for the patients and 0.63 (S.D. 0.21) for the controls (difference $t(22)=-2.91$, $p<0.01$) (figure 1). Within the patient group, there was one subject with right cerebral dominance (lateralization index -0.4), which is an unusual finding for a right-handed subject (Springer et al. 1999). This subject differed more than three times the standard deviation from the group mean and can therefore be regarded

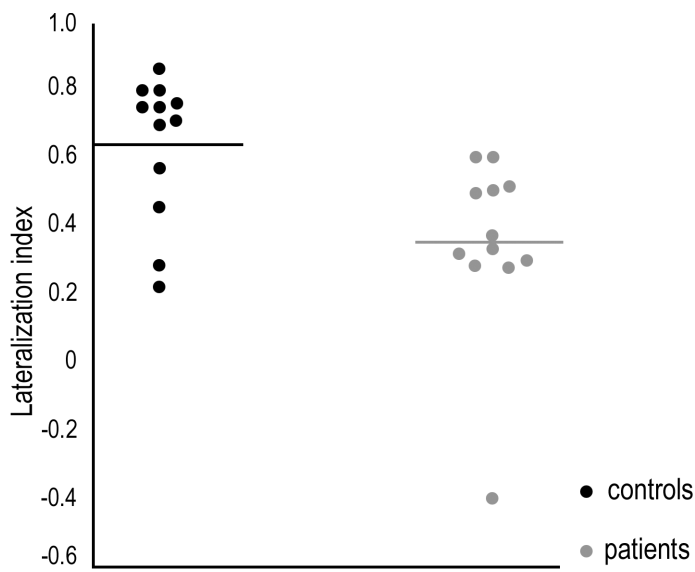

figure 1. Distribution and mean values of the lateralization index of controls (black) and patients (gray).

an outlier. When this patient was excluded, the difference in mean lateralization index between the groups remained significant (t(21)=-2.41, p<0.01).
There was no significant difference in the size of the VOI's (i.e. the total volume of separate VOI's within each hemisphere) between the groups (right hemisphere VOI's: t(22)=0.09, n.s., left hemisphere VOI's: t(22)=0.31, n.s.), nor was there a difference in VOI size between the right and left hemisphere (paired t-test: t(23)=0.13, n.s.).
Examples of junctional scans of a patient and a control subject are shown in figure 3.
There was no significant correlation between task performance and language lateralization or right hemisphere activation (Pearson correlation: rho=-0.12, n.s.; rho=0.036, n.s. respectively). After exclusion of the outlier, these correlations remained insignificant.
Finally, a significant negative correlation was found between the lateralization index and the severity of auditory hallucinations (Pearson correlation: rho=-0.54, p<0.05), after exclusion of the outlier (figure 2).

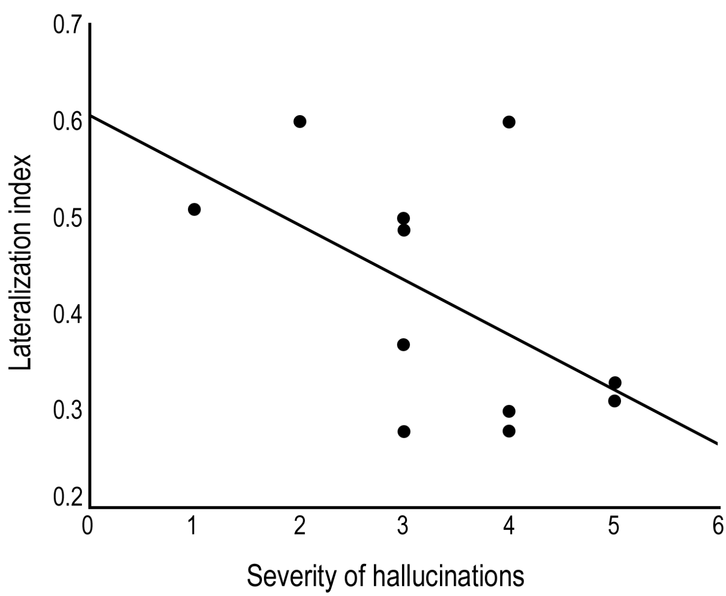

Figure 2. Correlation between language lateralization and severity of hallucinations.

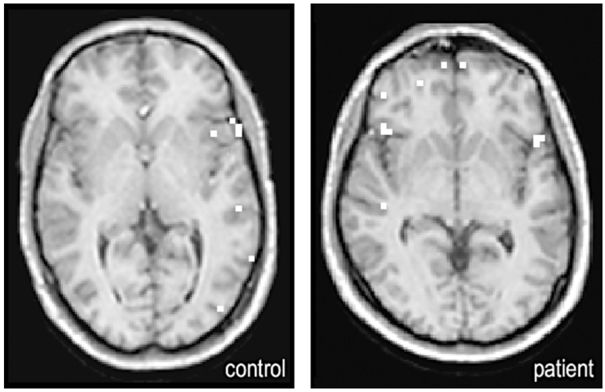

Figure 3. Examples of functional scans of a control subject and a patient.

DISCUSSION

Language lateralization was assessed with functional MRI in 12 schizophrenic patients and compared to that of 12 healthy subjects. Language lateralization was strongly reduced in the patient group, to almost half the value of that of the control group. This finding suggests that language processing is more bilateral in schizophrenic patients and supports the findings of several dichotic listening studies (Bruder et al. 1995; Kugler et al. 1982; Loberg et al. 1999). As fMRI allows for assessment of activity levels in the brain, we were able to determine that the reduced laterality was due to an increase in language-related activity in the right hemisphere in patients, and not to decreased activity in the left hemisphere. This finding suggests that the decreased degree of language lateralization in schizophrenic patients is due to increased contribution of right-hemisphere structures, which may reflect a failure to inhibit the non-dominant hemisphere, rather than a hypofunctional left hemisphere.

Language activation in schizophrenia has also been studied with functional imaging on similar tasks by other groups (Curtis et al. 1998; Frith et al. 1995; Yurgelun-Todd et al. 1996), but these reports gave no or insufficient data on activation in the right cerebral homologues, which makes it impossible to compare them to our findings. Several Positron Emission Tomography (PET) studies did include measurements in right cerebral homologues and showed decreased language lateralization in schizophrenia as well. A PET study by Lewis et al. (1992) reported a decrease in left frontal activity during verbal fluency, resulting in a reversed frontal dominance in schizophrenia. Another PET study by Spence et al. (2000) contrasted activity on a paced verbal fluency task against word repetition, but interpreted the results in terms of connectivity only. After re-analysis of those data, a reduction in lateralization was found in schizophrenic patients (Crow, 2000), but no conclusions were drawn regarding left cerebral hypoactivity or right cerebral hyperactivity. In a recent PET study with an un-paced verbal fluency protocol (Artiges et al. 2000) reduced lateralization in schizophrenia was also observed, which was attributed to both decreased left frontal activity and increased activity of the right-sided frontal areas. In contrast with these earlier studies, we did not find evidence of reduced activity in the left hemisphere. One important factor in functional imaging studies is the type of language task that is used. An un-paced verbal fluency task, for instance, may be problematic if patients cannot generate enough words, as language activity will then not be maintained throughout the task period, potentially resulting in reduced language-related brain activity. The current tasks prompted subjects for each individual word, and as such is less sensitive to failure to self-generate multiple words. This may explain why some groups find hypoactivity in the left hemisphere (eg. Lewis et al. 1992; Artiges et al. 2000). Indeed, decreased frontal activity was not detected when schizophrenic patients were compared to controls matched for performance (Frith et al. 1995). Another potential source of discrepant findings is the selection of patients. When comparing our study to that of Artiges et al. (2000), the mean total score on the PANSS items for negative symptoms was considerably lower (13, S.D. 3.7) than that of the sample of Artiges and colleagues (33.6, S.D.8.0). Increased right-sided language activity was a major finding in both studies, and this may be related to the fact that severity of positive symptoms was quite similar (15, S.D. 4 and 14.5, S.D. 5.6 respectively). This suggests some relationship between symptoms and language-related brain activity patterns, i.e. negative symptoms may be associated with decreased activity in the left hemisphere, whereas positive symptoms may be associated with increased activity in the right hemisphere.

The enhanced contribution to language processing of the right hemisphere may be caused by a genetic factor. Annett (1992), for instance, postulated that normal lateralization, right handedness and normal cerebral asymmetry are coupled to a dominant allele, i.e. the "right shift factor". According to this theory, in the absence of this right shift factor handedness, asymmetry and lateralization develop in a random fashion. The right shift factor is thought to accomplish cerebral lateralization by disrupting the growth of right-sided language-related cortex, rather than through enhancement of these areas in the left hemisphere (Annett 1999). Indeed, the asymmetry of the planum temporale normally observed in healthy right-handed subjects, is not the result of a larger left planum, but of a selective decrease in size of the right planum (Galaburda and Geschwind 1981). It has been suggested that schizophrenia is associated with an anomaly of the genetic mechanism that controls lateralization (Crow et al. 1989). An abnormality of the right shift factor has been hypothesized to play a role in mechanisms that promote proneness for psychosis (Crow 1999; Annett 1999). Structural MRI studies appeared to support this notion, in reporting reduced planum temporale asymmetry in schizophrenic patients. Interestingly, this reduction of asymmetry is due to a relatively large right planum in patients, in the presence of a normal-sized left planum (Shapleske et al. 1999).

The third finding of this study was a negative correlation between degree of lateralization and severity of hallucinations. This is in agreement with the reported association between hallucinations and reduced REA in dichotic listening studies (Wexler 1986; Wexler et al. 1991). It has been postulated that relatively high language activity of the right hemisphere may predispose for the emergence of hallucinations (Nasrallah 1985). This is in agreement with studies that found a more associative and less prototypical way of language processing in the right hemisphere in normal subjects (Chiarello et al. 1990; Egorov and Nikolaenko, 1996; Nagakawa 1991; Rodel et al. 1992), and with dichotic listening studies which reported an association between decreased REA and a loosening of associations in both healthy (Leonhard and Brugger 1998) and schizotypal subjects (Poreh et al. 1993).

The results of this study need to be interpreted with some caution, mainly because the sample size is limited, and because the group of patients is not representative in several ways. Firstly, only men were studied. Since men and women may have different lateralization patterns (Shaywitz et al. 1995), the present findings cannot be extrapolated to female patients. Secondly, only actively psychotic patients on clozapine were selected. The choice of psychotic patients, in whom auditory hallucinations were a prominent feature, was deliberate, as it enabled us to investigate a potential association between (positive) symptom severity and degree of lateralization. As a result, it is not clear whether reduced laterality is also present in schizophrenic patients with other symptom profiles. Thirdly, as all patients were on medication, it is possible that medication affected the results and that other types of medication may produce different results. A possible medication effect on language lateralization has not been studied with functional imaging techniques, but a dichotic listening study reported that withdrawal and reinstatement of medication did not affect the REA (Gruzelier and Hamond 1980). An additional limitation of the study is that performance was measured for only one of the two language tasks. One could argue that patients did not perform the verb generation task adequately, but this is unlikely, as one would then expect to find reduced brain activity levels, which was not the case in the present study.

In summary, this study provides evidence that cerebral dominance for language processing is reduced in schizophrenic patients with positive symptoms. This reduction is associated with enhanced activity in the right hemisphere, suggesting that language-related regions in that hemisphere are not adequately suppressed. No evidence was found for hypoactivity in the left language regions, suggesting that those are not impaired. The correlation between degree of language lateralization and severity of hallucinations suggests that decreased lateralization may be a factor in the predisposition for psychosis.

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Part 2 Language lateralization in schizophrenia

CHAPTER 10

Language lateralization in women with schizophrenia

Schizophr Res. 2003 Apr 1;60(2-3):183-90

ABSTRACT

Gender differences in schizophrenia are among the most consistently reported findings in schizophrenia research. However, the biological substrate underlying these gender differences is still largely unknown. Differences in language lateralization between men and women may underlie some gender differences in schizophrenia.
In previous functional imaging studies, language lateralization was found to be decreased in male schizophrenia patients as compared to healthy males, which was due to enhanced language activation of the right hemisphere as compared to the healthy males. It could be hypothesized that decreased language lateralization in schizophrenia is gender specific; i.e. decreased lateralization in male patients and normal lateralization in female patients.
To test this hypothesis, language activation was measured in 12 right-handed female patients with schizophrenia and 12 healthy females and compared to findings in 12 male patients and 12 male controls of an earlier study.
Language lateralization was significantly lower in the female patients (0.44) as compared to the female controls (0.75), which was due to increased activation of the right sided language areas (patients: 19 voxels, controls: 8 voxels), while left hemisphere activation was similar in patients and controls. When these data are compared to the male patients and controls, both patient groups had lower lateralization than their healthy counterparts, but there was no difference between male and female patients. In both sexes, decreased lateralization resulted from increased right hemispheric language activation, which suggests a failure to inhibit non-dominant language areas in schizophrenia. These findings indicate that lower language lateralization in women is not likely to underlie gender differences in schizophrenia.

INTRODUCTION

As is well known, gender is an important factor in schizophrenia, since differences in age at onset and course of schizophrenia between male and female patients are among the most consistent findings in schizophrenia research (Leung and Chue 2000). The most striking gender difference is the age of onset (first appearance of psychotic symptoms), which is typically around five years later in females (Jablensky et al.1992). Secondly, symptom profile is different between the sexes, with men having more negative symptoms and women having more paranoid psychosis and more affective symptoms (World Health Organization 1973, 1975). Thirdly, male patients are reported to have poorer premorbid social competence (Lewine 1981). Finally, female patients generally respond better to treatment and outcome is also better in female than in male patients (Sikich and Todd 1988; Leung and Chue 2000). The biological substrate(s) underlying these gender differences in onset and course of schizophrenia are still largely unknown, though estrogens are hypothesized to play an important role (DeLisi et al. 1989). Gender difference in language lateralization is another factor that could be speculated to underlie some of the gender differences in schizophrenia (Ragland et al. 1999; Gur et al. 2000).

Several functional imaging studies found higher language lateralization in healthy men as compared to women (Shaywitz et al. 1995; Pugh et al. 1996; Gur et al. 2000; Kansaku et al. 2001). However, other studies, including the large study by Frost et al. (1999), found no gender difference in language lateralization (Price et al. 1996; van der Kallen et al. 1998). Though results are inconsistent, there is some evidence that women may have a more bilateral pattern of cortical language representation, which could provide more "brain reserve" to counter a possible left hemisphere dysfunction in schizophrenia (Sikich and Todd 1988).

In schizophrenia, left cerebral dominance may be decreased. This is suggested by the higher incidence of left-handedness, decreased structural asymmetry of language-related areas and decreased perceptual asymmetry on the dichotic listening paradigm in schizophrenia (for a quantitative review see Sommer et al. 2001a). Several functional brain imaging studies provide information on language lateralization in schizophrenic patients. Lewis et al. (1992) reported decreased left frontal activity during verbal fluency, resulting in reversed frontal dominance in schizophrenia. Crow (2000) re-analyzed the data of a study by Spence et al. (2000) and reported reduced lateralization in schizophrenic patients. Artiges et al. (2000) also observed reduced lateralization in schizophrenia using a verbal fluency protocol. In an earlier study of our group, language lateralization was decreased in male schizophrenic patients (Sommer et al. 2001b). In that study, decreased lateralization in the patient group resulted from increased language-related activation of the right hemisphere, while language activation of the left hemisphere was similar in patients and controls. Furthermore, decreased language lateralization correlated with increased severity of hallucinations. The latter finding suggests that decreased language lateralization may play a role in the etiology of psychosis, at least of hallucinations.

It is not clear whether the results obtained in male schizophrenia patients can be extrapolated to female patients with schizophrenia, since neurobehavioral laterality indices, i.e. performance on motor, sensory, and spatial and verbal cognitive tests, were reportedly different in male and female schizophrenia patients (Ragland et al.1999). Furthermore, a possible gender difference in language lateralization may be a factor underlying some of the gender differences in onset and course of schizophrenia. It could be hypothesized that decreased language lateralization in schizophrenia is gender specific (i.e. decreased lateralization in male schizophrenia patients and normal lateralization in women with schizophrenia). To test this hypothesis, we studied language lateralization in female schizophrenia patients and compared the results to the data from the earlier study in male patients.

METHODS

Subjects

Twelve women were included that fulfilled DSM-IV criteria for schizophrenia, paranoid subtype, as determined by an independent psychiatrist using the Comprehensive Assessment of Symptoms and History (CASH) and History Schedule for Affective Disorder and Schizophrenia Lifetime version (SADS-L) (Andreasen et al. 1992). Patients with comorbid depression were excluded. The mean age of the patients was 33.6 (s.d. 8) and the mean age at onset (first appearance of psychotic symptoms) was 28 (s.d. 5). Patients with diagnosis of drug dependence or substance abuse in the three months prior to entry were excluded. All patients were on atypical antipsychotic medication: six patients used clozapine (mean dose 339 mg, s.d. 67), five patients used

olanzapine (all 15 mg) and one patient used risperidone (3 mg). No additional medication was used, except oral contraconceptives in five patients.
The Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) was used for symptom assessment immediately prior to the scan session. Presence and severity of several positive and negative symptoms were scored over the last two weeks. Ratings were carried out by a physician and a second rater who had been trained for the interview. Scores were determined by means of consensus.
Twelve healthy women aged 32 (s.d. 12), who were free of medical or neurological illness, were also included. Subjects met Research Diagnostic Criteria for "never mentally ill" according to the CASH and SADS-L interview and had no first or second degree relatives with schizophrenia. The section "substance abuse" from the CASH was used to determine whether subjects met the DSM-IV criteria for substance dependence, in which case they were excluded. Seven females from the control group used contraconceptive pills.
Parental educational levels were measured by the total number of years of education. No significant differences in parental educational level were found between patients and controls
All subjects were right-handed as assessed with the Edinburgh Handedness Inventory (Oldfield 1971). Mean score on the Edinburgh Handedness Inventory was 0.92 (s.d. 0.1) for the patients and 0.92 (s.d. 0.2) for the controls. Four patients and four controls had left-handed first-degree relatives. The primary language of all subjects was Dutch.
After complete description of the study to the subjects, written informed consent was obtained.

Tasks

Tasks and scan technique are described in detail by Ramsey et al. (2001). Briefly, two word tasks were used: the verb-generation task and the reverse-read semantic decision task. For the verb-generation task a noun appeared on the screen every 3.6 seconds. The subject was instructed to generate a verb that was appropriate for that word. To avoid head motion, silent vocalization was used.
For the reverse-read task, the subject had to read words that were spelled from right to left (but not in mirror-image print). These words also appeared once every 3.6 seconds. The reversed spelling of the words is thought to avoid direct orthographic word recognition and put more

emphasis on phonologic decoding. The subject was instructed to vocalize the word silently and push a button if the word was an animal. For the reverse-read task performance was recorded by a computer. Both tasks were performed during 10 periods of 29 seconds, alternated with 29 seconds rest. During the rest condition, subjects were instructed to keep their eyes open while fixating on an asterisk in the center of the screen. A simple button-press task (i.e. respond to an asterisk, which appeared at the same rate as the targets) was used as a baseline condition for the reverse-read task.

Scans

Functional scans were acquired with a Philips ACS-NT 1.5 Tesla clinical scanner, using the blood oxygen level dependent (BOLD) sensitive, navigated 3D PRESTO pulse sequence (Ramsey et al. 1998; van Gelderen et al. 1995), with the following parameter settings:

TE/TR 35/24 ms, flip angle 9°, FOV 225 x180x91 mm, matrix 52x64x26, voxel size 3.51 mm isotropic, scan time per fMRI volume 2.4s. Following the fMRI procedure an anatomical scan was acquired (3d-FFE, TE/TR 4.6/30 ms, flip angle 30°, FOV 256x256x180 mm, matrix 128x128x150, slice thickness 1.2mm).

fMRI Analyses

The outer two slices (most dorsal and most ventral) of the transaxial fMRI volumes were not analyzed, since registration causes signal fluctuations at the edges of the volume. Functional scans started and ended seven seconds later than the task to compensate for the delay of the vascular response. All scans, including the subjects' anatomical volume, were registered to the last volume of the last block to correct for head movements and translated and rotated to the standard brain from the Montreal Neurological Institute (Collins et al. 1994) without scaling. Brain activation maps were obtained by analyzing the fMRI scans acquired during both tasks together. Advantages of this combined task analysis are discussed by Ramsey et al. (2001). Functional images were analyzed on a voxel by voxel basis using multiple regression analysis (Worsley and Friston 1995) with one factor coding for activation (task versus rest), and three for signal drift (due to scanner hardware). The regression coefficient for activation was converted to a t-value for each voxel, yielding a t-map. Significant activation was then determined in each voxel by applying a threshold. The threshold corresponded to a p-value of 0.05, Bonferroni-corrected for the total number of voxels in the brain, and amounted to a t-value of approximately 4.5 (depending on the number of voxels for each individual). Five volumes of interest (VOI) were manually delineated bilaterally, on the structural MRI of each brain, blind to statistical results. Manual delineation was performed in sagittal orientation using the DISPLAY tool from the Montreal Neurological Institute. The VOI's comprised Brodmann area (BA) 44 and 45 (Broca's area and its contralateral homologue), middle temporal gyrus (BA 21), superior temporal gyrus (BA 22, 38, 41, 42 and 52), supramarginal gyrus (BA 40) and angular gyrus (BA 39). Together, these VOI's encompassed the main areas where language processing of visually presented words is thought to be mediated (Springer et al. 1999; Perry et al. 1999).

In each VOI the number of active voxels was determined. For subsequent analyses the VOI's were combined, yielding one measure of language-related activation for each hemisphere.

A lateralization index was calculated, defined as the difference in number of active voxels in the left versus the right hemisphere (within the VOI's) divided by the total sum of activated voxels in both hemispheres.

For the patient group, correlations between the lateralization index and the score on the main psychotic symptoms, i.e. delusions (item one of the PANSS) and hallucinations (item three of the PANSS), were calculated and tested for significance (bivariate correlations, tested one-sided).

Comparison to the male patients and controls

The data of the male patients and controls were obtained two years ago (Sommer et al. 2001b). Since then, our method of measuring language lateralization has been updated in two aspects. Firstly, the dorso-lateral prefrontal cortex (DLPC) is no longer considered to be a language area and is therefore no longer included as a VOI for language activation. Secondly, there has been a renewal of the statistical software. In order to make the male data exactly comparable to the present data in females, the raw scan data were re-analyzed with the new statistical package and with exclusion of the DLPC as a VOI.

Lateralization indices and summed language activation in the VOI's of both hemispheres of both sexes were analyzed in an ANOVA, testing a main effect for Gender, a main effect for Diagnosis and a Gender-by-Diagnosis interaction. A direct comparison (independent t-test) between male and female patients was also performed since this test has more discriminative power than the ANOVA.

RESULTS

Symptoms
The mean total PANSS score at the time of scanning was 60 (s.d. 12). The mean subscore on all positive items of the PANSS was 16 (s.d. 5) and the mean subscore on all negative items was 13 (s.d. 4). This indicates that symptom severity in the female patients is in the same range as symptom severity in the study on male patients (total score: 60, positive subscore: 15, negative subscore: 14).

Performance
Performance on the reverse-read task was reduced in the patient group: mean of 20 errors (s.d. 8) on 128 trials, versus 10 (s.d. 6) for the controls ($t(22)=2.2$, $p<0.05$). This was similar to performance in the male study (21 and 8 errors respectively)

Manual segmentation
There was no significant difference in the size of the VOI's (i.e. the total volume of all VOI's within each hemisphere) between the groups, nor was there a difference in total VOI size between the right and left hemisphere.

Activation pattern in the females
Mean activation in the language areas of the left hemisphere was not significantly different between patients (49 voxels, s.d. 32) and controls (50 voxels, s.d. 35).
The mean activation in the language areas of the right hemisphere was significantly elevated in the patients (19 voxels, s.d. 15), as compared to the controls (8 voxels, s.d. 7), $t=2.4$, $p<0.05$. The mean lateralization index of the patients (0.44, s.d. 0.23) was significantly lower than that of the controls (0.75, s.d. 0.2), $t=3$, $p<0.01$.

Correlation with symptom severity
Decreased language lateralization was significantly correlated with increased severity of delusions (rho= -0.54, $p<0.05$), but not with the severity of hallucinations (rho= -0.36, n.s.).

Comparison males and females

When the lateralization indices of these women are compared to the indices of the male patients and controls, a main effect for Diagnosis emerged ($F(2,44)=13.1$, $p<0.001$) and a main effect for Gender ($F(2,44)=4.6$, $p<0.05$), but no Gender by Diagnosis interaction ($F(2,44)= 0.2$, n.s.). Lateralization indices of all four groups are plotted in figure 1.

For the language activation in the VOI's of the left hemisphere, no main effects and no interaction emerged. For the language-related activation in the VOI's of the right hemisphere a significant main effect for Diagnosis ($F(2,44)=10.8$, $p<0.005$), but no main effect for Gender and no interaction emerged.

In the direct comparison between male and female patients no differences were found in lateralization index ($t=-1.2$, n.s.), neither in left hemisphere language activation ($t=-0.1$, n.s.) nor in right hemisphere activation ($t=0.5$, n.s.)

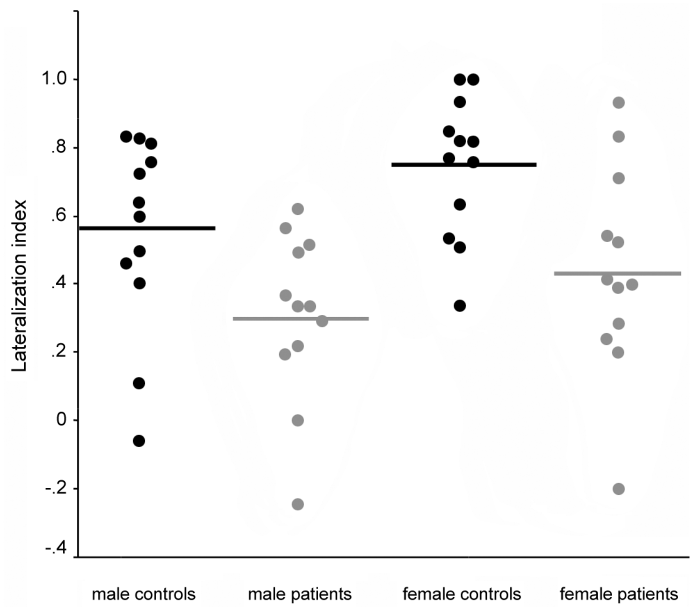

Figure 1
Language lateralization in healthy men (black), men with schizophrenia (grey), in healthy women (black) and in women with schizophrenia (grey)

DISCUSSION

Language lateralization was studied in 12 female patients with schizophrenia and 12 healthy females. Lateralization was decreased in the patients as compared to healthy women, which resulted from increased activation of right hemispheric language areas in the patient group. Activation of left hemispheric language areas was similar in both groups. When the results of this study are combined with the results of our previous study in male patients (Sommer et al. 2001b), lateralization was decreased in patients of both sexes as compared to their healthy counterparts, but there was no difference in language activation between female and male patients. Women, as a group, had higher degrees of language lateralization than men, which is probably a chance finding. In both patient groups, decreased language lateralization was due to increased language activation of the right hemisphere, while left hemisphere language activation was normal. These results suggest that decreased language lateralization in schizophrenia is not gender specific. It is therefore not likely that gender differences in language lateralization underlie gender differences in age at onset and course of schizophrenia.

Decreased lateralization was correlated to the severity of delusions, which suggests that relatively increased participation of right hemisphere areas for language may lead to delusional thinking. Indeed, an association was reported between decreased language lateralization, as measured with dichotic listening tests and increased loosening of associations in healthy (Leonhard and Brugger, 1998) and in schizotypal subjects (Poreh et al. 1993).

Other functional imaging studies that assessed language activity in patients with schizophrenia either studied only men (Artiges et al. 2000; Curtis et al. 1999; McGuire et al. 1996; Lewis et al. 1992), or did not analyze male and female patients separately (Ragland et al. 2001; Crespo-Facorro et al. 1999; Dye et al. 1999; Frith et al. 1995; Wood et al. 1990; Yurgelun-Todd et al. 1996; Spence et al. 2000). Only the early functional imaging studies by Gur et al. (1983 and 1985) provided separate data on language activity in male and female patients. In these studies language lateralization was lower in female patients as compared to healthy females. In men, language lateralization was not found in the patients, nor in the control group. However, these studies were among the first functional imaging studies in schizophrenia and

the signal to noise ratio may have been relatively low, which can explain the unusual finding of absent language lateralization in healthy males.
In the present (female) and the previous (male) study (Sommer et al. 2001b), activation of right sided language areas was significantly increased in schizophrenia patients, while language activation of the left hemisphere areas was normal. This activation pattern could result from a more bilateral cortical representation of language functions, or it could result from a failure to inhibit non-dominant language-related areas. With fMRI it is not possible to differentiate between activation from critical language areas (i.e. areas were lesions would lead to aphasia) and activation from additional areas (i.e. areas that are not essential for language function). The pattern of language activation of the schizophrenia patients, with increased activation of the right hemisphere and normal activation of the left hemisphere, differs from the activation patterns reported for healthy women. Studies that reported decreased lateralization in women (Shaywitz et al. 1995; Pugh et al. 1996; Gur et al. 2000; Kansaku et al. 2001), found that women showed increased language activation in the right hemisphere, which was coupled with decreased language activation in the left hemisphere, although not all functional imaging studies on language found lower lateralization in women as compared to men (Price et al. 1996; van der Kallen et al. 1998; Frost et al. 1999). The difference in activation patterns between healthy women with low lateralization (i.e. a shift in language activation from the left to the right hemisphere) and schizophrenia patients with low lateralization (i.e. additional right hemisphere activation with normal left hemisphere activation) could imply that decreased lateralization in healthy women reflects a more bilateral cortical language representation, while decreased lateralization in schizophrenia patients results from a different mechanism. Increased language activation of the right hemisphere in schizophrenia, in the absence of decreased language activation in the other hemisphere, may reflect a failure to inhibit the non-dominant language areas, while the critical language areas are located at their regular site in the left hemisphere.
However, the results of this study need to be interpreted with caution, mainly because the sample size is limited. Furthermore, all patients were using atypical antipsychotic medication. It is not clear whether antipsychotic medication has an effect on language activation, and whether this effect is different for atypical and typical antipsychotics.
An additional limitation of the study is that performance was measured for only one of the two language tasks. One could argue that patients did not

perform the verb generation task adequately. However, this is unlikely, as one would then expect to find reduced brain activity levels, which was not the case in the patients of this study.

In summary, language lateralization was decreased in female schizophrenia patients as compared to controls, which was due to increased activation of the right hemisphere. No difference in language lateralization between female and male patients was found. Thus, it appears unlikely that the gender differences in onset and course of schizophrenia are related to a gender difference in language lateralization. The consistent finding of increased right-sided language activation in schizophrenia may be explained by a failure to inhibit non-dominant language areas.

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Part 2 Language lateralization in schizophrenia

CHAPTER 11

Language lateralization in monozygotic twin pairs discordant for schizophrenia

British journal of Psychiatry feb. 2004

ABSTRACT

In previous functional magnetic resonance imaging (fMRI) studies, schizophrenia patients showed decreased language lateralization, resulting from increased activation of the right hemisphere as compared to controls. In this study, we aimed to determine whether decreased lateralization and increased right cerebral language activation constitute genetic predispositions for schizophrenia.

Language activation was measured with fMRI in 12 right-handed monozygotic twin pairs discordant for schizophrenia and 12 healthy right-handed monozygotic twin pairs, who were matched for sex, age and education. We found that language lateralization was decreased in discordant twin pairs as compared to healthy twin pairs. The groups did not differ in activation of the language-related areas of the left hemisphere, but language-related activation in the right hemisphere was significantly higher in the discordant twin pairs than in the healthy pairs. Within the discordant twin pairs, language lateralization was not significantly different between patients and their non-schizophrenic co-twins. This suggests that decreased language lateralization constitutes a genetic predisposition for schizophrenia.

INTRODUCTION

In two functional Magnetic Resonance Imaging (fMRI) studies we reported that language lateralization was decreased in male (Sommer et al. 2001) and female (Sommer et al. 2003) schizophrenia patients as compared to healthy controls. This was caused by increased language-related activation in the right-sided homologues of Broca's and Wernicke's area in the patients than in the controls. Activation in the language-related areas of the left hemisphere was similar in both groups.

The increased activation of the right cerebral homologues of the language areas in schizophrenia patients may be a predisposing (genetic) factor for schizophrenia. Alternatively, it could be a result of the disease, or of the use of antipsychotic medication.

In this study we aimed to determine whether decreased language lateralization is a genetic predisposition for schizophrenia or if it reflects aspecific functional disturbance caused by schizophrenic cerebral pathology. Therefore, language activation was assessed with fMRI in monozygotic twin pairs discordant for schizophrenia using the same protocol as in the earlier studies. Since monozygotic twin pairs are genetically identical, traits that reflect increased genetic vulnerability for schizophrenia will be present in both twins, while characteristics that are secondary to the disease or medication are absent in the non-schizophrenic co-twins.

METHODS

Subjects

Twelve monozygotic twin pairs discordant for schizophrenia or schizo-affective disorder were included. Diagnosis was established using DSM-IV criteria as determined by an independent psychiatrist using the Comprehensive Assessment of Symptoms and History (CASH) and History Schedule for Affective Disorder and Schizophrenia Lifetime version (SADS-L) (Andreassen et al. 1992).

At the time of scanning, six patients were psychotic, as indicated by a score of more than two on one or more of the following PANSS items: hallucinations, delusions, suspisiousness or grandiosity. None of the schizo-affective patients was depressed or manic at the time of scanning. Hallucinations, if present, were experienced infrequently (once a day or several times a week). In the group of discordant twin pairs, the co-twins of the patients by exclusion had never experienced hallucinations or delusions as assessed in the CASH and SADS-L interview. However, the non-schizophrenic co-twins were not necessarily free of other psychiatric disorders. Clinical data of the patients and their co-twins are listed in table 1.

Of the non-schizophrenic co-twins, one subject was clinically depressed at the time of scanning. In the discordant twin pairs, the mean time after onset of the first psychotic episode of the schizophrenic twin was 17 years, s.d. 10. Belmaker et al. (1974) reported that approximatly 70% of monozygotic twin pairs become concordant for schizophrenia within four years of the first twin's hospitalisation. Therefore, it is unlikely that the discordant twin pairs will become concordant for schizophrenia in the future.

Twelve healthy monozygotic twin pairs were included that were matched pair-wise for gender, age and education. Subjects with medical or neurological illness were excluded. Subjects met Research Diagnostic Criteria for "never mentally ill" according to the CASH and SADS-L interview.

In all twin pairs monozygosity was confirmed by genotyping, using ten highly polymorphic markers (Wijmenga et al. 1998). All twins were native Dutch speakers and all were right-handed as assessed with the Edinburgh Handedness Inventory (Oldfield 1971). Familial left-handedness was scored positive if one or more first-degree relative(s) preferred the left-hand for writing. Educational levels were measured by the total number of years of education. Information on birth weight, gestational age at birth and chorionicity was collected from a questionnaire filled out by the mothers of the twins. Demographic data of the patients, the co-twins and the healthy twin pairs are detailed in table 2. After complete description of the study to the subjects, written informed consent was obtained that had been approved by the human ethics committee of the University Medical Center Utrecht.

Symptom assessment

The Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) was used for symptom assessment immediately prior to the scan session. Mean scores on the positive and negative items of the PANSS are listed in table 1.

Table 1. Clinical characteristics of the discordant twins

	Proband (n=12)	**Co-twin (n=12)**
DSM-IV diagnosis	2 Schizo-affective disorder, 10 schizophrenia (1 catatonic, 1 disorganized, 8 paranoid)	1 major depression, 2 dystymia from which one also had alcohol dependence, 1 schizotypal personality disorder
First psychotic symptoms	Age 25, s.d.4	—
Medication at time of scanning	3 olanzapine (2:10mg, 15mg), 1 risperidone (4mg), 2 clozapine (350 mg, 100mg), 3 pimozide (2:4mg, 6mg), 2 zuclopentixol (15mg, 20mg), 1 perfenazine (10mg)	1 clomipramine 100mg and lithium 1200mg, 1 fluvoxamine 100 mg
Psychotic at time of scanning	6 subjects	—
Total score positive PANSS items	17 s.d. 7	—
Total score negative PANSS items	19 s.d.8	—

Scans

Functional scans were acquired with a Philips ACS-NT 1.5 Tesla clinical scanner, using the blood oxygen level dependent (BOLD) sensitive, navigated 3D PRESTO pulse sequence (Ramsey et al. 1998) with the following parameter settings: TE/TR 35/24 ms, flip angle 9°, FOV 180x225x91 mm, matrix 52x64x26, voxel size 3.51 mm isotropic, scan time per fMRI volume 2.4 s. Following the fMRI procedure, an anatomical scan was acquired (3d-FFE, TE/TR 4.6/30 ms, flip angle 30°, FOV 256x256x180 mm, matrix 128x128x150, slice thickness 1.2mm).

Activation tasks

Tasks and scan technique have been described in detail by Ramsey et al. (2001). Briefly, two word tasks were used: a paced verb-generation task and a semantic decision task. For the verb-generation task a noun appeared on the screen every 3.6 seconds. The subject was instructed to generate a

Table 2. Demographic data

	discordant pairs	control pairs
Gender	5 male pairs, 7 female pairs	5 male pairs, 7 female pairs
Mean age (years)	42 s.d. 10	37 s.d. 12
Familial Left-handedness	In 9 twin pairs	In 4 twin pairs
Mean gestational age at birth	36 weeks s.d. 4	37 weeks s.d. 3
Chorionicity	6 monochorionic, 1 dichorionic, 4 unknown	4 monochorionic, 2 dichorionic, 6 unknown

	Patient	Co-twin	Healthy twin 1	Healthy twin 2
Mean birth weight (grams)	2486 s.d. 564	2403 s.d. 492	2628 s.d. 553	2819 s.d. 447
First born	6	6	6	6
Education (years)	11.9 s.d. 2.8	12.2 s.d. 2.6	12.1 s.d. 2.7	12.0 s.d. 3.0

verb that is appropriate for that noun. To avoid head motion, silent vocalization was used. During the baseline condition of the verb generation task subjects were instructed to fixate on a number of squares projected on the screen at the same frequency as the words.

For the semantic decision task, the subject had to decide if the concrete noun presented on the screen is an animal. Affirmative responses were given by pushing an air-mediated button with the right hand. The control task included the same number of button press responses, which were cued with a fixed number of asterixes that appeared with random intervals. Performance was recorded with a computer. Both tasks were performed during 10 periods of 29 seconds, alternated with 29 seconds of baseline conditions. Tasks were projected in a fixed order: the verb generation task first and the semantic decision task second.

Combined task analysis

Brain activity maps were obtained by analyzing the fMRI scans acquired during both tasks together, i.e. one t-map was derived from each subject during the performance of both tasks.

The rationale for combined analysis, which is similar to the "conjunction analysis" described by Price and Friston (1997), is that it combines methodological advantages of two tasks.
Lateralization varies between individuals, but also between tasks (Curtis et al. 1999). In an earlier study in healthy volunteers (Ramsey et al. 2001) we found that lateralization is generally low for semantic categorization tasks. When a task yields only low lateralization indices, as with semantic categorisation, its is difficult to detect a difference in lateralization between groups. In contrast, healthy volunteers showed high lateralization of language activity on a verb generation task. However, the verb generation task has the disadvantage that performance can not be recorded (at least not in our lab). Combined analyses of these two tasks yields relatively high lateralization, and also provides a performance measurement.
We have previously shown that such an analysis improves reliability of the subsequently computed laterality index, as compared to that obtained with individual task analyses (Ramsey et al. 2001).

fMRI Analyses

The outer two slices (most dorsal and most ventral) of the transaxial fMRI volumes were not analyzed, since registration causes signal fluctuations at the edges of the volume. Functional scans started and ended seven seconds later than the task to compensate for the delay of the vascular response. All scans, including the anatomical scan, were registered to the last volume of the last block to correct for head movements and translated and rotated to the standard brain from the Montreal Neurological Institute (Collins et al. 1994) without scaling. Functional images were analyzed on a voxel by voxel basis using multiple regression analysis (Worsley and Friston 1995) with one factor coding for activation (task versus rest), and three for signal drift (due to scanner hardware). The regression coefficient for activation was converted to a t-value for each voxel, yielding a t-map. Significant activation was then determined in each voxel by applying a threshold. The threshold corresponded to a p-value of 0.05, Bonferroni-corrected for the total number of voxels in the fMRI scan volume, and amounted to a t-value of approximately 4.5 (depending on the number of voxels for each individual).
Ten volumes of interest (VOI) were manually delineated on the structural MRI scan of each subject, blind to diagnosis and to the statistical results. Manual delineation was performed in sagittal orientation using the DISPLAY tool from the Montreal Neurological Institute.

For manual delineation, the following landmarks were used: lateral fissure, its ramus anterior and ramus ascendens and the sulcus temporalis superior. The VOI's selection was based on the activation pattern of healthy subjects scanned with this protocol (Ramsey et al. 2001) and comprised the inferior frontal gyrus pars orbitalis and pars opercularis: Brodmann area (BA) 44 and 45, middle temporal gyrus (BA 21), superior temporal gyrus (BA 22, 38, 41, 42 and 52), supramarginal gyrus (BA 40) and angular gyrus (BA 39). Together, these VOI's encompassed the main areas where language processing of visually presented words is thought to be mediated.

In each VOI the number of activated voxels was determined. For subsequent analyses the VOI's were combined, yielding one measure of language-related activation for each hemisphere. Finally, a lateralization index was calculated, defined as the difference in the number of activated voxels in the left versus the right hemisphere (within the VOI's) divided by the total sum of activated voxels in the VOI's of both hemispheres (activation left-sided VOIs – activation in right-sided VOIs / total activation in all VOIs). In fMRI scans there generally is a large variability in the total activation a subject shows when presented with a task. The lateralization index was used to correct for this large spread. This index divides the difference between left-sided and right-sided activation by the total number of activated voxels. Therefore, the relative measure of the lateralization index is less susceptible to differences in signal to noise ratio than an absolute activation measurement, such as the language activation of the right hemisphere could be.

Statistical Analyses

For the discordant twin pairs, the data of the schizophrenic twins were placed in the first column (first twins) and data of the non-schizophrenic twins in the second column (second twins). Control twin pairs were divided in two subgroups based on birth order of the discordant twin pair that they were matching, i.e. if the affected twin was born first, then the first born twin of the control pair was also placed in the first column, and vice versa. In this way, control pairs were also matched for birth order.

To assess if language lateralization differed between discordant and healthy pairs, lateralization indices of the discordant pairs (schizophrenia patients and co-twins) were compared to the control pairs in a repeated measurement ANOVA. If significant differences emerged, language activation per hemisphere was compared between discordant and control pairs, to test

whether decreased lateralization resulted from decreased left hemisphere activation, or from increased activation of the right hemisphere.
Possible differences between discordant and control pairs in the activation of specific VOI's were evaluated in a repeated measurements MANOVA.
To test the possible effects of schizophrenia or of antipsychotic medication use on language lateralization, the schizophrenic and non-schizophrenic twins of the discordant pairs were compared using a paired T-test. If significant differences emerged, language activation per hemisphere was also compared.
To test the possible effect of increased genetic risk for schizophrenia on the lateralization index, the non-schizophrenic co-twins of the discordant pairs were compared with the control twins, that were matched for birth order, using an independent t-test. If the difference was significant, differences in activation per hemisphere were also tested.
Finally, an effect for Gender on the lateralization index was tested for significance in the discordant and control twins separately, by means of a repeated measurements ANOVA.
All results reported are based on two-tailed tests of statistical significance.

RESULTS

Performance

Performance on the semantic decision task was not significantly different between the discordant and the healthy twin pairs: mean of 6 errors, s.d. 5 on 128 trials for the discordant pairs and 5, s.d. 3 for the healthy pairs.

Language activation

Discordant vs Control twin pairs

For the lateralization index a significant main effect for Group (discordant vs control twin pairs) was found ($F(1,22)=13.3$, $p<0.001$). The main effect for Twin (first and second twins) was not significant ($F(1,22)=2.9$, $p=0.1$), nor was the Twin x Group interaction ($F(1,22)=2.0$, $p=0.17$). Differences in the lateralization index are shown in figure 1.
Summed language-related activation in the VOI's of the left hemisphere was similar for both groups (main effect for Group: $F(1,22)=1.2$, n.s., main effect for Twin: $F(1,22)=0.05$, n.s, Twin x Group interaction: $F(1,22)=0.03$, n.s.). For the summed language-related activation in the VOI's of the right hemisphere, a significant main effect for Group was found ($F(1,22)=5.0$,

p=0.02). No significant main effects for Twin (F(1,22)=0.17, n.s.) or Group x Twin interaction were found for the activation of the right hemisphere (F(1,22)=0.34, n.s.).
For the number of activated voxels in the separate VOI's the main effect for Group (F(9,198)=0.8, n.s.), the main effect for Twin (F(9,198)=0.04, n.s.) and the Group x Twin interaction (F(9,198)=1.3, n.s.) were not significant.

Schizophrenic vs non-schizophrenic twins
Language lateralization was not significantly lower in the schizophrenic twins as compared to their non-schizophrenic co-twins: t=-1.9, df=11, p=0.09. Infact, there was a trend towards lower language lateralization in the non-schizophrenic co-twins.

Non-schizophrenic co-twins vs control twins
Language lateralization was significantly lower in the non-schizophrenic twins from the discordant pairs than in the control twins: t=4.0, df=22, p=0.001. This decreased lateralization in the non-schizophrenic co-twins resulted from a trend towards increased language activation in the right hemisphere

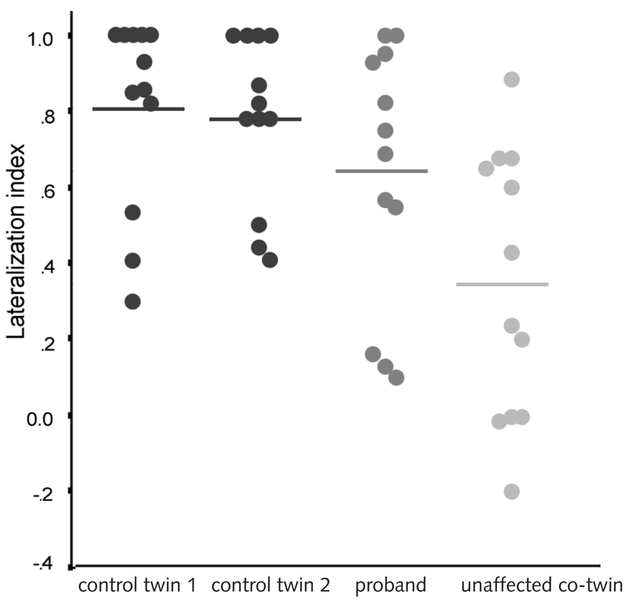

Figure 1
Language lateralization indices in 12 control twin pairs (black), 12 probands (dark grey) and their 12 non-schizophrenic monozygotic co-twins (light grey).

of the non-schizophrenic co-twins as compared to the control twins: t=2.7, df=22, p=0.1, while language activation in the left hemisphere was similar in both groups: t=0.6, df=22, p=0.54.
To preclude the possibility that the effect on lateralization reflected higher psychopathology in the non-schizophrenic twins from the discordant pairs rather than increased genetic risk, the analyses were repeated after excluding the four co-twins with psychiatric disorders. Results were essentially the same: the difference in lateralization index remained significant: t=4.4, df=16, p=0.003, there was a trend towards higher language activation of the right hemisphere in the non-schizophrenic co-twins as compared to the controls: t=1.7, df=17, p=0.1, and language activation of the left hemisphere was equal in both groups: t=0.5, df=17, p=0.65.

Gender
No significant main effect for Gender on the lateralization index was found in the discordant twin pairs, nor in the healthy twin pairs (p>0.55).

DISCUSSION

This study compared the language activation patterns on basic word processing tasks of monozygotic twin pairs discordant for schizophrenia to those of healthy monozygotic twin pairs. We found that language lateralization was decreased in the discordant twin pairs, which was caused by increased activation of the right hemisphere homologues of the language areas, while activation in the language-related areas of the left hemisphere was similar in healthy and discordant pairs. Furthermore, the non-schizophrenic twins had lower language lateralization than control twins.
The corollary of these results is that decreased language lateralization and increased language-related activation of frontal, temporal and parietal areas of the right hemisphere appear to constitute a genetic risk factor for schizophrenia. There also appeared to be a trend towards lower language lateralization in the non-schizophrenic twins as compared to their diseased twins. This may be a medication effect, since all schizophrenic twins used antipsychotic medication, which may have corrected their decreased degree of lateralization to a subnormal level. Currently, this hypothesis is being tested in a medication study, from which the results are not yet available.

Comparison to other studies

Several functional imaging studies measured language activity patterns in patients with schizophrenia (Lewis et al.1992; Frith, et al, 1995; McGuire et al, 1996; Woodruff et al. 1997; Curtis et al. 1999; Artiges et al. 2000; Spence et al. 2000; Kircher et al, 2001; Sommer et al. 2001, 2003). Apart from the previous studies of our group, five functional imaging studies provided information on language lateralization. Lewis et al.(1992) reported decreased left frontal activity in a Single Photon Emission Computed Tomography (SPECT) study of 25 schizophrenia patients during verbal fluency, resulting in reversed frontal dominance. Woodruff et al. (1997) compared the fMRI activation patterns of 15 schizophrenia patients to those of eight healthy subjects while listening to speech. They found reduced activation of the left superior temporal gyrus and increased activation of the right middle temporal gyrus in the patients as compared to controles. Dye et al. (1999) found no difference in PET language activation paterns between six schizophrenia patients and 10 healthy controls on a verbal fluency task. In a Positron Emission Tomography (PET) study by Spence et al. (2000) 10 schizophrenia patients showed more bilateral activation of the frontal areas on a paced verbal fluency task at a qualitative level (Crow 2000). On formal comparison increased activation in the right hemisphere in the patients was not statistically significant. Artiges et al. (2000) also observed reduced lateralization in 14 schizophrenia patients using an un-paced verbal fluency PET protocol. Decreased lateralization was due to both decreased left frontal language activity and increased language activity of the right-sided frontal areas. However, an un-paced verbal fluency task may be problematic if patients cannot generate enough words, as language activity will then not be maintained throughout the task period, potentially resulting in reduced language production and hence reduced language-related brain activity. Indeed, decreased left frontal language activity was not detected when schizophrenic patients were compared to controls with equally poor performance (Frith et al. 1995; Curtis et al. 1999). While the decreased left-sided language activity described by Artiges et al. (2000) may reflect low performance, increased language-related activity of the right hemisphere in schizophrenia patients can not be explained by poor task performance. Thus, increased language-related activity of the right hemisphere may be a functional characteristic of schizophrenia, or a characteristic of the genetic predisposition for schizophrenia.

Language activation has not been studied previously with functional imaging techniques in monozygotic twin pairs with schizophrenia, but several studies used the dichotic listening paradigm to estimate language lateralization in relatives of schizophrenia patients. This method measures perceptual asymmetry on language stimuli, but provides no information on the involvement of each hemisphere in language processing.

Ragland et al. (1992) studied perceptual asymmetry in 18 monozygotic twin pairs discordant for schizophrenia and seven healthy twin pairs. In contrast to our results, Ragland et al. found decreased language lateralization in the affected twins as compared to their unaffected co-twins, while lateralization of the unaffected twins was not significantly different from that of the healthy twins. The difference between Ragland's study and the present one may result from a lack of power in the Ragland et al. study, since the standard deviation of their lateralization indices was fairly large.

Two groups studied language lateralization with dichotic listening tests in other first-degree relatives of schizophrenia patients. Grosh et al. (1995) studied language lateralization in 18 parents of schizophrenic patients. Lateralization in the parents was significantly decreased as compared to healthy controls, to a similar degree as that in their schizophrenic offspring. Hallet et al. (1986) assessed language lateralization in 22 children of schizophrenic parents. Consistent with the findings of Grosh et al. (1995) and with the present study, they reported significantly lower lateralization in children of patients as compared to 22 children of unaffected parents.

Language activity in the right hemisphere

Our results suggest that increased activation in the contralateral homologues of the language-related areas is not a necessary factor for schizophrenia to develop, given the strong left cerebral dominance for language in some schizophrenia patients of our sample. Neither is increased language-related activation in homologue areas of the right hemisphere sufficient to cause schizophrenia, given the absence of psychotic symptoms in the unaffected co-twins of the patients. However, in combination with other factors more bilateral language activation may facilitate the occurrence of language-related psychotic symptoms, such as auditory verbal hallucinations, thought insertion and thought disorder (Nasrallah 1985). Therefore, it would be useful to gain more insight into the role of the right-sided homologues of the language areas.

Current knowledge on the brain organization for language functions is based on data from two different types of studies (Binder et al. 1996). The first type establishes a link between language functions and brain organization by associating disrupted function of a brain area with a change in linguistic behavior, usually a deficit. Such studies identify a brain area as "critical" for a certain aspect of language, which means that aphasia results when a critical area is damaged. This type of studies, which includes descriptions of different kinds of aphasia and their corresponding lesions, observations using the carotid sodium-amytal (Wada) procedure and findings with intra-operative electrical stimulation indicated that Broca's area (BA 44 and 45 of the left hemisphere) and Wernicke's area (the upper part of the superior temporal gyrus of the left hemisphere) are in most subjects critical language areas (Grodzinsky et al. 2000).

The other type of studies record physiological measures of brain activity while subjects are engaged in tasks that address certain language functions, such as PET and fMRI. Changes in such physiological parameters during a language task may also be detected at sites that are not critical for that language function, but may be activated for aspecific supporting functions. Examples of areas that are frequently found to be activated during language tasks with functional imaging, but that do not produce aphasia when lesioned are the anterior cingulate gyrus and the superior frontal gyrus (Binder et al. 1997).

When the left hemisphere is anaesthesized during the Wada procedure, right-handed subjects are generally not able to speak or to read (Rasmussen and Milner 1976). The left hemisphere can thus be defined to be critical for language. Aphasia is generally not present after aneathezising the right hemisphere of right handed subjects. In these subjects, the right hemisphere thus appears not to contain critical language areas. In contrast, in approximately 30% of left-handers the right hemisphere does have critical language areas, since they become aphasic after anaestezising the right hemisphere (Rasmussen and Milner 1976). A common approach in aphasia and Wada test research is to divide subjects into "exclusively left dominance", "bilateral language" and "exclusively right dominance" categories (Binder et al. 1996). However, functional imaging studies show that there is considerable variation, even among healthy right-handed subjects, in the relative contribution of the right hemisphere to basic language tasks, varying on a continuum from almost exclusively left hemisphere activity to bilateral processing and in rare cases right cerebral dominance (Binder et al.

1997; Frost et al. 1999). Considering this, the increased language activation in the homologue areas of the right hemisphere in our discordant twin pairs can be interpreted in two ways. Firstly, language functions of the discordant twin pairs may have a fundamentally different cortical organisation with a more bilateral distribution of critical language areas. Indirect support for this explanation is provided by structural MRI studies in schizophrenia, reporting decreased asymmetry of the Sylvian fissure and the planum temporale, though not all studies found significant differences (reviewed by Sommer et al. 2001). Such a more bilateral distribution of critical language areas is frequently encountered in left-handed subjects (Knecht et al. 2001; Pujol et al. 1999). Possibly, the discordant schizophrenic twin pairs are similar to healthy left-handers, in that they also have a more bilateral cortical representation of language functions. However, the activation patterns of the discordant twin pairs argue against this explanantion. In an earlier study of our group eight healthy left-handed subjects were scanned with the same protocol as in the present study, and compared to eight healthy right-handers (Ramsey et al. 2001). The left-handed subjects indeed showed increased language activation of the right hemisphere, which can be assumed to arise from a more bilateral representation of critical language functions. However, language-related activation of the left hemisphere was decreased in the healthy left-handed subjects, i.e. the left-handers displayed a shift in language activation from the left to the right hemisphere. Other functional imaging studies that compared larger samples of left-handed and right-handed volunteers also found increased language activation of the right hemisphere in tandem with decreased language activation of the left hemisphere (Pujol, et al, 1999; Knecht et al. 2000). In contrast to this activation pattern in healthy left-handers, the discordant schizophrenic twin pairs of this study showed an additional increase in language activation of the right hemisphere, while left hemisphere language activation remained normal (i.e. high). Therefore, another interpretation of our data is more plausible, namely that language representation in the discordant twin pairs is not similar to that in healthy left-handers. Instead, the language activation pattern in the discordant twin pairs may reflect the use of additional cortical areas in the right hemisphere while the critical language areas are located at their regular sites in the left hemisphere. The additional activation of homologue areas in the right hemisphere is probably not essential to carry out the word tasks, since the language areas of the left hemisphere show normal task-related activation. In fact, increased language activation of the right hemisphere areas may result from insufficient inhibition of these non-dominant areas.

Limitations

Theoretically, we cannot differentiate between genetic effects and the effects of shared environmental influences on decreased language lateralization in the discordant twin pairs of this study, since the results are not compared to findings in dizygotic discordant twin pairs. However, for this type of research the comparison to dizygotic twin pairs may be less effective, since environmental factors that are generally shared in both monozygotic and dizygotic twin pairs, such as upbringing, nutrition, education and sociocultural circumstances are unlikely to have any effect on cerebral dominance (Hicks and Kinsbourne 1976; Bryden and Allard 1981).

An additional limitation of the study is that performance was measured for only one of the two language tasks. One could argue that patients did not perform the verb generation task adequately. However, this is unlikely, as one would then expect to find reduced brain activity levels, which was not the case in the patients of this study.

Finally, the affected twins were a heterogene group. Firstly, both schizophrenia and schizo-affective patients were included. Furthermore, symptom severity and type and dose of antipsychotic medication varied. All three factors may have influenced the relative contribution of the right hemisphere to language activity.

In summary, monozygotic twin pairs discordant for schizophrenia display lower language lateralization, caused by higher language-related activation in the homologue areas of the right hemisphere as compared to healthy monozygotic twin pairs, while activation of the left sided language-related areas is equal in both groups. Decreased language lateralization in the discordant twin pairs may be a functional substrate of their genetic predisposition to develop psychotic symptoms of schizophrenia.

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Part 2 Language lateralization in schizophrenia

CHAPTER 12

Lateralization of hallucinations

J Psychiatry Neurosci. 2003 May;28(3):217-8

ABSTRACT

Several studies reported decreased language lateralization in schizophrenia, wich has been linked to psychotic symptoms. Possibly, language activation of the right hemisphere may become misperceived and lead to auditory verbal hallucinations. To test this hypothesis, functional imaging studies of auditory verbal hallucinations were reviewed in a meta-analysis. The results showed that the language areas of the left hemisphere showed more activity during hallucinations than the right-sided homologues. This finding does not support a right hemisphere origin of auditory verbal hallucinations.

INTRODUCTION

The finding of decreased cerebral asymmetry in schizophrenia, first observed by Crow et al. (1989), has been replicated with several techniques (for reviews see Shapleske et al. 1999; Sommer et al. 2001a). In addition, functional imaging studies reported decreased lateralization of language-related activation in schizophrenic patients as compared to healthy controls (Artiges et al. 2000, Sommer et al. 2001b). Several structural and functional studies correlated decreased asymmetry to psychotic symptoms (e.g., Sommer et al. 20016, Sommer et al. 2003). It could be hypothesized that inner speech, originating from right cerebral homologues of the language areas is perceived as auditory hallucinations. Self-produced language activity normally leads to inhibition of language perception areas (McGuire et al. 1996). When this inhibitory mechanism is failing, verbal thoughts may not be recognised as originating from the self and erroneously be attributed to an external source (Frith 1992). Indeed, inhibition of language perception might be more prone to failure when language activity is derived from an unusual site, i.e. from contralateral homologues areas in the right hemisphere. This hypothesis can be tested by reviewing studies meta-analytically that report functional activation in schizophrenia patients while experiencing hallucinations.

METHOD

The following inclusion criteria were used: valid functional imaging technique, bilateral measurement of activity, right-handed patients with diagnosis of schizophrenia, hallucination-related activity measured either in a block design or with event-related fMRI protocols. Because we are interested in laterality of the verbal component of auditory hallucinations, analysis was restricted to activity in areas that are known to be involved in language: Brodmann areas 21, 22, 38, 39, 40, 41, 42, 44, 45, and 52 (Ramsey et al. 2001). Significant hallucination-related activity was statistically integrated and compared between areas in the left and the right hemisphere using the logaritmic Risk Ratio method (Shadish & Haddock, 1994).
In order to be less dependent on statistical thresholds of the individual studies, data were also analysed with a vote counting method, which compares the number of language-related areas that is significantly activated between the right and left hemisphere.

RESULTS

Five studies met our inclusion criteria: Woodruff et al. 1995 (1 subject), Silbersweig et al. 1995 (5 subjects), Dierks et al. 1999 (3 subjects, from which 2 right-handed), Lennox et al. 2000 (4 subjects), and Shergill et al. 2000 (5 subjects).
Only three studies could be included in the Risk Ratio analysis: Dierks et al. (1999), Lennox et al. (2000) and Shergill et al. (2000), since the Woodruff et al. (1995) study provided insufficient data and the study by Silbersweig et al. (1995) did not report activity in language-related areas at all. The resulting mean, weighted Risk Ratio (left/right) was 3.42 (k=3, total N=11), implying stronger activity of left hemisphere language areas, with a 95% Confidence Interval ranging from 2.89 to 4.81.
All five studies could be included in the vote counting analysis. This analysis also demonstrated that more left hemisphere (n=14) than right hemisphere (n=7) language-related brain areas were significantly activated during auditory verbal hallucinations.

Table 1. Main results of the included studies

Study	Patients	Left hemisphere	Right hemisphere
Woodruff et al. (1995)	1	0	2
Lennox et al. (2000)	4	3	0
Silbersweig et al. (1995)	5	0	0
Dierks et al. (1999)	2	7	1
Shergill et al. (2000)	5	4	4

CONCLUSION

Using two different methods, our results showed that language-related areas in the left hemisphere were significantly more activated than the right sided homotope regions.
Thus, the hypothesis that auditory verbal hallucinations arise from a right hemisphere source of language production (inner speech) and are subsequently perceived as originating from an external source is not supported by the available evidence.

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Summary and discussion

In this thesis, the role of language lateralization in the pathogenesis of schizophrenia is investigated. As with many brain mechanisms studied in schizophrenia, there were gaps in our knowledge on language lateralization in the healthy brain. Therefore, the first part of this thesis is dedicated to aspects of language lateralization in healthy subjects. These studies are essential to interpret subsequent findings in schizophrenia patients.

Since both clinicians and brain researchers may not always be familiar with the details of language lateralization, the aspects of language lateralization relevant to this thesis are discussed in chapter 1.

Chapter 2 presents a hypothetical model on the evolution of language lateralization. In this model, the unilateral development of Broca's and Wernicke's area in most human brains is thought to have resulted from transcription factors that have an expression pattern restricted to the left hemisphere.

In chapter 3, language activation patterns of healthy subjects performing several language tasks are compared. It was concluded that the combined language task protocol is most apt to study cerebral lateralization in schizophrenia. This method was used for all further functional MRI studies in this thesis.

After the method was established, three other aspects of language lateralization in healthy subjects were assessed and described in the following three chapters.

In chapter 4, the issue of sex differences in language lateralization was studied in a meta-analysis. Although women are generally believed to have a more bilateral pattern of language representation than men, our meta-analysis on language activation patterns of 377 men and 442 women yielded no significant difference between healthy men and women. This implies that the sex difference in language lateralization in healthy adults is very small or non-existent.

Chapter 5 is focused on another topic of dispute: language lateralization in monozygotic twin pairs. Approximately 20% of monozygotic twin pairs are discordant for handedness, which is virtually the same percentage as dizygotic twin pairs. Since handedness is genetically determined (Hicks and Kinsbourne 1976), this is an unexpected finding. Handedness is related to language lateralization and thus, language lateralization may also show discordance in an unexpectedly high percentage of monozygotic twin pairs. To test this prediction, language lateralization was studied in 12 monozygotic twin pairs that were concordant for right-handedness and in 13 monozygotic twin pairs of discordant handedness. All concordant right-handed pairs were left cerebral dominant for language and showed high resemblance for the degree of lateralization. From the twin pairs that were discordant for handedness, the majority also showed high correspondence for language lateralization, similar to the handedness concordant group. However, five handedness discordant twin pairs showed large differences in the degree of language lateralization and even opposite cerebral dominance. It is hypothesized that left-handedness and right or bilateral language dominance in these "mirror-imaged" twin pairs is a result of early embryological determination of asymmetry that was disrupted by the splitting process of monozygotic twinning. The finding that monozygotic twin pairs of discordant handedness can show opposite patterns of cerebral lateralization may have implications for studies that use twins to investigate the relative contribution of genes and environment in cerebral diseases, such as schizophrenia. Decreased language lateralization may be a predisposing factor to develop schizophrenia (Green et al. 2003). The twin with disrupted (i.e. right or bilateral) dominance may thus have a higher risk to develop the disorder than his co-twin with "standard" (i.e. left) cerebral dominance. Such an unequal risk for monozygotic twins of these mirror-imaged pairs may also exist for other cerebral diseases, such as depression, autism and dyslexia (Bruder et al. 2003). Mirror imaging is estimated to occur in 35% of monozygotic twin pairs that are discordant for handedness (Springer and Searleman 1978). Therefore, mirror-imaging in twin studies could lead to an underestimation of the genetic contribution to diseases in which hemispheric lateralization may play a role in the aetiology. For future twin studies on diseases that could be dependent on cerebral lateralization we recommend to include only concordant right-handed twin pairs.

In chapter 6, a challenge study in healthy subjects is described that tests the association between language lateralization and cerebral dopamine concentrations. In rats, the striatum of the dominant hemisphere was found to have higher dopamine levels than the non-dominant striatum (Glick and Shapiro 1984). The concentrations of dopamine in the two rat striata normally differ by about 15%, but this asymmetry could be increased to approximately 25% following administration of amphetamine, which resulted in enhanced directional preference in level pressing and turning behavior (Glick and Shapiro 1984). If cerebral dominance in humans would also be related to differences in striatal dopamine concentrations, this would be an important issue for studies on schizophrenia. For example, antipsychotic medication would be expected to have major impact on lateralization, and groups could only be compared if they had equal doses of similar antipsychotic medication. To assess the influence of differences in cerebral dopamine concentrations on human lateralization, ten volunteers participated in a double blind cross-over study that compared functional scans under placebo condition to scans of the same subjects two hours after administration of 0.25 mg/ kg dextro-amphetamine. The scans during the amphetamine condition showed increased activation in several language-related areas of both hemispheres, which may reflect increased vigilance. However, amphetamine challenge had no significant effect on lateralization, which implies that dopamine does not play a key role in language lateralization.

In part II of this thesis, the studies on schizophrenia are described.
Chapter 7 provides an introduction for those readers who are not familiar with the clinical and epidemiological aspects of schizophrenia.
In chapter 8, the literature on possible associations between schizophrenia and cerebral lateralization are summarized in a meta-analysis. The results showed that schizophrenia patients are more frequently non-right-handed (i.e. left-handed or ambidexter) than healthy subjects. Also, non-right-handed children have a somewhat higher chance to develop schizophrenia in adulthood than their right-handed peers. Furthermore, the planum temporale (the upper surface of the temporal lobe that largely overlaps with Wernicke's area) was more symmetrical in patients with schizophrenia than in healthy subjects. In addition, dichotic listening tests generally reported a decreased Right Ear Advantage (REA) in schizophrenia. All three findings suggest that language lateralization is more bilateral in schizophrenia patients, compared to healthy controls. Decreased language lateralization in schizophrenia has generally been considered to reflect a dysfunction of the left hemisphere in schizophrenia. However, this is not in agreement with the findings of the meta-analysis on asymmetry of the planum temporale. Decreased asymmetry of the planum temporale in schizophrenia was not caused by a smaller left planum, but due to a larger right planum. This may reflect a failure to inhibit development of language-related areas in the non-dominant hemisphere rather than a compensation for an underdeveloped left hemisphere.
In chapter 9, the first patient study is described. The lateralization pattern of language functions was assessed in 12 male schizophrenia patients and 12

matched controls. The results were evident: language lateralization is decreased in schizophrenia and this is caused by increased activity of the right cerebral homologues of Broca's and Wernicke's area. Language activation of the left sided language areas was equal in patients and controls. Furthermore, decreased lateralization correlated to increased severity of auditory hallucinations in this patient group. This may suggest that language lateralization is a state phenomenon that temporarily decreases during psychosis and may normalize after remission of psychosis. However, other studies found that structural asymmetry was also decreased in schizophrenia (chapter 8), which suggests a more stable decrease in lateralization. Since the first patient study consisted solely of men, the study needed replication in a female sample.
In chapter 10, the results are described of functional language activation scans in 12 female schizophrenia patients and 12 female control subjects. Similar to the findings in men, schizophrenia was associated with decreased lateralization, which resulted from increased language activity of the right hemisphere as compared to healthy volunteers. When these results are compared to the findings in the male patients study, no sex differences in lateralization emerged. In the female patient study, a correlation was observed between decreased lateralization and increased severity of delusions. The correlation with the severity of hallucinations failed to reach significance, possibly because only few female patients were suffering from hallucinations in the days prior to the fMRI scan.

At this point, there was consistent evidence that language lateralization is decreased in patients with schizophrenia. But it was not clear what the significance of decreased language lateralization in schizophrenia may be. All participating patients were using antipsychotic medication. This medication is known to affect several language functions (Docherty and Gottesman 2000), and may also have altered language lateralization. The correlation with the severity of positive symptoms suggests that decreased lateralization may be a state phenomenon accompanying psychosis. Possibly, cerebral ordering systems, such as the thalamic gating mechanism, may become malfunctioning during psychosis (Andreasen 1997). This could result in dysfunction of cortical systems, which may cause both decreased language lateralization and psychosis. Thus, decreased lateralization could be a feature that is associated with psychosis, without having a role in its etiology. On the other hand, decreased lateralization could antedate psychosis.

Decreased lateralization could thus be a risk factor that predisposes the brain for the development of psychosis and may even have a role in the pathogenesis of psychosis. To differentiate between these two possibilities, one would have to assess lateralization in subjects that later develop psychosis. Given the incidence of 1% for schizophrenia, it would take a great effort to study the association between language lateralization and schizophrenia in a prospective design. An alternative strategy is to study monozygotic twin pairs that are discordant for schizophrenia. The non-schizophrenic twin is genetically identical to the schizophrenic twin, but has never suffered from psychosis. This twin will have all the genetic predisposing factors, but not the phenomena that are secondary to the disease or to its treatment.

In chapter 11, language lateralization was measured in 12 monozygotic twin pairs discordant for schizophrenia and 12 healthy monozygotic twin pairs, who were matched for sex, age and education. All participating twin pairs were right-handed. Language lateralization was decreased in the discordant twin pairs as compared to the healthy twin pairs. Language lateralization in the unaffected co-twins of the patients was significantly lower than in control twins. Within the discordant twin pairs, there was a trend towards decreased language lateralization in the non-schizophrenic co-twins as compared to the patients. This may be a medication effect. All schizophrenic twins used antipsychotic medication and this could have corrected their decreased degree of lateralization to a subnormal level. A study is currently undertaken in which language lateralization is measured in medication naive schizophrenia patients, and then again when the patients are taking antipsychotic medication for eight weeks. This study may reveal the effect of antipsychotic medication on language lateralization, and may also shed light on the stability of individual degrees of lateralization when psychotic symptoms have subsided.

The finding of decreased language lateralization in the non-schizophrenic co-twins suggests that decreased language lateralization constitutes a genetic predisposition for schizophrenia. The discordant pairs did not differ from control pairs in the activation of the language-related areas of the left hemisphere, but language-related activation in the right hemisphere was significantly higher in the discordant twin pairs than in the healthy pairs. Possibly, the language activation pattern in schizophrenia patients reflects the use of additional cortical areas in the right hemisphere, to compensate for the left sided language areas that are less efficient in handling language functions. The slightly lower degree of language lateralization in the non-schizophrenic co-twins as compared to the affected twins may then reflect an even more successful compensation mechanism than in their schizophrenic twins. Alternatively, the language activation pattern in the discordant twin pairs may reflect a failure to inhibit homologue cortical areas in the right hemisphere while the language areas of the left hemisphere are functioning normally. The additional right hemisphere activation may be disadvantageous for language functioning, and may even give rise to language-related psychotic symptoms.

Normal language dominance may be accomplished by a gating mechanism of the thalamus, which selectively facilitates the cortical areas that are specialized for a language function, while inhibiting the contralateral homologue areas (chapter 1). Lesions of the left thalamus, especially of the ventrolateral and pulvinar nuclei are known to cause language deficits consisting of paucity of spontaneous speech, perseverations, dysnomia and neologisms with intact comprehension and repetition (Reynolds et al. 1978). Electro-stimulation of the dominant ventrolateral thalamus during brain surgery leads to activation of the dominant language areas while the contralateral homologues are inhibited (Ojemann 1975). Left-handed subjects have a more bilateral thalamo-cortical facilitation (Ojemann 1975), which may underlie their more bilateral representation of language functions. In Parkinson patients treated with stereotactic thalamotomy, language lateralization increased during direct electrical stimulation of the left ventrolateral thalamus and subsequently decreased after thermocoagulative destruction of this nucleus. These effects are absent when stimulation and coagulation is applied to the right ventrolateral thalamus (Hugdahl and Wester 2000). Thus, the language activation pattern observed in the discordant twin pairs of the present study may result from a failure of the thalamus to perform its normal inhibitory activity on the non-dominant cortical areas. Because the thalamic inhibitory mechanism is failing, inappropriate language activity, originating from the right hemisphere, may emerge. When this "release" language activity is not integrated correctly, subjects may wrongly attribute this self-generated language activity to an external source. Language-related psychotic symptoms such as auditory verbal hallucinations and formal thought disorder may result from incorrect integration of language activity of the right hemisphere (Nasrallah 1985). Therefore, the excess language-related activation in the right hemisphere found in the discordant twin pairs may be a functional substrate of their increased risk to develop psychosis.

In order to test whether language activity in the right hemisphere of schizophrenia patients is a necessary compensation mechanism or a disturbing failure of inhibition, transcranial magnetic stimulation (TMS) is currently used to assess dysphasia after stimulation of right sided language areas in schizophrenia patients. If the right-sided language activation is necessary to maintain normal language functions, patients may become dysphasic when the right sided homologue of Broca's area is stimulated. Alternatively, if right-sided language activation is causing language-related psychotic symptoms, TMS may give relieve of these symptoms. In this case, TMS could further be tested as a therapeutic instrument for persisting auditory verbal hallucinations. However, results of this study are not yet available.

In chapter 12, meta-analysis was performed on functional imaging studies that have measured cerebral activity during auditory verbal hallucinations in schizophrenia patients. The aim was to test whether cerebral activation during auditory verbal hallucinations is indeed derived from frontal and temporal areas in the right hemisphere. Of the included studies, some reported more extensive activation of the right hemisphere and others reported predominantly left sided activity. Most of the included studies had very small sample sizes and the applied scanning protocols were heterogeneous. The meta-analysis showed that the language areas of the left hemisphere are more frequently activated during hallucinations than the homologue areas of the right hemisphere. This finding does not support the hypothesis that verbal hallucinations arise from inappropriate language activity of the non-dominant hemisphere. Still, the included studies were too small and their results too heterogeneous to fully reject the hypothesis.

In conclusion, this thesis showed that language lateralization is decreased in schizophrenia and that it constitutes a genetic predisposition for the disease. Several issues need further investigation. These include the influence of medication on lateralization and the stability of individual lateralization patterns over periods of variable clinical states. However, the most pressing question is whether the increased language activity of the right hemisphere found on fMRI scans of schizophrenia patients reflects a useful compensation mechanism or a disturbing failure of inhibition.

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Nederlandse samenvatting

Lateralisatie en schizofrenie

De twee hersenhelften, de hemisferen, van het menselijke brein verschillen zowel in vorm als in functie. In sommige hersenfuncties, zoals taal, rekenen, fijne motoriek en ruimtelijk inzicht is de ene hersenhelft beter dan de andere. Deze specialisatie van de hersenhelften wordt lateralisatie genoemd. De hersenhelft die gespecialiseerd is in taal wordt de dominante hemisfeer genoemd.

De anatomische verschillen tussen de hersenhelften zijn het grootste in de gebieden die bij taal betrokken zijn. Het planum temporale, het horizontale oppervlak van de bovenkant van de slaapkwab, is bij de meeste mensen duidelijk groter in de linker dan in de rechter hersenhelft. De fissuur van Sylvi, de diepe groeve tussen de voorhoofdskwab en de slaapkwab, is links over het algemeen langer en minder stijl dan aan de rechter kant.

De mate waarin de hersenhelften qua anatomie en functie van elkaar verschillen is niet voor ieder mens gelijk. Mensen met een “hoge lateralisatie graad” gebruiken vrijwel uitsluitend de linker hersenhelft voor taal. Bij hun zullen ook de anatomische verschillen meer uitgesproken zijn. Maar er zijn ook mensen bij wie de rechter hersenhelft een even belangrijke rol heeft voor taalfuncties dan de linker; dit zijn mensen met bilaterale taal representatie. Dan zijn er ook nog mensen bij wie de rechter hersenhelft dominant is voor taal. In de algemene bevolking is bij ongeveer 75% van de mensen de linker hersenhelft dominant voor taal. Bij 20% van de bevolking zijn de taal functies gelijkelijk over beide hersenhelften verdeeld, en bij slechts 5% is de rechter hersenhelft dominant voor taal.

Bij linkshandige mensen komt bilaterale taalrepresentatie en dominantie van de rechter hersenhelft vaker voor dan bij rechtshandigen. Ook van vrouwen wordt wel gesteld dat zij gemiddeld een lagere lateralisatie graad van taal hebben. In een meta-analyse van de literatuur hierover (hoofdstuk vier) kon dit echter niet bevestigd worden.

De grote spreiding in de lateralisatie graad van taal in de algemene bevolking is opvallend. Een kleine beschadiging of afwijking van de hersenen kan al grote functie stoornissen veroorzaken. Toch leidt een complete afwezigheid van asymmetrie (bilaterale taalrepresentatie) of een omkering van de gebruikelijke asymmetrie (rechter taal dominantie) meestal niet tot enige

functie stoornis. Ondanks veel onderzoek is niet aangetoond dat mensen met een lateralisatie patroon dat afwijkt van de standaard slechter zijn in bepaalde vaardigheden. Dat deze mensen speciale talenten zouden hebben, bijvoorbeeld meer ruimtelijk inzicht of meer creativiteit, is ook nog niet overtuigend aan getoond.
In een aantal studies werd een relatie gevonden tussen enkele psychiatrische ziekten, zoals autisme, dyslexie, aandachtstekortstoornis met hyperactiviteit (ook wel ADHD) en schizofrenie en een afwijkend lateralisatie patroon.

Het doel van dit proefschrift is het verhelderen van de associatie tussen taal lateralisatie en schizofrenie. Daarbij is gebruik gemaakt van functional Magnetic Resonance Imaging (fMRI) om de taalactiviteit van de hersenen in beeld te brengen. Bij deze methode wordt een hersenscan gemaakt terwijl de proefpersoon taaltaken uitvoert. Deze taken actieveren bepaalde delen van de hersenen, waaronder de taalgebieden van Wernicke en van Broca. Deze geactieveerde gebieden zullen beter doorbloed worden tijdens de taak ten opzichte van de rustperiodes. De scan is zo ingesteld dat dit verschil in doorbloeding met behulp van statistische toetsen bepaald kan worden. De plaatsen waar de doorbloeding significant hoger was tijdens het uitvoeren van de taak worden gemarkeerd op de MRI scans. Zo ontstaat een activatie patroon.

In hoofdstuk drie wordt beschreven hoe taal lateralisatie het beste met fMRI gekwantificeerd kan worden. De meest stabiele maat werd gevonden wanneer de taalactiviteit van twee of meer taaltaken gecombineerd wordt. Deze methode werd in de fMRI studies van dit proefschrift steeds toegepast.

Het lijkt waarschijnlijk dat hersendominantie voor een groot deel erfelijk bepaald is. Linkshandigheid, dat geassocieerd is met bilaterale of rechter hersenhelft dominantie, komt vaak in families voor. De handvoorkeur (links,- of rechtshandigheid)van een kind blijkt bepaald te worden door de handvoorkeur van de biologische ouders, maar niet door die van de adoptie ouders. Dit geeft aan dat het kind niet de handvoorkeur van zijn verzorgers na doet, maar dat handvoorkeur bepaald wordt door erfelijke aanleg (de genen). Van eeneiige tweelingen, die precies dezelfde erfelijke aanleg hebben, zou je dan ook verwachten dat ze steeds de zelfde handvoorkeur hebben. Het blijkt echter dat ongeveer 20% van de gezonde eeneiige tweelingen niet dezelfde handvoorkeur heeft. Het zou dus kunnen dat eeneiige tweelingen ook niet altijd dezelfde hersendominantie hebben. Hiernaar is nog weinig onderzoek gedaan. In hoofdstuk vijf wordt beschreven hoe dit met behulp van fMRI onderzocht werd. Vijfentwintig gezonde eeneiige tweelingparen namen deel aan dit onderzoek, twaalf van gelijke handvoorkeur (allen rechtshandig)en dertien van ongelijke handvoorkeur (de één rechtshandig en de ander linkshandig).

Bij alle twaalf tweelingparen van gelijke handvoorkeur was de linker hersenhelft dominant voor taal. De lateralisatie graad van tweelingen van een paar leken sterk op elkaar. Bij de tweelingparen van ongelijke handvoorkeur werden twee patronen gevonden: bij acht tweelingparen was zowel bij de rechtshandige als bij de linkshandige tweeling de linker hersenhelft dominant voor taal. Bij de andere vijf tweelingparen van ongelijke handvoorkeur was de hersendominantie sterk verschillend: bij de rechtshandige tweeling was steeds de linker hersenhelft dominant, terwijl de links-handige tweelingbroer of zus een afwijkend dominantie patroon had: taal dominantie in de rechterhersenhelft (bij drie personen) of bilaterale taal representatie (bij twee personen). Deze vijf tweelingparen met verschillende taaldominantie hadden geen andere familieleden die linkshandig waren.

Er bestaat dus een kleine groep eeneiige tweelingen (naar schatting zo'n 8%) die sterk van elkaar verschillen in functionele hersenorganisatie. Dit verschil kan mogelijk verklaard worden doordat er een verstoring optreedt tijdens de splitsing van het oorspronkelijke embryo in twee embryo's (de tweeling-splitsing). Eeneiïge tweelingen ontstaan doordat een embryo in een vroeg stadium (0-14 dagen na de bevruchting) in tweeën deelt. Wanneer die splitsing relatief laat plaats vindt is het embryo al in het blastula-stadium: een hol bolletje, dat zich gaat innestelen in de baarmoeder. Echter, dit holle embryo is mogelijk al asymmetrisch.
Bepaalde erfelijke factoren zijn vooral tijdens de embryonale fase actief, dit zijn de homeobox genen. Deze genen regelen de aanleg van de juiste structuren op de juiste plaats en op het juiste tijdstip. Enkele van deze homeobox genen zijn slechts aan één kant van het embryo actief. Zij zorgen voor de juiste asymmetrie in het lichaam: het hart links, de lever rechts etc. Wanneer het embryo deelt kunnen er twee ongelijke helften ontstaan: in de ene helft zijn de asymmetrie-genen wel actief, in de andere helft niet.

Bij de tweeling die geen actieve genen voor asymmetrie mee krijgt kan de ontwikkeling van de links-rechts asymmetrie verstoord worden.

Deze bevinding zou consequenties kunnen hebben voor het schizofrenie onderzoek, omdat de erfelijkheid van schizofrenie vaak bepaald wordt met behulp van tweelingstudies. Indien schizofrenie inderdaad geassocieerd is met een verminderde lateralisatie, dan zouden eeneiige tweelingen met een sterk verschillend lateralisatie patroon niet dezelfde kans op schizofrenie hebben. De tweeling met bilaterale of rechter hersendominantie kan mogelijk een grotere kans op schizofrenie hebben. Hierdoor zouden tweelingstudies een onderschatting kunnen geven van de werkelijke genetische basis van schizofrenie.

Schizofrenie is een ernstige psychiatrische ziekte die over de hele wereld voorkomt bij ongeveer 1-2% van de bevolking. Schizofrenie wordt gekenmerkt door periodes van psychose, waarin patiënten hallucineren (iets waarnemen dat er niet is) en/of lijden aan wanen (hardnekkige overtuigingen die niet waar zijn). Daarnaast is er meestal sprake van negatieve symptomen: patiënten worden apathisch, tonen minder interesse en hebben weinig energie.
Het is niet duidelijk welk proces in de hersenen schizofrenie veroorzaakt. Wel bestaan er verschillende theorieën over de onderliggende hersenafwijkingen. Een van die theorieën stelt dat de lateralisatie graad van taal te laag is bij schizofrenie. De relatief hoge taalactiviteit van de rechter (niet-dominante) hersenhelft zou de bron van gehoorshallucinaties kunnen zijn. Deze theorie wordt in dit proefschrift getoetst.

In hoofdstuk acht wordt een overzicht gegeven van de literatuur over schizofrenie en lateralisatie. Hierin komt naar voren dat mensen met schizofrenie vaker linkshandig zijn. Daarnaast werd met behulp van bepaalde neuropsychologische testen gevonden dat de lateralisatie graad van taal waarschijnlijk lager is bij schizofrenie. Als laatste werd gevonden dat patiënten met schizofrenie een minder uitgesproken asymmetrie hebben van het planum temporale en van de fissuur van Sylvi. Deze drie bevindingen zijn indirecte aanwijzingen dat de lateralisatie graad van taal gemiddeld lager is bij schizofrenie patiënten dan bij gezonde mensen.

In hoofdstuk negen werd de taallateralisatie van 12 mannelijke patiënten met schizofrenie vergeleken met die van twaalf gezonde mannen. De patiënten hadden gemiddeld een lagere lateralisatie graad dan de vrijwilligers. Patiënten die veel last hadden van hallucinaties (bijna altijd werden stemmen gehoord) hadden een lagere lateralisatie graad dan patiënten die minder last van hallucinaties hadden.
In hoofdstuk tien werden vrouwelijke patiënten vergeleken met vrouwelijke vrijwilligers en werd hetzelfde gevonden als bij de mannen: gemiddeld een lagere lateralisatie graad bij de patiënten.

Om na te gaan of verlaagde lateralisatie een mogelijke oorzaak is van schizofrenie, of juist een gevolg van de ziekte werd onderzoek gedaan naar tweelingen met schizofrenie. Twaalf eeneiige tweelingparen waarvan één schizofrenie heeft en de ander niet en twaalf gezonde eeneiige tweeling paren waren bereid mee te doen. Voor deze studie werden alleen de scans van rechtshandige tweelingparen gebruikt. Taallateralisatie bleek niet alleen verlaagd bij de tweelingen met schizofrenie, maar ook bij hun gezonde tweelingbroer of zus. Dit bewijst dat de lage taal lateralisatie niet een gevolg is van schizofrenie, maar al voor het begin van de ziekte aanwezig is. Mogelijk kan het een rol spelen in het ontstaan van een psychose.

In hoofdstuk twaalf wordt een samenvatting (meta-analyse) gegeven van de vijf op dit moment beschikbare studies die hersenactiviteit gemeten hebben op het moment dat patiënten hallucinaties ervoeren. Twee studies vonden dat voornamelijk de linker hersenhelft actief was, terwijl de andere studies juist vonden dat de rechter hersenhelft meer geactiveerd werd. Op basis van deze gegevens kan niet geconcludeerd worden dat taalactiviteit in de rechterhersenhelft de bron is van gehoorshallucinaties. Echter, de beschreven studies hadden elk maar weinig patiënten onderzocht en hun bevindingen waren sterk verschillend, waardoor deze hypothese ook niet met zekerheid uitgesloten kan worden.

Concluderend kan gesteld worden dat in dit werk aanwijzingen gevonden werden dat de lateralisatie graad van taal verlaagd is bij schizofrenie en dat dit geassocieerd is met de erfelijke aanleg voor schizofrenie. Of de verlaagde lateralisatie graad ook een directe oorzaak is voor het ontstaan van een psychose is nog niet duidelijk.

CURRICULUM VITAE

Iris Sommer werd geboren op 31-8-1970 te Roermond. In 1988 werd het V.W.O. diploma behaald aan het Bisschoppelijk College Schöndeln in Roermond. Van 1989 tot 1991 volgde zij de studie Gezondheidswetenschappen aan de Rijks Universiteit te Maastricht. Hiervan werd in 1989 het propadeuse examen behaald en in 1990 het tweede jaar voltooid, in de richting biologische gezondheidskunde. Van 1990 tot 1994 volgde ze de studie geneeskunde aan de Vrije Universiteit te Amsterdam, waarvoor in 1994 het doctoraal Cum Laude behaald werd. Tijdens de co-schappen werkte ze aan onderzoeksprojecten bij de vakgroepen neurologie, kinderneurologie en psychiatrie van de Vrije Universiteit Amsterdam. In 1997 werd het arts examen Cum Laude behaald, eveneens aan de Vrije Universiteit te Amsterdam.
Van 1997 tot 2002 werkte zij als promovendus aan het Universitair Medisch Centrum Utrecht. Het onderzoeksgebied was "Taalactivatie bij schizofrenie, gemeten met functionele M.R.I.". Het hieruit voortgekomen proefschrift wordt op 27 januari 2004 openbaar verdedigd.
In september 2003 werd een subsidie aanvraag voor verder onderzoek naar dit onderwerp gehonoreerd door de Hersenstichting Nederland.
Sinds september 2002 is zij in opleiding tot psychiater aan het Universitair Medisch Centrum Utrecht.

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DANKWOORD

Als eerste wil ik mijn promotor en copromotor bedanken. Jullie waren respectievelijk de rechter en linker hemisfeer van dit werk: *"The left hemisphere is analytic, detailed and logic, the right hemisphere is holistic, global and synthetic. Both hemispheres are capable of most functions and differ only in the relative efficacy of individual processing."* *(Goldberg 1990)*
René, je gaf me de kans om zelf hypothesen op te stellen en te toetsen. Ik denk dat ik daarom met zo veel plezier aan dit onderzoek gewerkt heb. Ondanks je volle agenda was je altijd beschikbaar voor hulp en wist je problemen binnen vijf minuten op te lossen. Bedankt voor je vertrouwen en je enthousiasme voor het onderzoek.
Nick, het was een eer om bij de Nederlandse *Doctor fMRI* in de leer te zijn.
Ik ben blij dat ik alle onderdelen van het scannen zelf geleerd heb.
Dank voor je geduld mij dat bij te brengen.

Dan het fMRI team: Martijn Jansma, bedankt voor de tijd die we samen achter WAVE en MEL doorbrachten. René Mandl, veel dank voor je hulp met alles dat onder Unix draait. Jouw kamer was een vaste plek om even stoom af te blazen. Hans Hoogduin, door jou werden we echt een fMRI *team*. Tamar, het was altijd leuk om met je te scannen en jouw scans mislukken nooit!

De onderzoekers en psychiaters van het schizofrenie project wil ik allen hartelijk danken voor hun hulp met het voorbereiden en uitvoeren van dit onderzoek. Een aantal van jullie wil ik persoonlijk bedanken: André, nadat ik de concurrentie slag met jou had opgegeven bleek je een heel leuke kameraad. Dank voor de leerzame samenwerking. Bob, ik mis de lunch met jou, ook al was die altijd veel te vroeg. Veel dank voor je hulp met de amfetamine studie. Wiepke en Esther, dank voor jullie hulp bij de selectie van proefpersonen. Mechteld, ik keek echt uit naar de middagen dat jij ook op de AIO-kamer werkte, al waren die niet het meest productief. Jacob, bedankt dat je bereid was om in te springen als kliniek en onderzoek moeilijk te combineren waren. Marjon Scholten, voor emancipatoire kwesties kon ik altijd bij jou terecht, bedankt voor je grote inlevingsvermogen. Jean-Paul, bedankt voor de stimulerende discussies over schizofrenie. Ik ben er heel trots op dat jij mij een echte onderzoeker vindt.

Floris, Michiel, Doortje, en Hanneke die mee hielpen met de scanstudies wil ik heel hartelijk bedanken voor hun inzet. Wim Verrijp, hartelijk dank voor je bewerking van de figuren en de prachtige voorkant.
De laboranten van radiologie: Desirée, Marion, Jürgen, Jan, Greetje en de anderen, bedankt voor de deskundige hulp en goed gezelschap tijdens de lange fMRI scans.

Anke Bouma, de overleggen met jou waren hartelijk en inspirerend.
Tim Crow, without you I would probably never have heard of language lateralization in schizophrenia. Thank you for promoting this interesting and testable hypothesis.

Veel dank ben ik ook verschuldigd aan de proefpersonen die deelnamen aan de fMRI sessies. Vooral de patiënten, die geheel belangeloos meededen. Voor sommige tweelingen was het al de zoveelste keer dat ze gevraagd werden voor een onderzoek. Fantastisch dat jullie toch bereid waren mee te doen.

Leo Smit, Eric Wolters en Witte Hoogendijk, met wie ik de eerste onderzoekservaring opdeed, wil ik danken voor hun inspirerende voorbeeldfunctie.

Dan wil ik het thuisfront bedanken. Hans, Mies en Marjo, de dinsdag was een lange, productieve werkdag omdat jullie dan voor de kinderen zorgden. De meeste scans zijn dan ook op dinsdag gemaakt. Mies, ik wil je ook bedanken voor het bijschaven van mijn steenkolen-Engels. Kan ik al inschrijven voor de vervolg cursus?
Hans en Joycelyn, twee jaar lang ging Julie op donderdag met veel plezier bij jullie spelen. Ik ben jullie daar dankbaar voor. Brigitte, als er iets mis liep belde ik jou en nam je één of twee kinderen alvast mee naar huis. Je bent de beste buurvrouw die je kunt hebben.
Floor, met jou kon ik alles bespreken, bedankt voor je trouwe vriendschap.

Papa en mama, jullie hebben me vrij gelaten in mijn keuzes. Juist die afwezigheid van ouderlijke druk maakte het leuk om te studeren. Pappa, niemand kan zo duidelijk uitleggen waar mijn proefschrift over gaat als jij. (Wie niets van dit boekje begrepen heeft kan met mijn vader contact opnemen.) Bedankt voor jullie interesse en aanmoediging.

Julie en Simon, jullie zijn lief. Promovendus en moeder zijn was een prima combinatie.
Robert, mijn lief, ik vind je geweldig. Bedankt voor je steun en relativering.