Impact of Language (Re-)organization on Cognitive Functions in Patients with Congenital Left-Hemispheric Lesions

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(f)MRI	(functional) Magnetic Resonance Imaging
AR	Autoregressive model
BOLD	Blood Oxygen Level Dependent
CNS	Central Nervous System
CP	Cerebral Palsy
CSF	Cerebrospinal Fluid
EPI	Echoplanar Image
FDR	False-discovery Rate
FEF	Frontal Eye Fields
FIQ	Fullscale IQ
FWE	Familywise Error
FWHM	Full Width at Half Maximum
GM	Grey Matter
HAWIE-R	Hamburg-Wechsler Intelligenztest für Erwachsene, Revision
IQ	Intelligence Quotient
LI	Laterality Index
MCA	Medial Cerebral Artery infarction
MNI	Montreal Neurological Institute
PET	Positron Emission Tomography
PIQ	Performance IQ
PV	Periventricular lesion
SPL	Superior Parietal Lobule
TA	Time of Acquisition
TE	Time of Echo
TR	Time of Repetition
VIQ	Verbal IQ
WAIS	Wechsler Adult Intelligence Scale
WM	White Matter

Zusammenfassung

Hintergrund: Frühe Läsionen der linken Hemisphäre führen häufig zu einer rechtshemisphärischen Sprachorganisation. Die betroffenen Kinder zeigen Verzögerungen in der Sprachentwicklung; im Jugend- oder Erwachsenenalter sind jedoch keine sprachlichen Auffälligkeiten mehr festzustellen. Andererseits zeigen viele Patienten mit frühen linkshemisphärischen Läsionen Defizite in räumlich-visuellen Fertigkeiten, die normalerweise von der rechten Hemisphäre kontrolliert werden. Für diesen paradoxen Befund gibt es zwei Erklärungsansätze: a) „Crowding“, also eine „Überfüllung“ der rechten Hemisphäre, und b) unspezifische Läsionseffekte.

Methoden: Die vorliegende Arbeit untersuchte mit Hilfe von neuropsychologischen Methoden und funktioneller Bildgebung die Auswirkungen früher linkshemisphärischer Hirnläsionen auf der Verhaltensebene und auf der Ebene der funktionellen Neuroanatomie. Patienten mit angeborenen linkshemisphärischen Hirnläsionen und gesunden Kontrollpersonen wurden eine neuropsychologische Testbatterie vorgegeben, sowie während einer funktionellen Magnetresonanztomographie verbale und nonverbale Aufgaben.

Ergebnisse: Patienten mit frühen linkshemisphärischen Hirnläsionen können Defizite in visuospatialen Fertigkeiten zeigen, sofern ihre Läsion eine Reorganisation von Sprachfunktionen in die rechte Hemisphäre verursacht hat. Bei diesen Patienten sind die visuospatialen Defizite keine unspezifische Auswirkung der Läsion an sich, denn die Läsionsgröße korrelierte nicht mit den Leistungen in nicht-motorischen visuospatialen Aufgaben. Das Ausmaß der rechtshemisphärischen Sprachbeteiligung korrelierte dagegen signifikant mit nicht-motorischen visuospatialen Fertigkeiten. Auf der Ebene der funktionellen Neuroanatomie zeigten diese Patienten keine Reorganisation nonverbaler Funktionen von der rechten in die linke Hemisphäre oder innerhalb der rechten Hemisphäre. Jedoch teilten verbale und nonverbale Funktionen kortikale Netzwerke in einem größeren Ausmaß, als dies bei den Kontrollpersonen der Fall war.

Schlussfolgerung: Die neuropsychologischen Defizite von Patienten mit frühen linkshemisphärischen Hirnläsionen scheinen mit einer verstärkt gemeinsamen Nutzung kortikaler Netzwerke durch verschiedenartige Aufgaben im Zusammenhang zu stehen.

Abstract

Background: Early left hemispheric brain lesions often induce right hemispheric organization of language functions. The children thus affected show delays in language development, but an apparently normal language outcome when they are adolescents or adults. Many patients with early left hemispheric brain lesions, however, show persistent deficits in visuospatial skills, which are usually mediated by the right hemisphere. This paradox finding has been explained by a) a "crowding" of the right hemisphere, or b) considered to be due to unspecific lesion effects.

Methods: The present work examined with neuropsychological methods and functional neuroimaging the consequences of early left-hemispheric brain injury on the behavioral and the functional neuroanatomical level. Patients with congenital left-hemispheric brain lesions and normal controls were examined with a neuropsychological test battery and with verbal and nonverbal tasks in functional MRI.

R*esults:* It was shown that patients with early left hemispheric brain lesions may experience deficits in visuospatial functions, if their lesion induced a reorganization of language to the right hemisphere. The visuospatial deficits are, in these patients, not an unspecific consequence of the brain lesion, as lesion size did not correlate with visuospatial skills without motor component. The degree of right-hemispheric involvement in language production, however, correlated significantly with pure visuospatial skills. On the level of functional neuroanatomy, these patients with lesion-induced right-hemispheric language organization did not show any signs for reorganization of nonverbal functions from the right to the left hemisphere, or within the right hemisphere. In fact, verbal and nonverbal functions shared cortical tissue to a larger extent than was found in the control group.

Conclusions: The neuropsychological deficits of patients with early left hemispheric brain lesions seems to be associated with an increased sharing of cortical networks by functionally different tasks.

1 Introduction

The human brain demonstrates a remarkable plasticity all over the life span, which is thought to be greatest during the initial phases of development. Structural and functional flexibility enables the developing brain to counteract adverse events like unilateral insults which, in adults, often lead to severe cognitive and motor impairments.

Patients who have suffered brain damage before birth or during early childhood often surprise by a comparatively good cognitive outcome. Language functions seem to be particularly protected from lesion effects, even when the traditional left hemispheric language areas are damaged.

The scope of the present study is to examine the consequences of pre- and perinatally acquired left-hemispheric focal brain lesions on the neuropsychological level and on the level of functional neuroanatomy. By this approach, the complex interplay of lesion size, extent of functional reorganization, motor impairment and neuropsychological performance will be illustrated.

2 Theoretical Background

2.1 Localization and Lateralization of Cognitive Functions

The relationship between brain structures and cognitive functions has always been a predominant issue in neuropsychology. From Franz Joseph Gall's first phrenological approaches via Broca's and Wernicke's observations of the behavioral effects of specific brain lesions, up to the modern neuroimaging techniques, the predominant goal has always been to understand where in the brain our cognitive and psychological functions can be found.

Research on functional reorganization in patients with neurodevelopmental disorders cannot do without an understanding of structure-function relationships in the normal developing brain. Therefore, in this first introductory chapter, I will start with a review of theories on structure-function-relationships and lateralization of cognitive functions in general, and with respect to neuronal development. After that, a set of cognitive functions known to be lateralized to a certain extent will be described in more detail. The locations of structures and areas mentioned in the next paragraphs are illustrated in Figure 2.1.

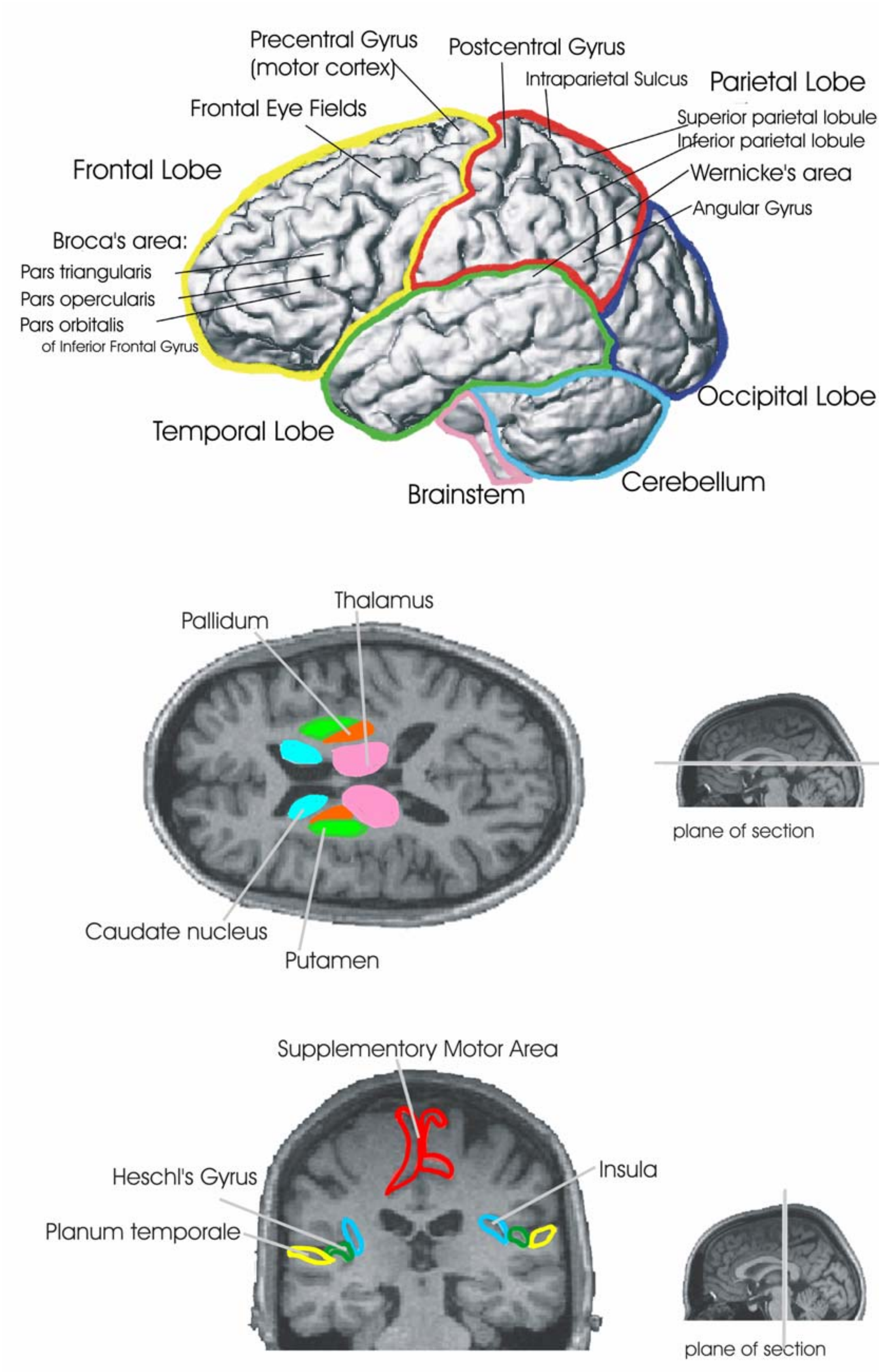

Figure 2.1: Anatomical structures and functional areas mentioned in the text. Top: lateral view; middle: horizontal view; bottom: coronal view. All illustrations are derived from a T1-weighted dataset (resolution = 1.5x1x1mm^3) of the author's brain. The lateral view has been computed with the SPM2 software.

2.1.1 Structure-Function Relationships

Lesion studies have been the traditional neuropsychological approach towards the understanding of structure-function relationships in the brain. By observing the clinical deficits caused by damage to a specific structure, it is possible to examine which structures are essential for the maintenance of a specific cognitive function. In this way, essential areas for language production (Broca, 1861) and language comprehension (Wernicke, 1874) have been identified already in the 19th century. The traditional neuropsychological lesion-approach lead to a rather simple interpretation of the brain's organization: it implied a one-to-one-mapping of cognitive functions to specific structures. This assumption has, at first, been corroborated by neuroanatomical research, which delivered cortical parcellation schemes based on histological criteria (e.g. Brodmann, 1909). Cortical modularity on the cytoarchitectonic level is well established (Mountcastle, 1997). Also neurophysiological studies using invasive recordings from animals could gain clear information on very specific tasks of specific neural populations (e.g. visual cortex neurons firing only in response to a specific orientation; Mansfield, 1974).

Since the early 1990s, fMRI (functional magnetic resonance imaging) offers, by measuring changes of blood-oxygen-level-dependent (BOLD) signals, non-invasive, whole-brain, high-resolution measurements of regionally specific changes of brain activity which are correlated with certain components of a cognitive task. Cognitive neuroscience quickly adopted this technique for the still not sufficiently answered question of structure-function relationships in the brain. It became soon evident that functional neuroimaging reveals many structures which are involved in the processing of a given cognitive task, but it could not explain causal relations. Major parts of neuroscience have therefore been aiming at the more modest goal of establishing mere correlations between structure and function. The idea of one-to-one-mapping of function-to-structure, however, still implicitly lead the interpretation of their results (Stephan, 2004). By now, every single brain structure seems to have many functional labels attached, leading to an abundance of one-to-many and many-to-one structure-function relationships (for a review see Price & Friston, 2002). Again, neuroanatomy can help to understand this situation: No cortical area operates in isolation. Rather each area is connected with a large number of regions by association fibers, so that the activation of a single given structure is always dependent on contextual variables (Stephan, 2004), including activation of other, connected structures. These findings lead, slowly, to a trend reversal in goals and interpretation of neuroscience studies: In recent years, some tools have been made available which allow the exploration of functional imaging data for functional connections and thereby of systems (e.g. Dynamic Causal Modelling; Friston et al., 2003). The role of general system theory is increasingly emphasized in the area of functional imaging (Stephan, 2004). The model of *degenerate neuronal systems* assumes that multiple neuronal systems might be capable of producing the same behavioral response, either by employing alternative cognitive strategies, or by using alternative networks for the implementation of the same cognitive strategy (Noppeney et al., 2004). This approach can parsimoniously explain interindividual differences in functional imaging data, which has long been regarded as mere random noise, or nuisance activation. Even more, it can explain the brain's remarkable robustness to damage: If one structure is lesioned, the remaining ones can still support a particular function. Thus, neuropsychological and functional imaging studies can be combined to understand the nature of neuronal systems: By exploring behavioral deficits caused by lesions (either permanent lesions in neurological patients, or transient lesions, caused by repetitive transcranial magnetic stimulation), neuropsychology can identify which structures of a previously identified network are essential for a function. Functional neuroimaging, on the other hand, can unravel alternative networks in patients who have lesions but have kept or regained the function usually subserved by the lesioned structure (Noppeney et al., 2004).

Structure-function-relationships (regardless if the functions are organized in modules or systems) have to be molded during neuronal development. While most neurons have, at birth, reached their destinations within the cortex, the neocortices of newborns are less structurally differentiated compared to those of adults (Johnson, 1999). Especially the connectivity between different areas is at birth still immature (Johnson, 2001).

How the human brain arrives at the differentiation we know from adult neuropsychology has been discussed in the last twenty years, recently using also the aid of computational neuroscience approaches. Traditionally, a *maturational perspective* had been employed: As soon as a brain region becomes mature, a particular skill becomes functional. However, the dynamic changes in patterns of activation as seen in functional imaging studies on children and adults cannot be explained by such a static system (Johnson, 2001). More complex approaches have therefore to be employed. The *mixture of experts* approach assumes computational heterogeneity in the initial neuronal substrate. The components which best fit a given cognitive domain will win the competition with their neighboring assemblies and come to specialize in the processing of this domain (Jacobs, 1991). Also experience is a determining factor in the specialization process: neural pathways evolve to process specific classes of information only when they received appropriate input (Stiles, 1988). A similar approach is *neural selectionism*, which takes into account the initial over-production of neuronal substrate. During learning, connections which are functional are stabilized, and connections not needed are weeded out (Plaut, 2002). Finally, the *wave of plasticity* approach is based on neural modeling, comparing the brain to computational models. Plasticity is reduced over time with one part of the system losing its plasticity earlier than the other. The later maturing units can use the functions computed by units which mature earlier as input and may therefore arrive at more complex and abstract computational functions (Shrager & Johnson, 1996).

All these theories converge to an explanation of the acquisition of new cognitive functions during childhood as a result of emerging patterns of interactions between different regions (Johnson, 2001).

2.1.2 Laterality

Hemispheric specialization has been shown early for language functions (Broca, 1861; Wernicke, 1874), a fact which lead to intensive research on hemispheric dominance. This discussion got even socio-philosophic traits in assigning the hemispheres "Western"/"analytic" (left) or "Eastern"/"emotional" (right) characters (Paredes & Hepburn, 1976). In an extensive review of the then current literature, however, Bradshaw & Nettleton came to the conclusion that the left hemisphere is specialized for time-dependent, sequential analysess, and therefore also for verbal processing. The right hemisphere might, in their opinion, not show any specialization per se, but takes over what the left hemisphere can not handle due to occupation of processing space by e.g. language functions (Bradshaw & Nettleton, 1981). The functional asymmetry of the hemispheres has been attributed to structural differences between the hemispheres which are influenced by genetic and environmental factors in the course of development (Geschwind & Galaburda, 1985).

Different views have been proposed regarding the development of hemispheric asymmetry: The *progressive lateralization model* asserts that functional lateralization emerges from an initial bihemispheric base (Lenneberg, 1967), whereas the *invariant lateralization model* implies hemispheric specialization being present already at birth (Kinsbourne, 1975). On the anatomical level, larger areas have been described in adults for the left planum temporale and for the left pars opercularis of the frontal lobe (Geschwind & Galaburda, 1985). The planum asymmetry is already present in the fetus and newborn (Chi et al., 1977), a fact which has been interpreted as genetic predisposition of the left hemisphere for language functions (Geschwind & Galaburda, 1985). However, these differences seem to get more pronounced in the course of development (Wada et al., 1975), which has been interpreted in the framework of a left-right maturational gradient, favoring a more rapid left-hemispheric development (Corballis & Morgan, 1987).

On the functional level, developmental studies were for a long time dependent on dichotic listening or tachistoscopic viewing tasks as means for assessment of hemispheric specialization. The results of these studies favor the invariant lateralization model, with the left hemisphere always being specialized for the processing of verbal stimuli, and with the right hemisphere being even in young children specialized for the processing of nonverbal stimuli (Kerr Hahn, 1987). A drawback of Kerr Hahns review, however, might be the dichotomous interpretation of the results of the dichotic listening tasks: The assignment of a dichotic listening result to the categories “right ear advantage” or “left ear advantage” does not leave any room for development of hemispheric specialization along a dimension of laterality. This fact has become obvious with the advent of functional neuroimaging studies, which can not only assess pure dominance of one hemisphere over the other, but the respective proportions of involvement in the solution of a given task. Studies employing functional MRI could indeed find evidence for the progressive lateralization model for verbal and nonverbal functions (Holland et al., 2001; Overy et al., 2004).

2.1.3 Localization and Lateralization of Specific Cognitive Functions

2.1.3.1 Verbal Functions

There is a broad consensus that language is, in most right-handers and in a substantial part of left-handers, controlled by the left hemisphere (Cabeza & Nyberg, 2000; Knecht et al., 2000; Price, 2000). This functional asymmetry has neuroanatomically been related to a larger left planum temporale (Steinmetz et al., 1989) and a larger left pars triangularis of the frontal lobe (Foundas et al., 1996). Although women had been suspected to show different patterns of hemispheric dominance for language (Shaywitz et al., 1995), a recent thorough meta-analysis could not find any significant differences in language lateralization between men and women (Sommer et al., 2004).

Regarding the development of functional lateralization of language, two competing hypotheses have been put forward: The *equipotentiality* hypothesis was inspired by findings that children can develop normal language functions despite hemispherectomy of the entire left hemisphere. It assumes that both hemispheres are equally able to sustain language functions, with lateralization determined gradually in the course of development (Lenneberg, 1967). This view was soon challenged by studies suggesting that early left hemisphere lesions do lead to subtle but persistent language deficits (B. T. Woods & Carey, 1979): The hypothesis of *irreversible determinism* was born. These two extremes were, mainly in the 1990s, brought together in the *emergentist view*. This theory is supported by a whole range of developmental neuropsychology studies, combined with structural and/or functional neuroimaging. These studies could show that children can experience initial delays in language development after early focal lesions, regardless of the hemisphere affected, but that they come to a clinically normal level of language skills, with only subtle deficits persisting (Bates & Roe, 2001; Chilosi et al., 2001). The emergentist view states that the infant brain contains strong biases which, in the absence of early brain damage, lead to an eventual left-hemispheric specialization for language. However, these biases are "soft", and can be overcome (Bates & Roe, 2001).

The extent of lateralization is different in specific language processes. In the next paragraphs I will outline structure-function-relationships with regard to language perception, production, and verbal memory.

2.1.3.1.1 Language perception

Language perception is dependent on primary auditory cortex, which is situated within Heschl's gyrus in the depth of the lateral sulcus (Kahle, 1991). Primary auditory perception is depending on bilateral auditory cortices (Belin et al., 1999), and language perception employs bilateral temporal lobes, however with a preponderance of the left hemisphere (Hickok & Poeppel, 2000). This principle has been found even in sleeping 3-month-old infants (Dehaene-Lambertz et al., 2002), and more pronounced in children aged 6 to 16 years, who listened to stories read to them in their native language (Wilke et al., 2005). Case studies on brain-lesioned patients with severe language comprehension deficits pointed to left superior temporal gyrus (Wernicke's area) as the area most involved in language comprehension (Wernicke, 1874). Recent studies could show, however, that Wernicke's area might not be the primary location of language comprehension, but that left-hemispheric temporo-parietal regions might be more critical for comprehension at a linguistic-semantic level (Binder et al., 1997).

2.1.3.1.2 Language Production

The first observations of Dr. Broca pointed to left prefrontal cortex as being extremely important in language production (Broca, 1861). Focal lesions of Broca's area in adults lead to impairment of language production, with language perception being spared (Damasio & Geschwind, 1984). By now a substantial amount of neuroimaging studies employing positron emission tomography (PET) or fMRI have examined the functional neuroanatomy of language production. Speech motor control is subserved by two networks: A "preparative loop" comprises cortical (supplementary motor area, dorsolateral prefrontal cortex including Broca's area, anterior insula) and cerebellar (superior cerebellum) structures, whereas the "executive loop" recruits cortical (motor cortex), subcortical (thalamus, putamen/pallidum, caudatum), and cerebellar (inferior cerebellum) structures (Riecker et al., 2005). Silent word generation, i.e. when subjects are asked to only think of words, leads to activation of the same areas, however, with a more pronounced left hemispheric dominance (Friedmann et al., 1998; Riecker et al., 2000). Semantic processing has consistently been shown to employ regions in the left inferior parietal lobe, including the angular gyrus (Price, 2000). Organization of language production resembles that of adults already in young children (Sachs & Gaillard, 2003; Wilke et al., 2005), but lateralization towards the left hemisphere increases until adulthood (Holland et al., 2001).

2.1.3.1.3 Verbal Memory

According to Baddeley's model (Baddeley, 1986, 1988), working memory consists of three components: a phonological loop for the maintenance of verbal information, a visuospatial sketchpad for the maintenance of visuospatial information, and a central executive for attentional control.

Extensive research on the neuronal organization of memory has taken place in recent years. For tasks requiring verbal and semantic memory, increased activity has almost always been found in prefrontal (Broca's area; phonological processing) and in inferior parietal cortex (phonological loop), with lateralization towards the left hemisphere (Cabeza & Nyberg, 2000).

2.1.3.1.4 Non-semantic aspects of language, and music-processing

There are also some components of language which are controlled predominantly by the right hemisphere. These are the processing of prosody (George et al., 1996), metaphors (Bottini et al., 1994), and jokes (Wild et al., 2003). Comprehension of prosody relies mainly on pitch perception (Ladd et al., 1985). Pitch discrimination and memory have been shown to be mediated by right inferior frontal cortex (Zatorre et al., 1992). Melody processing has been found to develop towards a right hemispheric preponderance during childhood (Overy et al., 2004), with 10-year-olds showing the same structures activated as adults (Koelsch et al., 2005).

2.1.3.2 Nonverbal functions

With the left hemisphere being in charge of verbal functions, the right hemisphere was soon suspected to be the "nonverbal" part of the brain. Structural differences between the hemispheres, with a larger parietal "area-EG" (i.e. the dorsal lip of the inferior parietal lobule) in the right hemisphere have been associated with a right hemisphere superiority for visuospatial functions (Eidelberg & Galaburda, 1984). The following paragraphs illustrate cognitive functions lateralized to the right hemisphere.

2.1.3.2.1 Visuospatial Skills

It is widely accepted that visuospatial skills show a right hemisphere preponderance (Vogel et al., 2003). Spatial working memory has been shown to rely on right prefrontal (Smith & Jonides, 1999) and right superior parietal cortex (Smith et al., 1996; Zarahn et al., 2000), not only in adults but also in children aged 8 to 10 years (Nelson et al., 2000; K. M. Thomas et al., 1999). In lesion studies, spatial neglect is known to be one of the best clinical indicators of damage to right hemisphere cortex (Karnath et al., 2004), pointing to a strong right hemispheric involvement in visual attention. By neuropsychological studies, the process of mental rotation of objects has been identified as a function primarily subserved by the right parietal cortex (Corballis, 1997; Deutsch et al., 1988; Harris et al., 2000; Ratcliff, 1979). The parietal cortex is not only involved in mental rotation, but also in visual search. Superior parietal activation has been detected in relation to basic visual search processes (Leonards et al., 2000; Shulman et al., 2003), and to visuospatial attention shifts (Corbetta et al., 1993; Corbetta et al., 1995; Petersen et al., 1994), which are basic processes employed in visuospatial search tasks. In everyday life, the focus of visual attention is shifted by the use of saccadic eye movements. These movements are believed to be controlled by the frontal eye fields (FEF), an area in lateral premotor cortex (Fox et al., 1985). Even when no overt eye movements are required, the FEFs have been shown to be activated during shifts of visual attention (Muggleton et al., 2003). The endogenous modulation of visual attention is mediated by a fronto-parietal network involving FEFs and intraparietal sulcus (Corbetta & Shulman, 2002), with the FEF involvement probably lateralized to the right hemisphere (Mayer et al., 2004).

2.1.3.2.2 Executive Functions

The “central executive system” is one component of Baddeley’s model of working memory (Baddeley, 1988). Executive processes are involved in the regulation of functions operating on the content of working memory. Executive processes can be divided into *attention/inhibition, task management, planning, monitoring,* and *coding* (Smith & Jonides, 1999). This taxonomy suggests that executive functions must be a rather independent unit, which is facilitating not only working memory, but also cognitive problem solving in general. The “central executive system” has been located in the prefrontal cortex, with lateralization depending on the processing modality (Duncan et al., 2000). One particular component of the central executive is modulation and maintenance of attention, which has been shown to rely on a network of frontal and superior parietal structures (Coull, 1998; Culham & Kanwisher, 2001; Lawrence et al., 2003; Lewin et al., 1996; Pardo et al., 1991), often showing a right-hemispheric preponderance (Posner & Petersen, 1990), regardless of the processing modality being employed (Corbetta & Shulman, 2002; Deutsch et al., 1987). Other studies have, however, found modality-specific lateralization, with verbal and phonetic processes being lateralized to a left fronto-parietal network (Paulesu et al., 1993), and visual vigilance (Pardo et al., 1991), and spatial attention in a right fronto-parietal network (Battelli et al., 2003).

2.2 Development and Plasticity of the human brain

The following chapter is concerned with human brain development and with the plasticity of the central nervous system in particular. The latter can, to a certain extent, protect cognitive functions from the impact of early brain lesions. The development of children with early brain lesions has been an important source of information for developmental neuropsychologists. Therefore, the major brain lesions affecting fetuses and children are explained, and the developmental consequences are set out.

2.2.1 Development, Learning and Plasticity

Brain development is the product of a complex series of adaptive processes operating within a genetically organized, but continually changing context (Stiles et al., 2005). While the gross structure of the human brain is constituted within the third trimester of pregnancy, the fine-tuning of synapses and neural connections continues well into adulthood. Probably one of the most important factors for early cognitive development is myelination of the neural fibers, which helps in optimizing the speed of information transfer. The myelination of axons increases significantly during childhood and into adulthood (Durston et al., 2001). Between the age of four and 20 years, the proportion of white matter accordingly increases, while grey matter proportion, representing neural cell bodies, increases before adolescence and decreases again after adolescence (Giedd et al., 1999). During childhood and adolescence different regions experience bursts in grey matter development, with frontal and parietal lobes showing a developmental peak at the age of 12, temporal lobe at the age of 16, and with occipital lobe grey matter increasing through age 20 (Giedd et al., 1999). These decreases of grey matter after a long phase of neurogenesis are an important factor in human development: The pruning of synapses happens in accordance with the principle “use it or lose it”, meaning that unused pathways are dismantled (Huttenlocher, 1984; Webb et al., 2001). The “overproduction” of neural substrate during brain development is crucial for the remarkable plasticity of the developing brain. This plasticity allows the brain to react with “hardware changes” to disadvantageous insults during development.

2.3 Congenital Brain Damage

2.3.1 Etiologies

Due to the long time the human brain needs to constitute its final structure, it is particularly vulnerable to adverse influences during development. Pathogenic influences before birth may cause abnormalities or lesions which show special patterns consistent with the time of insult (Krägeloh-Mann, 2004). During the first and second trimester of pregnancy, brain pathology is characterized by malformations (cf. Figure 2.2), which can be genetically determined or acquired (Barkovic et al., 2001). Once the “gross architecture” of the brain is established at the beginning of the third trimester, disturbances of brain development predominantly result in lesions. Causes are mainly inflammatory-ischemic and/or infectious events. While during the early third trimester white matter is especially affected, towards birth, lesions affect cortical or deep gray matter in most cases (Krägeloh-Mann, 2004).

Brain lesions of the third trimester of pregnancy are prevalent especially in preterm-born children. Periventricular lesions, like periventricular leukomalacias or periventricular infarction are the major neuropathology in preterms (Krägeloh-Mann et al., 1999). To a lesser extent, these lesions can also be seen in term-born children (Figure 2.2), but then probably of prenatal origin (Krägeloh-Mann et al., 1995). Children suffering severe birth asphyxia show completely different lesional patterns: Acute perfusion failure in term or near to term born infants may cause lesions of the basal ganglia and thalamus. Often also the central region and the hippocampus are affected as well (Krägeloh-Mann, 2004). More sustained or chronic repetitive perfusion failures may cause cortico-subcortical lesions following the border zones of the major cerebral arteries (Krägeloh-Mann, 2004).

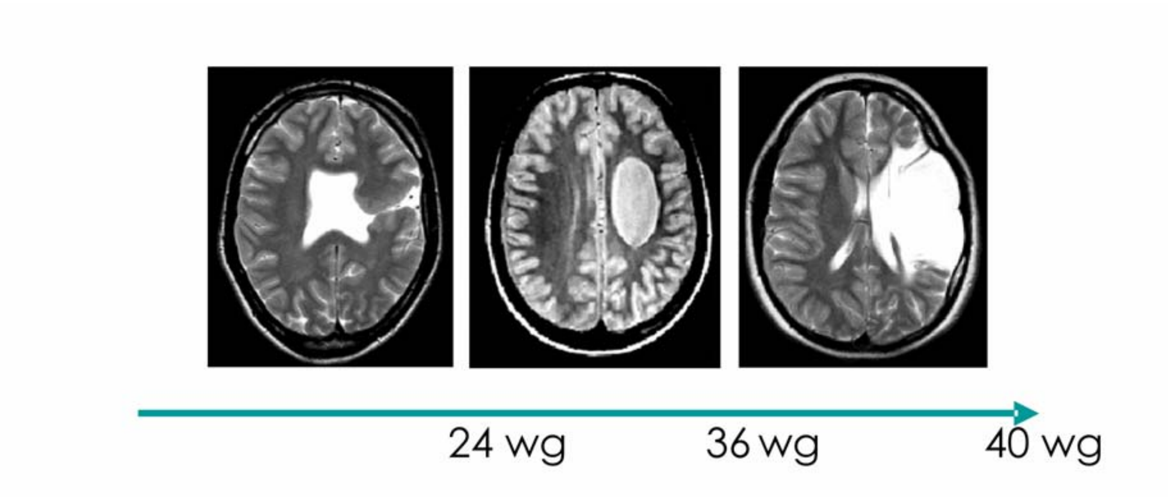

Figure 2.2: Patterns of brain damage typical for different gestational ages; examples show unilateral lesions. wg = weeks of gestation. From left to right: Malformation (schizencephaly), typical for the first and second trimester; periventricular lesion, typical for the early third trimester; cortico-subcortical infarction, typical for the late third trimester and term. T2-weighted images of adult patients who participated in studies of the *SFB 550-C4* research project.

2.3.2 Prevalence

The previous chapter elucidated the multiplicity of early brain pathology, comprising various etiologies and characteristics. This is probably one of the reasons for the relative scarcity of epidemiologic data. Estimates are, however, that 25% of all fetuses are affected by developmental diseases of the central nervous system (CNS), and a large proportion of stillbirths may be caused by severe developmental disorders. Furthermore, 40% of all infant mortalities are suspected to arise from insults during the prenatal period (Aicardi, 1998).

Brain damage causing cerebral palsy (CP) comprises a substantial part of all early pathologies of the CNS, even though not in all children with CP a definite cause for the symptoms can be proven (Krägeloh-Mann et al., 1995). In preterm-born children, bilateral spastic CP is the main major disability, usually caused by periventricular brain lesions (Krägeloh-Mann et al., 1999). The pan-European multicenter-study for the collaboration of CP surveys and registers is probably the most comprehensive source for epidemiologic data on congenital brain damage. Here, over an 11-year period, the overall birth cohort prevalence for CP was 2.08/1000 live births. Of the affected children, 30% had unilateral, 55% had bilateral symptoms. As low birth weight is mainly related to low gestational age, thus reflecting immaturity, it is not surprising that birth weight is a determining factor for CP prevalence: The rate of neonatal survivors suffering CP was 72.6/1000 in the group of children who weighed <1500g, among those weighing 1500 - 2499g it was 11.1/1000, and in the "heaviest" group of children weighing 2500g and more only 1.2/1000 children had CP (SCPE, 2002).

2.3.3 Consequences

In adults, damage to brain tissue leads to clinical deficits which often are predictable from site and extent of the lesion. As neuropsychological functions are being sculpted during CNS development, the relation between damage to a developing structure and impaired functions (which implies, in most cases impaired *development* of functions) is not always as clear as in adult patients. In adult patients, neuropsychologists usually have the working-hypothesis of *residual normality*, meaning that the non-damaged systems can work normally and only functions which are affected directly by the lesion are specifically impaired. This assumption is made also in children, nurtured particularly by the findings of undamaged tissue compensating for endangered functions. However, in the developing brain a system compensating for early damage may not follow the normal path of development (M. Thomas & Karmiloff-Smith, 2002), but it may show alternative individual patterns (Stiles et al., 2005). Superficially intact abilities after congenital lesions have been shown to rely on atypical cognitive processes which may be not as efficient as the typical ones (M. Thomas & Karmiloff-Smith, 2002). With studies using computational modeling, some authors came to the conclusion that damage to one route of a system entails that "the other route will not develop normally." (M. Thomas & Karmiloff-Smith, 2002).

Severe generalized disturbances during the initial phases of brain development show a particularly disadvantageous outcome for motor and cognitive development (Krägeloh-Mann, 2004). Around 73% of children with bilateral CP present mental retardation in addition to their motor impairment, 20% suffer from severe visual impairment, and 28% have epileptic seizures (Krägeloh-Mann et al., 1993). In contrast to diffuse or bilateral lesions, focal unilateral lesions lead to far more variable outcomes, depending on time of insult, lesion size, and lesion site (Krägeloh-Mann, 2004). Epileptic seizures have been shown to be the largest jeopardy for cognitive development in these children (Muter et al., 1997). Seizure activity may negatively influence cognitive functions (Henkin et al., 2005; Lindgren et al., 2004), and even cortical representations of functions can be altered by epileptic activity (Janszky et al., 2003). Also antiepileptic medication can impair cognitive development (Svoboda, 2004).

If unilateral lesions affect motor areas of the brain, i.e. motor cortex, pyramidal tracts, or basal ganglia, unilateral CP of the contralateral side is to be expected (Krägeloh-Mann, 2004). The cognitive outcome of children with unilateral lesions is usually much better than that of children with bilateral or diffuse lesions. Several studies have shown selective impairment of performance IQ in children with focal brain lesions, indicating problems in visuospatial functions, attention, and/or processing speed (Muter et al., 1997; Vargha-Khadem et al., 1992). Deficits like these are found in adults almost only in patients with right hemispheric brain lesions, with hemispatial neglect being the most pronounced symptom of deficits in visual attention (Karnath et al., 2004). In the next chapter, the causes for these unexpected findings in children are discussed in more detail.

2.4 Neuronal Compensation: Capacity and Limitations

The long time the human brain needs to constitute its final structure has been stated previously as a cause for the particular vulnerability to developmental disturbances. However, the relatively long phase of constitution holds for the developing brain a much wider range of opportunities to cope with insults than which are at hand for the mature brain. Cortical plasticity is considered to be the main source of recovery from brain insults, employing mechanisms of neurochemical, receptor and neuronal structural changes (Bach-y-Rita, 1990).

2.4.1 Brain lesions acquired by adults

The most common cause of adult disability in the United States is stroke, with hemiparesis of one or both sides being the most common neurological deficit (Cramer, 2003). Stroke patients may recover from the initial symptoms to a certain degree, however, complete recovery is rare. The source of recovery is believed to be the reorganization of brain functions, which occurs over weeks to months following stroke. Cortical reorganization in adults presents variable strategies. Hemiplegic patients often recruit a distributed motor network even for simple motor tasks, with recruitment of bilateral motor cortex, with increased recruitment of secondary cortical areas (supplementary motor area and premotor cortex), and/or with recruitment of peri-lesional tissue (Cramer, 2003). In language recovery after aphasia, recruitment of peri-lesional tissue has been shown to be employed (Heiss et al., 1999; Warburton et al., 1999), but also right hemispheric activation in areas homotopic to the left hemisphere language zones has been found in patients with destroyed left hemispheric language areas (Heiss et al., 1999; Rijntjes & Weiller, 2002; Weiller et al., 1995). To arrive at a maximum of functional recovery, however, specific procedures in terms of specific rehabilitation are necessary in adults (Bach-y-Rita, 1990).

2.4.2 Early brain lesions

With Margaret Kennard showing astonishing recoveries of baby monkeys who had been lesioned in their motor-cortices (Kennard, 1936), a very simple view of early cortical resistance, dubbed by Hans-Lukas Teuber the "Kennard Principle" (Teuber & Reudel, 1962), dominated the discussion on cortical plasticity: Early brain lesions were almost considered "harmless" with regard to cognitive functions. However, it soon became clear that there are manifold exceptions to the "Kennard Principle". Children with early brain lesions may react with severe mental retardation or unexpected abnormal behavior (e.g. mirror-movements), which is not observed in adult patients at all (Schneider, 1979). These exceptions have been explained already by Margaret Kennard herself with a possible alteration of neural *connections* after lesions, a view which then did not receive much interest due to the lack of histological evidence (Schneider, 1979).

2.4.2.1 Motor functions

Children with lesions acquired prenatally or early in life often present with CP (Krägeloh-Mann, 2004). The residual motor function, however, is often much better than what would be the outcome of the same lesion in an adult. Reorganization of motor functions after unilateral lesions is obviously more flexible in the developing brain, with outcome depending on time, size, and site of the insult (Staudt et al., 2004). Being still in the constitutional phase, the developing brain has more opportunities of real "hardware modifications" than would be possible in an adult brain. In a substantial proportion of patients with congenital brain lesions, motorcortex has been found to be reorganized to the unaffected hemisphere (M. Rey et al., 1988; Vandermeeren et al., 2003), and ipsilateral cortico-spinal projections to the paretic limbs were demonstrated (Staudt, Grodd et al., 2002). Furthermore, gestational age at the time of insult correlated significantly with the efficacy of reorganization, as depicted in hand motor function scores (Staudt et al., 2004). In patients with congenital unilateral white-matter lesions, a dissociation of efferent and afferent fibers could be shown, with motor execution being reorganized in the hemisphere ipsilateral to the paretic hand, and primary somatosensory representation being situated in the affected hemisphere (Staudt et al., submitted).

2.4.2.2 Language and cognition

Neuropsychological test profiles of patients with early lesions can not always be predicted by the adult model of lesion-function correlations. Whereas deficits in visuospatial skills after early right hemispheric lesions are in line with the adult model (Muter et al., 1997; Trauner, 2003; Vargha-Khadem et al., 1994), a contrary finding is that children with *right hemispheric* lesions experience delays in language acquisition (Aram et al., 1985; Feldman et al., 1992; Snitzer Reilly et al., 1998; Thal et al., 1991; Vicari et al., 2000). On the other hand, young children with left hemispheric lesions behave concordantly with the adult model, in showing delays in language development (Chilosi et al., 2001; Feldman et al., 1992; Snitzer Reilly et al., 1998; Thal et al., 1991; Vicari et al., 2000). By school-age or adolescence, however, these formerly language-delayed children show a remarkable 'recovery', with only subtle, if any, deficits persisting (Bates & Roe, 2001; Feldman et al., 1992). Children who acquire a left-hemispheric lesion during early childhood do show mild and transient aphasias. The clinical picture, however, is much different from that of adults with analogous injuries (Snitzer Reilly et al., 1998). Communicative skills are spared even in the extreme case of early hemispherectomy, where children can establish or regain language function to a sufficient clinical level (Vargha-Khadem et al., 1991). Lenneberg set up a schedule for the consequences of early lesions, which comprises a critical period within which language sparing is possible: Children younger than three years can (re-)acquire language rapidly and completely. Children between the ages of three and ten years often do show aphasia, but they recover completely. Lesions suffered after the age of ten years usually cause persistent impairments which are similar to what we know from adult patients (Lenneberg, 1967). Studies on patients with intractable epilepsy, who underwent the Wada-procedure, could show that the preservation of language functions may be the consequence of abnormal language organization in the right hemisphere (Rasmussen & Milner, 1977; Rausch & Walsh, 1984; M. Rey et al., 1988; R. P. Woods et al., 1988). Possible determinants for the reorganization-pattern seem to be site and onset of the lesion. While early lesions often cause a reorganization of language to the right hemisphere, lesions acquired later in childhood may rather lead to intrahemispheric maintenance of language (Hécaen, 1976; Satz et al., 1988). Within the group of patients affected by congenital lesions, lesions comprising the fronto-temporal language areas lead more often to interhemispheric (re-)organization, whereas in periventricular lesions, language often remains in the left hemisphere (Brizzolara et al., 2002). With the fused dichotic listening test, also lesion size could be connected to reorganization: The larger the lesion, the stronger was the atypical left ear advantage in the study (Brizzolara et al., 2002). Studies employing neuroimaging techniques which are able to map the precise topography of cortical activation, supplied evidence for recruitment of right hemisphere areas which are homotopic to left hemisphere language areas of normal right-handers (Booth et al., 1999; Müller et al., 1998; Staudt, Lidzba et al., 2002). In children with periventricular lesions, the degree of right-hemispheric language organization correlated significantly with the extent of damage to the facial portion of the pyramidal tract (Staudt et al., 2001). In children with early lesions to Broca's and Wernicke's areas, another fMRI study could demonstrate the recruitment of perilesional brain tissue for language production (Liegeois et al., 2004).

The preservation of language skills by reorganization to the right hemisphere does seem to come at the cost of deficits in visuospatial tasks, as depicted in performance IQ (Muter et al., 1997; Vargha-Khadem et al., 1994), and being traditionally regarded as indicators of right-hemisphere-mediated functions. These paradoxical data reveal that developing brains react in many cases very differently to insults than adult brains.

2.4.2.3 The "Crowding Hypothesis"

The findings of language reorganization to the right hemisphere and of visuospatial deficits in children with early left hemispheric brain lesions lead to the formulation of the "crowding hypothesis": "*All in all, these findings suggest a definite hemisphere specialization at birth, with a curious greater vulnerability to early lesions for those capacities that depend, in an adult, on the right hemisphere – as if speech were relatively more resilient or simply earlier in getting established. Yet this resiliency is purchased at the expense of non-speech functions as if one had to admit a factor of competition in the developing brain for terminal space, with consequent crowding when one hemisphere tries to do more than it had originally been meant to do." (p.73)* (Teuber, 1974).

This hypothesis assumes that if the right hemisphere mediates both verbal and nonverbal functions, the nonverbal functions must be either "crowded out" (Loring et al., 1999) of their original locations or share the neural substrate with verbal functions. Also the hypothesis of "reversed laterality" has been put forward, which means the interhemispheric reorganization of nonverbal functions to the left hemisphere. Having to deal with inferior neural substrate, these functions are then impaired (Korkman & von Wendt, 1995; Loring et al., 1999).

By now, a growing body of evidence has come to confirm the notion that patients with early left hemispheric lesions may show deficits in visuospatial functions and spared language skills. An alternative to the "crowding" explanation, however, could be that brain lesions themselves have an unspecific effect on visuospatial skills: Neuropsychological tests which are sensitive to right-hemispheric brain damage are also sensitive to diffuse brain impairment (Lee & Hamsher, 1988). Therefore, lesion size could be the true determining factor in producing visuospatial impairments in patients with early left hemispheric brain lesions.

Experiments examining the relationship between language reorganization and neuropsychological profiles have resulted in controversial conclusions. In studies using the Wada-test to determine language dominance, epileptic patients with atypical (right hemispheric or bilateral) language representations have shown larger deficits in visuospatial functions than patients with normal left hemispheric language organization (Billingsley & Smith, 2000; Loring et al., 1999; Strauss et al., 1990). In hemiplegic children without epilepsy, language dominance has been assessed by the dichotic listening task. Here, children with atypical left ear advantage did not show any deficits in nonverbal tasks as compared to children with normal right ear advantage (Korkman & von Wendt, 1995). Both types of studies, however, have caveats which limit the interpretability of the results: In epileptic patients, cognitive representations (Janszky et al., 2003) as well as cognitive functioning (Henkin et al., 2005; Lindgren et al., 2004) are influenced by seizure activity. Thus it seems questionable whether implications on cognitive functions drawn from data on epileptic patients are valid also for non-epileptic subjects. The dichotic listening task which has been used in non-epileptic, hemiplegic children, assesses language perception, which is, to some extent, bilateral (Hickok & Poeppel, 2000) and thus not particularly prone to be reorganized due to left hemispheric brain damage. It is also heavily influenced by attentional factors and thus, especially in children, less reliable than the Wada-procedure in assessing language dominance. Functional MRI has the advantage of being non-invasive and it can localize language representation with a reasonable reliability. The literature on language representation assessed by fMRI in patients with early unilateral brain lesions is still limited and the studies have been restricted to the description of functional activation patterns in the patients, with little information on neuropsychological profiles. The patients showed normal nonverbal intelligence with slight language impairments (Booth et al., 1999), or normal overall intelligence with slightly lower performance IQ than the control group (Staudt, Lidzba et al., 2002). Unfortunately, due to small groups and limited neuropsychological tests, language (re-)organization patterns could not be directly related to neuropsychological outcome.

3 Scope and Hypotheses

3.1 *Scope of this work*

The present work was set up to explore the neuropsychological and functional neuroanatomical consequences of lesion-induced right-hemispheric language organization in patients with pre- and perinatally acquired focal lesions of the left hemisphere, who did not have a history of epileptic seizures. To attain this goal, three sequential studies were performed, which will be presented and discussed in the following chapters.

Study 1: Visuospatial deficits in patients with early left-hemispheric lesions and functional organization of language: Consequence of lesion or reorganization?

The assumption that lesion-induced right hemispheric language organization is the reason for visuospatial deficits in patients with early left hemispheric language has, up to now, been based on studies on epileptic patients or on studies without any direct test of language lateralization. The interpretability of these studies must therefore remain rather limited.

Two competing hypotheses try to explain visuospatial deficits in patients with lesion-induced right hemispheric language organization:

H1.1: Language reorganization from the left to the right hemisphere induces scarcity of neural substrate in the right hemisphere, thus impairing visuospatial functions (Teuber, 1974).

H1.2: Brain lesions have an unspecific effect on cognition, with visuospatial functions being most vulnerable to impairment (Lee & Hamsher, 1988).

In study 1, the relationship between anatomy (structural and functional) and neuropsychological profiles was examined in patients with early left hemispheric focal brain lesions, and without a history of epileptic seizures, who had participated in fMRI studies of the Tübingen children's hospital (Staudt et al., 2001; Staudt, Lidzba et al., 2002).

Study 2: Paradigms eliciting right hemispheric fronto-parietal activation in fMRI

Patients with lesion-induced right hemispheric language organization have been shown to recruit fronto-parietal areas which are homotopic to left hemisphere language regions (Staudt, Lidzba et al., 2002). There is a broad consensus that the right hemisphere is involved in or even specialized for nonverbal functions, however, the specific functions of right fronto-parietal areas have not been described in a way which allowed simple adoption for a study on neurological patients.

Therefore, in study 2, five paradigms were developed, adapted for use in the fMRI environment, and evaluated with respect to their ability to elicit predominantly right fronto-parietal activation in healthy right-handed volunteers.

Q2.1: Which cognitive functions are, in the healthy brain, subserved by areas recruited for language production in lesion-induced right hemispheric language organization?

Study 3: Organization of non-verbal functions in lesion-induced right hemispheric language

Based on the knowledge of cortical reorganization of language functions to the right hemisphere in patients with early left hemispheric lesions, assumptions on a "functional crowding" in the right hemisphere have been put forward. Whereas the cortical representation of language functions has been studied and described in patients with lesion-induced right hemispheric language organization, the topography of the cortical organization of nonverbal functions in these patients has remained largely unexplored.

Study 3 examines the cortical organization of nonverbal functions in patients with lesion-induced right-hemispheric language organization. Regarding the nonverbal functions, two alternative hypotheses can be put forward:

H3.1: Nonverbal functions are reorganized interhemispherically ("reversed laterality") or intrahemispherically ("crowding out").

H3.2: Nonverbal functions share the right-hemispheric neural substrate with language functions, thus leading to areas shared by verbal and nonverbal tasks ("crowding").

4 Study 1: Visuospatial deficits in patients with early left-hemispheric lesions and functional organization of language: Consequence of lesion or reorganization?

4.1 Hypotheses

In studying the relations between functional/anatomical MRI data and neuropsychological performance of patients with early left-hemispheric lesions, the following hypotheses were examined:

H1.1: Language reorganization from the left to the right hemisphere induces scarcity of neural substrate in the right hemisphere, thus impairing visuospatial functions (Teuber, 1974).

Predictions:

P1.1.1: Visuospatial skills are impaired in patients with lesion-induced right-hemispheric language organization as compared to patients with left-hemispheric or bilateral language organization.

P1.1.2: Visuospatial skills correlate with the degree of right-hemispheric language involvement in patients with left-hemispheric lesions.

H1.2: The visuospatial deficits are an unspecific effect of the brain lesion (Lee & Hamsher, 1988).

Predictions:

P1.2.1: Visuospatial skills are impaired in patients with and without lesion-induced right-hemispheric language organization as compared to normal controls.

P1.2.2: Visuospatial skills correlate with lesion-size in patients with left-hemispheric lesions.

4.2 *Subjects and Methods*

4.2.1 Subjects

Fourteen adolescent and young adult patients (age range 16 to 27 years, 8 women) had participated in fMRI studies of the Tübingen children's hospital on language organization. Written informed consent of all participants (for the two underage patients, also written informed consent of the parents) and approval of the local ethics committee were obtained, according to the 1964 Declaration of Helsinki. A characterization of the patients is shown in Table 4.1. The (f)MRI procedures and 7 of the patients (P3, P4, P5, P8, P11, P13, P14) have been described in detail elsewhere (Staudt et al., 2001). In the meantime, seven more patients had been recruited and assessed with the same fMRI protocol.

All patients had acquired focal left-hemispheric lesions pre- or perinatally. Three of the patients had infarctions in the territory of the left medial cerebral artery (MCA); the remaining 10 patients had left-sided periventricular white matter lesions (PV). One patient was excluded due to development of epileptic seizures; none of the remaining patients had a history of epilepsy. Structural T1-weighted datasets of the 13 patients who were included in the study are depicted in Figure 4.1.

All patients had unilateral spastic CP on the right side (c.f. SCPE, 2000). Hand motor function scores (assessed by a paediatrician; c.f. Staudt et al., 2004) are shown in Table 4.1. Due to their CP, all patients were strongly left-handed (laterality indices ranging from -80 to -100 according to the Edinburgh Inventory; Oldfield, 1971). Native language of all participants was German, and all patients except two had attended regular schools. Two patients with MCA infarction had attended schools for motor handicapped children. School performance was within the normal range for all patients.

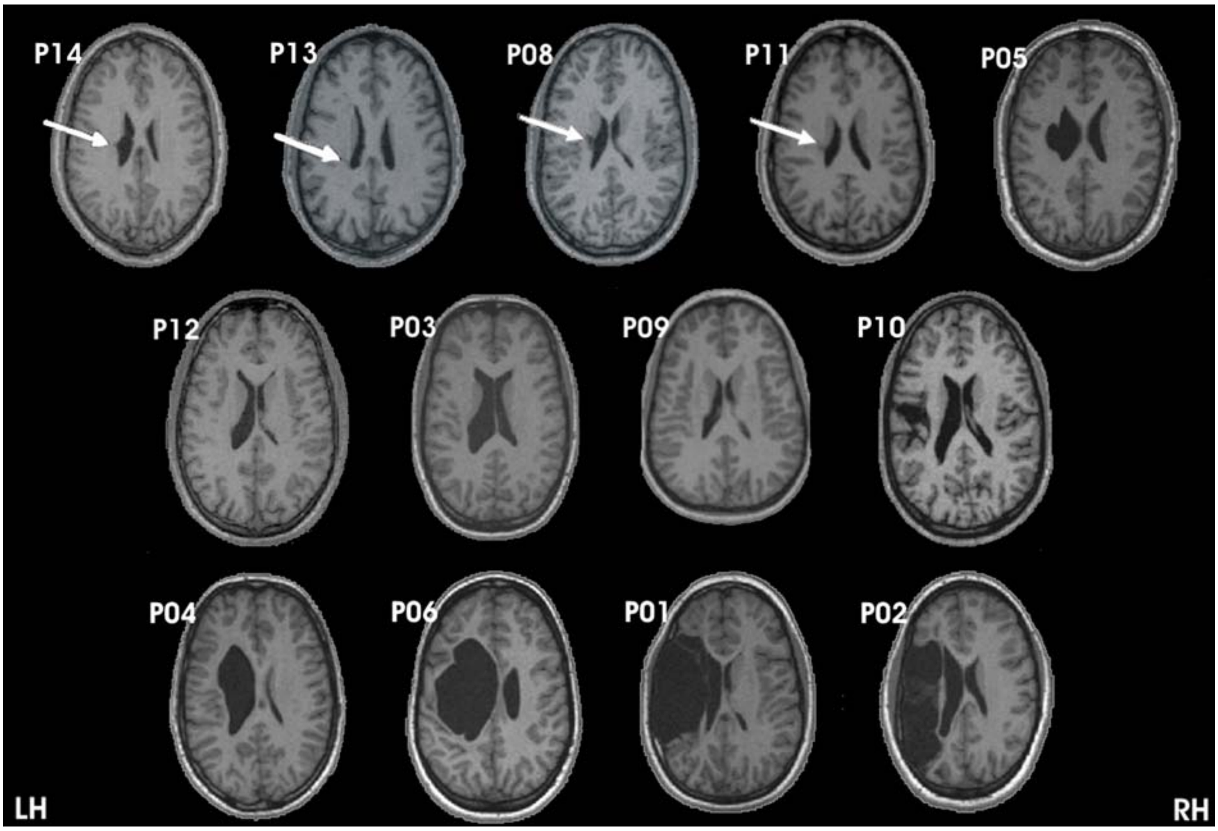

Figure 4.1: Axial slices of the T1-weighted datasets of patients. Periventricular lesions can be identified as irregular dilatations of the left lateral ventricles; arrows indicate the gliotic scars in the small lesions. Images are arranged according to lesion size (starting top left with the smallest lesion).

From a pool of 30 healthy right handed young adults, who had been recruited from students and clinical staff, thirteen age-, sex-, and verbal IQ-matched controls were selected to take part in the study. Verbal IQ was used as matching criteria instead of full-scale IQ, because the patients were expected to be impaired in performance IQ, due to their CP, to functional "crowding", or to lesion effects.

Table 4.1: Patient characterization

Patient no.	gender	age	pathology	Hand motor function
P1	f	17	MCA	4
P2	f	16	MCA	3
P3	f	26	PV	2
P4	f	27	PV	2
P5	m	21	PV	3
P6	f	19	PV	2
P7*	f	27	MCA	3
P8	m	25	PV	2
P9	f	21	PV	1
P10	m	18	MCA	1
P11	f	23	PV	2
P12	m	18	PV	1
P13	m	24	PV	1
P14	m	20	PV	1

f=male; f=female; MCA=infarction of the middle cerebral artery; PV=periventricular lesion; *Patient excluded due to development of epileptic seizures. Hand motor function scores, as assessed with the sequential finger opposition task: 1=normal performance; 2=slow or incomplete performance; 3=inability to perform any independent finger movement; 4=no active grasping.

4.2.2 Neuropsychological protocol

General measures

All participants performed the full German version of the WAIS, the HAWIE-R (Tewes, 1994), supplying full-scale IQ (FIQ), verbal IQ (VIQ), and performance IQ (PIQ) data. Additionally, a set of neuropsychological assessments was obtained from patients and controls.

Language

Three different verbal fluency tasks were performed by all participants.

<u>Word-Chain Task</u> (Staudt, Lidzba et al., 2002): Given a starting word, subjects generated chains of words which start with the last letter of the pervious word (e.g. Do**G**-**G**arde**N**-**N**eighbo**R**-**R…**). In German, generating word-chains

requires phonetic rather than orthographic decisions in most cases, as the spelling of most German words corresponds with their pronunciation. In four trials with duration of 60 seconds, the number of generated words was recorded; duplicates within one block were subtracted from the total.

Categories (Monsch et al., 1992): Subjects were asked to separately generate as many words as possible for the categories of *animals, fruits*, and *vegetables*; 60 seconds were allowed for each category. The total number for all three categories less the number of duplicates was recorded.

Letters (Benton & Hamsher, 1989): Subjects generated as many words as they could think of which started with the letters *F, A*, and *S*; 60 seconds were allowed for each letter, words for names or numbers were not allowed. The total number for all letters less the number of duplicates or errors was recorded.

Visuospatial functions

All subjects performed standardized tasks on visual short-term and long-term memory, and mental rotation. An important factor is that none of these tasks requires bimanual manipulation, so that the patients with CP were not penalized for their motor disability, as compared with the control group.

Block-tapping test (Schelling, 1997): On a block-board containing 9 cubes in a standardized arrangement, sequences of blocks are tapped by the examiner, which increase consecutively in length. Subjects then repeat the sequences; the longest sequence with two or more correct replications is recorded as the visuospatial memory span.

Rey-Osterrieth Complex Figure (A. Rey, 1941): The complex figure was first copied, and after 60 minutes reproduced from memory. Subjects were *not* instructed to remember the figure while copying. Recorded were number and gross quality of 18 defined details, maximum score was 36 (Lezak, 1995).

Tube figures (Stumpf & Fay, 1983): Subjects processed 21 tasks with two figures each of transparent cubes containing a cable. One figure depicted the front view, the other figure depicted the same cube from a different view (back, left, right, top, bottom). Subjects decided which view was presented in the second figure; time limit was 12 minutes for all tasks. The number of correct responses was recorded.

Neglect tests (Ferber & Karnath, 2001): Subjects performed the *letter cancellation* and the *bells task* without time limit. Numbers of misses in the left and right quartiles of the sheet were compared.

To obtain comparable scores for all test procedures, raw scores were subjected to a z-transformation.

4.2.3 (f)MRI data acquisition and processing

Data acquisition: All patients were assessed by fMRI with the word-chain task (Staudt, Lidzba et al., 2002), using a 1.5 Tesla Siemens Scanner. The task was arranged in a block design with four alternating epochs each of covertly generating word-chains and silent rest. Epoch length was 48 seconds, in which 6 volumes (whole brain multislice echo-planar imaging sequence, repetition time (TR) = 8 seconds, acquisition time (TA) = 4.87 seconds, echo time (TE) = 84 ms, 27 axial slices, 1 mm gap, 2x2x5 mm^3 voxel size) were recorded in a sparse sampling procedure to allow auditory instruction in the pauses between the scans. A total of 48 volumes were obtained in 384 seconds (6 min, 24 sec). Additionally, a structural T1-weighted 3D-dataset was acquired from all patients (TR = 1300 ms, TE = 3.93 ms, 144 slices, 256x256 base resolution, 1x1x1.25 mm^3 voxel size, 15° flip angle).

Structural and functional MRI data of all patients were processed with SPM2 (Wellcome Department of Imaging Neuroscience, UCL, London, U.K.) in order to gain uniform measures for lesion extent and laterality index.

Data preprocessing: Functional data was first preprocessed using the SPM2 default parameters unless otherwise specified. The images of every subject were spatially realigned to eliminate movement artifacts. To allow inter-subject comparison, data was normalized using templates provided by the Montreal Neurological Institute (MNI; Brett et al., 2002). After smoothing with a Gaussian filter of full width at half maximum (FWHM) = 12 mm, the functional data was subjected to a voxel-based statistics according to the general linear model (Friston et al., 1995) to assess activation contrasts for the different tasks. First level single subject statistics were assessed by contrasting the activation condition with the rest condition. For modeling the experiment, basic box-car functions were convolved with the haemodynamic response function. To account for technical or physiological noise and intersubject activation variability, the functional data was subjected to a high-pass filter of 128 sec and to global scaling.

Lesion extent: For assessment of lesion-size an automated volumetry procedure analogue to the one suggested by (Staudt et al., 2003) was used. Using SPM2 algorithms the linearly normalized T1-weighted structural data was segmented into compartments of grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). This process produces probability maps in which each voxel is assigned a probability ($0 \leq p \leq 1$) of correct assessment. As the patients' lesions produced unilateral loss of WM (periventricular lesions) or GM and WM (MCA infarctions) the ratio of $(GM+WM)_{left}/(GM+WM)_{right}$ was used to express lesion extent.

Laterality index: Laterality indices (LI) of language activation for each subject were calculated by integrating the sum of voxel values, as expressed in the spmT-maps of the activation>control contrasts, on both sides of the brain (disregarding 5 mm left and right of the interhemispheric fissure). As gross activation levels were very variable between subjects, an adaptive thresholding procedure was used to define "interesting" voxels (i.e. those which contribute significantly to the task as opposed to noise) for each subject as those voxels with above-average intensity values (Wilke & Lidzba, submitted). The laterality index was calculated with LI = (left-right)/(left+right), leading to values between -1 and +1. Negative values express right hemispheric preference.

4.2.4 Correlations between structural, functional, and behavioral data

Patients were assigned to different groups to compare behavioral data with respect to language lateralization: LIs were divided at the median, to obtain one group of right-hemispheric-language (RH-language), and one group of left-hemispheric or bilateral language (LH-/bilateral language).

IQ and z-scores in verbal and visuospatial tasks were compared between both patient and control groups, and tested for significant main effects using the non-parametrical Kruskal-Wallis H-test. Post-hoc comparisons between the groups were conducted using the Scheffé-test.

Within the patient group, Pearson's correlations were calculated for LI and visuospatial tasks, for LI and verbal fluency tasks, as well as for LI and IQ-data. Significance was tested one-tailed, as H1.1 predicted effects with regard to lower visuospatial performance with stronger right-hemisphere-involvement in language production.

Spearman rank correlations were calculated for lesion ratio rank and visuospatial tasks (PIQ, block-tapping test, tube-figures test, Rey Copy, and Rey Recall), for lesion ratio rank and verbal fluency tasks, as well as for lesion ratio rank and IQ-data. Significance was tested one-tailed, as H1.2 predicted a negative correlation between lesion extent and visuospatial performance.

4.3 Results

4.3.1 Patient characterization

Table 4.2 contains lesion ratios and laterality indices of all patients; Figure 4.2 illustrates the assignment to one of the two groups according to median LI.

Table 4.2: Lesion sizes and word-chain laterality indices for all patients

Patient no.	**$(GM+WM)_{left}/(GM+WM)_{right}$**	**LI**
P1	0.7569	-0.52
P2	0.7144	-0.91
P3	0.9538	-0.48
P4	0.8981	-0.41
P5	0.9608	-0.42
P6	0.8770	-0.55
P8	0.9655	-0.38
P9	0.9450	-0.42
P10	0.9335	0.34
P11	0.9639	0.31
P12	0.9606	0.52
P13	0.9655	0.14
P14	0.9678	-0.09

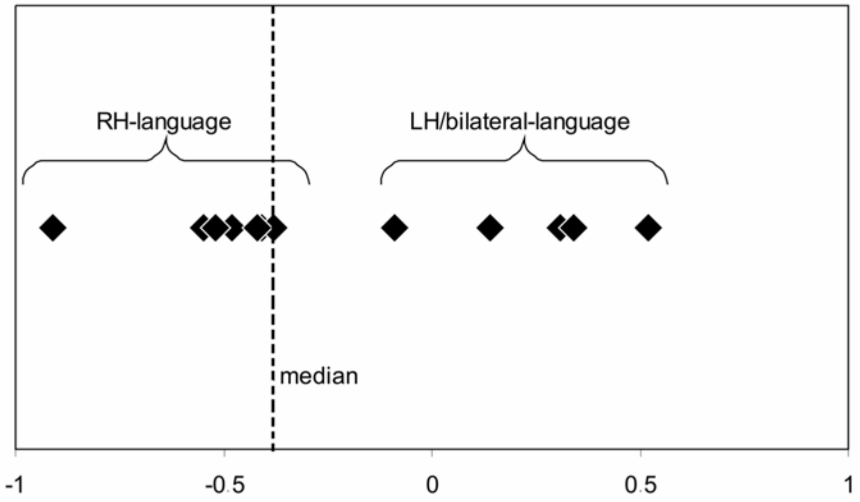

Figure 4.2: Laterality indices of single patients and assignment to the two patient groups.

4.3.2 Behavioral data: Group comparisons

The Kruskal-Wallis H-Test revealed a significant main effect of PIQ (p<0.05), whereas the other IQ-measures did not differ significantly between the groups, implying successful matching of the groups for VIQ. The post-hoc Scheffé procedure pointed to the RH-language group as showing significantly lower PIQ than the control group (Table 4.3).

Table 4.3: Performance in IQ measures and (z-transformed) neuropsychological measures

Measure	**RH-language**	**LH-/bilateral language**	**Controls**	***p* value**
Verbal IQ	105.75±17.08	106.00±17.80	107.69±12.72	n.s.
Performance IQ	96.88±11.57	107.00±7.19	112.92±12.98	<0.05[a)]
Word-chains	-0.14±1.26	-0.08±1.29	0.12±0.81	n.s.
Categories	0.04±1.00	-0.23±1.15	-0.03±0.95	n.s.
Letters	0.39±0.80	-0.56±1.41	-0.03±0.95	n.s.
Block-tapping test	-1.07±0.94	0.70±0.74	0.31±0.66	<0.005[a),b)]
Tube-figures test	-0.89±0.94	0.53±0.77	0.32±0.90	<0.05[a),b)]
Rey Osterrieth Copy	-0.54±0.94	0.20±0.10	0.31±0.65	n.s.
Rey Osterrieth Recall	0.03±1.26	-0.13±0.14	0.02±0.98	n.s.

[a)]significant difference between RH-language and Controls; [b)]significant difference between RH-language and LH-/bilateral language

None of the verbal fluency tasks differed significantly between the groups (Table 4.3). In the nonmanipulative visuospatial tasks, however, the block-tapping test and the tube figures test revealed significant main effects (block-tapping: p<0.01, tube figures test: p<0.05; Kruskal Wallis H-test), whereas groups did not differ in visuospatial perception (Rey Osterrieth Copy) or visuospatial long term memory (Rey Osterrieth Delayed Recall). Post-hoc Scheffé showed that the RH-language group scored significantly worse both in the block-tapping and in the tube figures tests than did the control group and the LH-/bilateral language group (Table 4.3). Figure 4.3 depicts the groups' mean scores for the visuospatial tasks.

Patients did not show any signs of spatial neglect: both letter cancellation and bells tests were solved without error by all patients and controls.

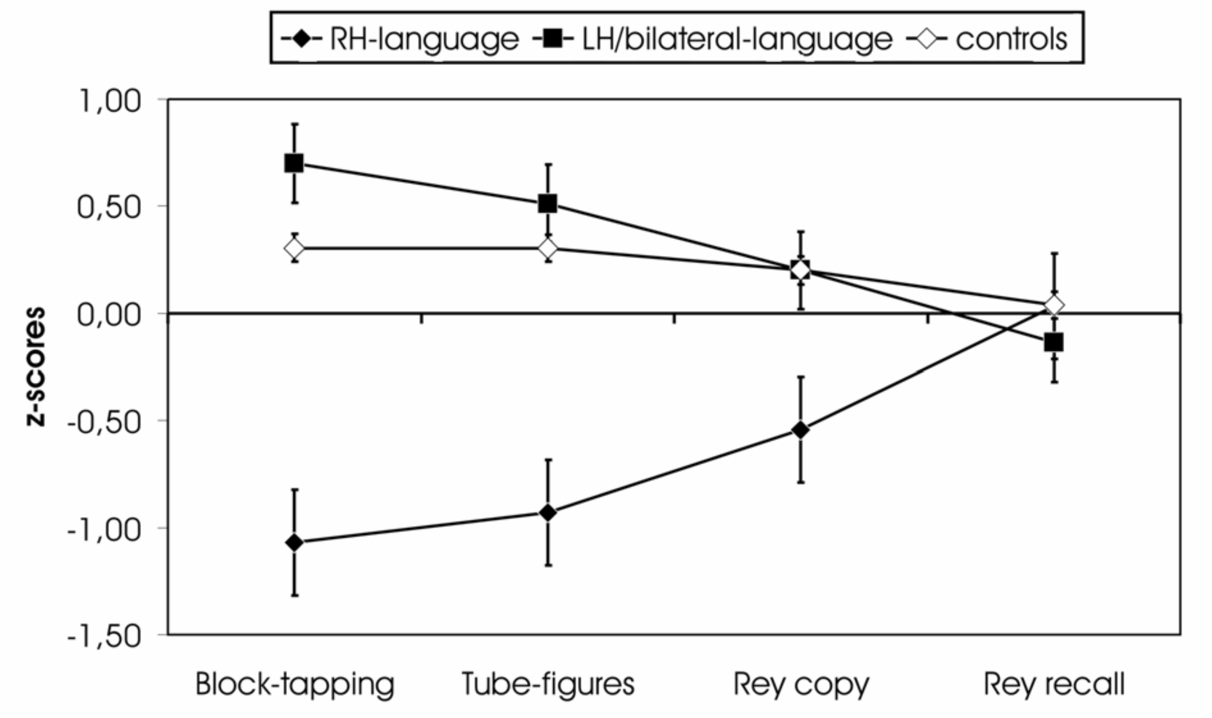

Figure 4.3: Means and standard errors for the visuospatial tasks

4.3.3 Behavioral data: correlations

Correlation coefficients are depicted in Table 4.4. Lesion ratio correlated significantly with PIQ (r=-.577, p<0.05, Spearman rank, one-tailed). Also LI correlated significantly with PIQ (r=.487, p<0.05, Pearson, one-tailed). As this correlation was suspected of being mediated by deficits in hand motor function, an additional correlation analysis of hand motor function with PIQ, visuospatial functions, and lesion size was conducted. As expected and shown in Figure 4.4, hand motor function correlated significantly with PIQ (Spearman rank r = -.561, p<0.05, one-tailed), but not with visuospatial functions (Spearman rank for block-tapping r = -.212, p=0.487; Spearman rank for tube-figures r = -.354, p=0.235, one-tailed). Hand motor function did, however, correlate significantly with lesion size (r = .490, p<0.05, one-tailed).

Table 4.4: Correlations of structural, functional, and behavioral data

	PIQ	Block-tapping	Tube-figures	Rey Copy	Rey Recall
Lesion ratio					
Spearman rank	-.577*	-.154	-.146	-.160	-.190
one-tailed p	.020	.307	.317	.602	.534
LI					
Pearson's r	.487*	.615*	.500*	.224	-.027
one-tailed p	.046	.013	.041	.231	.465

*p<0.05, one-tailed

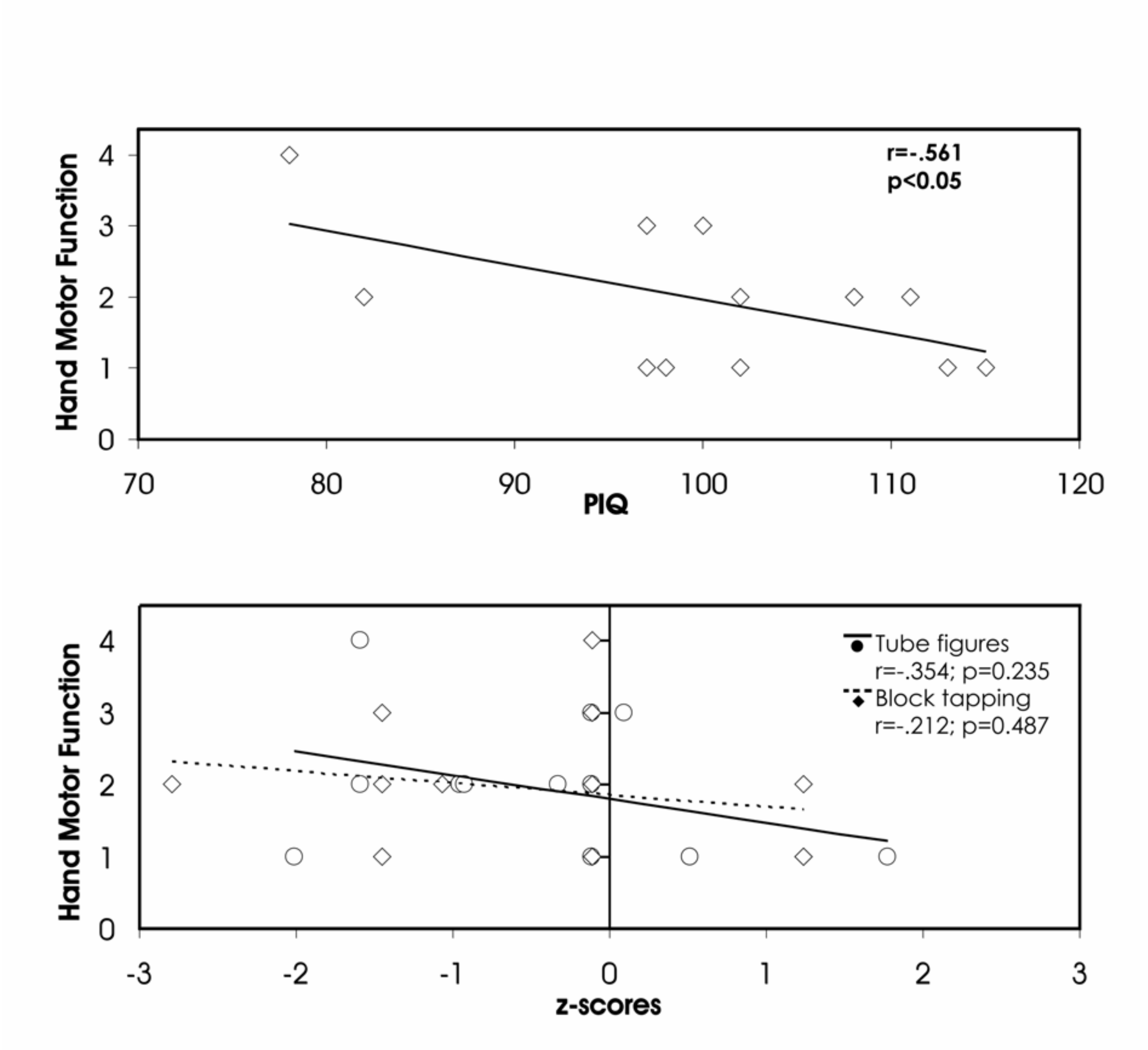

Figure 4.4: Scatterplots illustrating the correlations between Hand Motor Function and Performance IQ (top) and visuospatial tasks (bottom).

Lesion ratio did not correlate significantly with any of the visuospatial tasks, whereas LI correlated significantly with the block-tapping and the tube figures tasks (Figure 4.5): The more right-hemisphere preference in the word-chain task, the lower the visuospatial memory span and the worse the mental rotation skills. No significant correlations were found for the other visuospatial tasks.

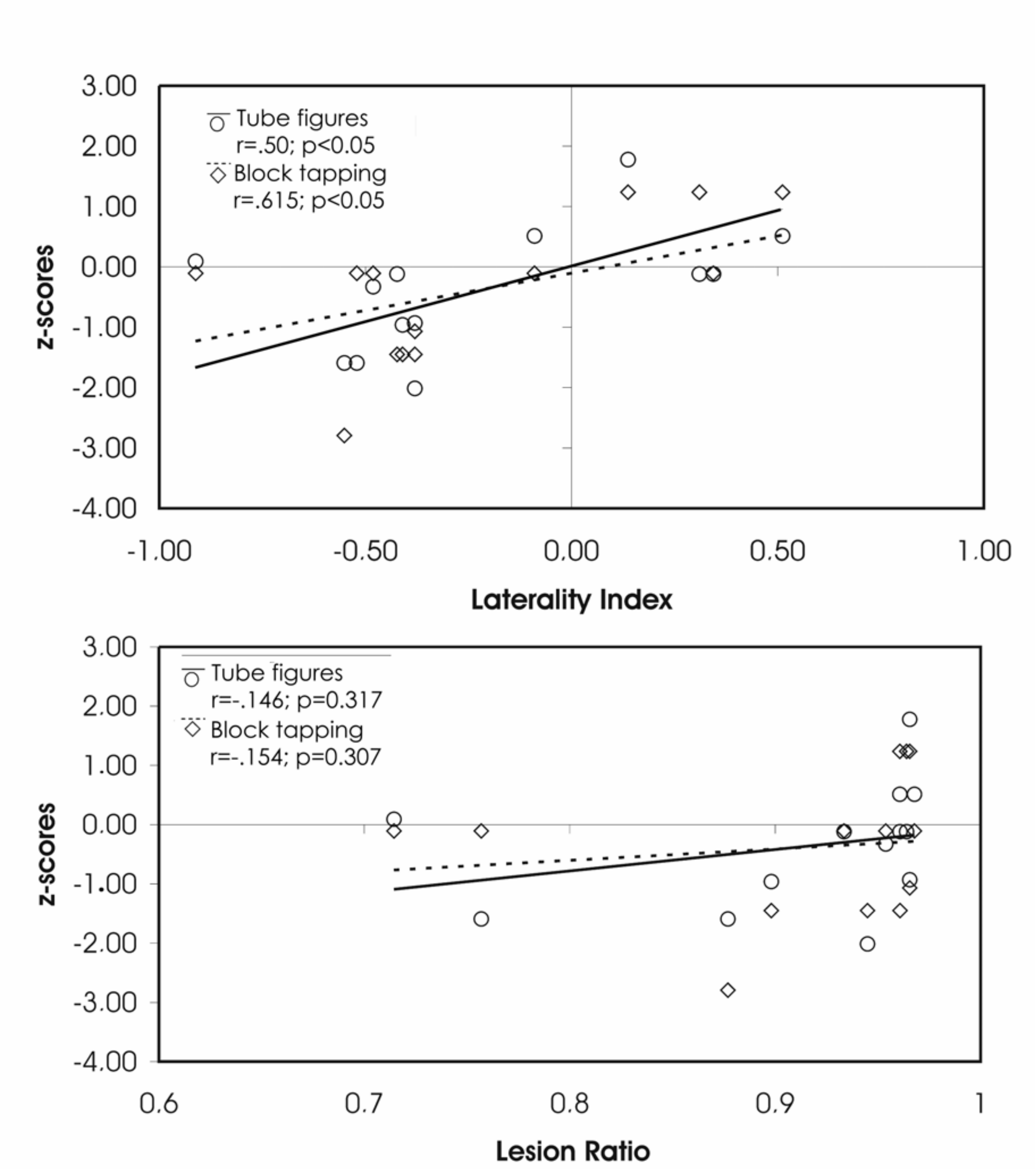

Figure 4.5: Scatterplots illustrating the correlations between Laterality Index (top) and Lesion Ratio (bottom) and the visuospatial tasks.

4.4 Discussion

The results of Study 1 corroborate H1.1: Language reorganization to the right hemisphere impairs visuospatial functions (Teuber, 1974). In this study, visuospatial skills were impaired in patients with lesion-induced right-hemispheric language organization as compared to patients with left-hemispheric or bilateral language organization (P1.1.1 confirmed). Furthermore, visuospatial skills correlated with the degree of right-hemispheric language involvement (P1.1.2 confirmed). H1.2, however, has to be refuted: The visuospatial deficits are not just an unspecific effect of brain lesion (thus not in line with the findings of Lee & Hamsher, 1988). Visuospatial skills were not impaired in patients without lesion-induced right-hemispheric language organization as compared to normal controls (P1.2.1 discarded). And the level of visuospatial skills did not correlate with the lesion-size (P1.2.2 not confirmed).

Only performance IQ showed a correlation with lesion ratio, and correlations of lesion ratio with all other measures were very low. Performance IQ was, on the other hand, shown to be dependent on hand motor function. Impaired hand motor function strongly influences the speed in which manual tasks can be solved, and thus, the lower performance IQs did very probably not reflect cognitive, but rather manipulative impairment. It was also shown that lesion extent is correlated with hand motor function, and thus it is not surprising that patients with larger lesions, having less hand motor function, score lower in certain subtests of the performance scale.

5 Study 2: Paradigms eliciting right hemispheric fronto-parietal activation in fMRI

5.1 Scope

In this exploratory study, paradigms were developed and evaluated for usage in the fMRI environment, which were thought to elicit predominantly right-hemispheric activation of fronto-parietal networks.

Q2.1: Which cognitive functions are in the healthy brain subserved by areas recruited for language production in lesion-induced right hemispheric language organization?

The study should detect paradigms suitable for the use in a clinical context. The paradigms should therefore meet the following criteria:

C2.1: The paradigms shall be potentially solvable also for patients with visuospatial deficits.

C2.2: The paradigms shall gain robust and consistent activations on a single subject level.

5.2 Subjects and Methods

5.2.1 Subjects

Eleven adult volunteers were recruited from hospital staff and among medical students of the University of Tübingen. All of them exhibited right-hand preference with laterality indices >+50 (range +70 to +100) in the Edinburgh Handedness Inventory (Oldfield, 1971), and had normal vision. None had a history of neurological or psychiatric disorders, and none had previous experience with the stimuli and tasks. One subject was excluded because of abnormalities revealed on the T1 MRI scan, and another because of loss of the data. This left 9 subjects (5 women), with a mean age of 25.4 years (SD 3.5 years) for subsequent data processing. Informed written consent was obtained from all participants in accordance with the Declaration of Helsinki and the requirements of the local ethics committee.

5.2.2 Stimulus presentation

For stimulus presentation, instructions, and recording of behavioral responses, the Presentation® software (Version 0.53, http://www.neurobs.com) was used. Visual stimuli were presented to the subjects by projection onto a screen that was viewed via a tilted mirror located on the head coil of the scanner. Auditory stimuli were presented via the standard air-conducting headphones of the MRI scanner. Subjects responded by pressing MRI-compatible response-buttons held in the right hand. All participants were instructed and trained outside the scanner, and their understanding of the task was ensured by performance of test runs. Each new task was introduced by a reminder which appeared on the screen.

5.2.3 Paradigms and Designs

Five paradigms were designed to elicit cognitive processes mediated by the right hemisphere, and modified for use in the MRI scanner. In order to gain a method viable also in the clinical context, the paradigms were designed in a block-design which promises robust signals also in single-subject analyses. To allow for good compliance in patients with neuropsychological deficits, emphasis was put on a low degree of difficulty.

Mental Rotation of objects has been reported to rely heavily on right hemispheric processing (Ratcliff, 1979). Therefore, this task was used as "reference paradigm", with right hemispheric dominance to be expected. As mental rotation is a process which poses a challenge especially to neurological patients (Tomasino et al., 2003), also visual search paradigms were developed which were designed in a manner to find a tradeoff between difficulty and lateralization. The *Visual Search / Animals* task was expected to be easy and entertaining, but on the other hand it held the possibility of verbalizing the search process, leading to activation of a verbal, rather than a visuospatial network. The *Visual Search / Complex* task was difficult to verbalize, but also it required a higher degree of visuospatial skills. The *Visual Search / Symbols* task was also designed to make verbalization difficult, and to encourage subjects to search systematically by arranging the symbols in a matrix.

To provide a task which is a) suitable for vision-impaired persons, and b) close to right hemispheric language functions, the *Memory for Pitch Information* paradigm was developed. Perception of and memory for pitch is a function mediated by RH structures (Zatorre, 2001), and is regarded as a basis for the understanding of emotional prosody (Ladd et al., 1985).

In the ***Mental Rotation*** paradigm (Figure 5.1A), subjects judged as quickly as possible whether two 3D objects composed of cubes were identical or mirror-imaged. In the *activation condition* one of the shapes was rotated, and, therefore, mental rotation was invoked in accomplishing the task. In the *control condition* none of the objects was rotated. Stimuli were presented for 9 sec each.

In the ***Visual Search/Animals*** task (Figure 5.1B), subjects judged as quickly as possible whether or not an integral part of an animal depiction was missing (*activation condition*, Fig. 1B) or whether the image was upside-down or not (*control condition*). Stimuli were presented for 9 sec each.

In the ***Visual Search/Complex*** task (Figure 5.1C), a modification of the Rey Osterrieth-Complex Figure was used (A. Rey, 1941). In each trial, subjects judged as quickly as possible whether one of two presented figures lacked a detail or not (*activation condition*) or was rotated or not (*control condition*). Stimuli were presented for 9 sec each.

For the ***Visual Search/Symbols*** task (Figure 5.1D), subjects were presented with a target symbol in the middle of the screen (1000 ms), followed by a black-and-white masking image (500 ms). In a 3x3 matrix of symbols, subjects then searched for the target symbol and judged whether it was present or not (7500 ms). In the *activation condition,* the symbol was present in 50% of the cases, at some place other than the center. In the *control condition,* the symbol was exactly in the middle of the matrix, about which the subjects were not told beforehand.

Also the ***Memory for Pitch Information*** task (Figure 5.1E) was built in a subtraction-design. Three different kinds of sounds (rising in pitch from 400-600 Hz, falling in pitch from 600-400 Hz, continuous at 500 Hz) were presented in a quasi-randomized manner, each sound lasted 50 ms, inter-stimulus-interval was 2450 ms. *Activation condition*: Subjects pressed a button whenever they heared a sound which was the same as the one before the previous one. *Control condition*: Subjects pressed a button whenever they heared a sound rising in pitch.

The paradigms were presented in block designs with activation, control and rest conditions alternating in 4 cycles. Activation and control blocks of the visual paradigms lasted for 46 sec each (containing 5 trials and a 1-sec instruction screen), in the rest condition, subjects fixated a cross positioned in the middle of the screen for 9 sec.

For the auditive task, activation and control blocks lasted 50 sec each (containing 19 stimuli and a verbal instruction), in the rest condition, subjects listened to the sounds without task for 20 sec. The cycle control-activation-rest was presented 4 times.

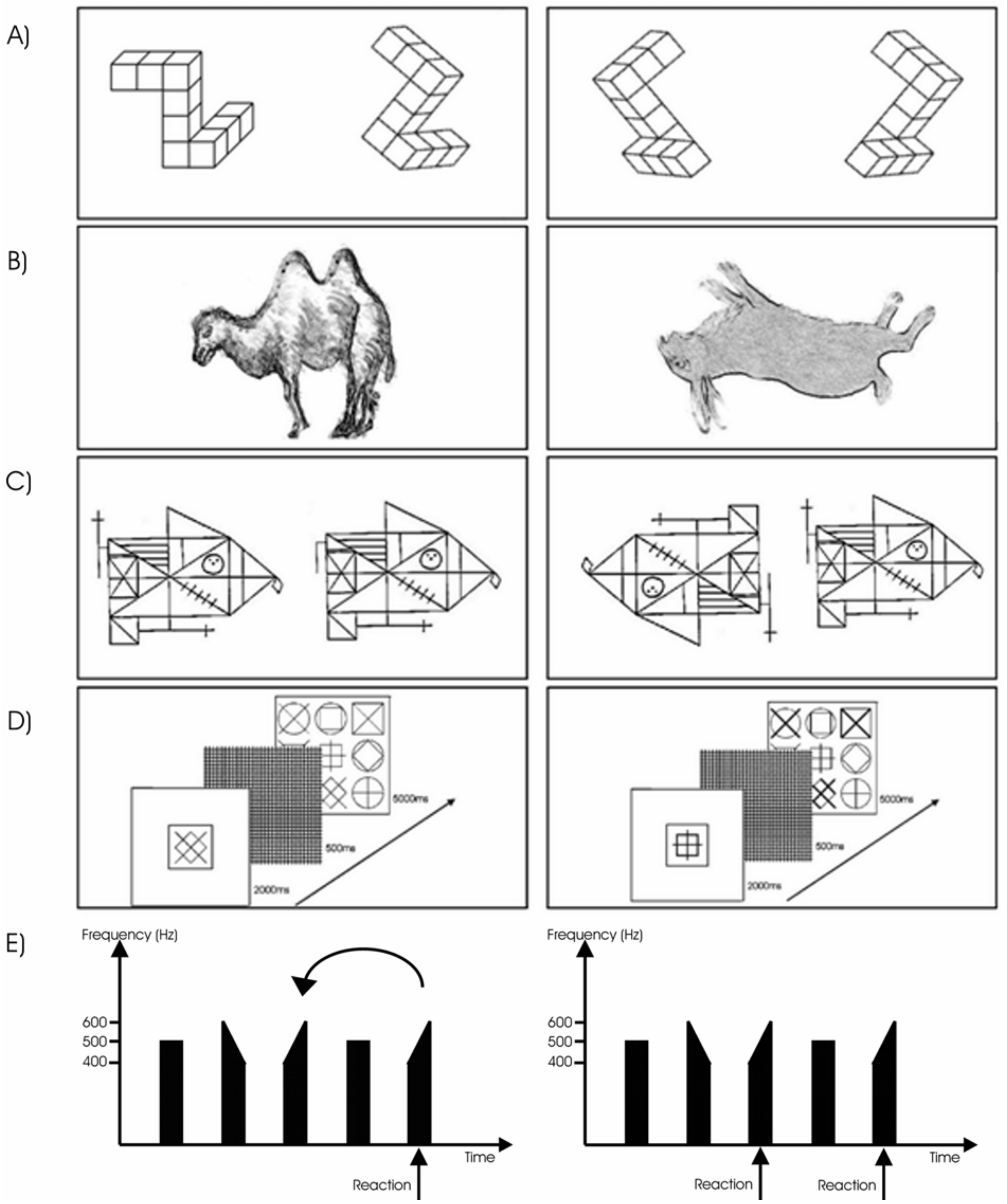

Figure 5.1: Examples for the stimuli used in activation (left panel) and control (right panel) conditions. A) Mental rotation; B) Visual Search / Animals; C) Visual Search / Complex; D) Visual Search / Symbols; E) Memory for Pitch Information

5.2.4 fMRI procedure

MRI measurements were performed on a 1.5 Tesla scanner (Siemens Vision; Erlangen, Germany). Functional imaging data was acquired using a whole-brain multislice echo-planar imaging (EPI) sequence (Klose et al., 1999): TR = 3 sec, TA = 2.9 sec, TE = 39 ms, 4-mm slice thickness, 1-mm gap, 28 axial slices, in-plane matrix 64x64, voxel size 3x3x5 mm^3. A total of 137 volumes were acquired for the visual paradigms. This led to a total scanning time of 411 sec (6 min, 51 sec). For the auditive paradigm, a total of 169 volumes were acquired, leading to a scanning time of 507 sec (8 min, 27 sec). The first five volumes of each session were discarded to allow for stabilization of longitudinal magnetization. Structural images were obtained as T1-weighed 3D-datasets (128 contiguous sagittal slices, in-plane matrix 256x256, voxel size 1x1x1.5 mm^3).

5.2.5 Statistical analysis

Data analysis was performed using SPM2 (Wellcome Department of Imaging Neuroscience, London, UK). Functional data were realigned to correct for movement, coregistered with structural data, and spatially normalized using templates provided by the Montreal Neurological Institute (MNI; Brett et al., 2002). For statistical evaluation, data were smoothed with a Gaussian filter of FWHM = 9 mm for single-subject analysis and with a filter of FWHM = 12 mm for group analysis. Data were subjected to a high pass filter (128 sec cutoff) and corrected for serial autocorrelations with an autoregressive model (AR(0.2)). For the depiction of differences between activation and control conditions, a height threshold of $p<0.05$, FWE-corrected (familywise error; Nichols & Hayasaka, 2003) for multiple comparisons and an extent threshold $k>10$ voxels were chosen for single-subject data. To show also activation patterns common to the group, random effects analyses were conducted. As the groups per paradigm were small (n=5), an approach not to correct for multiple comparisons was employed, which has been used before for small samples (Ullsperger & von Cramon, 2004).

Rather than using voxel counts as has been suggested before (Holland et al., 2001; Staudt et al., 2001), Laterality Indices (LI) were calculated with the sums of T-values above the threshold for FDR-corrected (false discovery rate; Genovese et al., 2002) $p<0.05$ on either side of the brain. Activation strength as reflected in the voxel value takes into account different degrees of contribution to the correlation of task and neural response as detectable in the functional images (Adcock et al., 2003). The interhemispheric fissure (2.5cm left and right of the midsagittal plane) was excluded from the analysis. The LI = (right-left)/(right+left) results in values between -1 and +1, and positive values for left hemispheric lateralization.

Anatomically defined regions of interest for frontal, parietal, and fronto-parietal cortex were used which conform to MNI space and are publicly available (Tzourio-Mazoyer et al., 2002). The fronto-parietal region of interest was employed because paradigms should be found which show a lateralization to the RH in frontal and parietal areas, to be of further use in the assessment of patients with lesion-induced RH language organization. The T-values provide only an indirect measure of neurobiological processes and might vary in different regions not only on grounds of activation strength but of different variables which are not easy to control. Therefore, the frontal and parietal activation maps were inspected separately for their laterality.

Differences in laterality between paradigms and regions were tested for significance using the nonparametrical Kruskal-Wallis H-test. Post hoc comparisons were conducted using the Scheffé procedure.

5.2.6 Behavioral data analysis

Mean reaction times and correct responses were recorded for all paradigms and conditions. Differences between conditions were analyzed using the non-parametrical Mann-Whitney U-Test for ordinal data.

5.3 Results

5.3.1 fMRI Data

Four of the five paradigms (*Mental Rotation, Visual Search / Animals, Visual Search / Complex, Memory for Pitch Information*) consistently elicited suprathreshold ($p<0.05$, FWE-corrected) activations of occipital, parietal, and frontal structures in the single subjects. The *Visual Search / Symbo*ls task elicited variable patterns, with mainly occipital activation in most subjects. Figure 5.2 illustrates an example of the single subject activation patterns, for the *Visual Search / Comple*x task. The exact coordinates of the activation maxima common to the group (random effects analysis, $p<0.001$, uncorrected) within standard MNI-space are provided in Appendix A, Table 1.

For the group level only clusters surviving an uncorrected threshold of $p<0.001$ are reported.

The *Mental Rotation* task evoked bilateral occipital activation on group level and in 3/5 subjects, also bilateral activation of the superior parietal lobule (4/5 subjects), and right- and/or left-hemispheric activation of the middle frontal gyrus part of the precentral cortex (3/5 subjects).

The *Visual Search / Animals* task elicited activation of right occipital lobe (4/5 subjects) and right superior parietal lobule (5/5 subjects).

For the *Visual Search / Complex* task (Figure 5.2) the global maximum was found for the group in the right middle frontal gyrus part of the precentral cortex (present in 3/5 subjects). Suprathreshold areas were also bilateral superior parietal lobule (right > left; this activation was supra-threshold in 5/5 subjects), and bilateral occipital lobe (5/5 subjects).

The *Visual Search / Symbols* task showed large between-subject variability, resulting in very low group activation levels. Small clusters of activation are found in bilateral occipital lobe (present in 4/5 subjects), no other cluster was suprathreshold in more than one subject.

For the auditory *Memory for Pitch Information* task the global maximum of group activation was found in right superior parietal cortex (suprathreshold in

5/5 subjects). Additional clusters of activation were found in right premotor cortex (4/5 subjects) and in right medial frontal cortex (3/5 subjects).

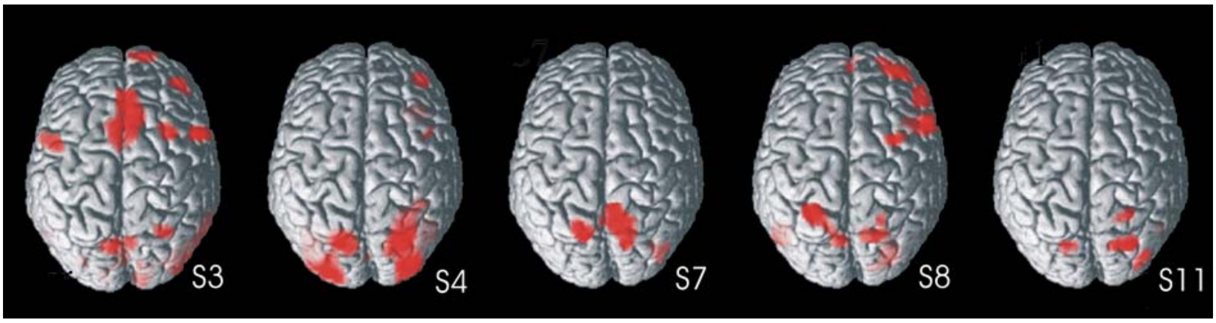

Figure 5.2: Activations patterns of single subjects for the Visual Search / Complex task ($p<0.05$, FWE-corrected, extent threshold $k>10$ voxels; overlaid on the SPM2 single subject brain surface).

Laterality indices are shown in Figure 5.3 and Table 5.1. A significant main effect was revealed for fronto-parietal and parietal LIs (Kruskal-Wallis $p<0.05$). Whereas the *Visual Search / Symbols* paradigm elicited bilateral activation or slight left-hemisphere preference in all subjects, predominantly right-hemispheric activation was seen for all subjects in the *Visual Search / Animals* (post-hoc Scheffé $p<0.05$), *Visual Search / Complex* (post-hoc Scheffé trend $p=0.095$), and *Memory for Pitch Information* (post-hoc Scheffé trend $p=0.068$) paradigms. For the *Mental Rotation* paradigm, three of the subjects showed a moderate right hemispheric laterality, one subject showed bilateral activation, and one subject showed left hemispheric laterality.

Table 5.1: Laterality indices for single subjects per paradigm at an FDR-corrected threshold of $p<0.05$. Negative values indicate higher T-values in the RH than in the LH.

		S1	S2	S3	S4	S5	Mean	SD
Mental Rotation	frontal	-0.066	-0.142	-0.266	n/a	-0.999	-0.368	0.18
	parietal	-0.379	0.419	-0.082	0.212	-0.754	-0.116	0.27
	fronto-parietal	-0.249	-0.002	-0.185	0.326	-0.895	-0.201	0.08
Visual Search / Complex	frontal	-0.359	-0.268	-0.683	-0.393	-0.150	-0.370	0.37
	parietal	-0.477	-0.574	0.052	0.091	-0.358	-0.253	0.42
	fronto-parietal	-0.393	-0.312	-0.16	-0.28	-0.304	-0.289	0.40
Visual Search / Animals	frontal	0.0705	-0.582	-0.311	-0.266	-0.386	-0.294	0.21
	parietal	-0.625	-0.784	-0.149	-0.28	-0.502	-0.468a)	0.23
	fronto-parietal	-0.15	-0.724	-0.226	-0.272	-0.446	-0.363b)	0.20
Visual Search / Symbols	frontal	0.605	0.13	0.345	0.335	-0.273	0.228	0.29
	parietal	0.41	0.273	0.255	-0.034	0.363	0.253a)	0.15
	fronto-parietal	0.573	0.259	0.306	0.049	0.037	0.245b)	0.20
Memory for Pitch Information	frontal	-0.309	-0.169	-0.0832	-0.479	0.772	-0.054	0.49
	parietal	-0.248	-0.349	-0.325	-0.57	-0.115	-0.321	0.17
	fronto-parietal	-0.281	-0.27	-0.239	-0.528	-0.0847	-0.281	0.28

a),b) Scheffé-test for post-hoc comparisons: $p<0.05$. S4 did not show any suprathreshold frontal activation for the Mental Rotation paradigm.

Frontal and parietal laterality indices did not differ for the visual search paradigms, but in the *Mental Rotation* paradigm frontal activation was more right hemisphere dominant than the parietal activation in three out of five subjects, whereas in the *Memory for Pitch Information* paradigm, parietal activation was consistently right hemispheric lateralized, with frontal activation being left hemispheric or bilateral in three out of five subjects.

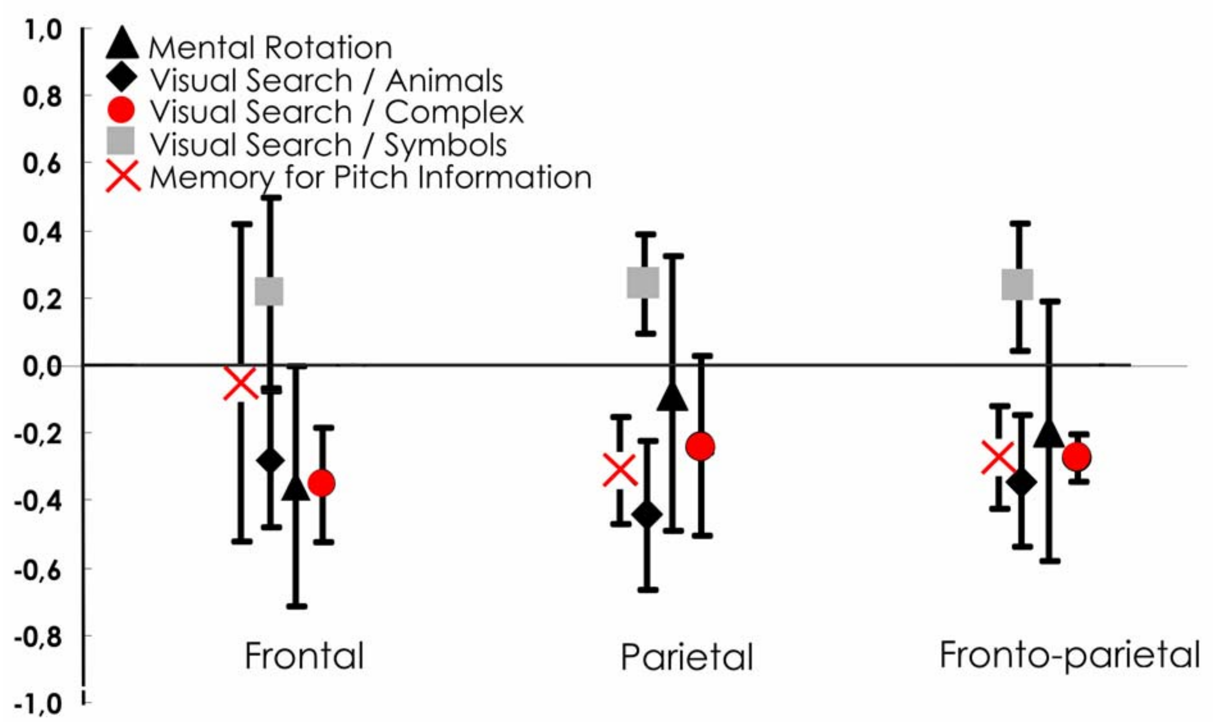

Figure 5.3: Means and standard deviations for the laterality indices elicited by the different paradigms.

5.3.2 Behavioral Data

In all administered tasks, performance of all participants was above chance level. For all tasks activation and control conditions differed significantly in their respective difficulties: response time was significantly longer in the activation than in the control conditions (*Visual Search / Complex*; *Visual Search / Animals*; *Visual Search / Symbols*; *Mental Rotation*); and in four out of five paradigms (*Visual Search / Complex*; *Visual Search / Animals*; *Visual Search / Symbols*; *Memory for Pitch Information*) the number of correct responses was significantly greater in the control as compared to the activation conditions (Mann Whitney U-test; Table 5.2).

Table 5.2: Mean reaction times and correct responses for the paradigms used in the study and difference between conditions (Mann-Whitney U-test).

	Reaction Times (ms)					**Correct Responses (%)**				
	Activation		Control			Activation		Control		
	mean	SD	mean	SD	p	mean	SD	mean	SD	p
Mental Rotation	4314	785	2273	699	<0.005	86.00	7.23	97.33	4.35	=0.075
Visual Search / Animals	3321	1128	1491	332	<0.005	74.85	7.19	93.87	4.25	<0.005
Visual Search / Complex	5199	1051	1693	400	<0.005	80.69	6.0	97.33	3.65	<0.001
Visual Search / Symbols	2349	412	1028	161	<0.005	82.22	7.51	97.84	3.52	<0.005
Memory for Pitch Information	944	125	848	101	=0.175	71.25	27.46	98.75	2.80	<0.01

SD=standard deviation

5.4 Discussion

Study 2 set out to identify cognitive functions which are in the healthy brain subserved by areas recruited for language production in lesion-induced right hemispheric language organization (Q2.1). The results show that mental rotation, complex visual search processes and nonverbal auditory memory are mediated by bilateral fronto-parietal networks, which were in four of the paradigms lateralized to the right hemisphere. Right hemispheric lateralization was more pronounced and consistent on single subject level in the new *Visual Search / Animals, Visual Search / Complex,* and *Memory for Pitch Information* tasks than in the already established *Mental Rotation* task. Robust and consistent activation on the single subject level is essential if the task is to be used in the clinical context (C2.2). As mental rotation of objects poses a particular challenge to many neurological patients (Tomasino et al., 2003), it was necessary to develop visuospatial paradigms which were easy to solve but still elicited a sufficient level of brain activation. The *Visual Search / Animals*, and the *Visual Search / Complex* paradigms met this criterion, with performance well above chance-level in normal volunteers (C2.1). As not all potential subjects possess accurate vision, a non-visual paradigm (*Memory for Pitch Information*) was also developed and shown to be sufficiently solvable by the volunteers.

In a neuropsychological study trying to examine fine-grained cognitive processes, a block design as used here would be a very coarse technique. Obviously, the visual search paradigms did not only tap basic visual search processes, particularly with the complex stimuli used. Also the *Memory for Pitch Information* task did not only tap memory for pitch, but also attention and executive control. The purpose of this study, however, was to find paradigms which reflect complex cognitive processes on one hand, but are easy to solve on the other hand. Furthermore, they should elicit predominantly right-hemispheric fronto-parietal activation on a single-subject level. Two of the visual search tasks and the auditive task fulfil these conditions. The inconsistent lateralization pattern elicited by the *Visual Search / Symbols* paradigm can probably best be explained by the assumption that search for symbols addresses analytic processes more than holistic or visuospatial processes in some subjects. Analytic, as opposed to holistic processing is a function attributed mostly to the left hemisphere (Van Kleeck, 1989).

The activation patterns observed in the *Visual Search / Comple*x and the *Visual Search / Animals* tasks fit well into the body of literature regarding the cognitive processes required for the performance of the tasks. The activation of the superior parietal lobule (SPL) can be explained by the endogeneously triggered visual search process (Leonards et al., 2000; Shulman et al., 2003), which employs spatial attention shifts (Corbetta & Shulman, 2002), spatial selection processes (Shibita & Ioannides, 2001), and spatial memory (Smith et al., 1996; Zarahn et al., 2000). Also in the *Mental Rotation* Paradigm, SPL activation was to be expected (Corballis, 1997).

The activation of the FEFs in the visual paradigms is in line with findings on the engagement of these areas in saccadic eye movements (Fox et al., 1985), in visual search processes (Muggleton et al., 2003), and in visuospatial orienting, the latter showing right hemispheric preponderance (Mayer et al., 2004). As subjects were not compelled to fixate their gaze, saccadic eye movements certainly happened, especially in the *Mental Rotation, Visual Search / Complex, and Visual Search / Symbols* tasks, where two images were to be compared or a matrix had to be searched.

The SPL activation in the *Memory for Pitch Information* paradigm seems puzzling on first sight, as the task did not involve visual or spatial information or processes at all. The explanation for this activation must rather lie in the area of executive functions and attentional control: The *Memory for Pitch Information* task places heavy demands on working memory, attentional control and internal task monitoring processes. These demands are lighter in the control condition. The executive system, and particularly attentional control, however, has been located in a fronto-parietal network, predominantly of the right hemisphere (Sarter et al., 2001).

It is indisputable that the results of a random effects analysis in a small group cannot be taken for granted without further analyses of the single subject data. In the present sample, however, the single subjects' results corroborate the weak but reasonable activation patterns in the random effects group analysis. E.g. all subjects presented supra-threshold superior parietal activation predominantly of the right hemisphere in the *Visual Search / Complex* and the *Memory for Pitch Information* tasks. Four of five subjects showed predominantly right-hemispheric SPL activation in the *Visual Search / Animals* task, and three of five subjects in the *Mental Rotation* task. Also the other activation clusters for these paradigms were on the one hand to be expected and are corroborated on the other hand by single subject data. The statistical analysis of the laterality indices further corroborates the group results, also with respect to the frontal and parietal regions of interest.

That the random-effects analysis did not yield significant results after correction for multiple comparisons may be caused by interindividual differences which are easily explained by the complexity of the tasks, which may elicit different specific processes in individual subjects.

Study 2 resulted therefore in three nonverbal tasks suitable for usage in the planned study on patients with early left hemispheric brain injury. From them, the *Memory for Pitch Information* task was chosen because not all patients considered for the study possessed accurate vision. As visual paradigm, the *Visual Search / Complex* task was chosen, as the patients to be assessed were adults. For children, the *Visual Search / Animals* task might be more suitable.

6 Study 3: Organization of nonverbal functions in lesion-induced right-hemispheric language

6.1 Hypotheses

Study 1 corroborated the hypothesis that right-hemispheric language involvement is a decisive factor influencing visuospatial deficits in patients with early left hemispheric lesions. The neuroanatomical causes for these deficits have been hypothesized more or less vaguely – as “crowding” (Teuber, 1974), “crowding out” (Loring et al., 1999), or “reversed laterality” (Korkman & von Wendt, 1995). A direct exploration of the cortical organization of nonverbal functions in patients with lesion-induced right-hemispheric language organization, however, has yet to be undertaken. In Study 2, four fMRI paradigms were found to be suitable to consistently elicit predominantly right hemispheric fronto-parietal activations in normal right-handers, and from these one visual and one auditive paradigm were chosen for the use in Study 3.

Study 3 examines the cortical organization of nonverbal functions in patients with lesion-induced right-hemispheric language organization. Regarding the nonverbal functions, two alternative hypotheses can be put forward:

H3.1: Nonverbal functions are reorganized interhemispherically (“reversed laterality”) or intrahemisperically (“crowding out”).

H3.2: Nonverbal functions share the right-hemispheric neural substrate with language functions, thus leading to areas shared by verbal and nonverbal tasks (“crowding”).

6.2 *Subjects and Methods*

6.2.1 Subjects

Six young adults (five women, age range from 16 to 27 years) with pre- or perinatally acquired lesions of the left hemisphere, who had taken part in Study 1, participated in this new fMRI study. Strict inclusion criteria were applied: Patients had to have well-defined unilateral and focal lesions of the left hemisphere, and right hemispheric language organization in fMRI. None of the patients suffered from epilepsy or neurological diseases apart from a right-sided unilateral spastic CP (SCPE, 2000). All patients showed a strong left-hand preference: Laterality Indices ranged from -80 to -100 in the Edinburgh Handedness Inventory (Oldfield, 1971). In the course of Study 1, all patients had been assessed with an intelligence test (HAWIE-R). Verbal IQs of all patients were normal or above-average, performance IQ was below average (>1 standard deviation below mean) in two of the patients, and normal in four. Patient characteristics are shown in Table 6.1.

Table 6.1: Patient characterization

Patient no.	**gender**	**age**	**pathology**	**Verbal IQ**	**Performance IQ**
P1	F	17	MCA	92	78
P2	F	16	MCA	91	97
P3	F	26	PV	119	108
P4	F	27	PV	92	102
P5	M	21	PV	112	100
P6	F	19	PV	114	82

M=male; F=female; MCA=infarction of middle cerebral artery; PV=periventricular lesion

Thirty healthy right handed controls were recruited from hospital staff and students to identify six (Laterality Indices ranged from 80 to 100) who could be closely matched to a patient each by age, sex, and IQ data (HAWIE-R; (Tewes, 1994), forming the control group for the fMRI experiment. Verbal IQ data were used as matching criteria, as deficits in performance IQ had to be expected in the patient group, due to either visuospatial deficits or, even more, to impairments in bimanual manipulation.

All participants were native speakers of German. Informed consent of the participants (for the two underage patients also informed consent of the parents) and agreement of the local ethics committee were obtained, according to the Declaration of Helsinki.

6.2.2 fMRI-Tasks

Participants performed three different tasks. To ensure comparability of activation patterns in the two groups, a "ceiling effect" was deliberately introduced to task performance by choosing a low degree of difficulty. All paradigms were presented in block-designs, with activation and rest / control conditions alternating in four cycles.

A) Word-Chain task (Staudt et al., 2001). Given a starting letter, subjects silently produced word-chains with every word starting with the last letter of the preceding word (Example: Do**G**-**G**arde**N**-**N**eighbo**R**-**R**…). Four blocks of silent word-generation, each triggered by an aurally presented starting letter, were alternated with four blocks of silent rest. Each block lasted 48 sec, total scanning time was 384 sec. As performance could not be monitored during the scanning session, subjects performed the same task outside the scanner, and the number of generated words was documented.

B) Visual Search task (cf. Study 2; Figure 5.1A). This task was built in a subtraction-design using the Rey Osterrieth Complex Figure (A. Rey, 1941). Activation condition: Subjects compared two versions of the figure and decided whether both figures were complete or whether one figure lacked a detail (5 trials of 9 sec in 45 sec). Control condition: Two complete figures were presented in a rotated manner, either both looking in the same direction or in different directions. Subjects decided here if both figures show the same orientation (5 trials in 45 sec). In a short Rest condition subjects fixated a fixation cross (6sec). The cycle Control-Activation-Rest was presented 4 times, total scanning time was 396 sec.

C) Memory for Pitch Information task (cf. Study 2; Figure 5.2E). Again, this task was built in a subtraction-design. Three different kinds of sounds (rising in pitch from 400-600 Hz, falling in pitch from 600-400 Hz, continuous at 500 Hz) were presented in a quasi-randomized manner, each sound lasted 50 ms, inter-stimulus-interval was 2450 ms. Activation condition: Subjects press a button whenever they hear a sound which is the same as the one before the previous one (duration of block: 50 sec). Control condition: Subjects press a button whenever they hear a sound rising in pitch (duration of block: 50 sec). Rest condition: Subjects listen to the sounds without task (duration of block: 20 sec). The cycle Control-Activation-Rest was presented 4 times, total scanning time was 492 sec.

6.2.3 Stimulus presentation

For stimulus presentation, instructions, and recording of behavioral responses, the Presentation® software (Version 0.53, http://www.neurobs.com) was used. Visual stimuli were presented to the subjects by projection onto a screen that was viewed via a tilted mirror located on the head coil of the scanner. Auditory stimuli were amplified and transmitted via the standard MRI air-conduction headphones. Subjects responded by pressing MRI-compatible response-buttons held in the left hand. All participants were instructed and trained outside the scanner, and their understanding of the task was ensured by performance of test runs. Each new task was introduced by a reminder projected onto the screen.

6.2.4 fMRI data acquisition

We used a Siemens 1.5T Sonata (Siemens, Erlangen, Germany) scanner to acquire whole brain 3D anatomical data sets (TR = 1300 ms, TE = 3.93 ms, 144 slices, 256x256 base resolution, 1x1x1.25 mm^3 voxel size, 1.25 mm slice thickness, 15° flip angle), and whole brain functional echoplanar images (TR = 3 sec, TA = 3 sec, TE = 52 ms, 28 slices, 64x64 base resolution, 3x3x4 mm^3 voxel size, 4mm slice thickness, 1mm gap to prevent cross-talk, 90° flip angle). The *word-chain* task was presented a second time with the sparse-sampling approach as used in a previous study (Staudt, Lidzba et al., 2002): TR = 6 sec, TA = 2400 ms, leaving 3600 ms of silence in which the starting letters were presented aurally.

For the *Word-Chain*, *Visual Search*, and *Memory for Pitch Information* paradigms were acquired 133, 137, and 169 volumes each with repetition time=3 sec, for the word-chain paradigm were acquired another 69 volumes with the sparse-sampling approach. The first 5 scans were discarded for the first three sessions, whereas the first 2 scans were discarded for the sparse-sampling word-chain session, to account for stabilization of the magnetic field.

6.2.5 Data analysis

6.2.5.1 Structural Data

Data was analyzed using SPM2 (Wellcome Department of Imaging Neuroscience). The patients' structural datasets were coregistered with the mean of the realigned functional images to allow the presentation of single subject results.

For assessment of lesion-size the same automated procedure as in Study 1 was used (Staudt et al., 2003): Using SPM2 algorithms the normalized T1-weighted data were segmented into compartments of grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). This process produces probabilistic maps in which each voxel is assigned a probability ($0 \leq p \leq 1$) of correct assessment.

To assess lesion-size, the total of grey and white matter (GM+WM) volume was used, because the group contained patients with periventricular WM lesions as well as cortico-subcortical lesions, which differ in relative grey and white matter loss. The ratio of (GM+WM) volume in the left and right hemisphere: $(GM+WM)_{left}/(GM+WM)_{right}$ is a normalized measure for lesion extent in the patient group.

6.2.5.2 Functional Data

Functional data was preprocessed using the SPM2 default parameters unless otherwise specified. The images of every subject were spatially realigned to eliminate movement artifacts. To allow inter-subject comparison, data was normalized using templates provided by the Montreal Neurological Institute (MNI; Brett et al., 2002)). Since normalization of pathological brain data is a critical step (Brett et al., 2002), the effects of nonlinear normalization were assessed by calculating the Jacobian determinant j for each voxel, which indicates the volume change experienced during normalization. As j is a value representing either increase or, by negative values, decrease of volume, the mean of $|j|$ in each segementation compartment was used to depict absolute volume changes.

After smoothing with a Gaussian filter of FWHM = 12 mm, the functional data was subjected to a voxel-based statistics according to the general linear model (Friston et al., 1995) to assess activation contrasts for the different tasks. First level single subject statistics were assessed by contrasting the activation condition with the rest condition (*word-chain* task), or with the respective control conditions (*visual search* and *memory for pitch information*), in the latter cases treating the rest condition as condition of no interest. For modeling the experiment, basic box-car functions were convolved with the haemodynamic response function. To account for technical or physiological noise the functional data was subjected to a high-pass filter of 128 sec. Furthermore, correction for autocorrelations was employed using an autoregressive (AR(0.2)) model and individual activation strength was rescaled by means of global scaling.

To assess activation patterns common to all individuals of each group, fixed-effect analyses were conducted. On the second level, paired t-tests were conducted to test for differences between the groups.

Laterality indices (LI) were calculated for each subject and activation>control contrast by integrating the sum of voxel values on both sides of the brain (disregarding 5mm left and right of the interhemispheric fissure). The equation

LI=(left-right)/(left+right) leads to negative values for predominantly right-hemispheric activation. As language activation was to be expected in fronto-parietal areas (Staudt, Lidzba et al., 2002), and the main interest was laid on interactions between language and nonverbal functions, the contrasts were masked in a manner to leave only frontal and parietal activation. As gross activation levels were variable between subjects and in particular between both groups (the patients showing less activation than the controls) an adaptive thresholding procedure was used to define "interesting" voxels (i.e. those which contribute significantly to the task as opposed to noise) for each subject as those voxels with above-average intensity values.

To address the question of cortical areas shared by language and nonverbal functions, a conjunction analysis was used applying the Minimum Statistic / Conjunction Null-hypothesis approach. This approach is designed to reveal only those areas which are significantly activated in all specified contrasts (Nichols et al., 2005). The percentage of voxels activated in both tasks as compared with those voxels activated only in the nonverbal functions was used as measure for shared use of cortical areas. For the word-chain task, the functional data collected with TR = 3 sec was used for this procedure, to ensure comparability with the other paradigms.

6.2.5.3 Intercorrelations of structural and functional data

In the patient group, correlations between lesion extent ($(GM+WM)_{left}/(GM+WM)_{right}$) and LIs were calculated, and between lesion extent and shared cortical area.

6.2.6 Behavioral data

During fMRI, hit rates and reaction times were recorded. Differences in behavioral data between the groups were analyzed using non-parametrical Mann-Whitney U-tests.

6.3 *Results*

6.3.1 Behavioral Data

All patients were able to perform as well as controls in all fMRI tasks. None of the behavioral measures showed significant differences between the groups (Table 6.2).

Table 6.2: Behavioral data of patients and controls in the activation conditions

		Hit MPI (%)	RT MPI (ms)	Hit VS (%)	RT VS (ms)	WC (total number)
Patients	mean	67.71	956.11	69.33	5609.46	63.67
	SD	15.01	247.19	13.83	411.72	20.40
Controls	mean	76.04	878.26	72.78	5724.35	64.33
	SD	27.22	90.11	5.74	699.93	13.29
Mann-Whitney U-Test		p=0.240	p=0.699	p=0.662	p=0.792	p=1.000

Hit=Hit Rate, RT=Reaction time, SD=Standard deviation; MPI=Memory for Pitch Information; VS=Visual Search; WC=Word-chain

6.3.2 fMRI

6.3.2.1 Patient characterization

Figure 6.1 shows axial slices of the T1-weighted structural datasets of the patients, depicting the respective lesions. Lesion sizes are variable, as is shown in Table 6.3 by the lesion ratios ($(GM+WM)_{left}/(GM+WM)_{right}$).

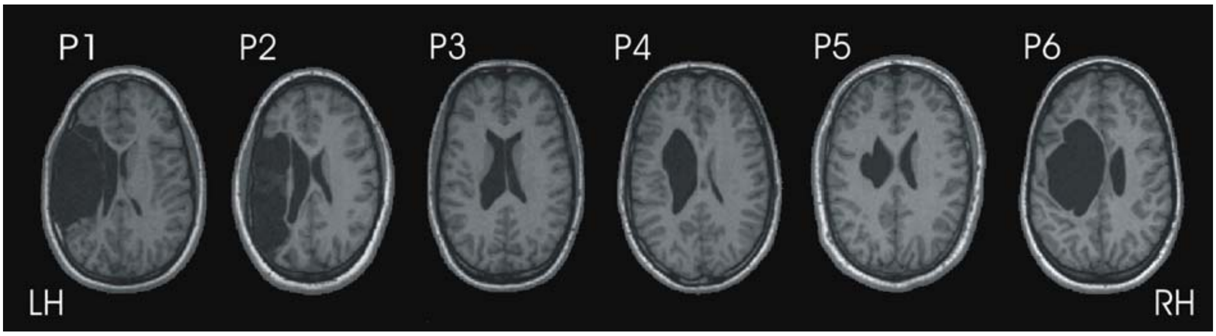

Figure 6.1: T1-weighed datasets of patients with lesion-induced right-hemispheric language production

Qualitative inspection of the deformation maps confirmed that nonlinear warping was most pronounced around the lesions. The average volume changes caused by deformation during nonlinear warping are shown in Table 6.3. In accordance with their larger lesions, average deformations exceeded the range of controls in P1 (left fronto-parietal and right frontal), P2 (left and right fronto-parietal), and P4 (left fronto-parietal).

Table 6.3: Lesion ratios* and volume-changes by nonlinear normalization, shown by mean deformation-factor |j|. Bold print indicates higher factors than in the control group

	Lesion ratio*	Left frontal			Left parietal			Right frontal			Right parietal		
		GM	WM	CSF	GM	WM	CSF	GM	WM	CSF	GM	WM	CSF
Patients													
P1	0.7569	**0.44**	**0.43**	**0.40**	**0.47**	**0.43**	0.43	**0.43**	**0.44**	**0.44**	0.45	0.45	0.45
P2	0.7144	**0.52**	**0.53**	**0.51**	**0.53**	**0.51**	**0.49**	**0.49**	**0.50**	**0.49**	**0.51**	**0.51**	**0.51**
P3	0.9538	0.37	0.38	0.36	0.42	0.41	0.37	0.37	0.37	0.35	0.39	0.39	0.39
P4	0.8981	**0.41**	**0.42**	**0.40**	**0.46**	**0.43**	0.39	0.39	0.34	0.34	0.40	0.39	0.40
P5	0.9608	0.35	0.35	0.35	0.35	0.35	0.33	0.33	0.34	0.33	0.35	0.35	0.36
P6	0.8770	0.33	0.32	0.31	0.35	0.34	0.35	0.35	0.35	0.35	0.38	0.37	0.38
Controls													
min		0.29	0.29	0.27	0.32	0.33	0.32	0.30	0.31	0.28	0.31	0.31	0.31
max		0.40	0.40	0.39	0.43	0.42	0.43	0.39	0.40	0.38	0.47	0.48	0.46

*$(GM+WM)_{left}/(GM+WM)_{right}$

6.3.2.2 fMRI activation data

MNI-coordinates of major activation sites in all paradigms and groups are shown in Appendix B, Table 1.

6.3.2.2.1 Language

The word-chain data has been acquired with two different EPI sequences, one with a sparse-sampling approach (repetition time = 6 sec), the other one with the same sequence as the other paradigms (repetition time = 3 sec). The results do not differ qualitatively, in uncovering the same areas of activation. However, activation strength and dispersion are slightly higher with the latter sequence, reflecting the higher statistical power gained by the double amount of scans per block. As the group data is intended to replicate a previous study, which used a sparse-sampling approach, data acquired with TR = 6 sec will be reported here.

The results of the *Word-Chain* task replicated a previous study (Staudt, Lidzba et al., 2002): Normal controls show activation of a predominantly left-hemispheric fronto-parietal network during silent word generation (SPM2: fixed-effect analysis, $p<0.05$, FWE-correction). The frontal part of the network consists of inferior frontal gyrus and premotor cortex, the parietal part is located in the inferior parietal lobule.

The patient group shows the same fronto-parietal activation pattern, only predominantly in the right hemisphere, comprising areas homologous to the ones activated by normal controls (Figure 6.2A). The activation of the patients' dominant hemisphere is not as exclusive as in the controls: Patients show co-activation of left hemisphere homologues, especially in premotor and parietal areas.

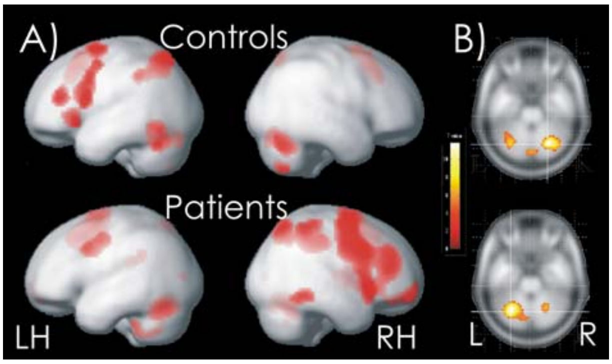

Figure 6.2: SPM2 fixed-effects analysis ($p<0.05$, FWE-corrected, extent-threshold $k>50$ voxels) for the word-chain task (activation>rest). A) Activation patterns overlaid on the SPM2 smooth average template; B) Cerebellar activation (axial slice $z=-27$) overlaid on the SPM2 T1 template.

The group results are corroborated by the single-subject data. Single-subject activation patterns are variable, but consistent with the group pattern: All participants show activation of frontal and/or parietal areas of the left (controls) or the right (patients) hemisphere. Whereas the activation pattern of the controls is exclusively left-hemispheric on the chosen threshold, three out of six patients show left-hemispheric co-activation of homologue areas.

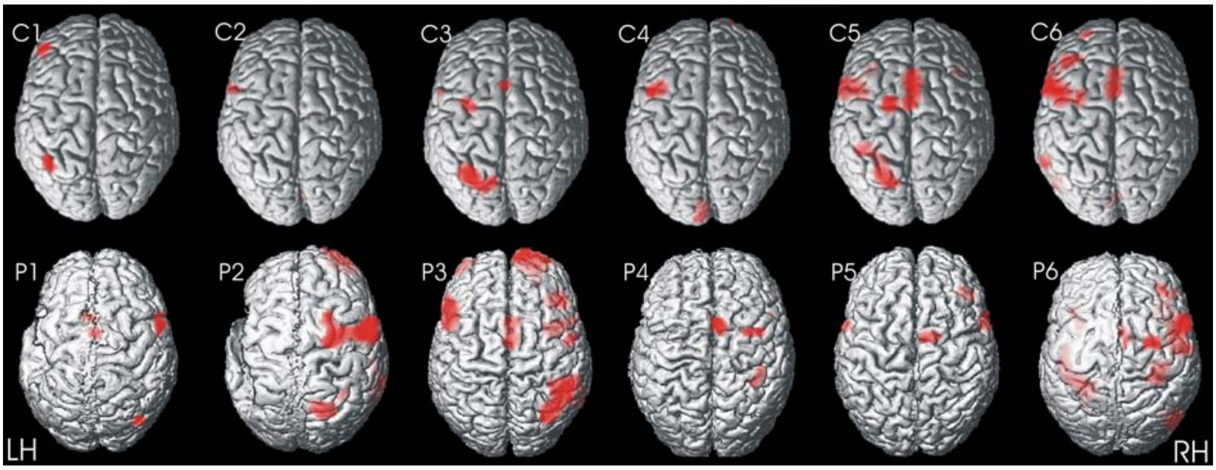

Figure 6.3: Single-subject results of controls (top panel) and patients (bottom panel), overlaid on patients' individual grey-matter surfaces, and on the SPM2 single-subject standard surface for the controls. Significance threshold: $p<0.05$, FWE-corrected, extent threshold $k>10$ voxels.

An additional finding is cerebellar activation: In accordance with previous reports on right-hemispheric cerebellar activation in language production tasks (Riecker et al., 2000), controls show strong activation in right hemispheric superior cerebellum (Figure 6.2B, top panel). Patients, again, show the same activation spot, only in the left hemisphere (Figure 6.2B, bottom panel).

The random effects analysis (paired T-test) comparing patient and control groups shows for the patient group significantly more activation in right hemispheric premotor cortex and middle frontal gyrus ($p<0.001$, uncorr.; Figure 6.4, top panel). The converse contrast (controls > patients) does not yield any significant result on the uncorrected $p<0.001$ threshold.

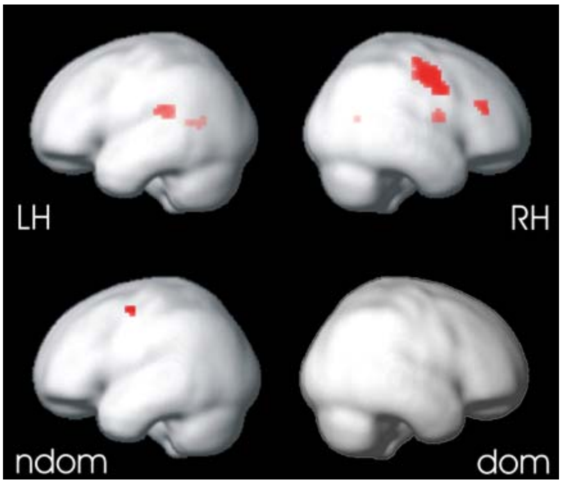

Figure 6.4: Random effects analyses (SPM2; p<0.001, uncorrected) depicting areas activated significantly more in patients than in controls (top panel). The bottom panel shows areas activated more in the dominant (dom) and nondominant (ndom) hemispheres of patients vs. controls.

As patients and controls showed almost mirror-image activation patterns, a second random-effects analysis was conducted between patient and *flipped* control data. Again, the data replicate the previous study: Patients show a small cluster in the premotor cortex of their nondominant hemispheres, with higher activity in comparison with the nondominant hemispheres of the controls (Figure 6.4, bottom panel). This is in accordance with a more bilateral activation pattern in three of the patients (c.f. Figure 6.3).

6.3.2.2.2 Memory for Pitch Information

Patients and controls show almost identical activation patterns for this paradigm: Both groups show activation of a predominantly right-hemispheric network of fronto-parietal areas, including prefrontal, premotor, and superior parietal cortex (Figure 6.5A). Single subject results corroborate the group analysis: Four of the controls and three of the patients show suprathreshold fronto-parietal activation patterns, with right-hemisphere predominance. One patient (P4) did not show any suprathreshold activation, one showed frontal activation in the right hemisphere, and one showed parietal activation in the right hemisphere. Of the controls, one showed bilateral parietal activation, and one left hemispheric parietal activation (Figure 6.6A). A random effect analysis does not show any significant differences between the groups, even on a very liberal threshold of p<0.05, uncorrected.

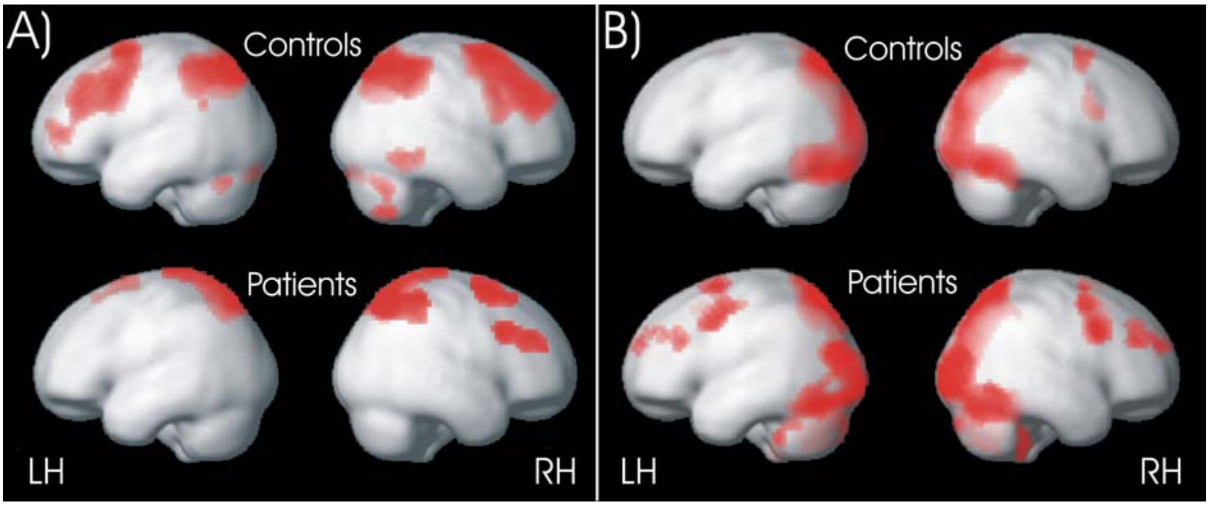

Figure 6.5: Results of fixed-effects analyses (p<0.05; FWE-corrected; extent-threshold k>50 voxels) for patient and control groups overlaid on the SPM2 smooth-average template. A) Memory for Pitch Information; B) Visual Search / Complex

6.3.2.2.3 Visual Search

Again, patients and controls show almost identical patterns of activation in the fixed-effects group analysis (Figure 6.5B). In both groups, the activation>control contrasts reveal fronto-parietal networks including middle frontal, premotor, and superior parietal cortex. Whereas the frontal activation is restricted to the RH in controls, patients activate a bilateral network. On the single subject level, all participants except one patient showed a fronto-parietal activation pattern, predominantly of the right hemisphere (Figure 6.6B). The comparison between the two groups does not yield any significant results at p<0.05, uncorrected (random-effects analysis).

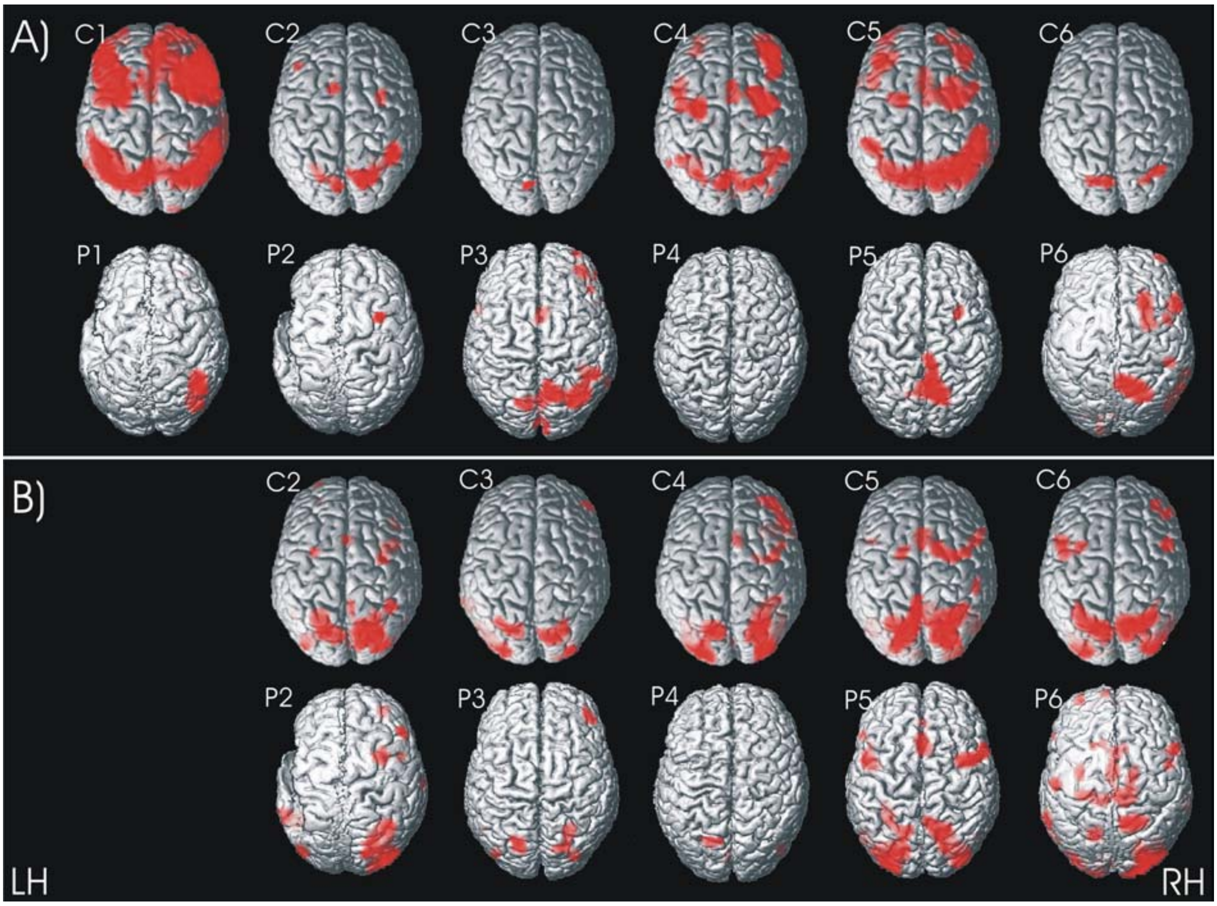

Figure 6.6: Single-subject results of controls (top panels) and patients (bottom panels), overlaid on patients' individual grey-matter surfaces, and on the SPM2 single-subject standard surface for the controls. Significance threshold: $p<0.05$, FWE-corrected, extent threshold $k>10$ voxels. A) Memory for Pitch Information Paradigm; B) Visual Search Paradigm. P1 could not solve the visual task due to low visual acuity.

6.3.2.2.4 *Laterality*

Laterality indices are depicted in Figure 6.7. As expected, patients and controls differed significantly in language dominance. All patients showed a strong right-hemispheric dominance for the *Word-Chain* task (mean LI: -0.550, range -0.912 to -0.410), whereas controls showed a strong left-hemispheric dominance (mean LI: 0.518, range 0.362 to 0.684; Mann-Whitney U-test p<0.0001). Differential tests for frontal and parietal activation show the same results: Patients' activation is right-hemisphere lateralized frontally (mean LI: -0.557), and parietally (mean LI: -0.608), whereas controls' activation is left-hemisphere lateralized frontally (mean LI: 0.530) as well as parietally (mean LI: 0.558; Mann-Whitney U-tests: p<0.005).

Also in the *Memory for Pitch Information* task patients showed a stronger preference for the right hemisphere (mean LI: -0.420, range -0.754 to -0.186), whereas controls presented a more bilateral pattern (mean LI: -0.055, range -0.302 to 0.202; Mann-Whitney U-test p<0.01). Separate inspection of frontal and parietal activation patterns show a more pronounced difference in the parietal activation (mean LI patients: -0.495, range -0.778 to -0.244; controls: -0.208, range -0.353 to 0.157; Mann Whitney U-test: p<0.05), than in the frontal activation (mean LI patients: -0.503, range -0.732 to -0.08; controls: -0.363, -0.171 to 0.267; Mann Whitney U-test: p=0.818).

There was no significant difference between the two groups with regard to laterality for the *Visual Search* paradigm. Patients showed a bilateral pattern, with a tendency towards a right-hemispheric lateralization (mean LI patients: -0.088, range -0.422 to 0.097), whereas the controls' patterns were more right-hemispheric dominant (mean LI controls: -0.245, range -0.664 to -0.043; Mann-Whitney U-test: p=0.222). The differential analysis of frontal and parietal activation yields similar results, without significant differences.

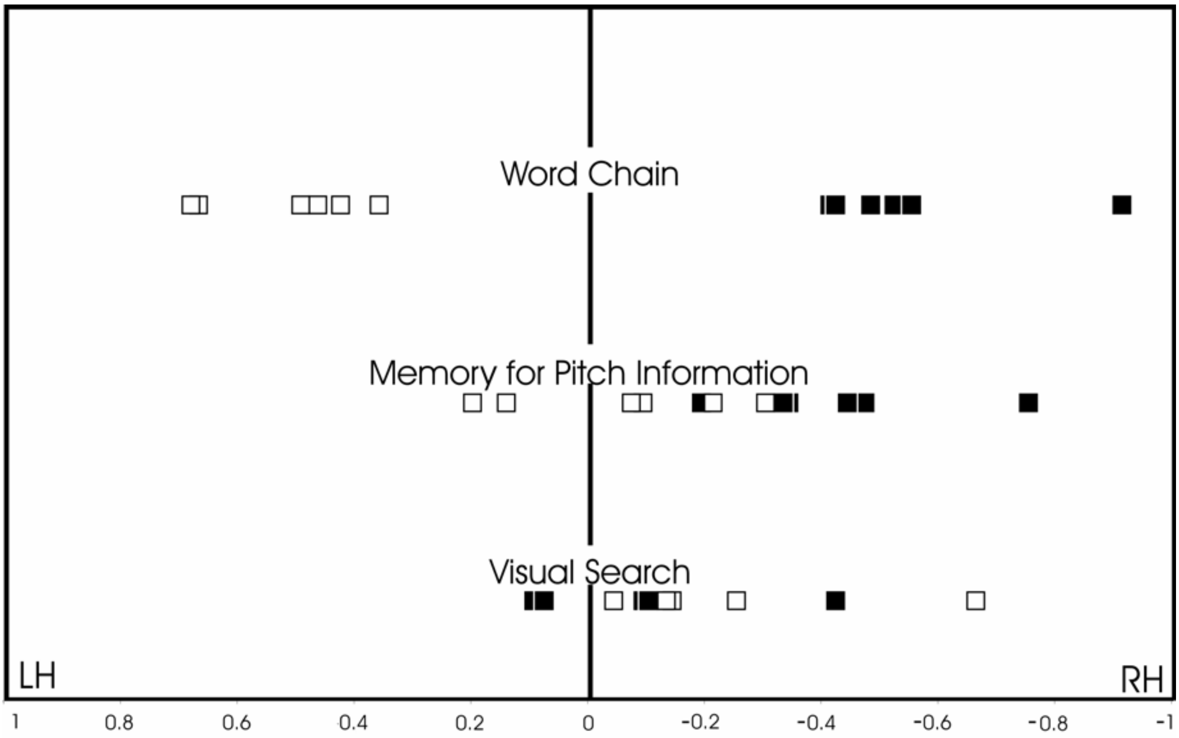

Figure 6.7: Laterality Indices for patients (solid squares) and controls (open squares) for the respective tasks.

6.3.2.2.5 *Shared use of cortical areas*

The conjunction analysis showed the shared use of cortical areas by language production and nonverbal functions in both groups. However, the size and the location of the commonly used areas differed strongly between patients and controls.

The areas activated during language production share a larger part of the memory for pitch information network in patients, than in controls (mean patients: 35.8%, mean controls: 5.16%), especially in the right hemisphere (mean patients: 46.69%, mean controls: 4.81%). Also for the visual search paradigm, patients show larger areas shared by language function in the right hemisphere (mean patients: 36.59%, mean controls: 10.23%). All reported results are significant on the $p<0.05$ level in the Mann-Whitney U-test.

The fixed-effects group analysis ($p<0.05$, FWE-corrected; Figure 6.8 and Appendix B, Table 2) reveals that in the patient group the right superior parietal lobule (SPL), middle frontal gyrus, and premotor cortex were activated significantly in all paradigms, verbal and non-verbal.

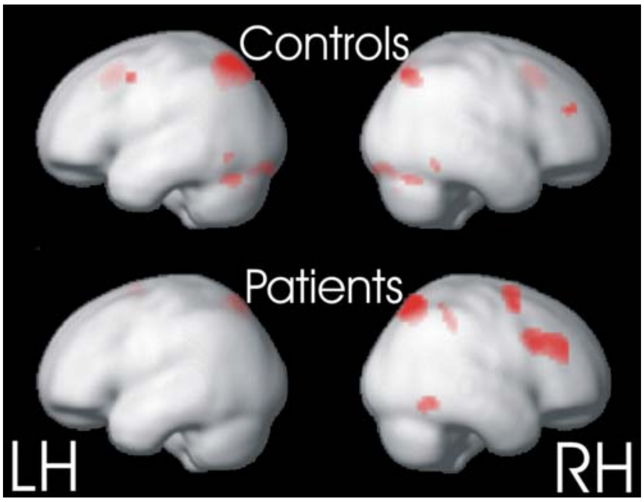

Figure 6.8: Results of fixed-effects group conjunction analyses ($p<0.05$, FWE-corrected), depicting areas commonly activated by verbal and non-verbal tasks.

Inspection of single-subject results ($p<0.01$, uncorrected; Figure 6.9) reveals that in all patients the right SPL was activated by verbal and nonverbal tasks, all patients but one showed common activation in middle frontal gyrus, and all patients but two showed common activation also in premotor cortex. In contrast, the control group activated bilateral (left > right) SPL and anterior cingulate cortex in all three paradigms (Fig 6.8 and Appendix B, Table 2).

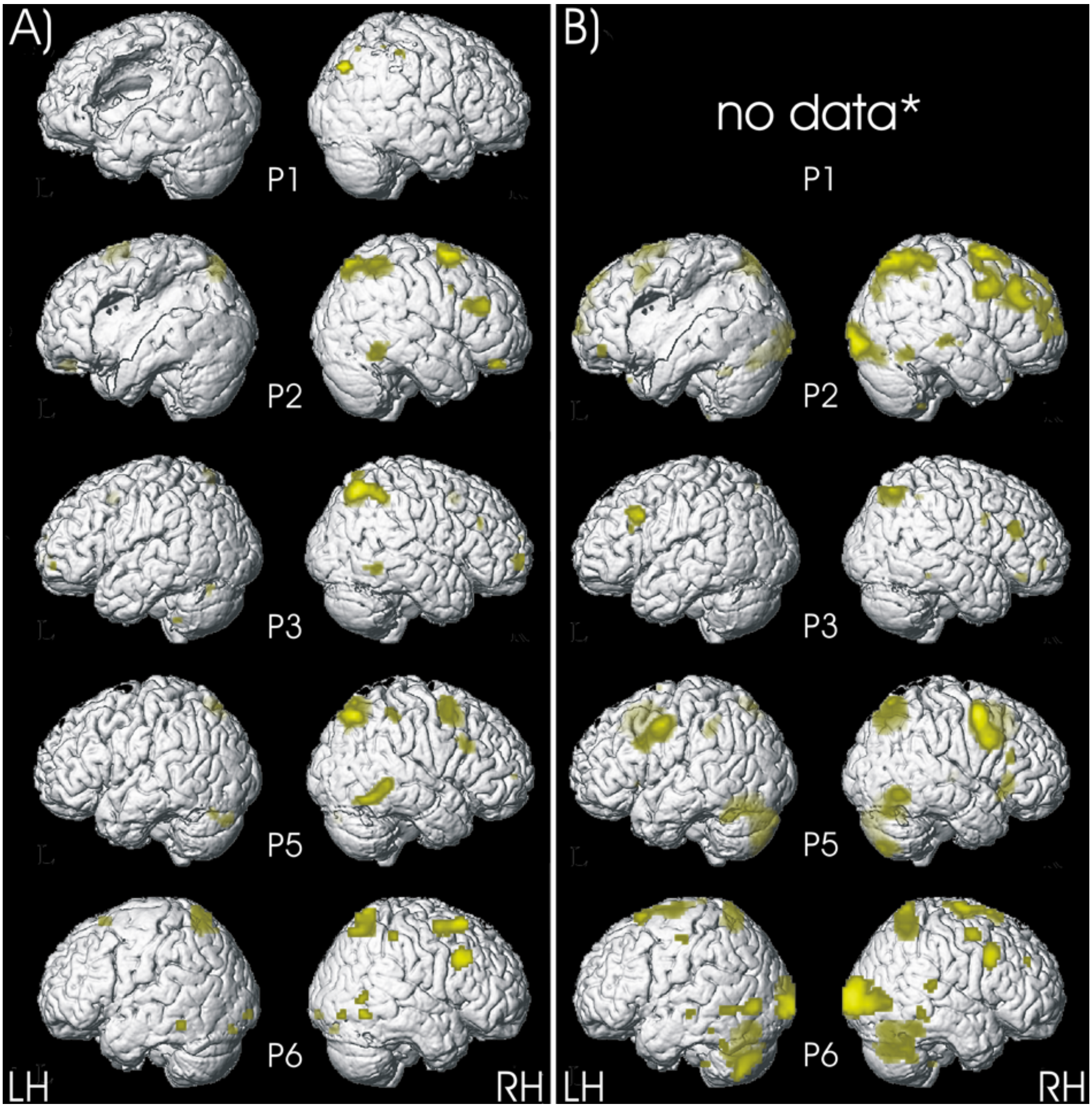

Figure 6.9: Results of conjunction analyses in single patients (p<0.001, uncorrected), overlaid on the individual 3D anatomical surfaces. A) Conjunction of word-chain and memory for pitch information; B) conjunction of word-chain and visual search / complex. *P1 did not perform the visual task due to low visual accuracy; P4 showed very low overall activations and therefore no suprathreshold conjunction results.

6.3.2.2.6 *Intercorrelations between structural and functional data*

Lesion ratios correlated significantly with LI in the Word-Chain task: The larger the lesion, the stronger was the right-hemispheric dominance (Spearman Rank r = .613, $p<0.05$). For the visual search paradigm, lesion size correlated significantly with LI in the parietal cortex: The larger the lesion, the stronger was the involvement of right hemisphere parietal cortex (Spearman Rank r = .900, $p<0.05$). No correlation was found between lesion ratio and LI in the memory for pitch information task, or between lesion size and overlap of functions.

6.4 Discussion

Study 3 indicates that in patients with lesion-induced right-hemisphere language organization, nonverbal functions are not reorganized, neither interhermispherically (Loring et al., 1999) nor intrahemispherically (Korkman & von Wendt, 1995; H3.2 is thus discarded). The results clearly show that nonverbal functions are organized in the right hemisphere, and mediated by the same areas as in normal controls. In fact, language functions share right-hemispheric cortical areas with nonverbal functions originally mediated by the right hemisphere. This confirms H3.1 and thus supports the crowding hypothesis (Teuber & Reudel, 1962).

Shared activation of cortical areas was found also in the control group, however, in patients, these areas were significantly larger. The main area of shared activation by verbal and nonverbal functions in both groups is the SPL. Conjunction analyses revealed that patients used the right SPL for all tasks, whereas controls used both SPL for all tasks. The SPL hosts multimodal attentional processes (Culham & Kanwisher, 2001) and common activation in different tasks is therefore not surprising. However, whereas controls showed only one more activation cluster in the anterior cingulate cortex (another region of higher attentional control; (Cabeza & Nyberg, 2000), the patients recruited also right premotor and middle frontal cortices for verbal, nonverbal memory, and visuospatial functions. In the control group, premotor and middle frontal cortex activation had been restricted to the LH in language production, whereas it remained in the RH in the visual search paradigm. In the patient group, however, this hemispheric dissociation was overridden by RH language organization.

The results in the language task replicate previous studies on lesion-induced RH language organization (Booth et al., 1999; Liegeois et al., 2004; Staudt, Lidzba et al., 2002), in showing that right hemispheric homologues of left hemispheric areas involved in language production were activated by the patient group in the language task. It was further shown that the reorganization of language production involved the entire fronto-parieto-cerebellar network, with the cerebellar part shifting from the right to the left hemisphere. As none of the patients of this study showed cerebellar damage, this shift of the entire network is remarkable, and further corroborates the notion of brain organization as a set of flexible networks (Stephan, 2004). The fact that not only the patients, but also the controls showed shared use of substrate for verbal and nonverbal tasks is in line with this notion.

To date, there have been no studies which directly tested the functional organization of nonverbal functions in patients with lesion-induced right-hemispheric language. The results of fixed-effects group analyses of small samples have, of course, to be interpreted with caution, as they can be biased by a single, strongly activating subject. When treating the single subjects of a group as fixed variables, the results can not be generalized beyond the study sample. For the sake of group homogeneity, however, strict inclusion criteria were introduced, thus leading to a small sample the data of which cannot be analyzed by means of random effects analyses. In this small but homogeneous group, a combination of fixed-effects analyses and qualitative inspection of single subject results seemed therefore to reveal more insight than a non-significant result of a random-effects analysis. Additionally, the results of the verbal task replicated precisely the results of a previous study using the same technique (Staudt, Lidzba et al., 2002).

When comparing neurological patients with normal controls, task difficulty is a sensitive issue: The broader network activated by patients irrespective of task specificity could be explained by the recruitment of cortical structures which mediate the higher cognitive effort to solve the tasks. However, the tasks were designed to be very easy; thus deliberately introducing a “ceiling effect”. The behavioural data makes clear that patients were as able to solve all three tasks on the same level as were the controls.

7 General Discussion

7.1 Results

The present work examined the consequences of early left-hemispheric brain injury at the levels of neuropsychology and functional neuroanatomy.

Study 1 showed that deficits in visuospatial functions in patients with early left hemispheric brain lesions were related to a reorganizational shift of language functions to the right hemisphere and not to lesion size. The visuospatial deficits are, in these patients, not an unspecific consequence of the brain lesion, as lesion size did not correlate with visuospatial skills. All patients with left hemisphere lesions showed a relative deficit in Performance IQ, regardless of their language organization pattern. This is, however, explained by their motor impairment as performance IQ was related to hand motor function, which in turn is related to lesion size. The lesion effects on performance IQ here are therefore neuropsychologically unspecific and depend on the patients' motor impairment. The degree of right-hemispheric involvement in language production, however, correlated significantly with nonmanipulative visuospatial skills, which were not correlated to hand motor function.

At the level of functional neuroanatomy, the patients with lesion-induced right-hemispheric language organization in Study 3 did not show any signs for reorganization of nonverbal functions from the right to the left hemisphere, or within the right hemisphere. In fact, verbal and nonverbal functions shared cortical tissue to a larger extent than was found in the control group. The neuropsychological deficits these patients showed in Study 1 might therefore be associated with this enhancement of cortical network sharing by very different tasks.

7.2 Methodological Issues

The present work was the first to examine neuropsychological deficits in patients a) without epilepsy, and b) with right-hemispheric language production proven by a reliable and valid technique, namely fMRI. In the introductory chapter the relative shortcomings of previous works on neuropsychological consequences of right-hemispheric language organization in patients with early left hemispheric brain lesions have already been discussed: Dichotic listening does not only tap temporal lobe language functions, but also different complex processing strategies employing large interhemispheric cortical networks (Jäncke & Shah, 2002). Attentional factors determine which cortical areas are involved in solving a dichotic listening task and which hemisphere has more influence (Jäncke & Shah, 2002). On the other hand, dichotic listening obviously can detect only lateralization of language *perception*, which has proven to be far less left-hemisphere lateralized than language production (Hickok & Poeppel, 2000). Furthermore, a study on adult patients with early left hemispheric brain lesions showed dissociation between reorganized right-hemisphere language production and un-reorganized bilateral language perception (Staudt et al., 2001).

The Wada procedure on the other hand is a rather reliable technique to assess language lateralization. Due to the invasiveness of the procedure, however, only patients with the prospect of neurosurgery are subjected to the Wada-test. The Wada-studies on right-hemispheric language organization have therefore comprised only patients suffering from severe epilepsy, which in itself poses a danger to cognitive development (Henkin et al., 2005). Epileptic discharges may even alter cortical representations of cognitive processes, as has been shown by Jantzsky et al. (2003). Also the influence of lesion size on the neuropsychological outcome has not yet been examined thoroughly: In the study of Loring et al. (1999), who examined retrospectively a large sample of epileptic patients with and without language reorganization, lesion size was not assessed systematically, so that the influence of lesion size on neuropsychological data remained undisclosed.

The cortical organization of nonverbal functions in lesion-induced right hemispheric language organization has by now been described only in one case study (Booth et al., 1999). Furthermore, the mental rotation task used in this study was obviously too difficult for the child assessed, leading to low performance and little overall activation. The use of relatively easy to solve nonverbal paradigms in the present work therefore provided reliable new data on the functional neuroanatomy of brains with reorganized language functions.

The present work, however, also suffers from some shortcomings and pitfalls. The demand to include only patients with well-defined unilateral focal lesions and without a history of epilepsy reduced the sample size considerably. With a small sample, statistical power and generalizability of the results are limited to some extent. On the behavioral level, the use of nonparametrical statistical procedures can counteract these disadvantages to a certain degree.
In the functional imaging study the combination of different approaches had to affirm the validity of the results: To allow generalization of the results of a group analysis, strictly speaking only a random effects analysis, with the results corrected for multiple comparisons, can gain reasonable results. In a small sample, however, especially in the case of patients who show certain aberrations from the "normal" brain, a random effects analysis will usually not lead to significant results, due to its sensitivity to interindividual differences. Using a fixed-effects analysis instead to identify areas commonly activated in one group hosts the danger of overestimating the activation-pattern of a single subject with strong activation. In the present work therefore single-subject data was inspected in addition and the group results were thereby validated. The results on the topography of right-hemispheric language organization replicated a previous work which had used the same approach (Staudt, Lidzba et al., 2002) and can therefore be considered valid.

A drawback of the fMRI technique which is often put forward especially by "traditional" neuropsychologists, is the indirectness of the data. In fact, with fMRI we cannot directly assess neuronal activity. The regional cerebral blood flow (rCBF) is a good index for regional neuronal activity (Raichle, 1987), and can be assessed by PET, employing radioactively marked substances. Brain activation is accompanied by increases of rCBF, which exceed local changes in oxygen uptake, so that, as a consequence, the regional concentration of *deoxyhemoglobin* diminishes (Fox & Raichle, 1986). As fMRI imaging can reveal intravascular magnetic susceptibility, which is dependent on the level of deoxyhemoglobin (Ogawa et al., 1992), it should correlate with rCBF. Cross-validation of fMRI with PET resulted in a reasonable congruence of the results of the two techniques (Paulesu et al., 1995), and it could be shown that the BOLD contrast reflects changes in the magnetic susceptibility mainly of the venules and veins of the brain (Seiyama et al., 2004). “Brain activity”, however, is still a rather vague description of the complex neuronal processes happening in the brain. In recent years, some research has taken place to find out more about the processes underlying rCBF increases or the BOLD response. Activity-dependent CBF as well as BOLD contrast increases are dependent on synaptic activity (as reflected in low frequency potentials), which is closely coupled to glucose uptake (Logothetis et al., 2001; Mathiesen et al., 1998). The hypothesis that BOLD reflects spiking activity, had to be refuted (Logothetis et al., 2001). Both BOLD contrast and rCBF increase with activity of excitatory, as well as *inhibitory* synapses (Mathiesen et al., 1998), and under certain haemodynamic conditions, fMRI does not detect brain activity at all (Seiyama et al., 2004). As with most experimental techniques, the study design is one of the most determining factors of what we detect with fMRI. Recently, the resting condition used in many fMRI studies has attracted the attention of methodological research. “Silent rest” as it is still widely used, provokes brain activity in large networks of heteromodal associative parietal and frontal cortical areas (Mazoyer et al., 2001), and especially temporal lobe has been activated during rest as much as during viewing novel and familiar pictures (Stark & Squire, 2001). These findings clarify that fMRI is well able to detect synaptic activity, but that the interpretation of fMRI findings depends on careful construction of the experimental design and has to be based on a sound theoretical background. In the present study, the development of elaborate tasks complementary to the activation condition was therefore an important step.

7.3 Implications

The results of the present work support a new trend in neuroscience: less modular thinking of strict structure-function relations and more considerations of functional networks in the brain. Findings that the cortex is organized in cytoarchitectonically distinguishable modules (Mountcastle, 1997), and clinical neuropychological studies describing which structures are essential in subserving a given cognitive function, had lead to the notion of functional specialization. In recent years, more and more studies, however, explore functional integration and neural networks, using neuroimaging techniques like functional MRI (Boksman et al., 2005; Penny et al., 2004; Welchew et al., 2005), diffusion tensor imaging (Snook et al., 2005; Tuch et al., 2003), or a combination of both (Baird et al., 2005). In the area of behavioral rehabilitation after brain lesions, the localizationist paradigm had difficulties to explain recovery from brain lesions. Here, the theory of *degenerate neuronal systems* offers a parsimonious explanation for cortical reorganization of cognitive functions: The lesion induces immediate plastic changes, which rely on the unmasking of a pre-existing, functionally latent system. This system can then replace the (partly or wholly) destroyed system and sustain the cognitive function instead. This might employ also the engagement of a different strategy, but with the same overall behavioral outcome. Lesions may, however, also induce long-term plastic changes which lead to the emergence of a new alternative system (Noppeney et al., 2004).

Similarly, the present work provides evidence for the employment of networks for the solution of different tasks. Patients with left-hemispheric cortico-subcortical or periventricular lesions showed reorganization of the entire language network to the other hemisphere: Processes sustained usually by left hemispheric prefrontal and inferior parietal structures were shifted to the right hemisphere, and cerebellar language processes were shifted from the right to the left cerebellar hemisphere. This cerebellar shift is particularly remarkable, as none of the patients suffered from a cerebellar lesion. If the cerebellar activation in these patients reflected a specialized and isolated process, why should it not stay in the cerebellar hemisphere which has been shown to be predisposed for articulation processing? Obviously, brain functions are organized in networks during brain development. A single brain structure may well be employed by a variety of functional processes, and the combination of structures leads to specific functions. Language seems to be organized in a bilateral network in the beginning, which is reflected in the fact that children with early brain lesions of whichever side suffer from delays in language development (Thal et al., 1991; Vicari et al., 2000). There might be a predisposition towards a left-hemispheric lateralization in healthy people, with language-relevant structures (e.g. planum temporale) being larger in the left than in the right hemisphere even before birth (Chi et al., 1977). During language development, the initially bilateral network accordingly develops an increasing left-hemispheric dominance (Holland et al., 2001). In children with left-hemispheric brain lesions this bias towards left hemispheric language processing can be overridden and the language network may establish a preference for the right cortical hemisphere (Lenneberg, 1967; Liegeois et al., 2004; Staudt et al., 2001; Staudt, Lidzba et al., 2002).

In the normal brain, distinct cognitive functions may activate sets of cognitive regions which are in part overlapping. The regions of the intersection might then either have two distinct functions, which can not be differentiated by the resolution of an fMRI sequence. They may also represent common processes such as increased attentional demands or general executive functions (Noppeney et al., 2004). Study 3 showed that in the control group, superior parietal lobule and anterior cingulate cortex were used for both verbal and nonverbal tasks. Superior parietal lobule and anterior cingulate cortex are known for their involvement in higher cognitive functions such as attention (Posner & Petersen, 1990) and cognitive control (Buchsbaum et al., 2005). Thus, in the normal controls, the overlapping areas represent unspecific higher cognitive functions, which are employed both by verbal and nonverbal tasks. The right-hemispheric preference for language functions in patients with early left-hemispheric brain lesions leads to an enhancement of the shared use of brain structures by different functions. In contrast to the controls, the patients used also right hemispheric premotor and medial frontal cortex for verbal and nonverbal tasks. In the controls, these areas showed a material-specific dissociation with verbal activation lateralized to the left and nonverbal activation lateralized to the right hemisphere.

Taken together, the findings of Study 1 and Study 3 suggest that it is this enhancement of shared use of cortical areas which impairs visuospatial functions in patients with lesion-induced right-hemispheric language organization. However, the notion of cortical areas being "crowded" or overtaxed seems difficult to reconcile with the idea of flexible networks mentioned before. The visuospatial deficits could as well reflect an abnormal development of the visuospatial pathways, which is, within the dynamic process of brain development, caused by the reorganization of language, and leads to the use of inefficient strategies to solve particular, visuospatial tasks. Joan Stiles reported a study on brain lesioned children, who showed, in the beginning, mild impairments in global visuospatial processing and in the comprehension of facial expression of emotional affect. The deficits were gradually alleviated during development, but the patients still used abnormal processes and strategies in the solution of visuospatial tasks (Stiles, 1988; Stiles et al., 2005).

To disentangle the questions of which neuronal and cognitive processes underlie functional (re-)organization in the developing CNS, further developmental studies employing neuropsychological, neuroimaging, and neuromodelling techniques will be needed

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8 References

8.1 Manuscripts of the Author resulting from the present work

Chapter 2: Theoretical Background

Lidzba,-K, Krägeloh-Mann,-I (2005) Development and lateralization of language in the presence of early brain lesions. Developmental Medicine and Child Neurology, Vol. 47, p724

Chapter 4: Study 1

Lidzba,-K, Staudt,-M, Krägeloh-Mann,-I (2001) Right-hemisphere language organization in patients with early left-sided brain-injury: Neuropsychological Profiles. Developmental Medicine and Child Neurology, Vol. 43, Suppl. 89, p22

Staudt,-M, **Lidzba,-K**, Grodd,-W, Wildgruber,-D, Erb,-M, Krägeloh-Mann,-I (2002) Right-hemispheric organization of language following early left-sided brain-lesions: functional MRI topography. NeuroImage, 16(4), p954-967

Lidzba,-K, Staudt,-M, Wilke,-M, Krägeloh-Mann,-I Visuospatial deficits in patients with early left hemispheric lesions and functional reorganization of language: Consequence of lesion or reorganization? Neuropsychologia in press

Chapter 5, Study 2

Lidzba,-K, Staudt,-M, Wilke,-M, Erb,-M, Grodd,-W, Krägeloh-Mann,-I (2004) Paradigms provoking right lateralized activation in fMRI. 10th Annual Meeting of the Organization of Human Brain Mapping 2004 in Budapest. Supplement on CD-ROM

Wilke,-M, **Lidzba,-K** (under review) On computing a lateralization index: a new toolbox to address and explore some unsettled issues. NeuroImage

Chapter 6, Study 3

Lidzba,-K, Staudt,-M, Wilke,-M, Grodd,-W, Krägeloh-Mann,-I (under review) Lesion-induced right-hemispheric language and organization of nonverbal functions. NeuroReport

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9 Appendix

A) Locations of Activation-Clusters in Study 2

Table 1: Regions showing significant activation (p<0.001, uncorrected) in the group analysis, with MNI-coordinates (MNI), T-value (T), and numbers of activated voxels (vox)

	Mental Rotation		**Visual Search/ Complex**		**Visual Search/ Animals**		**Visual Search/ Symbols**		**Memory for Pitch**	
Region	**MNI**	**T**	**MNI**	**T**	**MNI**	**T**	**MNI**	**T**	**MNI**	**T**
Occipital Lobe	-42,-57,-21	39.57	-21,-54,-15	27.93			-39,-90,0	11.01		
	60,-63,-18	24.99	57,-51,-6	17.71	42,-84,15	22.76	6,-90,33	12.81		
vox (left/right)	31/60		46/22		0/67		4/25		0/0	
Parietal Lobe										
Superior	-6,-75,60	11.80					-6,-78,60	10.02	24,-67,53	15.24
	9,-57,54	13.66	24,-60,57	14.21	24,-66,54	11.84			-6,-68,45	9.77
Inferior			-27,-48,48	8.41						
vox (left/right)	15/10		4/24		0/18		3/0		10/22	
Frontal Lobe										
Superior										
									30,63,3	11.91
Middle	-3,30,42	8.74								
	6,30,36	10.56	21,6,51	30.49					36,12,45	12.37
Inferior					-48,9,27	16.07				
							42,30,15	10.56		
vox (left/right)	6/3		0/53		6/0		0/6		0/28	

B) Locations of Activation Clusters in Study 3

Table 1:

Comparison of major activation sites (Fixed-effect Analysis, FWE-corrected p<0.05; cluster size >50 Voxels) in patients and controls, including T-values, stereotactic coordinates (MNI-space; negative x indicates left hemisphere) for all local maxima.

A) Word-chains

	Patients				**Controls**			
	left		right		left		right	
	x,y,z	T	x,y,z	T	x,y,z	T	x,y,z	T
Frontal								
premotor	-48,9,36	6.74	57,9,36	13.14	-42,9,27	8.72		
MFG			45,36,18	9.81	-45,36,21	6.45		
IFG			51,18,-9	6.86	-39,24,-3	7.61		
MeFG	-15,-33,21	5.07			0,21,48	7.67		
Parietal								
IPL			39,-39,42	9.94	-27,-66,51	9.09		
Temporal								
MTG			60,-48,-12	8.63				
Cerebellum								
	-30,-63,-27	11.28					24,-69,-24	11.88
	-27,-39,-42	5.04					33,-69,-54	6.86

MFG=middle frontal gyrus; IFG=inferior frontal gyrus; MeFG=mesial frontal gyrus; IPL=inferior parietal lobule; MTG=middle temporal gyrus

B) Memory for Pitch Information

	Patients				Controls			
	left		right		left		right	
	x,y,z	T	x,y,z	T	x,y,z	T	x,y,z	T
Frontal								
premotor			33,3,69	6.16			33,6,60	10.55
MFG			48,39,30	4.01				
Parietal								
SPL			15,-66,66	8.93			33,-66,57	14.69
Temporal								
ITG							60,-54,-15	6.92
Cerebellum					-36,-66,-30	5.47	39,-63,-54	7.33

MFG=middle frontal gyrus; SPL=superior parietal lobule; ITg=inferior temporal gyrus

C) Visual Search / Complex

	Patients				Controls			
	left		right		left		right	
	x,y,z	T	x,y,z	T	x,y,z	T	x,y,z	T
Frontal								
premotor	-54,3,45	7.39	60,15,36	7.69			39,3,63	5.78
MFG	-48,51,-12	6.45	45,48,30	6.32			42,6,27	6.43
MeFG	3,12,51	5.72						
Parietal								
SPL	-18,-72,57	10.67	15,-66,66	9.15	-15,-75,57	17.37	24,-72,54	19.30

MFG=middle frontal gyrus; MeFG=mesial frontal gyrus; SPL=superior parietal lobule

Table 2: Results of the Fixed-Effects Group analyses for the conjunction of all three paradigms, as tested for the Conjunction Null Hypothesis (p<0.05, FWE-corrected).

	Patients				Controls			
	left		right		left		right	
	x,y,z	T	x,y,z	T	x,y,z	T	x,y,z	T
Frontal								
premotor			27,0,66	4.20				
MFG			48,39,30	4.42	-51,6,45	3.62	42,45,24	3.96
Parietal								
SPL			21,-69,60	6.96	-33,-66,60	7.99	33,-72,48	4.51
IPL			39,-42,45	3.83				
Temporal								
ITG			63,-54,-12	4.64			54,-51,-15	3.46
Anterior Cingulate					0,15,48	4.50		
Cerebellum					-42,-63,-27	4.11	36,-66,-27	4.32