University of Trier

Faculty of Psychobiology

Hemisphere differences in language processing:

A neuroimaging study in men and in women, taking into account changes in progesterone level during the menstrual cycle

Doctoral Thesis

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by

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Abbreviations

ACC	anterior cingulate cortex
BOLD	blood oxygenation level dependent
Cu	cuneus
CVF	central visual half field
EEG	electroencephalography
EPI	echo planar imaging
EPSP	excitatory postsynaptic potential
fMRI	functional magnetic resonance imaging
FID	free induction signal
FOV	field of view
FSH	follicle stimulating hormone
FWHM	full width half maximum
GABA	γ-aminobytric acid
$GABA_A$	γ-aminobytric acid type A
GF	fusiform gyrus
GFi	inferior frontal gyrus
GFm	middle frontal gyrus
GFs	superior frontal gyrus
GL	lingual gyrus
GLM	general linear model
Glu	glutamate
GnRH	gonadotrophic releasing hormone
GOi	inferior occipital gyrus
GOm	middle occipital gyrus
GOs	superior occipital gyrus
GPrC	precentral gyrus
GTi	inferior temporal gyrus
GTm	middle temporal gyrus
GTs	superior temporal gyrus
HRF	haemodynamic response function
INS	insula
IPSP	inhibitory postsynaptic potential

LH	left hemisphere
LH*	luteinizing hormone
LI	lateralization index
LIA	luminescence immunoassay
LPi	inferior parietal lobule
LVF	left visual field
MCC	middle cingulate cortex
NMDA	N-methyl-D-aspartate
NMR	nuclear magnetic resonance
MDBF	Mehrdimensionale Befindlichkeitsfragebogen
MRI	magnetic resonance imaging
PCu	precuneus
PET	positron emission tomography
PHi	parahippocampus
RF	radio frequency
RH	right hemisphere
ROI	region of interest
RVF	right visual field
RVFA	right visual field advantage
Sca	calcarine sulcus
SMA	super motor area
SPECT	single photon emission computed tomography
TE	echo time
TR	repetition time
VWFA	visual word form area

Chapter 1

Introduction and objective of the thesis

1.1 Introduction

The human brain is characterised by two apparently symmetrical cerebral hemispheres. However, the functions attributed to each half of the brain are very distinct. A relative specialisation of the left hemisphere (LH) for language has been recognised since the late 19th century. Based on the data of aphasic patients, a "classical model" of language organisation in the LH was developed. This model proposes a frontal "expressive" area for planning and executing speech and writing movements (Boca's area, 1861), and a posterior "receptive" area for analysis and identification of linguistic sensory stimuli (Wernickes' area, 1874). In 1874, Jackson proposed an alternative concept of functional neuroanatomy of language which included an important role of the right hemisphere (RH). According to Jackson the RH plays a role in non-propositional or automatic speech, whereas in the LH the automatic use of words merges into a voluntary use of words.

In the mean time, a variety of methods have been employed to study hemispheric specialisation for language. Patients whose corpus callosum had been resected to prevent the spread of epileptic seizures from one hemisphere to the other allowed researchers to test each hemisphere in isolation. Studies on patients with brain damage restricted to one hemisphere gave insight into which language function the lesioned region was responsible for. In the past, intracarotoid amobarbital anaesthesia, also known as the Wada test, was a frequently applied invasive method to define the hemispheric language dominance prior to epileptic surgery (Wada and Rasmussen, 1960). Most laterality research has been performed on a behavioural level, using techniques such as dichotic listening or visual half-field presentation. The processing capability of each hemisphere is described in terms of reaction times and/or numbers of errors in response to stimuli presented in the contralateral visual field or ear.

In recent years there has been an explosion of research using non-invasive neuroimaging techniques to study language organisation both in patients and healthy subjects. Studies using these techniques have confirmed the role of the classical language-related regions within the LH; however, they have also suggested other important aspects of language organisation in normal adults. Firstly, language centres are not well-circumscribed homogenous areas, but rather consists of small, non-adjacent, focal spots specialised for specific components of language (Schwartz et al., 1996). Secondly, language processing activates a widespread cortical network, including not only the classic language areas (Binder et al., 1997; Gernsbacher and Kaschak, 2003).

Nowadays, it is known that the LH is functionally specialised for language processing in the majority of right-handed men (Poldrack et al., 1999). A much debated issue however is how language is organized in women as findings are rather ambiguous covering a range between predominant left and bilateral language organisation (Frost et al., 1999; Shaywitz et al, 1995). It is supposed that this ambivalent picture of language organisation in women might be associated with changes in gonadal steroid levels in blood during the menstrual cycle. Unfortunately, behavioural studies do not present a clear picture (Heister et al., 1989; Hausmann and Güntürkün, 2000) and the number of neuroimaging studies is limited (Veltman et al., 2000; Fernandez et al., 2003).

To the best of my knowledge there are no functional neuroimaging studies available investigating: (1) the processing of linguistic information initially received in the specialised, non-specialised or both hemispheres; (2) linking the associated brain activation pattern with progesterone levels during the menstrual cycle.

1.2 Objective and Outline of the Thesis

The major objective of the studies presented in this thesis was firstly to investigate, using event-related fMRI, different components of language processing after presentation of linguistic stimuli in the right visual field (RVF), left visual field (LVF) and central visual field (CVF). In a second step the effect of fluctuating progesterone levels during the menstrual cycle on language processing was examined.

After presenting the framework and the outline of this thesis in the present chapter (chapter 1), the second chapter (chapter 2) provides the theoretical background. The chapter on theoretical backgrounds contains two main parts. The first part "functional cerebral specialisation" starts with a broadly presentation of functional cerebral specialisation as a result of interhemispheric integration, and introduces the visual-half field technique as a behavioural method to study hemispheric specialisation. In a second step we focus on a specific cerebral lateralized function namely language processing. The neuroanatomical networks associated with different components of language processing as well as factors that might cause inter-individual variability in these networks are discussed. In addition some hypotheses on the origin of language organisation are introduced. The first part is closed by bridging the gap between functional cerebral lateralization and plasma progesterone levels. The second part explains the basic principles of functional magnetic resonance imaging

(fMRI). The various fMRI task designs are shortly described as well as different steps of the fMRI analysis conducted with SPM.

Chapter 3, chapter 4, chapter 5 present findings of my own fMRI studies. The visual processing of linguistic stimuli after initial reception in the left, right or both visual cortices is reported in chapter 3. Chapter 4 includes findings of the processing of language components: phonology and semantics after initial reception of the linguistic stimuli in the left, right or both visual cortices. The results of the last study investigating the effect of changing progesterone levels during the menstrual cycle on semantic and phonological processing are presented in chapter 5. Chapter 3, chapter 4 and chapter 5 are three independent manuscripts that will be submitted for publication in suitable journals. Each paper draft composes a separate abstract, introduction, methods, results and discussion to provide the occasional reader with the necessary information. To make reading of a single chapter more convenient, abbreviations are introduced anew in each manuscript.

In chapter 6, the major observations from the four previous chapters and their implications are summarized. In addition, a general discussion as well as suggestions for further research will be given.

The addendum includes the statistical analyses, to compare between studies for sex differences.

Chapter 2

Theoretical background

2.1 Functional cerebral specialisation

There is little dispute that the human cerebral hemispheres are anatomically asymmetric. Despite centuries of discussion, the precise nature of the functional asymmetry continues to be debated. Where the LH is characterised as being verbal, analytic, and intelligent, the RH is described as non-verbal, visuospatial, holistic, and creative (Harrington, 1987).

2.1.1 Interhemispheric integration

Even though the human brain shows a functional lateralization, in reality, most cognitive functions are processed by both hemispheres, by a process called interhemispheric integration. This interaction is possible due to the several commissural fibre tracts, which connect both hemispheres (Stephan et al., 2007).

Interhemispheric connections

The cerebral cortex contains the neural cell bodies, and the white matter beneath it contains the axons which connect the different cortex areas among each other as well as with regions of the central nervous system. These connections are known as tracts or fasciculi (Latin fasciculus = “little bundle”). The usual classification of cerebral fibre tracts divides them into three main categories (Brodal, 1981).

Projection fibres are fibre tracts linking an area of cerebral cortex to a lower structure. For afferent fibres, the principal projections run upwards from the projection nuclei of the thalamus. Efferent fibres, on the other hand, run downwards in one of two separate systems, the pyramidal tract and the extrapyramidal tract

Association fibres link one area of the cerebral cortex to another within the same hemisphere. Some are quite short, linking one gyrus to its immediate neighbours, but others are longer, linking regions to regions and lobes to lobes. The integrity of these pathways is vitally important to the healthy brain because they integrate its various sub-functions into a coherent whole.

Commissural fibres are commissural fibre tracts (or simply “commissures”). These are connections between (a) the two cerebral hemispheres, or (b) any pair of lateralized structures.

Corpus callosum (commissura magna cerebri)

Being the largest commissural fibre tract in the brain, the corpus callosum plays the dominant role in interhemispheric interaction (Levy, 1985; Hoptman et al., 1994). The corpus callosum appears late in phylogeny, as indicated by its presence only in placental mammals, which evolved more recently than other animals. Within the placental animals, the corpus callosum complexity would appear to augment with increasing complexity of the organism. The corpus callosum appears late in the ontogeny, at about the 4 months gestation (Rakic and Yakovlev, 1968). The myelination of the corpus callosum progresses slowly and, in humans, approaches adult levels only in puberty (Yakovlev and Lecours, 1967). This development of the corpus callosum may be mirrored by reductions in its size in aged humans (Cowel et al., 1992), consistent with the notion that later developing structures are more vulnerable to functional loss (Jackson, 1958).

Most callosal fibres connect homologous regions of the two hemispheres (homotopic fibres), although there also are connections between non-homologous areas (heterotopic fibres). The callosal heterotopic connections of a particular cortical area are made with regions which on the ipsilateral side have associated connections with that area, though usually not with all of such regions (Hedreen and Yin, 1981).

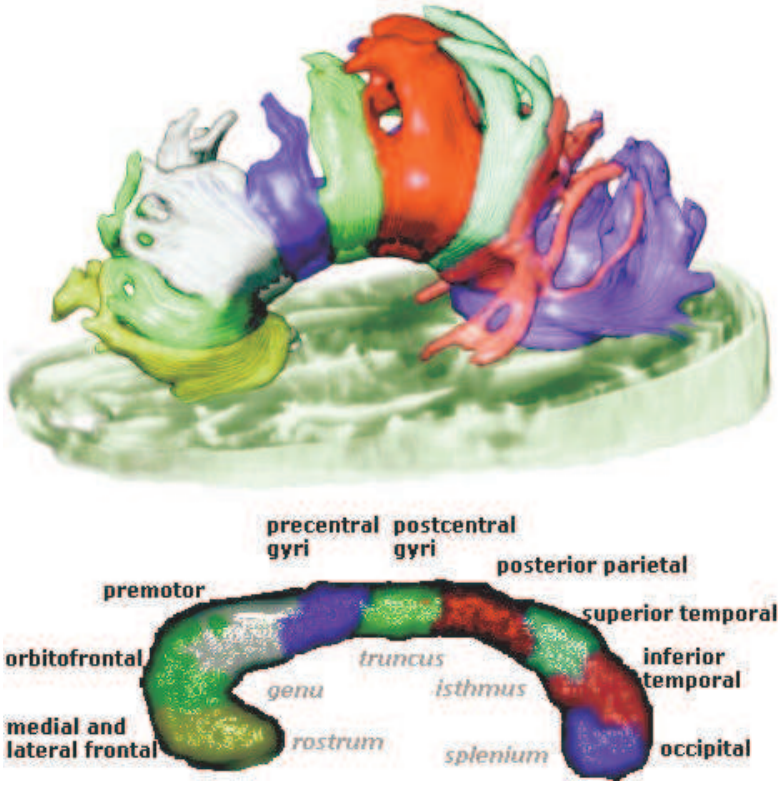


Fig 2.1: Topography of the corpus callosum (http://spie.org/).

The corpus callosum typically is divided into five parts; in rostral to caudal order: rostrum, genu, truncus, isthmus, and splenium (see Fig 2.1). Studies of callosal connections (Pandya and Seltzer, 1986) have revealed a well-ordered topography. Prefrontal callosal fibres cross in the rostrum (medial and lateral frontal regions) and genu (orbitofrontal regions). In the truncus of the corpus callosum the premotor and supplementary motor fibres of the frontal cortex cross just posterior to those of the prefrontal area. Connections between the temporal lobes cross still further posterior in the isthmus and splenium. The regions of the occipital cortex are connected by fibres which cross solely in the splenium.

The axon density in the corpus callosum, which is related to the level of myelination and the axonal diameter, is region dependent (LaMantia and Rakic, 1990; Aboitiz et al., 1992). The small, most non-myelinated axons are most frequent in genu and splenium, but hardly found in the posterior part of truncus; whereas the large, myelinated axons have the highest concentration in the posterior part of truncus and lowest concentration in genu and splenium.

The level of myelination is also region dependent in the corpus callosum: in genu about 20% of the axons are unmyelinated, in truncus and splenium about 5%.

The large majority of callosally projecting neurons probably exert a direct excitatory action on neurons of the contralateral hemisphere, using glutamate (Glu) and/or other excitatory amino acids as their neurotransmitters. Postsynaptically, they act on both N-methyl-D-aspartate (NMDA) and non-NMDA receptors. Monosynaptic excitatory postsynaptic potentials (EPSP) are the most frequent response elicited by callosal activation. These EPSP are frequently accompanied by long inhibitory postsynaptic potentials (IPSP), which are supposed to be mediated by local inhibitory interneurons as part of a feedforward inhibition circuit (Toyama et al., 1974). A small number of callosally projecting neurons have different physiological properties. It has been proposed that this population of neurons could have inhibitory effects by using γ-aminobutyric acid (GABA) as neurotransmitter (Conti and Manzoni, 1994).

Other commissural fibre tracts

The corpus callosum is the largest link between the cerebral hemispheres, but is assisted by: (a) the anterior commissure (or commissura rostralis), a diencephalic commissural tract situated just anterior to the thalami, over the optic chiasm; (b) the posterior commissure, a midbrain commissure situated just anterior to the tectum; (c) the commissura hippocampi (or commissura fornicis), which connects the hipocampi of both hemispheres; (d) the commissura habenularum, connecting of the habenular nuclei of both epithalami; and (e) the massa intermedia, a variable connection between the two thalamic masses across the third ventricle which is absent in about 20% of human brains (Brodal, 1981).

Mechanism of interhemispheric integration

Currently, three major theories on interhemispheric integration mechanism exist. The first theory is based on the notion of “information transfer” (Poffenberger, 1912). Asymmetrical information transfer supposes an asymmetrically enhanced information transfer from the non-specialised to the specialised hemisphere to ensure most efficient processing (Barnett and Kirk, 2005). Support for this hypothesis was provided by animal studies (Bures and Buresova, 1960), by behavioural studies both with split brain patients and with healthy volunteers (Gazzaniga, 2000; Marzi et al, 1991), but also by fMRI studies (Stephan et al., 2007). In this

context, information is asymmetrical transferred in both directions with the asymmetry degree related to the degree of specialisation of one hemisphere

Secondly, interhemispheric inhibition mediated by mutual inhibition between two homotopic brain regions as a general principle of brain function was first proposed by Kinsbourne (1970). From this view, specialisation of one hemisphere is equivalent to its being superior in suppressing the opposite hemisphere. Although interhemispheric inhibition has been found mainly for motor (Meyer et al., 1995) and visuospatial tasks (Fink et al., 2000), Kinsbourne suggested that it might underlie all lateralized processes, including language. Even though inhibition models predict that interhemispheric connection strengths should be negative in both directions. This does not necessarily mean, however, that two areas that affect each other by interhemispheric inhibition show decreased activity. Regional activations can coexist with interhemispheric inhibition if other (e.g. intrahemispheric) inputs to the area of interest are positive and dominant in magnitude.

A third possible interhemispheric integration mechanism concerns hemispheric recruitment. Banich and colleagues showed in behavioural experiments that hemispheric recruitment occurs as a function of computational complexity and attentional demands of the task performed (Banich, 1998; Belger and Banich, 1998; Weissman and Banich, 2000). To test this hypothesis a task was developed by Banich and Belger (1990). In this task participants are required to match letters either within a single hemisphere (within fields) or between hemispheres (across fields). Numerous studies (Banich, 1998; Belger and Banich, 1998; Weissman and Banich, 2000) with neurological intact individuals found for that for complex tasks such as name matching (e.g. “A” and “a”) performance is faster and more accurate on across-field trials compared to within trials, reflecting the advantage of interhemispheric division of labor.

The visual half-field technique

An overall problem when studying the functional specialisation of one hemisphere is how to isolate it. On one hand both hemisphere are connected by several commissures and are continuously interacting, on the other hand our sensory system is bilaterally represented in the brain.

Studies on patients with either partial (lobectomy and lesions) or completely (hemispherectomy) disabled hemisphere, gave insight into which function the lesioned region

was responsible for. Split brain patients whose corpus callosum had been resected to prevent the spread of epileptic seizures from one hemisphere to the other allowed researchers to test each hemisphere in isolation. In the past intracarotoid amobarbital anaesthesia, also known as the Wada test, was often applied to explore preoperative language lateralisation in case of epileptic surgery. The procedure, first described by Wada (Wada and Rasmussen, 1960), consists of unilateral injection of sodium amobarbital into the internal carotid, which temporarily anaesthetizes the hemisphere ipsilateral to the injection site. While one hemisphere is anaesthetized, cognitive functions of the hemisphere contralateral to the injection site can be tested. After the effect of the anaesthesia has dissipated, the process is repeated with the other hemisphere.

The problem with patient studies is that one must be attentive to the fact that following brain damage a reorganisation of the brain might take place. The functional cerebral specialisation for language processing, can also be studied in healthy subjects using behavioural methods such as dichotic listening or a visual half-field presentation. Both techniques are based on the observation that the hemisphere controlling language is more efficient than its counterpart in recognizing and reporting linguistic stimuli. During a dichotic listening task, stimuli, most commonly consonant-vowel syllables or monosyllabic words, are presented simultaneously to the participant via ear phones and the subject has to report what he/she has heard. Although there is a bilateral projection of auditory information to the cortex, the contralateral projections from each ear override ipsilateral projections, so that the left ear has better communication with the RH, whereas the right ear has preferential access to the LH (Kimura, 1967). To determine language lateralization, a laterality index, using the formula [(right ear - left ear)/ (right ear + left ear)] x 100, can be computed on the number of correct stimuli reported for each ear, where a positive index indicates right ear advantage, and a negative index indicates left ear advantage. With bilateral language representation no ear advantage or only a weak ear advantage is observed. Comparisons between dichotic listening and Wada have yielded a concordance ranging from 80 to 95 percent (Fernandes and Smith, 2000; Strauss et al., 1987). Similar results have been obtained from studies investigating the relationship between ear advantage and fMRI findings in healthy subjects (Hund-Georgiadis et al., 2002) and epileptic patients (Fernandes et al., 2006).

The technique

Visual half-field presentation involves the presentation of stimuli in the LVF or RVF for a very short time (about 200 ms) (Fig 2.2). This duration is chosen to minimize the possibility of saccadic eye movements. During the presentation of lateralized stimuli, the gaze of the participants is fixated on a centrally presented fixation cross. This technique takes advantage of the crossing of the nasal optic fibbers in the optic chiasma. Thus, stimuli presented in the LVF or RVF are initially processed in the contralateral hemisphere (Bourne, 2006). The processing capability of each hemisphere is described in terms of reaction times and/or numbers of errors in response to stimuli presented in the contralateral visual field or ear. Comparable with the dichotic listening task a laterality index can be assessed. The prediction is that individuals with LH language dominance will show a RVF advantage (RVFA) for a visual half-field task. People with RH language dominance will show the reverse advantage. A study by Hunter and Brysbaert (2008) compared data of a word and picture naming task using visual half-field presentation with a word generation task in the nuclear magnetic resonance (NMR) scanner. The results revealed a direct link between the VHF advantages and individual language lateralization.

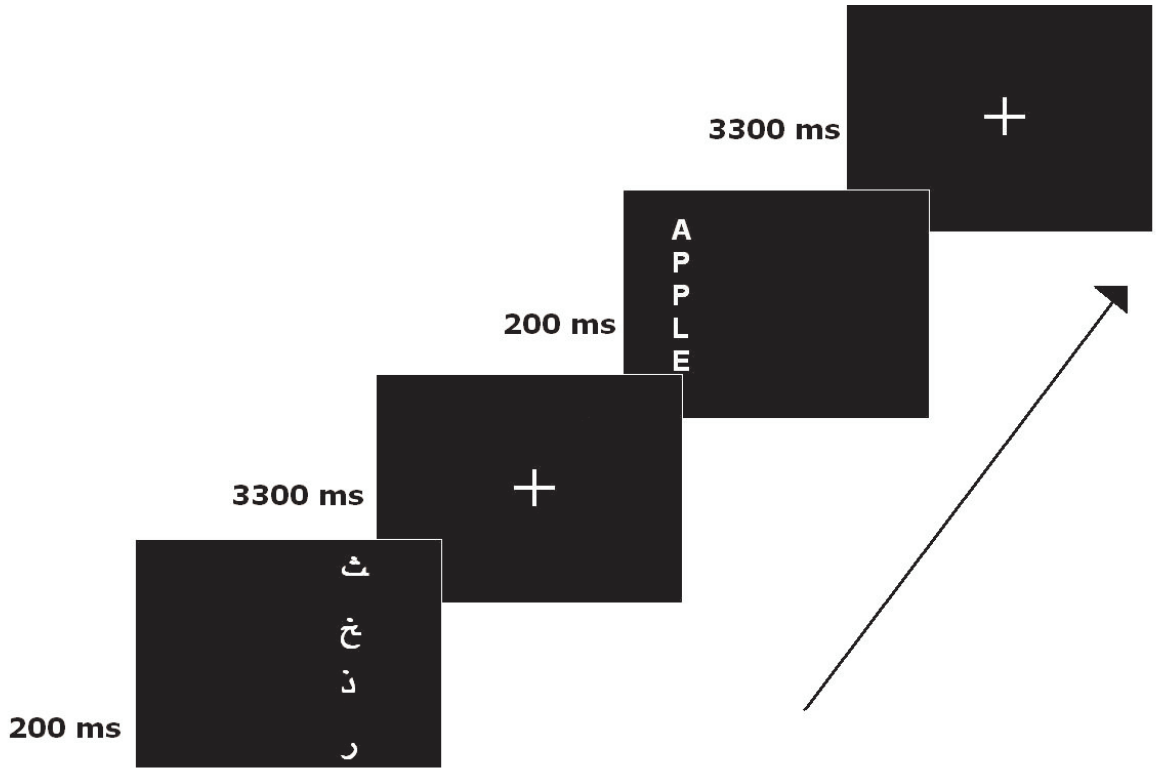


Fig 2.2: Example of the visual half-field presentation used for this thesis.

Anatomical background to visual half-field technique

The visual system is part of the nervous system. It interprets the information from visible light to build a representation of the world surrounding the body.

Light entering the eye is refracted as it passes through the cornea. The light then passes the anterior chamber and enters, through the pupil, the lens where it is focussed. The cornea and lens act together as a compound lens to project, after the light passed vitreous body, an inverted image onto the retina (Fig 2.3a and Fig 2.3b).

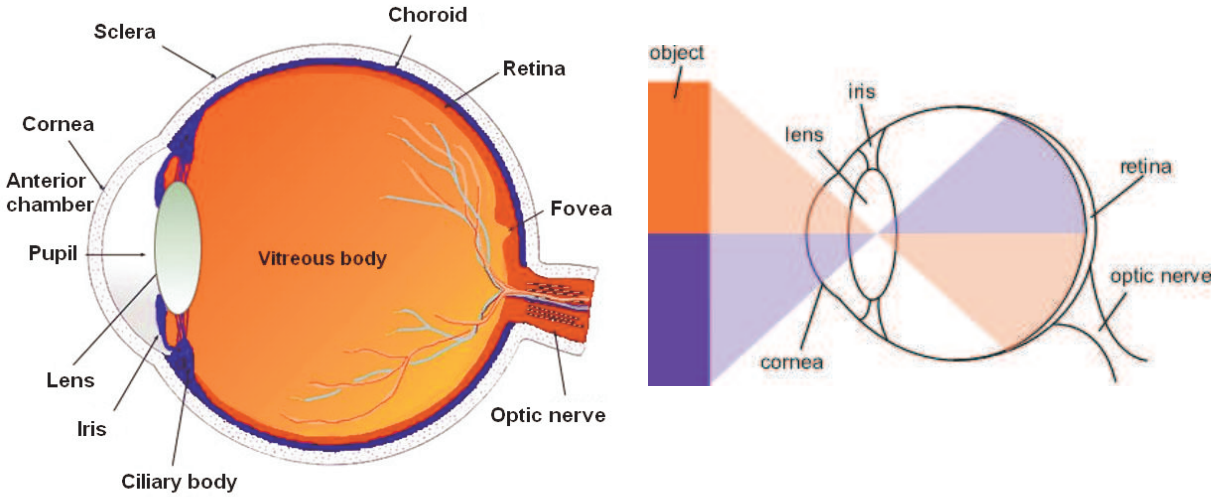


Fig 2.3a (left): Sagital section of the human adult eye (Modified from http://webvision.med.utah.edu/). **Fig 2.3b** (right): The image projected onto the retina is inverted due to the optics of the eye (http://en.wikipedia.org).

The retina consists of a large number of photoreceptor cells which contain a particular molecule: opsin. In humans there are two types of opsins, rod opsins and cone opsins. Either opsin absorbs a photon and transmits a signal to the cell through a signal transduction pathway, resulting in hyperpolarisation of the photoreceptor. Rods and cones differ in function. Rods are found primarily in the periphery of the retina and are particular sensitive to light. Cones are primarily found in centre or fovea of the retina. The main role of the cones is to distinguish details as well as colours. In fact there are three types of cones that differ in the spectrum of wavelengths they absorb; a first type absorbs short wavelengths (or blue light), a second type middle wavelengths (or green light), and a last one long wavelengths (or red

light). Together with opsin, another light-sensitive molecule is found in the photoreceptor cells, retinal. In the presence of light the retinal molecule changes configuration that causes a catalytic reaction and as a result a nerve impulse is generated (Goldstein_1997).

Besides photoreceptor cells the retina consists of four other main types of neuronal cells which synapse both among each other and onto photoreceptor cells: the horizontal cells, the amacrine cells, the bipolar cells and the ganglion cells. The photoreceptor cells synapse directly onto bipolar cells, which in turn synapse onto ganglion cells of the outermost layer. The horizontal cells and amacrine cells transmit information laterally; the horizontal cells connect the photoreceptor cells with each other, whereas the amacrine cells link with the ganglion cells. The processing in the retina includes the formation of receptive fields of bipolar and ganglion cells, as well as convergence and divergence from photoreceptor to bipolar cell. Finally different populations of ganglion cells send information to the brain: M (magnocellular)-ganglion cells, with large receptive fields that are sensitive to depth, indifferent to colour and rapidly adapt to a stimulus; P (parvocellular)-ganglion cells, with smaller receptive fields that are sensitive to colour and shape; K-ganglion cells, with very large receptive fields that are sensitive to colour and indifferent to shape or depth. The axons of the ganglion cells convergence at the blind spot, and form the optic nerve (Fig 2.3a and Fig 2.3b).

The optic nerves from both eyes meet at the optic chiasm at the base of the hypothalamus of the brain (Fig 2.4). At this point the fibbers of the nasal hemiretinae cross, whereas the fibbers of the temporal hemiretinae, covering a small region in the centre of the field of view project ipsilaterally. Information from the RVF travels in the left optic tract. Information of the LVF travels in the right optic tract. Each optic tract terminates in the lateral geniculate nucleus in the thalamus. The lateral geniculate nucleus consists of six layers. Layers 1, 4, and 6 correspond to information from one eye; layers 2, 3, and 5 correspond to information from the other eye. Layer one contains M-cells, which corresponds to the magnocellular cells, whereas layer 4 and 6 connected to the parvocellular cells of the opposite eye. By contrast layers 2, 3 and 5 connect to the magno- and parvocellular cells of the ipsilateral side. In between the six layers are smaller cells that receive information from the K-cells in the retina. A small part of the fibbers of the optic tract travels to superior colliculus, controlling eye movements.

The optic radiations carry information from the lateral geniculate nucleus to the primary visual cortex. A distinctive feature of the optic radiations is that they split into two parts on each side. One part (also called "Meyer's loop" or "Archambault's loop") must pass into the

temporal lobe by looping around the inferior horn of the lateral ventricle, whereas the other part travels straight back to the to the visual cortex (Goldstein, 1997).

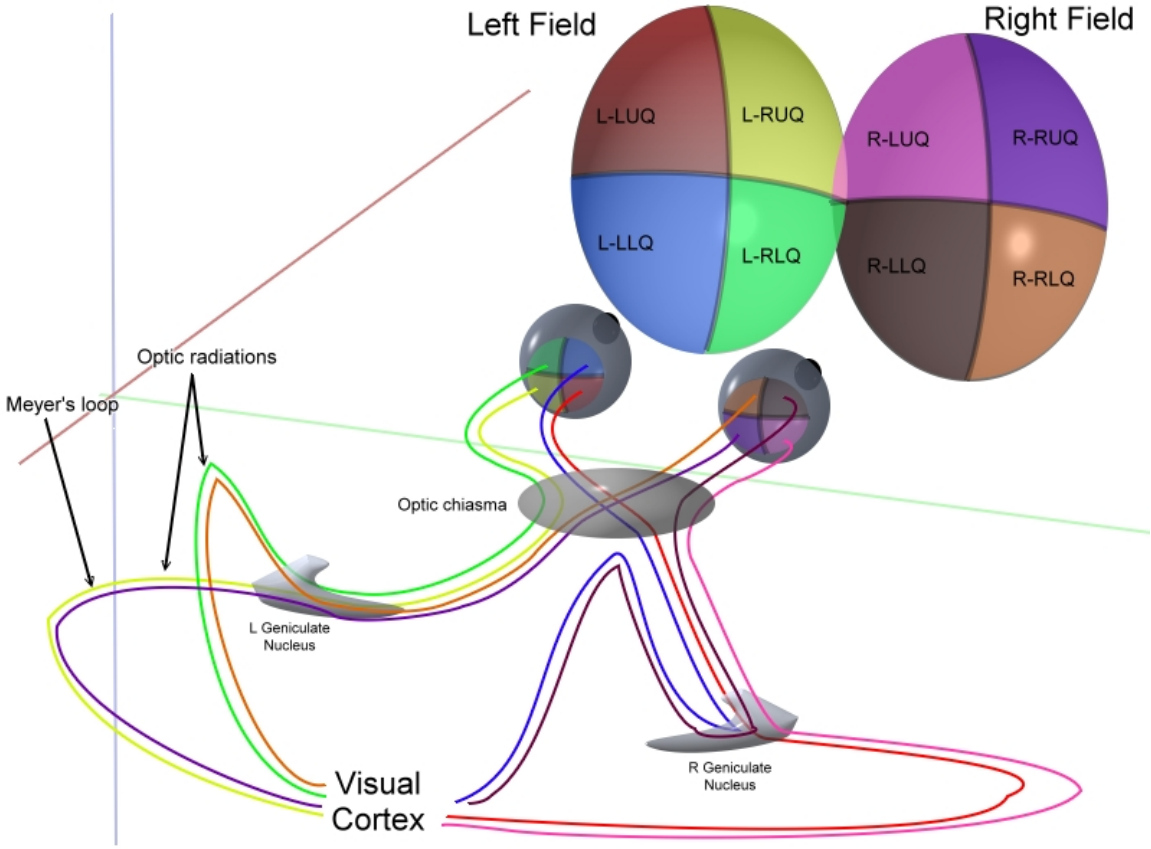


Fig 2.4: This image schematically represents the optic pathways from each of the 4 quadrants of view for both eyes simultaneously (LUQ = left visual half-field upper quadrant; LLQ = left visual half-field lower quadrant; RUQ = right visual half-field upper quadrant; RLQ = right visual half-field lower quadrant; L = left eye; R = right eye) (http://en.wikipedia.org).

2.1.2 Functional imaging of language processing in the brain

Human communication uses a variety of signals, including speech sounds and written symbols, but also gestures and facial expressions. “Language” refers to any system of communication involving arbitrary representation of information which enables us to describe our external environment and abstract thoughts (Price, 2000).

Components of Language processing

The effective use of language requires the interaction of sensory input and motor output systems, as well as more central components. The principal central components required for language are orthography (analysis of visual word forms), phonology (the analysis of word pronunciation) and semantics (the analysis of word meaning). Sensory input can be via auditory processing (for spoken words), visual processing (for written words), or tactile processing (Braille). Motor output enables the expression of concepts via articulation, writing, singing or drawing; it can either be self generated (in response to internally generated thought) or stimulus driven (e.g. in response to written or heard words) (Price, 2000).

Orthographic processing

Perceptual processing of written symbols has been studied using different kinds of stimuli such as unfamiliar, letter like characters "false fonts", single letters, non-words (letter strings with no phonological representation), pseudowords (letter strings with a phonological representation) and words. Although the calcarine cortex and adjacent medial occipital extrastriate regions are activated by printed word stimuli in contrast to non-visual stimuli, their activation has been interpreted as representing early visual information processing and has not been associated with language processing. Supported for this view has been found in the observation that activation of these visual areas does not differ between orthographically familiar and non-familiar character strings (Indefrey et al., 1997; Petersen et al., 1988; Price et al., 1994).

Using fMRI, a specific letter processing area in the left posterolateral fusiform or inferior occipital gyrus was observed by Puce et al. (1996). The letter stimuli, which consisted of unpronounceable consonant strings, were contrasted with faces and visual textures during a passive viewing paradigm. Studies using contrasts between letters and false fonts have yielded no clear consensus, with some showing activation differences in this region (Pugh et al., 1996) and others showing no differences (Indefrey et al., 1997).

In addition, Fujimaki et al. (1999) have shown that complex visual forms such as letters and pseudocharacters activate the occipital-temporal sulcus and the posterior inferiortemporal region bilaterally. These regions thus play a role in the early processing of visual linguistic stimuli.

Beyond orthographic processing, it has been proposed that visual linguistic input is translated into phonological form (e.g., Xu et al. 2001). Regions in and around Wernicke's area, including the supramarginal gyrus and the angular gyrus, have been implicated in this process, both with regard to being "word-form centres" (especially regions in and near the angular gyrus; Small et al. 1996) and/or being responsible for the actual translation process. Based on data of neuroimaging experiments (Jobard et al., 2003) and neuropsychological observations of patients with pure alexia (Cohen et al., 2003), an area located in the midportion of the left fusiform gyrus was proposed to be labelled the Visual Word Form Area (VWFA) (Cohen et al., 2000, 2002, 2003 and 2004; Dehaene et al., 2001, 2002 and 2004). The VWFA responds to words more than to other control shapes such as checkerboards or strings of consonants (Cohen 2002), and shows invariance for case change (Dehaene et al., 2001 and 2004). In children it shows a growing responsivity as a function of increasing expertise in reading (Maurer et al., 2006; Shaywitz et al., 2002). Vinckier et al. (2007), using fMRI, was able to detect a high degree of spatial and functional hierarchical organisation, with a posterior-to-anterior gradient as a function of stimulus complexity in the VWFA.

There remains some debate on the former issue. A series of conflicting studies of visual word processing (Petersen et al. 1990, Price et al. 1994, Pugh et al. 1996; Price and Devlin, 2003 and 2004), suggest that whereas the brain regions involved in processing particular aspects of the linguistic stimulus have been identified, there does not yet appear to be any evidence of a specific word-form processing region. However, Polk and Farah (2002) conducted an experiment in which participants read alternating casewords and pseudowords. These stimuli produced similar patterns of activation in the left-ventral visual cortex, suggesting the presence of a word-form area that pays attention to abstract orthographic patterns rather than strictly perceptual components of visually presented language.

Phonological processing

To isolate the brain regions associated with phonological processing from those specialised for semantic processing, psychological tasks have been designed that focus attention on a particular characteristic of the stimulus. The problem by this kind of paradigm is that once an experiment introduces a task that requires an attention-demanding strategy, also other, non-phonological processes (e.g. attention, verbal memory, etc.) will be involved.

When considering processing of phonological tasks two distinct regions of the inferior frontal cortex appear to be involved: the left frontal operculum (around the anterior insula and BA45) and a more posteriordorsal region of the inferior frontal gyrus near the premotor boundary (BA 44/6). The left inferior frontal operculum is activated when phoneme detection tasks are contrasted to fixation, when phonetic judgements are made on visually presented words, and when listening to words passively is contrasted to hearing reversed words (Price et al., 1996b). Consistent with these findings, activation was found in the left frontal operculum when phonetic judgement tasks were contrasted to passive listening (Zatorre et al., 1996), suggesting a fundamental role in phonemic perception. However, these findings do not explain why activation is not always detected in the left frontal operculum for passive word listening contrasted to silence (Price et al., 1996b). One possibility is that during silent conditions, the left frontal operculum is engaged in inner speech and auditory verbal imagery (McGuire et al., 1996). The more posterior dorsal region of the inferior frontal cortex has been observed for phoneme processing relative to passive listening (Zatorre et al., 1996), relative to semantic decisions (Démonet et al., 1994) and relative to non-verbal visual tasks (Paulesu et al., 1993).

Several studies have also demonstrated left lateralized or bilateral activation of the supramarginal gyrus for pseudowords relative to real words (Price et al., 1996a; Rumsey et al., 1997) as well as for some phoneme-processing tasks with both heard words and non-words. It is hypothesized that the left supramarginal gyrus might allow verbal short-term storage (Paulesu et al., 1993) or orthographic-to-phonological translation (Price, 1996a), but neither explanation accounts for all the available data.

Semantic processing

Functional imaging studies have employed a wide range of semantic tasks (e.g. semantic category decision on single words (Binder et al. 1995), word generation (Shaywitz et al., 1995) and picture naming (Bookheimer et al., 1995). Comparison of these studies is complicated by the fact that these different tasks have been used in combination with different control conditions including linguistic and non-linguistic stimuli. Nevertheless, together these studies implicate a number of regions in the performance of tasks involving word meaning.

Activation associated with such tasks has been strongly lateralized to the left hemisphere. The most consistently activated region was the inferio-temporal area. Activation was observed for

a semantic task contrasted to a phonological control task (Pugh et al., 1996), as well as for a semantic task relative to the non-linguistic task of hearing a tone (Démonet et al., 1992). This area is situated strategically between visual, auditory, and somatosensory centres, making it a reasonable candidate for a multimodal "convergence area" involved in storing or processing very abstract representations of sensory experience and word meaning.

In most studies on semantic processing the prefrontal cortex of the superior frontal gyrus was consistently activated (Démonet et al., 1992; Binder et al., 1997; Pugh et al., 1996). This region includes the medial aspects of BA 8 and BA 9. Language deficits associated with a lesion in this region suggest an impairment involving self-initiation of language (Rapcsak et al., 1994). Binder and Price (2001) hypothesized that this brain region initiates the process of semantic information retrieval. That this area is activated by semantic, relative to phonologic knowledge retrieval tasks, indicates either a specific role in initiating retrieval from semantic stores or that semantic knowledge retrieval makes stronger demands on the initiation mechanism than does phonologic retrieval.

Activation of the middle and inferior temporal gyrus of the LH is less consistent and appears to be more dependent on specific stimulus characteristics and task requirements. Whereas imaging studies using visual stimuli found activation in both middle and inferior temporal gyrus for the semantic relative to phonologic tasks (Pugh et al., 1996; Price et al., 1997). Functional imaging studies demonstrated that activation of the left middle and inferior temporal gyrus depends partly on the semantic category associated with the stimuli (Damasio et al., 1996). This evidence of category-specific organization in the ventrolateral and ventral temporal lobe strongly suggests the presence of concept-level representations in this region.

Involvement of the left inferior frontal gyrus in semantic processing has been a topic of considerable debate (Démonet et al., 1992; Petersen et al., 1988). The left inferior frontal gyrus is consistently activated during word production tasks (Petersen et al., 1988) and activation of this area was also observed in studies involving semantic tasks (mostly categorization tasks) contrasted with non-linguistic perceptual control tasks (Kapur et al., 1994; Demb et al, 1995). Most of the studies employing phonological control tasks failed to show differential activation of the left inferior frontal gyrus. One explanation is that left inferior frontal gyrus (particularly BA 44/6) activation reflects phonological or verbal short-term memory demands of the word generation and comprehension tasks employed in these studies (Paulesu et al., 1993; Démonet et al., 1992). Another explanation for the activation in

this region is that this activation reflects more general task demands related to linguistic knowledge retrieval.

A final region implicated in several semantic tasks is the cingulate cortex and precuneus. Although interpretation of these findings is unclear, part of this region coincides with retrosplenial cortex (Vogt, 1976), which has connections with hippocampus, parahippocampus and anterolaterodorsal thalamus (Suzuki and Amaral, 1994; Sripanidkulchai and Wyss, 1986). This connectivity pattern suggests involvement of the cingulate cortex in memory functions (Rudge and Warrington, 1991). Cingulate activation may therefore be related to memory-encoding processes that accompany semantic task performance (Craik and Lockhart, 1972). This could also account for activation observed in the left parahippocampus and hippocampus, structures closely tied to episodic memory encoding (Binder and Price, 2001)

Role of the right hemisphere

As discussed before, the majority of language functions are processed in the LH. The occurrence of structural damage to these language areas typically results, in the adult brain, in location related language disorders. For the recovery from such lesions, enhanced participation of the RH has been demonstrated as possible mechanism (Musso et al. 1999; Voets et al., 2005). However recovery from aphasia often remains incomplete and severe persisting disturbances are not uncommon. This situation is radically different when corresponding brain insults occur prenatal or during the first years of life. Affected children usually do not develop persistent aphasia even in cases with extensive LH lesions (Vargha-Khadem et al., 1985) or left hemispherectomies (Muter et al., 1992). So in case of LH lesions during the first years of life, the undamaged RH is able to take over language functions. Imaging studies showed that in patients with early LH damage, RH recruitment for language occurs in brain areas homotopic to the LH regions involved in language processing under normal circumstances (Staudt et al., 2002).

Apart from taking over -partly- language function after LH damage, a body of research has demonstrated specific RH linguistic abilities. Studies of healthy subjects as well as patients with lesions in the RH highlight the RH´s crucial role in the prosodic aspects of expressive and receptive language (Pell, 1999 and 2006; Buchanan et al., 1999). Prosody, the “melody of language”, encompasses those alterations in pitch, stress, and rhythm that allow us to

communicate meaning. Without prosody our articulation sounds monotonous and robotic. The RH is also associated with non-propositional speech. This form of spoken language involves verbalizations that neither involves generation of new ideas, nor the processing of such ideas into original, grammatical utterance (e.g. nursery rhyme) (Code, 1997; Ryding et al., 1987). By testing split brain patients Zaidel (1978) and Baynes et al. (1992) demonstrated that the disconnected RH possesses receptive language abilities and is capable of linguistic comprehension. Functional imaging research has confirmed that in comparison to the LH similar regions of activation occur in the RH. The right inferior frontal gyrus is active during the processing of abstract words and detection of emotional content in speech. The middle and superior frontal regions have shown activation during semantic decisions tasks. The right temporal regions are also associated with the processing of prosody (Gernsbacher and Kaschak, 2003-91).

A study by Fedio et al. (1997), using intracarotid injection of amobarbital, has demonstrated that while the hemispheres interact in the processing of semantic and orthographic information, the isolated RH is incapable of processing phonological information. These findings were confirmed by clinical data (Rapcsak et al., 1991; Chiarello and Church, 1986; Zaidel and Peters, 1981). Although the evidence above indicates that the RH lacks phonological processing capability, functional imaging research suggest that there might be a gender difference in the functional organization of phonetic processing. Shaywitz et al. (1995) found differences in the activation associated with a rhyme task. Whereas males showed activation that was strongly left lateralized in the inferior frontal gyrus, females showed bilateral activation in this region.

Inter-individual variability of language lateralization

Variability related to handedness

The available data on the relationship between hand preference and hemispheric specialisation for language are supplied by clinical data and recently by neuroimaging studies. An analysis of clinical cases with unilateral brain damage found 86-99% of right-handers to have a left hemispheric lateralization for language (Bryden et al., 1983). Using the carotid amytal infusion test, similar results were reported in epileptic patients (Rasmussen and Milner, 1977) and in individual with normal angiograms (Rossi et al., 1967). Whereas the incidence of left hemispheric dominance for language in right-handed individuals is probably as high as 95%,

left handers are more likely to have language controlled by the RH. Rasmussen and Milner (1975) reported only 70% of left handers having left hemispheric language lateralization, 15% having right hemispheric dominance for language and 15% having a bilateral representation. More recent functional imaging research estimates right hemispheric language dominance in 8-10% of left handers (Pujol et al., 1999; Szaflarski et al., 2002), rising to 27% for strong left-handed individuals (Knecht et al., 2000).

Variability related to gender

Gender has also been proposed as a cause of variation in language lateralization. In particular, it has been suggested that females have bilateral representation of language function, whereas males have a more left lateralized language organization (Gur et al., 2000). Such a theory would help to account for following observations; language impairments are following stroke are less frequent in females (Kimura, 1983); and developmental and reading disorders are twice as common in male children as female children (Flannery et al., 2000). However as Sommer et al. (2004) point out, such observations offer only indirect support for decreased language lateralization in women and functional imaging research is needed to directly access cortical language representation. Sommer et al. (2004) found in their meta-analysis of 14 functional imaging studies no significant difference between genders in language lateralization. So why do some studies find a decreased lateralization pattern in females (Gur et al., 2000, Shaywitz et al., 1995; Kansaku and Kitazawa, 2001; Jaeger et al, 1998) and others not (Sommer et al., 2004; Frost et al., 1999)? The discrepancies may reflect differences in hormonal state between the female populations tested. Across both functional imaging (Fernandez et al., 2003) and behavioural research (e.g. Heister et al., 1989; Rode et al., 1995; Hausmann and Güntürkün, 2000) it is demonstrated that patterns of lateralization in females are cycle dependent. Examining the role of the menstrual cycle phase in future studies on gender differences should provide a more consistent picture.

The origins of language lateralization

In the following section some models of the origins of hemispheric lateralization, focusing on language, will be presented. These models are often not limited to language. In fact hemispheric specialisation for language seems not to be independent of the lateralization of other cognitive functions (e.g. spatial processing) (Hécaen et al., 1981; Zatorre et al., 2002).

Thus, better understanding of hemispheric lateralization for language could provide important clues to brain organization in general.

Evolution of brain size

During the course of evolution brain size increased, requiring a better use of the intra-cranial space, resulting in cortical folding (Zilles et al., 1989). Hemispheric specialisation can also be considered as another way of sparing space. From a phylogenetic point of view symmetry is one of the principles of neural development. The presence of two hemispheres is related to the global symmetry of the body. On the level of primary motor processes and perception the necessity of functional separation of both hemispheres is clear. However integrated processes such as semantic processing are not directly tied to body symmetry. It has therefore been proposed that hemispheric specialisation developed because of the lack of space and the uselessness of symmetry for high level functions, of which language is one (Gazzaniga, 2000).

Anatomical asymmetry of the planum temporale as a basis to functional cerebral asymmetry for language

A first study on the anatomical asymmetry of the planum temporale was done by Geschwind and Levitsky (1968). The planum temporale is a structure located on the posterior surface of the temporal lobe. It is also part of a region which, when lesioned, leads to Wernicke's aphasia (Wise et al., 2001). Geschwind and Levitsky found the planum temporale to be larger on the left in 65 of 100 postmortem brains. Consequently, they supposed that this asymmetry in favour of the left was an anatomical marker of the left hemispheric specialisation for language. Later, considering the prenatal appearance of this asymmetry, Geschwind and Galaburda (1985) proposed that anatomical asymmetries were the basis on which functional hemispheric asymmetry specialisation developed.

Galaburda et al. (1987) re-analyzed the samples of brain used by Geschwind and Levitsky (1968) and computed correlations between the surface of the left and right planum temporale, represented by an asymmetry index. They found that the surface of the smallest planum temporale only was correlated negative to the asymmetry. Based on these results as well as on the fact that cerebral development implies neuronal loss, a new model was proposed.

According to this model, the two hemispheres start by having originally the same potential. Then, in most cases the right hemisphere undergoes a neuronal loss in the language areas, notably at the level of the planum temporale, leaving its homologue alone to take language in charge. In this hypothesis, atypical patterns of language specialisation would come from a limited degeneration of the right planum temporale. However, Josse et al. (2003) found a significant correlation not only between the size of the right planum temporale and its asymmetry but also between the LH and the asymmetry index. These findings do not exclude the hypothesis by Galaburda and colleagues (1987) of a relationship between the size of the right planum temporale and its asymmetry but also between the size of the left planum temporale and the asymmetry index.

The right shift theory

The right shift theory offered by Annett (1972 and 1996) postulates the existence of a gene with two alleles, one of which affects the distribution of asymmetries related language and handedness by favouring the LH. Homozygous subjects possessing the right shift allele show in most cases leftward asymmetries, whereas for homozygous subjects who do not possess this allele, asymmetries are distributed at random. In the case of heterozygote subjects, leftward asymmetries are more frequent than rightward asymmetries, but in comparison with the homozygote subjects at a lower occurrence rate.

Even though it is possible to make rather accurate predictions with this genetic model, the right shift theory was also criticized. First, according to Annetts' hypothesis, the probability for observing a left hemispheric specialisation for language should be the same in genetically identical subjects. In contrast, fMRI data of monozygotic twins with discordant handedness showed a higher probability for left hemispheric language organisation in the right-handed compared with the left-handed co-twins (Sommer et al., 2002). Secondly, Annetts' genetic model is based on an evolution, specific for humans. Corballis (1998 and 2003) argues that the left hemispheric dominance for language is an evolutionary trait. Several species such as frogs have a LH specialised for vocalisation (Bisazza et al., 1998). Consequently, Corballis proposes that the right-handedness in the majority of people might be due to the fact that, before the development of speech, hands were used for gestural communication.

Testosterone hypothesis

The testosterone hypothesis associates pathology and left-handedness with the sex hormone testosterone. Geschwind and Galaburda (1985) postulate that testosterone induces a delay in the development of the LH. This would make left hemispheric specialisation for both manual activities and language less likely in men. Furthermore testosterone would have a negative effect on the immune system. So, this hypothesis would account for the following: (1) there appears to be more left-handed men as women; (2) men and left-handers compared to women and right-handers seem to be more exposed to several pathologies. Support for an association between left-handedness and different pathologies was found by some studies (e.g. Coren and Halpern, 1991; Annett 1999). At the same time several pieces of evidence go against it. A meta-analysis by Porac and Searleman (2002) showed that left-handed people did not differ from right-handed ones regarding their physical and psychological health, nor their verbal cognitive capacity. Grimshaw et al. (1995) measured testosterone in the amniotic fluid (14^{th}-20^{th} week of gestation) and subsequently evaluated handedness and performed dichotic listening in the children. Their observations did not support the testosterone hypothesis.

Intra-uterine environment hypothesis

Previc (1991) proposed a theory based on the asymmetry of the intra-uterine environment. This asymmetry would induce a cranio-facial asymmetry causing the right middle ear to conduct certain sounds better as the left middle ear. In other words Prevics' hypothesis associates a right ear advantage, which can be observed with dichotic listening (Kimura, 1967), with the cranio-facial asymmetry as basis for the left hemispheric specialisation for language. Dichotic listening studies revealed a right ear advantage in 70%, a left ear advantage in 23% and no ear advantage in 7% of right handed subjects (Hättig, 2004). Therefore, it is suggested that factors other than the cranio-facial asymmetry would also influence the development of a left hemispheric specialisation for language.

2.1.3 Functional cerebral lateralization during the menstrual cycle

Both behavioural (Heister et al., 1989; Rode et al., 1995) and neuroimaging studies (Dietrich et al., 2001; Fernandez et al., 2003) have reported changes in functional cerebral lateralization during the menstrual cycle, however Veltman et al. (2000) did not observe such changes. A

visual half-field presentation study by Hausmann and Güntürkün (2000) revealed for all tasks (lexical decision, figural comparison, and face discrimination) a decreased lateralization during the midluteal phase compared to the menstrual phase. Based on these findings, they hypothezised that fluctuating steroid levels during the menstrual cycle do not affect a single hemisphere, but instead impair interhemispheric integration.

The progesterone-mediated interhemispheric decoupling hypothesis

The hypothesis of "progesterone-mediated interhemispheric decoupling" was proposed by Hausmann and Güntürkün (2000). This hypothesis suggests that progesterone attenuates the excitatory response of neurons to glutamate and augments the inhibitory response to GABA. Cortico-cortical transmission is partly based on a feedforward inhibition circuit (Fig 2.5) in which the glutamergic EPSP is mediated by a GABAergic IPSP (Conti and Manzoni, 1994). The effect of a rise in progesterone would result in a decrease in cortico-cortical transmission (inhibition) or functional hemispheric decoupling and thus to a temporal reduction in functional asymmetry.

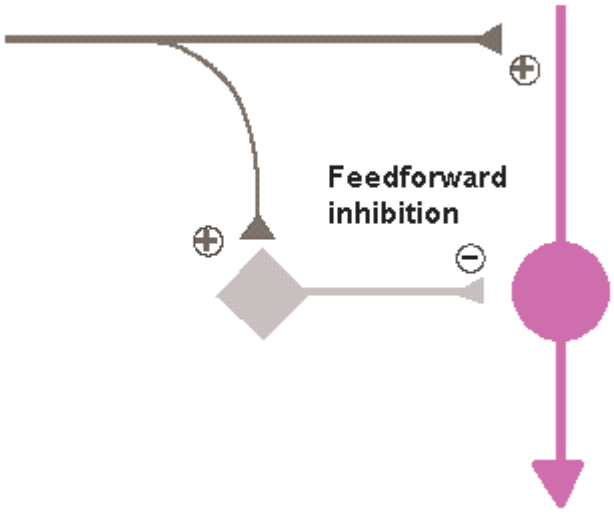


Fig 2.5: Feedforward inhibition. The involved excitatory neurons is black, the inhibitory interneuron is gray. In case of feedforward inhibition activates an extern excitatory neuron the main cell (pink). In the main time the excitatory neuron also activates the inhibitory interneuron. Thus, the main cell obtains almost simultaneously two synaptic influences, excitatory and inhibitory, whose effects superimpose. Modified from http://en.wikipedia.org.

It has been demonstrated that progesterone suppresses, in a dose dependent fashion, the glutamate-induced excitatory responses of neurons. This effect is due to the attenuation of non-NMDA glutamate-receptors without being mediated by an increase of GABA inhibition (Smith, 1991; Smith et al., 1987a). Progesterone is known to augment the inhibitory neuronal

response to GABA, in particular the 5-α- and 5-β-reduced metabolites of progesterone, allopregnanolone and pregnanolone. Thus, an increase of progesterone during the luteal phase could, after callosal activation, decrease the first excitatory EPSP, directly by decreasing non-NMDA receptor efficiency, and indirectly by augmenting the GABA responses.

Smith and colleaques showed that estradiol, contrary to progesterone, increases the glutamate response. However, estradiol combined with progesterone or progesterone applicated after estradiol pre-treatment down regulates glutamate receptors as with progesterone alone (Smith et al., 1987b).

Confirmation of the progesterone-mediated interhemispheric hypothesis was partly found by a behavioural longitudinal study which showed a relationship between high progesterone levels and reduced asymmetry for a figural comparison task due to a performance enhancement in the less specialised left hemisphere. Unfortunately, this effect could not be assessed for a semantic decision and face recognition task (Hausmann et al., 2002). Compton et al. (2004) tested the progesterone hypothesis by using a task requiring interhemispheric interaction. The results did not support the hypothesis that progesterone leads to interhemispheric decoupling. Another study of Hausmann et al. (2006) applied transcranial magnetic stimulation to the motor cortex and found a positive correlation between the duration of the ipsilateral silent period and progesterone level during the luteal phase. The ipsilateral silent period is a short period of suppression of ipsilateral tonic voluntary muscle activity due to transcranial magnetic stimulation application of the motor cortex (Wassermann et al., 1991). The ipsilateral silent period is assumed to be mediated cortically by a feedforward inhibitory circuit. A recent fMRI study (Fernandez et al., 2003) showed an increase of symmetrical activation in a semantic decision task which was positively related with progesterone levels. However the additional recruitment of areas in the non-specialised RH during the midluteal phase was specifically located in the superior temporal gyrus and the medial wall of the superior temporal gyrus. Fernandez and colleagues discussed that this cannot simply be explained by gonadal steroid hormone effects on commissural transmission, because neither region has a disproportional number commissural fibres.

The menstrual cycle

The menstrual cycle is a periodic cycle of physiological changes that occurs in the females of several mammals. The human female, unlike almost all other female mammals, has a menstrual cycle with a 'hidden' ovulation lacking obvious external physical changes (Dorit et al., 1991).

The hormonal regulation of the menstrual cycle

The menstrual cycle is counted from the first day of bleeding and its' length varies from 21 to 35 days with a mean time of ca. 28 days. The cycle is characterised by different phases: the follicular phase including menstruation, the ovulation and the luteal phase (Fig 2.6).

In a sexual mature woman, neurons in hypothalamus release in pulses of approximately 90 minutes the gonadotrophic releasing hormone (GnRH). GnRH stimulates the pulsatile secretion of the gonadotrophic hormones; the luteinizing hormone (LH^*) and the follicle stimulating hormone (FSH) in the anterior pituitary.

Already at the end of the luteal phase the concentration of FSH starts to rise. FSH stimulates the proliferation of ca. 20 follicles and induces the enzyme aromatase in their granulosa cells. This enzyme converts the androgens testosterone and androstendion, synthesised in the theca cells of the follicle and assimilated in the granulosa cells, into estrogens. The LH^* secretion is relative low, but LH^* activates enzymes in the theca cells that promote the synthesis of the androgens necessary for the production of estrogens in the granulosa cells. Estrogens within the follicle upregulate the FSH receptors, as such, the follicle with the highest estrogen concentration has the highest FSH sensitivity, and will be selected as the dominant follicle. All other follicles will undergo atresia. In the mid-follicular phase the estrogens control the LH^* and FSH secretion, by a negative feedback mechanism involving inhibine, whilst inducing more LH^*-receptors on the granulosa cells. As a consequence the granulosa cells start to synthesise progesterone, which is assimilated in the theca cells and is used as basis for an increase in androgen synthesis.

At the end of the follicular phase, the dominant follicle secretes enough estrogens to trigger the acute release of GnRH by the hypothalamus (positive feedback system), causing a rapid increase in FSH and LH^* secretion by the anterior hypothalamus. The FSH peak induces the meiosis of the ovum (ca. day 13). The LH^* surge starts around day 12 and may last 48 hours. The high concentration of LH^* weakens the wall of the follicle in the ovary. About 10 hours

after the LH* peak (ca. day 14) the follicle opens and the ovum is swept into the fallopian tube. This process is called ovulation

After ovulation, the residual follicle transforms into the corpus luteum under the support of FSH and LH* (start luteal phase). The corpus luteum produces progesterone in addition to estrogens. Both progesterone and estrogens inhibit the release of FSH and LH* at the hypothalamic level, rapidly reducing their plasma concentrations. This negative feedback system causes the decrease of progesterone and estrogens levels at the end of the menstrual cycle. Progesterone withdrawal leads to menstrual bleeding, and falling inhibin levels allow FSH levels to rise and to induce proliferation of a new group of follicles (Silbernagel and Despopoulos, 2001; Schmidt and Tews, 1990).

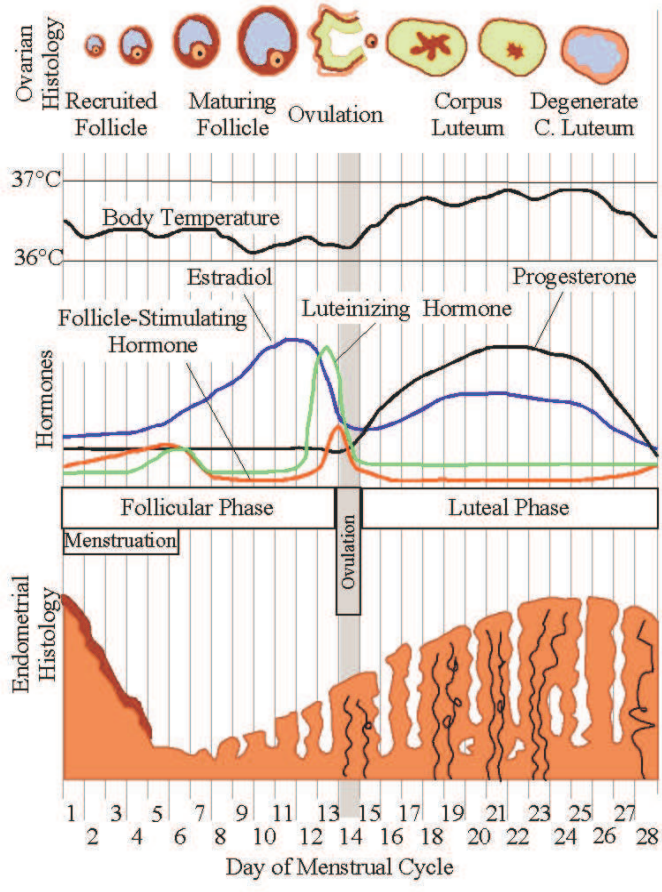


Fig 2.6: Representation of the variation through the menstrual cycle of the major hormones involved, basal body temperature, and relative endometrial thickness. Durations and values may differ between different females and different cycles. Modified from http://en.wikipedia.org.

Anovulation

Anovulation is the absence of ovulation and the associated progesterone peak during the menstrual cycle. Apparently normal menstrual flow can occur without a preceding ovulation. Sometimes, follicular development may start but due to the absence of the LH* surge or this increase being too small no ovulation takes place. In this case the menstrual bleeding results from a very thick endometrium caused by prolonged, continued high estrogens levels or triggered by a sudden drop in estrogen levels (Spence, 1997).

Cycle-dependent fluctuation in progesterone level

During the menstrual cycle plasma concentrations of progesterone fluctuate. Dighe and Hunter (1974) reported the following values: for the follicular phase 332 pg/ml; and for the midluteal phase 14.6 ng/ml. Due to diffusion of unbound progesterone from blood into saliva it is possible to measure progesterone in saliva. Salivary progesterone measurement is a valid and non-invasive method (Riad-Fahmy et al., 1982). Expected salivary progesterone values range for the follicular phase from 28 to 82 pg/ml, and during the luteal phase between 127 and 446 pg/ml (Riad-fahmy et al., 1982).

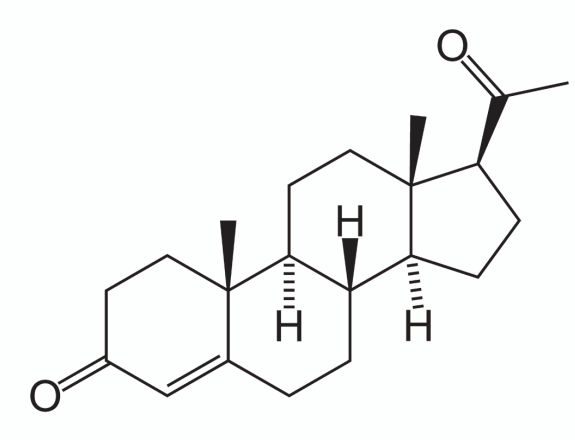
Salivary Progesterone levels can be assessed by luminescence immunoassay (LIA). LIA is based on the competition principle. An unknown amount of antigen present in the sample and a fixed amount of enzyme labelled antigen compete for the binding sites of the antibodies coated onto the wells. After incubation the wells are washed to stop the competition reaction. After addition of the luminescence substrate solution the intensity of the luminescence measured is inversely proportional to the amount of the antigen in the sample.

The female sex hormone: Progesterone

Progesterone is derived from PROGEstational STERoidal ketONE (Allen, 1970) and was independently discovered by four research groups (Allen, 1935; Hartmann and Wettstein, 1934; Slotta et al., 1934; Butenandt and Westphal, 1934).

Chemical structure of Progesterone

Progesterone (pregn-4-ene-3, 20-dione) consists of four interconnected cyclic hydrocarbons and contains ketone and oxygenated functional groups, as well as two methyl branches (Fig 2.7 and Fig 2.8). Like all steroid hormones, it is hydrophobic (Allen, 1970; Silbernagel and Despopoulos, 2001).



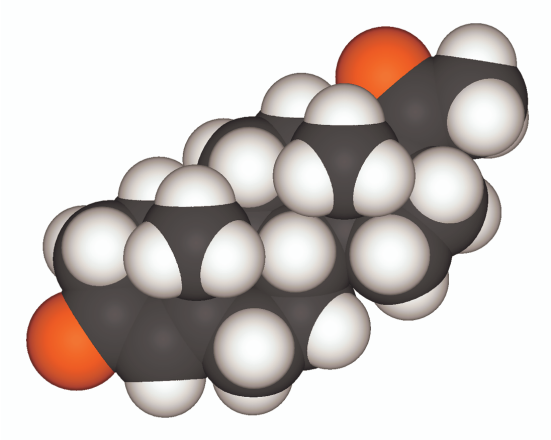


Fig 2.7 (left): Progesterone 2D skeletal (http://en.wikipedia.org). **Fig 2.8 (right):** Progesterone 3D (http://en.wikipedia.org).

Biosynthesis of Progesterone

Progesterone, like all other steroids, is synthesized from pregnenolone, a derivative of cholesterol (cholesterine) (see Fig 2.9). Cholesterol synthesized in the liver and adrenal glands from acetyl-CoA and can be transported in the blood by binding with lipoproteins. Cholesterol, containing 27 C-atoms, can be conversed in pregnenolone (21 C-atoms). By converting the 3-hydroxyl group of pregnenolone to a keto group and moving the double bond from C-5 to C-4, progesterone (21 C-atoms) is synthesized.

Progesterone is a female sex hormone. Simultaneously, progesterone is a precursor of the mineralcorticoids (11-desoxy-corticisterone, corticosterone and aldosterone), and after conversion to 17-hydroxy-progesterone, also of the glucocorticoids (11-desoxycortisol, cortisol) and androstenedione. The female sex hormones estrone and estradiol, as well as the male sex hormone testosterone can be synthesized form androstenedione (Silbernagel and Despopoulos, 2001).

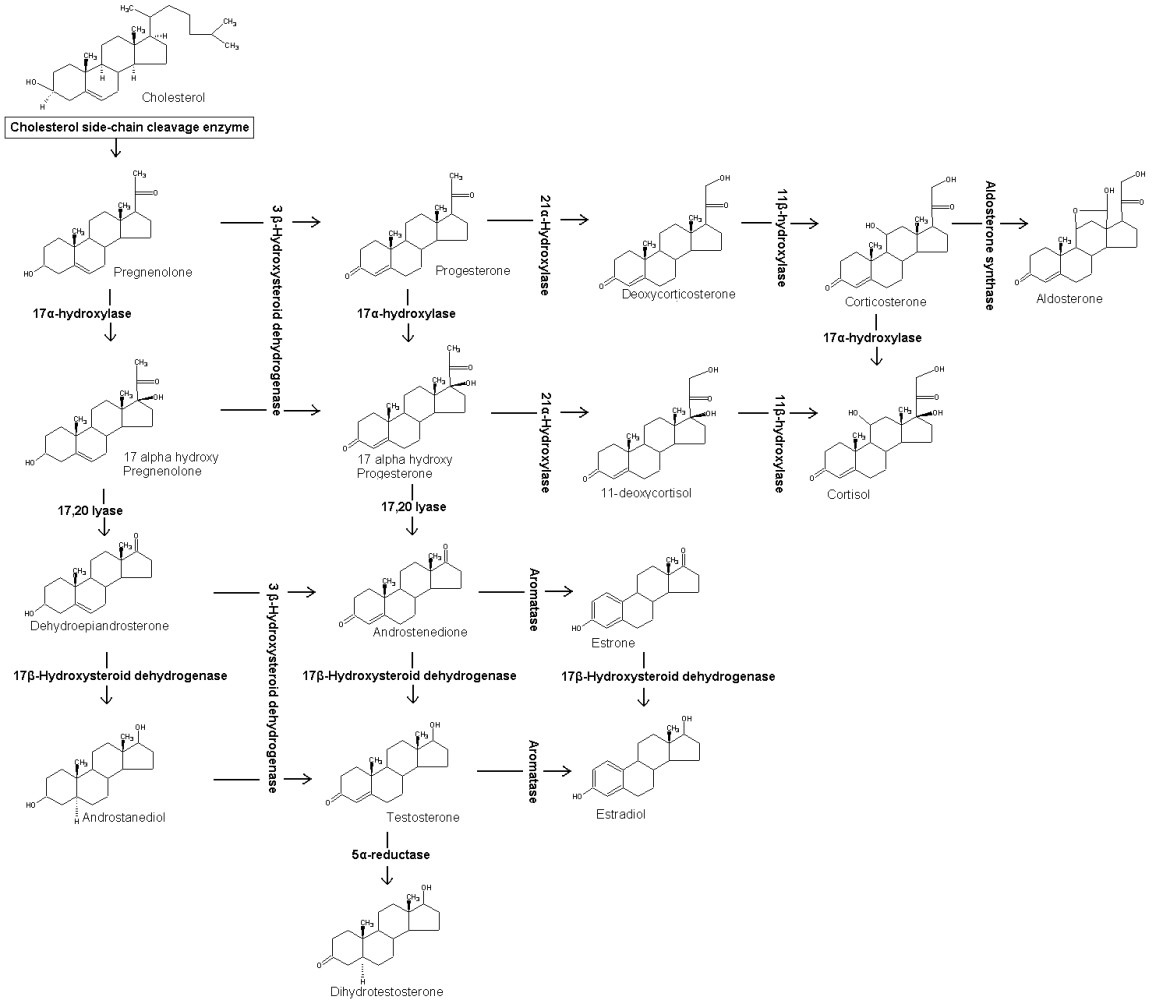


Fig 2.9: Biosynthesis of progesterone and other steroids (http://en.wikipedia.org).

Progesterone as steroid hormone

The major production side of progesterone is the corpus luteum in the ovary. It is thought that the gonadotrophic LH* stimulates the conversion of pregnenolone from cholesterol in the granulosa cells of the corpus luteum. In a second step, pregnenolone is converted to progesterone. When no fertilization occurs, the corpus luteum continues to enlarge for several days followed by regression of the gland and concomitant cessation of progesterone release (Silbernagel and Despopoulos, 2001; Murray, 1998). Another site of progesterone synthesis is the placenta. If fertilization occurs, the corpus luteum continues to grow and function for the first 2 to 3 months of pregnancy. Subsequently it will slowly regress as the placenta takes over the role of hormonal biosynthesis for maintenance of pregnancy (Silbernagel and Despopoulos, 2001; Murray, 1998). To a smaller extent, progesterone is produced in the

adrenal glands (Silbernagel and Despopoulos, 2001) and the brain (Greener, 2003; Schumacher et al., 2000, 2001). Once released, progesterone is bound in the blood by transcortin, a corticosteroid-binding globulin (Silbernagel and Despopoulos, 2001).

Progesterone is excreted primarily by the liver. Pregnanediol is one of the major metabolites of progesterone (Silbernagel and Despopoulos, 2001; Murray, 1998).

Progesterone exerts its action primarily through the progesterone receptor, which is an intracellular steroid receptor that specifically binds progesterone. The progesterone receptor has two main forms: progesterone receptor A and progesterone receptor B. The binding of progesterone with the PR induces a structural change with a following dimerization. The complex enters the nucleus and binds to deoxyribonucleic acid (DNA). There, transcription takes place resulting in formation of messenger ribonucleic acid (RNA) that activates cytoplasmic ribosomes to produce specific proteins. Although progesterone receptor A and progesterone receptor B share a nearly identical structure, they are functionally two distinct transcription factors, mediating their own response genes and physiological effects (Kastner et al., 1990).

Progesterone plays an important role in the human physiology. The hormone interacts both synergistically and antagonistically with estrogens; however the ratios of the two hormones vary widely in different target organs. Since both sex steroids work together in an intricate relationship, it is hard to define exactly the specific effects of each steroid on tissue and organs (Murray, 1998).

The main physiological roles of progesterone are in the reproductive system: 1) in the uterus and ovary: facilitation of fertilization by making the cervical mucus more permeable and implantation by converting the endometrium to the secretory stage, and maintenance of pregnancy by uterine growth and suppression of myometrial contractility; 2) in the mammary gland: development of lobular-alveolar structures in preparation for milk secretion and suppression of milk secretion before parturition; and 3) in the brain: regulation of sexually responsive behaviour (Murray, 1998; Graham and Clarke, 1997). In addition to the effects on the reproductive system, progesterone appears to influence also other aspects of human physiology for example: progesterone raises body temperature by about 0.3°C in both sexes (Murray, 1998); in the adrenal glands progesterone reduces the effects of aldosterone, increasing NaCl-excretion (Silbernagel and Despopoulos, 2001); and progesterone appears to

prevent osteoporosis (Wierman, 2007; Graham and Clarke, 1997). Tthe nervous system is also a site of action for progesterone.

Progesterone and its metabolites as neuroactive steroid hormones

The term "neurosteroid" was introduced by Baulieu (1991 and 1998) and is given to a steroid synthesized in the brain. The term "neuroactive steroid" refers to steroids which, independent of their origin, are capable of modifying neural activities. Neuroactive steroids bind and modulate different types of membrane receptors and may regulate gene expression via the progesterone receptor after intracellular oxidation (Paul and Purdy, 1992).

Progesterone which is formed peripherally by the corpus luteum and adrenal gland can because of its lipophilic nature cross the blood brain barrier (Hu et al., 1987). The 5α-reductase and/or 5β-reductase reduce progesterone to 5α-dihydroprogesterone (5α-DHP) and/or 5β-dihydroprogesterone (5β-DHP). These pregnane steroids may be further reduced to the neuroactive steroids 3α-hydroxy-5α-pregnan-20-one (or 3α, 5α-tetrahydroprogesterone; 3α, 5α-THP; allopregnanolone) and/or 3α-hydroxy-5β-pregnan-20-one (or 3α, 5β-tetrahydroprogesterone; 3α, 5β-THP; pregnanolone) by the 3α-hydroxysteroid oxidoreductase (Rupprecht, 1997). The biosynthesis of pregnanolone and allopregnanolone is regulated by negative feedback system in which the activation of γ-aminobutyric acid type A ($GABA_A$) receptors inhibits activities of the 5α/5β-reductase and 3α-hydroxysteroid oxidoreductase (Do-Rego et al, 2000; Mensah-Nyagen et al.1999).

Both pregnanolone and allopregnanolone modulate neuronal excitability as established positive allosteric modulators of the $GABA_A$ receptor, by increasing the frequency and/or duration of openings of the $GABA_A$-gated chloride channel (Lambert et al. 2003; Rupprecht 2003). Pregnanolone and allopregnanolone probably also activate gene expression via the progesterone receptor after intracellular oxidation (Rupprecht 2003). Recently, Greener (2003) and Schumacher et al. (2000 and 2001) showed evidence for de novo synthesis of the steroid progesterone from cholesterol in the brain.

These observations have led to the speculation that the major inhibitory neurotransmitter receptor in the central nervous system, $GABA_A$ receptor, may be influenced by both endocrine and local paracrine 'fine-tuning' by neuroactive steroids. Even though the $GABA_A$ receptor is widespread in the central nervous system, the actions of the $GABA_A$ receptor modulators are highly selective (Lambert et al., 2003). The $GABA_A$ receptor is composed of

five subunits selected from a palette that includes α1-6, β1-3, γ1-3, θ, δ, ε, θ and π (Barnard et al. 1998). Recent estimates suggested that the various subunit compositions underpins the existence of approximately 30 isoforms of the $GABA_A$ receptor that have distinct physiological and pharmacological properties and are heterogeneously expressed throughout the central nervous system (Sieghart and Sperk, 2002; Fritschy and Brunig, 2003).

In addition to $GABA_A$ receptors, other receptors have also been shown to be sensitive to progesterone and/or its metabolites. The serotonin receptor is negatively modulated by allopregnanolone and progesterone. Progesterone also modulates glycine receptors, nicotinic acetylcholine receptors, oxytocine receptor negatively and the kainate receptors positively (Rupprecht 2003; Dubrovsky, 2005).

Changes in circulating levels of progesterone (as during the menstrual cycle) have been correlated with depressive (Epperson et al., 2002), anxiolytic (Bitran et al., 1995) and convulsant effects (Smith and Woolley, 2004). At high doses, this steroid hormone is sedative and can act as an anaesthetic (Seyle 1941 and 1942; Rupprecht_2003).

2.2 FMRI

A number of techniques are available to image perceptual and cognitive processes in the human brain. The major ones are: positron emission tomography (PET), single photon emission computed tomography (SPECT), fMRI, and electroencephalography (EEG).

Both PET and SPECT are based on the use of radioligands which remain either within the blood stream or enter the brain and bind to receptors. Depending on the radioligand used, PET can demonstrate blood flow or glucose and oxygen metabolism reflecting the amount of brain activity in different regions. PET can through receptor specific binding of the radioligand, also be used to identify the brain sites where drugs and naturally occurring neurotransmitters act. In comparison to PET radioligands, SPECT radioligands deteriorate more slowly what makes this technique less expensive. PET is more multifunctional than SPECT and produces more detailed images with a higher degree of resolution, particularly of deeper brain structures.

Magnetic resonance imaging (MRI) is based on the variation in signals produced by protons (typically hydrogen protons) in the body when it is placed in a strong magnetic field. Using MRI, both surface and deep brain structures with a high degree of anatomical detail can be imaged, and minute changes in these structures that occur over time, can be detected. FMRI is the use of MRI to measure the hemodynamic response related to neural activity in the brain.

EEG is the neurophysiologic measurement of the electrical activity of the brain by recording from electrodes placed on the scalp or, in special cases, subdurally or in the cerebral cortex. The resulting traces are known as an electroencephalogram, and represent a summation of post-synaptic potentials from a large number of neurons. The greatest advantage of EEG is the temporal resolution. EEG can record patterns of neural activity occurring within fractions of a second after a stimulus has been administered. The biggest drawback to EEG is that it provides less spatial resolution than fMRI and PET do. As a result, a relative new technique Magnetoencephalography which combines the spatial resolution of a structural MRI scan with the temporal resolution of EEG is often used.

2.2.1 The basics of MRI

Over the past decade, fMRI has become a well-established non-invasive tool to investigate the functional properties of the brain. The theoretical background of fMRI is based on NMR of protons. H^+, a single proton, is most commonly used in MRI because the two main components of the body, water and fat, contain hydrogen. Pauli demonstrated, in 1924, that most atomic nuclei posses an angular momentum and a magnetic moment. However, it was not until Bloch and Purcell independently measured NMR absorption in bulk materials, work for which they jointly received the Nobel Price for Physics in 1952, that the existence of the nuclear spin was more clearly defined. Through the 1950's and 60's, NMR was primarily an analytical tool for chemists and physicists. The first demonstration of MRI was provided by Lauterbur, in 1924, who modified a spectrometer to provide spatially encoded signals through linear variation in the magnetic field. The first live human images using an Echo Planar Imaging sequence were reported by Sir Peter Mansfield in 1977. In 2003, Lauterbur and Sir Peter Mansfield jointly received the Nobel Price in Physiology or Medicine for their work.

Magnetic properties of nuclei

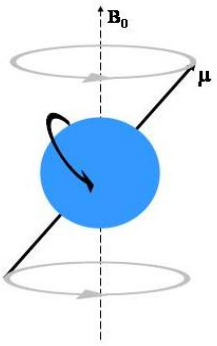


Fig 2.10: Precession of a spinning nucleus about the axis of an applied magnetic field B_0. The spinning nuclei induces an own magnetic field represented by the magnetic moment μ.

An atom is composed of positively charged (protons), negatively charged (electrons) and neutral particles (neutrons). Both the protons and the neutrons build the atomic nucleus and account for the bigger part of atomic mass. A nucleus with uneven atomic mass is electrically charged and spins around its axis (angular momentum or nuclear spin) (Fig. 2.10). Movement of an electrically charged particle induces a magnetic field with an axis coincident with the axis of the nuclear spin, and with a magnitude and direction represented by the magnetic moment μ.

Normally, the direction of these magnetic moments is randomly distributed. Thus, the sum of several spins gives a null net magnetization M. When an external, static magnetic field B_0 is applied two things happen simultaneously. Firstly, the magnetic moments align either parallel or anti-parallel with the direction of the applied field. These orientations correspond to different energy states, with a slight excess of the nuclear spins favouring the low energy (i.e. parallel) orientation. This small imbalance creates a net magnetization M oriented parallel to the applied field B_0. Since, the energy difference between the orientations is directly proportional to the field strength, increasing the applied field strength results in a proportional higher occupation of the parallel orientation and larger net magnetization. Secondly, spinning nuclei precess around the axis of the applied field. Precessing nuclei induce induce their own magnetic field. This precession, called a Larmor precession, has a characteristic frequency expressed as:

$$\omega = \gamma B_0 \qquad \text{(equilibrium state/orientation)}$$

where ω is the Larmor frequency in MHz, γ is a gyromagnetic constant which is specific for the nucleus involved (42.6 MHz/T for 1H) and B_0 is the magnetic field strength in T (Rinck et al, 2001; Cox et al, 1994).

Radio Frequency pulse and Free Induction Decay signal

The precessing net magnetization can be divided in a transverse (M_{xy}) and longitudinal (M_z) vector. In the equilibrium state $M_z = M$ and $M_{xy} = 0$ (Fig 2.11). Scince the spins do not rotate in phase the transverse magnetizations of each spin compensate each other and the sum of all transverse magnetization is null. The transverse magnetization can be made to induce a voltage in a receiver coil surrounding the sample. However, to be able to detect the net magnetization, it is necessary to tip it away from the equilibrium orientation toward the M_{xy}-plane. This can be achieved by applying a radio frequency (RF) pulse, matching the Larmor frequency. Following the pulse, the spins are still precessing with the Larmor frequency, but their precession is not longer at random but they precess in phase causing a net magnetization in the M_{xy}-plane.

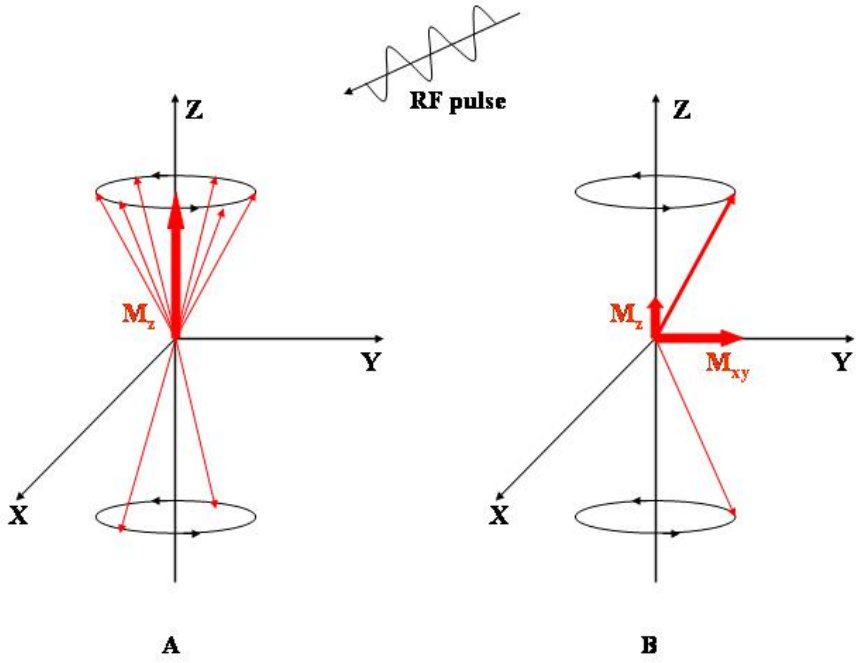


Fig 2.11: The precessing net magnetization M can be divided in a transverse (M_{xy}) and longitudinal (M_z) vector (A) in equilibrium, (B) after application of RF pulse.

When the RF pulse is switched off, the spins start returning to their equilibrium and emit a signal. This signal is called the Free Induction Decay (FID) signal, since it gradually decays due to the relaxation processes. After applying a Fourier transformation on the FID, one can analyse the signal for its frequency components in the NMR spectrum and determine the intensity of each frequency (Rinck et al, 2001; Cox et al, 1994).

Relaxation processes

After termination of the RF pulse, the nuclei start to lose the energy which was poured into the system by the RF pulse. During this process, which is called relaxation, both the longitudinal and transverse components of the net magnetization return to their equilibrium values. The relaxation processes, influencing the transverse and longitudinal magnetization components, occur exponentially but are independent of each other.

The longitudinal relaxation process is based on the energy exchange between excited nuclei and the lattice. This process is termed spin-lattice relaxation and is characterised by a value T_1, the spin-lattice relaxation time. T_1 is the time-constant which describes the time required for longitudinal magnetization to return to 63% of its original value (Fig 2.12).

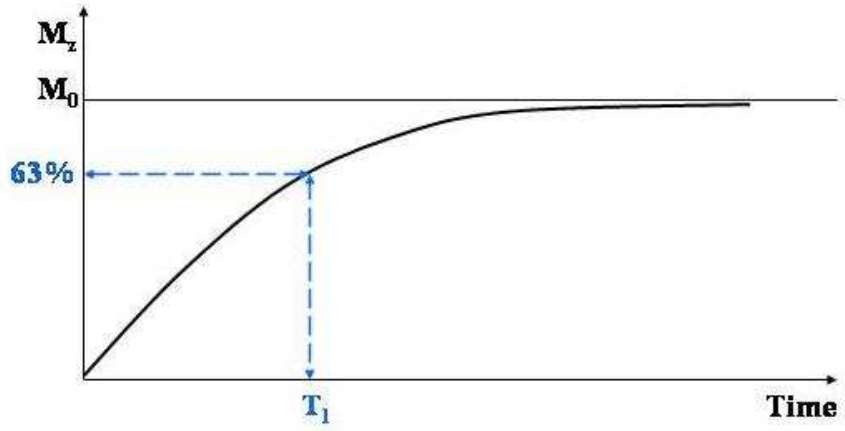


Fig 2.12: The longitudinal (spin-lattice) relaxation. T_1 is the time-constant which describes the time required for longitudinal magnetization to return to 63% of its original value.

During transverse relaxation, energy is transferred between nuclei in different energy states, creating random local magnetic field variations which, in turn, cause dephasing of the spins. This process is referred to as spin-spin interaction and is measured by T_2, spin-spin relaxation time. T_2 is the time-constant which describes the time required for tranverse magnetization to return to 37% of its original value. If the only contribution to the dephasing process were spin-spin interactions, the T_2 relaxation time could be readily determined. However, spin coherence is also affected by inhomogeneities in the applied magnetic field. The exponential decay in signal resulting from the combination of T_2 relaxation and field inhomogeneities is referred to as T_2* - the effective tranverse relaxation time (Fig 2.13) (Rinck et al, 2001; Cox et al, 1994).

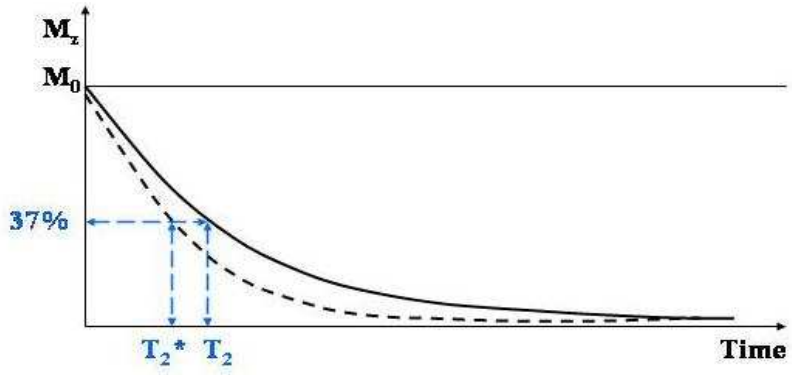


Fig 2.13: The transverse (spin-spin) relaxation. T_2 is the time-constant which describes the time required for transverse magnetization to return to 37% of its original value. T_2* is the effective transverse relaxation time as a combination of T_2 relaxation and field inhomogenities.

The decay of the MRI signal is tissue depending, which makes a distinction between different types of tissues in T_1, T_2 or T_2* weighted image possible (Fig 2.14).

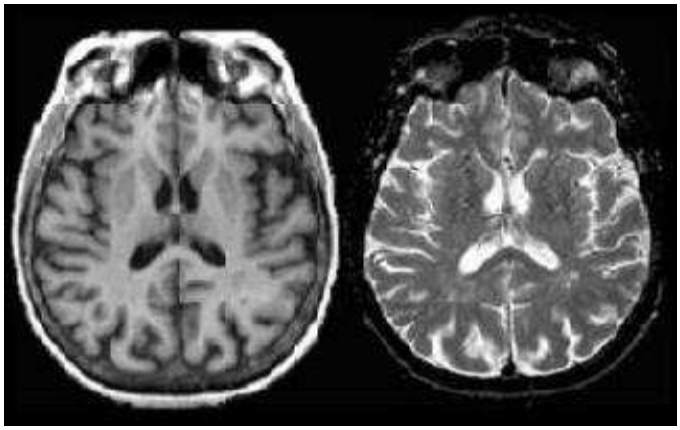


Fig 2.14: T_1 weighted image (left) and T_2 weighted image (right) (http:\\www.site.uottawa.ca).

Basic pulse sequences: Spin Echo and Gradient Echo

In the former description of the FID signal, it was assumed that the RF pulse and FID detection occur in one continuous, uninterrupted sequence. In fact, it is sometimes advantageous to not sample the FID directly, but rather to observe the signal as an echo. This is the reappearance of the signal a finite time after disappearance of the initial FID. Two approaches are routinely employed for creating an echo signal: spin echo and gradient echo.

The two dephasing processes which excited nuclei experience (spin-spin interaction and field inhomogeneities) are fundamental different. The spin-spin interaction which occurs between adjacent nuclei is a random, time-variant and irreversible process. Magnetic field inhomogeneities, however, exert a constant static influence on the spin system and therefore, in theory, can be accounted for. Measuring spin echo signal, instead of FID, permits more complete evolution of spin-spin interaction, while the influence of static field inhomogeneities can be corrected for. A 90° RF pulse flips the net magnetization into the transverse plane, where T_2* relaxation takes places (Fig 2.15). At time TE/2 (TE = echo time, the time between the beginning of the 90° pulse and the maximum amplitude of the first echo signal), a 180° pulse is applied, flipping the individual spins about the x-axis in mirror like fashion and the

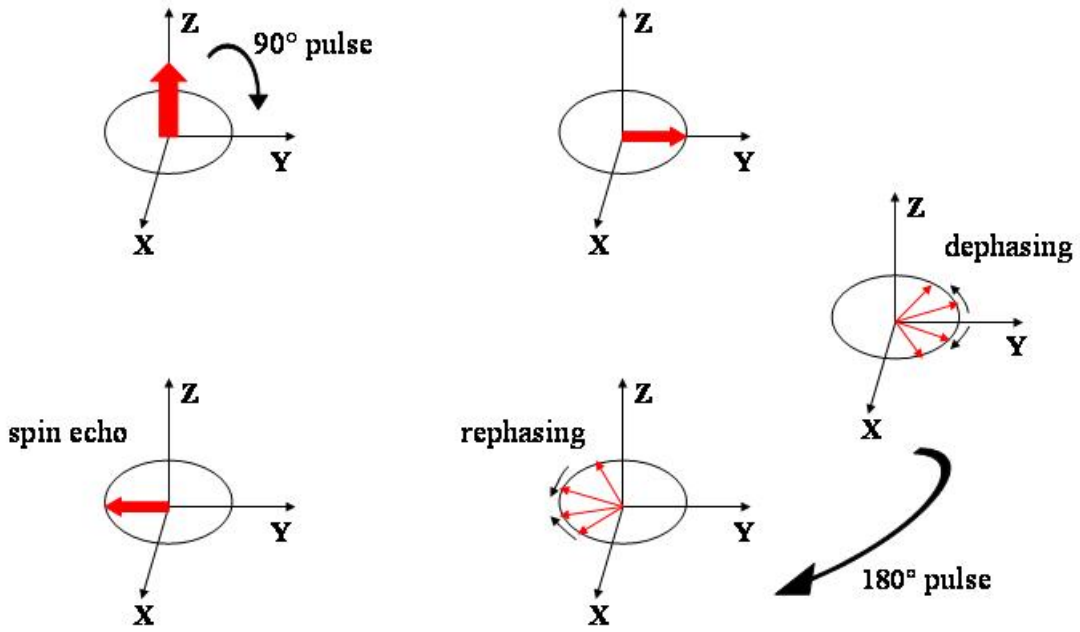


Fig 2.15: Spin echo pulse sequence

spins start to come back into phase. At time TE, the effect of static field homogeneities is cancelled out. The FID measured at time TE, is called an echo signal. The temporal interval between two RF-pulses at identical positions has been termed the repetition time (TR).

To create an echo, a 180° pulse is not necessarily needed; also field gradients can be used. This leads to gradient echo pulse sequence (Fig 2.16). Following the 90° RF pulse a gradient is switch on for a short a time. A gradient is a weak magnetic field which varies along each of the three main axes (x, y and z) and is superimposed upon the static magnetic field. After the

90° RF pulse, the spins starts to dephase and the application of the field gradient accelerates this process. By switching to the field gradient to the opposite polarization, the spins start to rephase until a gradient echo is formed. Importantly, a gradient echo pulse sequence does not cancel out the effects of field inhomogeneities. With a gradient echo pulse sequence the signal decay is determined by T_2* (Rinck et al, 2001; Cox et al, 1994).

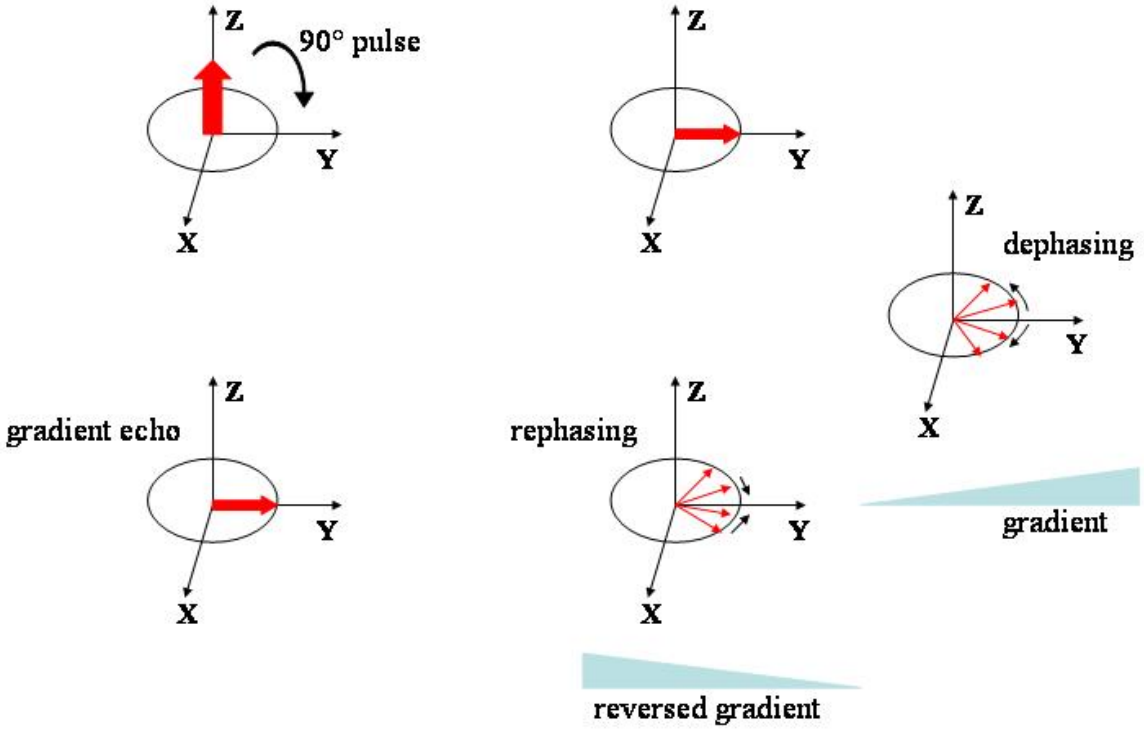


Fig 2.16: Gradient echo pulse sequence

Spatial encoding

To spatial localize the region of interest in the brain, three magnetic gradients are used: the slice selecting gradient, the readout or frequency encoding gradient and the phase-encoding gradient (Fig 2.17 and Fig 2.18). These three magnetic gradients are oriented orthogonal to each other. The slice selecting gradient is oriented along the z-axis, the frequency-encoding

gradient is oriented along the x-axis and the phase-encoding gradient is oriented along the y-axis.

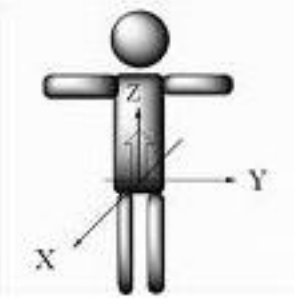
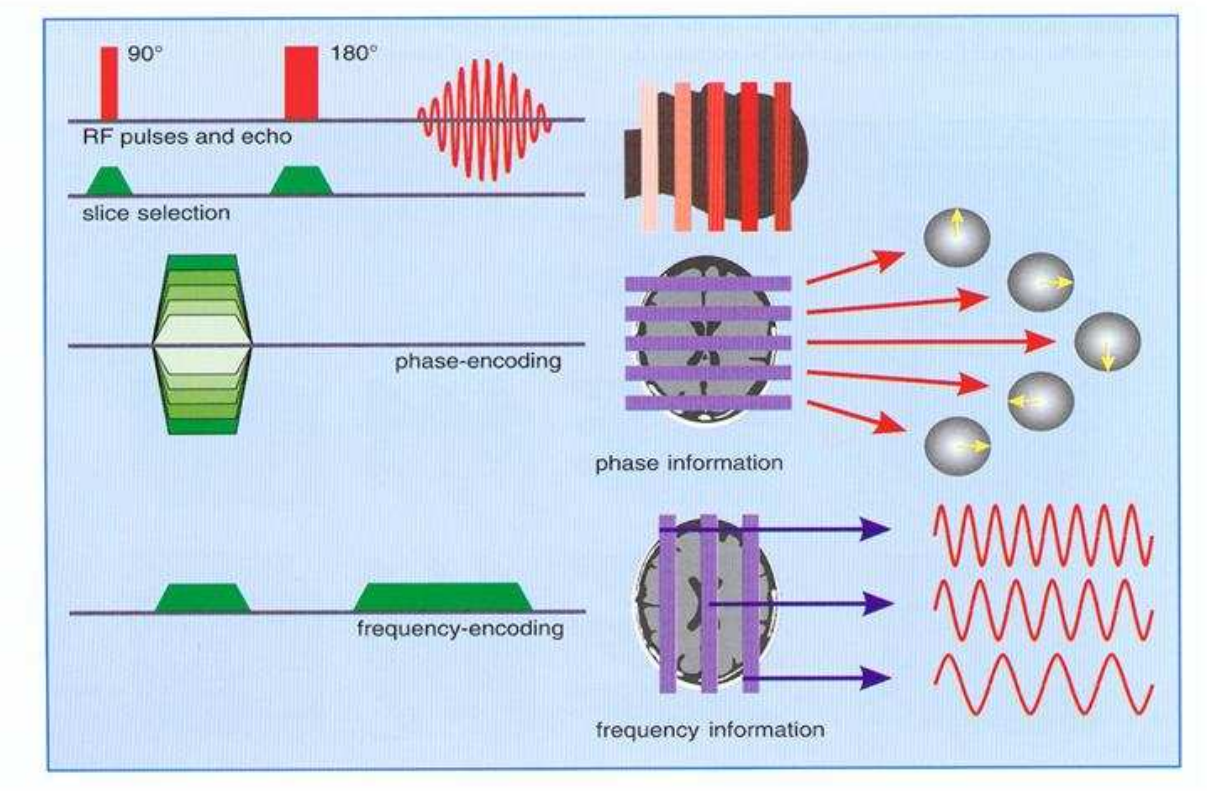


Fig 2.17 (left): Orthogonal orientation of the slice selecting gradient (z-axis), the frequency-encoding gradient (x-axis) and the phase-encoding gradient (y-axis)

Fig 2.18 (below): Spatial encoding for a spin echo experiment (Rinck et al., 2001)



The slice selecting gradient is briefly switched on at the same moment as the RF pulse is applied. This causes a linear variation in the magnetic field along the z-axis. The Larmor frequency of precession of the spins is proportional to the strength of the magnetic field. The result of this gradient is therefore that the precession frequency of the spins depends on the position along the z-axis. As said before, the frequency of the RF pulse needs to match the spins precession frequency to incline the net magnetization in the transverse plane. This means that by selecting an RF pulse with a specific range of frequencies, it is possible to

measure the relaxation in a specific 2D slice of the brain. By changing either the steepness of the gradient or frequency range of the RF pulse, slice thickness can be determined.
Spatial localisation in a slice is determined using phase and frequency encoding gradients. The phase encoding gradient is switched on for a brief period along the y-axis between the RF pulse and MRI signal measurement. Immediately after application of the RF pulse, no difference in phase has yet developed. Due to the phase encoding gradient the spins experience different magnetic field strengths along the y-axis and will start to precess at different frequencies. After the phase encoding gradient is switched off, the spins will precess at the same frequency again, but no longer in phase. Now, the phase of each spin will depend on its localisation along the y-axis.

The readout or frequency encoding gradient is applied along the x-axis during the measurement of the MRI signal. Before the frequency encoding gradient is applied all spins in the selected slice precess at the same frequency. The result of the frequency encoding gradient is the differentiation in precession frequency depending on the localisation of the spins along the x-axis in the selected slice.

After each signal component has experienced a different phase encoding and frequency encoding gradient, its exact spatial reconstruction can be specifically and precisely located by the Fourier transformation analysis. Spatial resolution is directly related to the number of phase encoding gradients used (Rinck et al, 2001; Cox et al, 1994).

k-Space

The k-space raw data matrix consists of an area to be filled with the information needed to form an MR image (Fig 2.19).

The coordinates of k-space are called spatial frequencies. They are filled depending on gradient strength of the frequency encoding and phase encoding gradient, moving from low gradient strength to zero gradient strength (centre) and further to high gradient strength. In a standard spin echo sequence, each 90° pulse creates a new line in the k-space. The length of

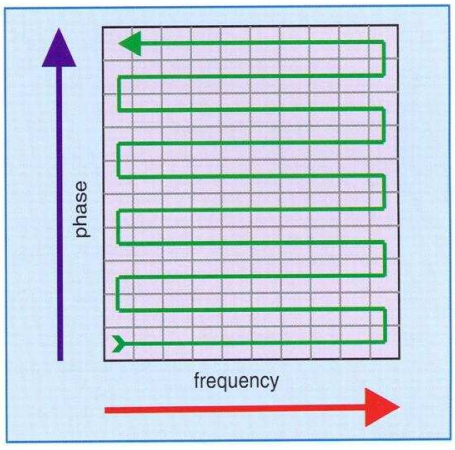


Fig 2.19: K-space (Rinck et al., 2001).

the line is determined by the strength of the frequency encoding gradient and the sampling time, whereas its position is defined by the strength of the phase encoding gradient. As soon as the k-space is filled, each data point is then Fourier transformed in the x-direction to extract frequency information. The second Fourier transformation is performed in the y-direction to extract phase information. The output is a matrix showing an image which corresponds to the bulk of MR signals from each point (Rinck et al, 2001; Cox et al, 1994).

Rapid imaging: Echo-Planar imaging

Echo Planar Imaging (EPI) is the fastest imaging sequence currently available and is the most commonly scanning technique used for fMRI. The EPI technique is based on the principles of a single RF pulse, followed by the rapid switching of a strong gradient to form a series of gradient echoes, each of which is given a different degree of phase encoding and thus can be reconstructed to form an image (Fig 2.20).

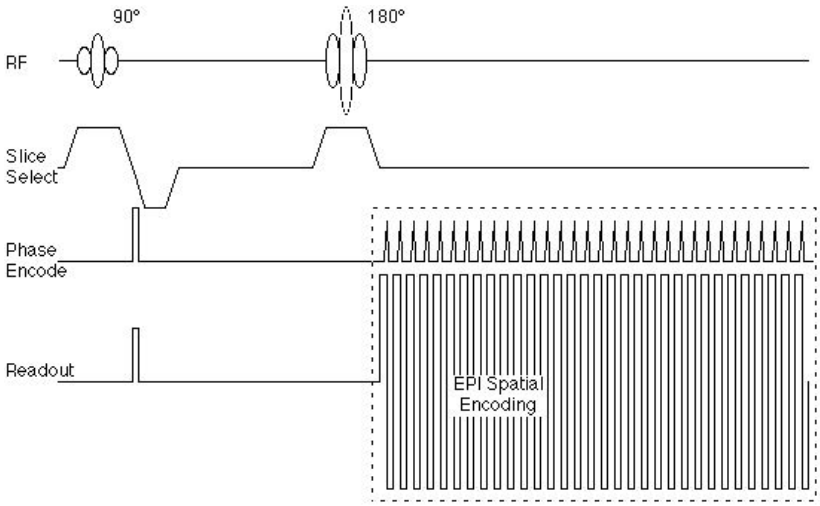


Fig 2.20: Echo planar imaging sequence (Cohen, 2000).

As comparison, a typical MR image is formed from 128 repeated samples and has an imaging time of more than 6.5 minutes; the EPI approach collects all of the image data, for an image of the same resolution, in 40 to 150 milliseconds (Fig 2.21). The faster imaging sequences help to reduce motion-related artefacts. The speed at which images are obtained can give unique insight into dynamic processes (Rinck et al, 2001; Cox et al, 1994).

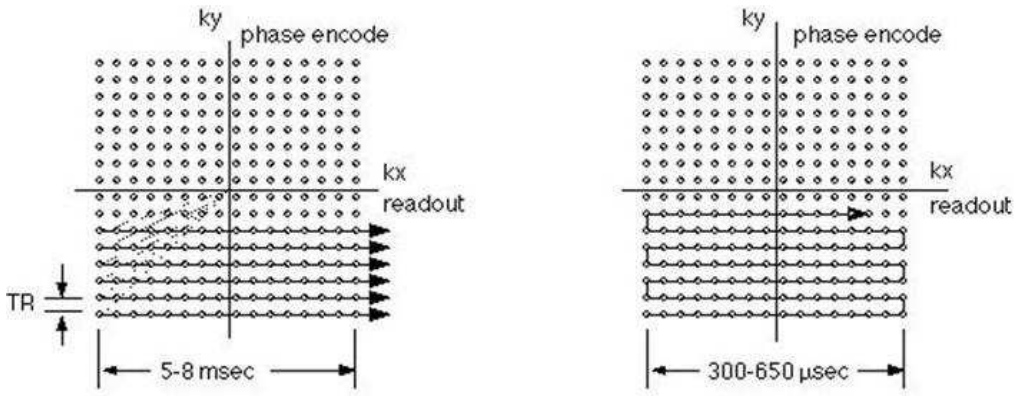


Fig 2.21: Filling of the K-space in conventional imaging (left) and echo planar imaging sequence (Cohen, 2000)

The MR image

A MR image consists of small elements, pixels, whose gray-scale intensity (brightness) is related to the amplitude of the MR signal arising from corresponding volume elements, voxels, in a tissue slice (Fig 2.22). The image matrix determines the number of pixels used to construct an image, determined by steepness of the read-out (frequency-encoding) gradient (x-axis) and the number of phase-encoding steps used (y-axis) for a given field of view (FOV). The actual volume of each voxel is defined by the field of view, the matrix size and the slice thickness selected.

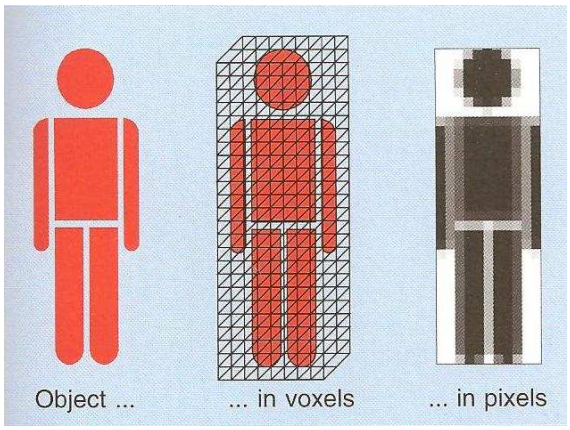


Fig 2.22: The MR image. To image an object, this object is mathematically divided into volume elements. In each volume element, the signals are averaged and turned into a anumber which represents a certain level on the grey scale. These numbers are used to create a picture consisting of pixels (Rinck et al., 2001).

The ability to resolve closely spaced anatomic details is defined as spatial resolution. Since the MRI signals from nuclei in a voxel are averaged, details within a voxel are lost during

image acquisition and reconstruction. Thus, one would expect that small voxel dimensions correlated with a greater amount of resolved fine detail. However, resolution alone does not determine whether a detail is distinguishable within an image, contrast and signal to noise ratio are also determining factors.

The contrast of an MR image is defined as the intensity difference between two tissues. It is a complex function of factors including inherent characteristics of the sample and the pulse sequence parameters.

The brightness of each pixel in an MR image is defined by the signal intensity of its corresponding voxel in the tissue slice. However, the detection coil in an MR imaging system also detects "noise". Noise is RF emissions from tissue surrounding the voxel. The signal intensity is determined by the number of excitated spins, and is directly proportional to voxel size. Noise, by comparison, is independent of the voxel size. Therefore, decreasing the voxel size decreases the signal to noise ratio or the pixel brightness (Rinck et al, 2001; Cox et al, 1994).

2.2.2 From neural activation to the fMRI signal

FMRI and MRI have in common that the signal is based on nuclear spin characteristics. FMRI enables the visualization of activated cortical brain regions during perceptual and cognitive processing. FMRI is mainly based on the linkage between neuronal activity and haemodynamic changes. Early fMRI studies had to use contrast agents to demonstrate changes in cortical perfusion. This disadvantage was resolved by the demonstration of fMRI acquisitions using Blood Oxygenation Level Dependent (BOLD) contrast (Ogawa, 1990).

Principle of the BOLD contrast

BOLD fMRI is a non-invasive method using an endogenous contrast mechanism, depending on differences in magnetic susceptibility between oxyhaemoglobin and deoxyhaemoglobin. The magnetic susceptibility is a mass for the impact of a substance on the magnetic field and influences the T_2* decay. Oxygenated arterial blood contains oxygenated haemoglobin, which is diamagnetic and has a small magnetic susceptibility effect. Therefore, oxyhaemoglobin does not significantly alter the regional magnetic field and does not greatly affect tissue T_2*. Deoxyhaemoglobin, is paramagnetic due to the four unpaired electrons, and disturbs the local

magnetic field in a region of tissue leading to the large observed magnetic susceptibility effect resulting in faster T_2* decay (Chen and Ogawa, 2000; Rosen et al., 1994)

The haemodynamic response function

The haemodynamic response function (HRF) (Fig 2.23) is the function of the BOLD fMRI signal against time in response to a temporary increase in neuronal activity (Bandettini, 2000; Weisskoff, 2000; Rosen et al., 1994).

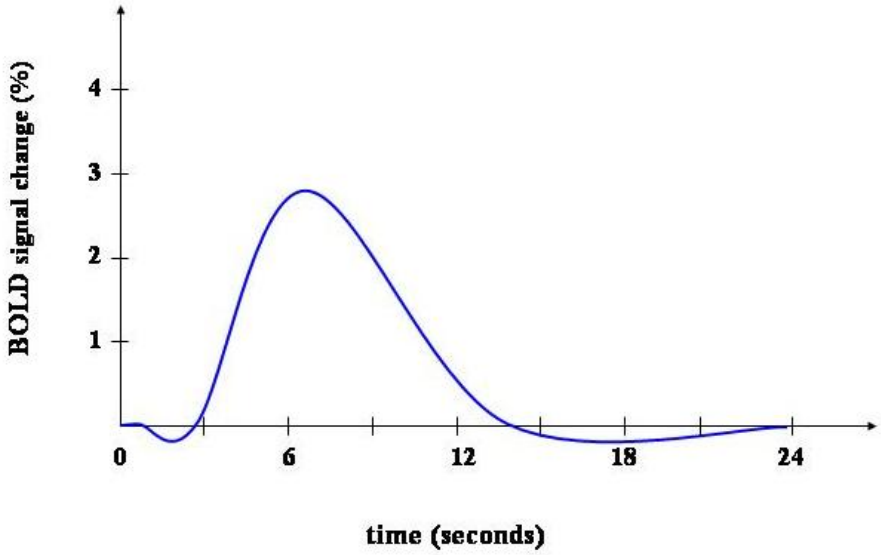


Fig 2.23: The haemodynamic response function (HRF).

When nerve cells are active they consume oxygen carried by haemoglobin in red blood cells from local capillaries. This causes initially a decrease in BOLD fMRI signal due to an increase in the relative level of deoxyhaemoglobin in the blood. This drop, however, is very small and not always found (Heeger et al. 2002; Detre et al. 2002). Following this initial decrease (approximately 500 ms to 2 s after onset of stimulation), the BOLD fMRI signal increases and reaches a maximum after approximately 6 seconds after onset of stimulation. This positive BOLD fMRI signal change is much larger as the initial decrease, as a result of an overshoot in oxyhaemoglobin. Namely, the blood flow in activated regions might increase by 20-40%, whereas the increase in oxygen consumption during an activated state of brain tissue is only 5%. The combination of these effects results in a decrease of the deoxygenated haemoglobin concentration in the neighbourhood of the activated neurons. Finally, the BOLD

fMRI signal declines with a late undershoot under the initial baseline value as a result of the cerebral blood flow after cessation of stimulation (Weisskoff, 2000; Rosen et al., 1994).

Spatial and temporal properties of the BOLD contrast

The spatial resolution of BOLD fMRI is about 2 to 5 mm, which is superior to many other neuroimaging techniques.

At best, the BOLD fMRI signal would reflect only the haemodynamic changes in the capillaries close to the localisation of the neuronal activity. However, the BOLD fMRI signal is sensitive to eventual contamination of large veins and arteries in the brain. The large arteries are fully oxygenated and therefore barely contribute to a change in signal since the BOLD fMRI signal measures the relative level of oxygenation. In contrast, draining veins are only 70% oxygenated. The decrease in relative oxygenation level in these large veins is larger than in the small capillaries close to the source of the neural activation. This means that the location of the maximum BOLD fMRI signal could be displaced, a few millimetres towards the large veins. Furthermore, usually these large veins drain an area of the brain that is larger the area of neural activation. This results in the activation area appearing larger than it really is (Bandettini, 2000).

The temporal resolution of the BOLD fMRI signal includes two factors the optimal stimulus presentation rate to realize a maximum BOLD fMRI signal change, as well as the optimal stimulus duration. In order to maximize both the signal and the number of activation cycles in a time course, an on/off switching rate study can be performed. Because the time to reach the baseline after cessation (off state) of activity is slightly longer than the time to reach the plateau during activation (on state), the signal becomes saturated in the on state with the faster on/off frequencies (Fig 2.24). Bandettini and Cox (1998) have shown that with a constant on/off rate of 2 s on and 2 s off, it is possible to induce a measurable hemodynamic response (Bandettini, 2000).

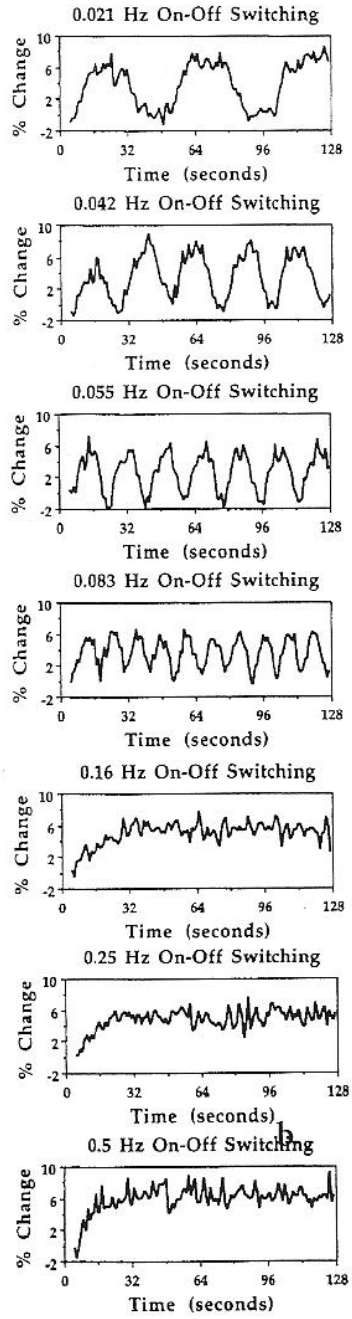


Fig 2.24: Signal of a region of interest in motor cortex obtained during he cyclic on/off finger movement. As the on-off frequency is increased from 0.024 Hz to 0.05 Hz, the activation-induced amplitude becomes decreased and the signal becomes saturated in the on state (Bandettini, 2000).

2.2.3 FMRI task design

When designing an fMRI experiment, one has to be conscious of the fact that the brain is continuously active. Only 1 to 10% of the variation in blood oxygenation level is actually task related. The optimal experimental design depends on the research question posed and maximizes both the statistical power and the power to infer. Two main types of experimental designs are used in fMRI research: block design and event-related design.

Block design

The first type of experimental design is the block design (Fig 2.25), also called boxcar design (Aguirre & D'Esposito, 2000). In the original block design two conditions are alternately presented in blocks during the experiment. Each block represents several trials of one condition.

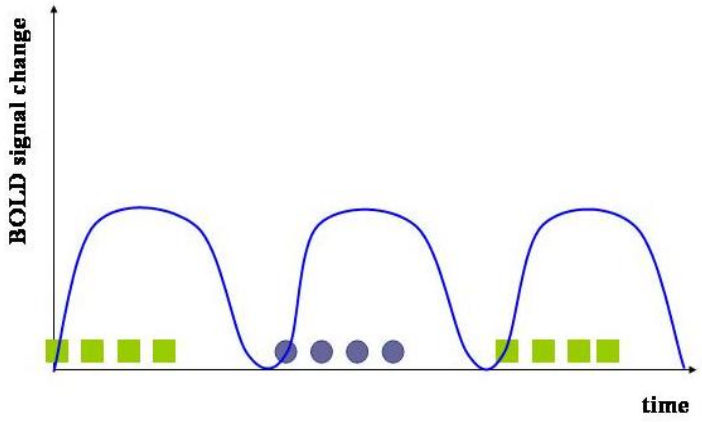


Fig 2.25: Block design with two conditions. Condition A in green and condition B in blue.

By making the conditions differ in only the cognitive process of interest, the fMRI signal that differentiates the conditions should represent this cognitive process of interest. This is the so-called subtraction paradigm (Posner et al., 1988). The subtraction paradigm relies upon two assumptions: "pure insertion" and linearity. Pure insertion represents the idea that a cognitive process can be added to a set of already active cognitive processes without affecting them. The second assumption off cognitive subtraction is that the transformation of neural activity into fMRI signal is linear (Zarahn et al., 1997).

In a block design, only one condition is presented in each block, randomization of stimulus types is not possible within a block. This makes the type of stimulus within each block very predictable. As a consequence, participants may become aware of the order of the events and might anticipate (Johnson et al., 1997).

Because of these weak points, block fMRI experiments are not capable of strong inference. Nevertheless, block designs also have a significant advantage namely their superior statistical power. The increase in fMRI signal in response to a stimulus is additive. This means that the amplitude of the HRF increases when multiple stimuli are presented in rapid succession. When each block is alternated with a rest condition in which the HRF has enough time (optimal block length 14-20 s) to return to baseline, a maximum amount of variability is

introduced in the signal. Therefore, block designs offer considerable statistical power (Zarahn et al., 1997).

When more than two conditions are included in the design several options, on how to order these blocks in the block design, are open (e.g. fixed: A-B-C-A-B-C-A-B-C; or random: A-C-C-B-A-B-C-B-A). Though, randomization of the block order decreases the statistical power (Aguirre & D'Esposito, 2000).

Event-related design

In an event related design the course of the HRF following each stimulus presentation is estimated (Fig 2.26). The multiple HRF's following a single type of stimulus can be averaged. The signal change in the BOLD fMRI signal following a single stimulus presentation is small; resulting in a low statistical power for event related designs (Dale and Buckner, 1997; Josephs et al, 1997 and Zarahn et al., 1997).

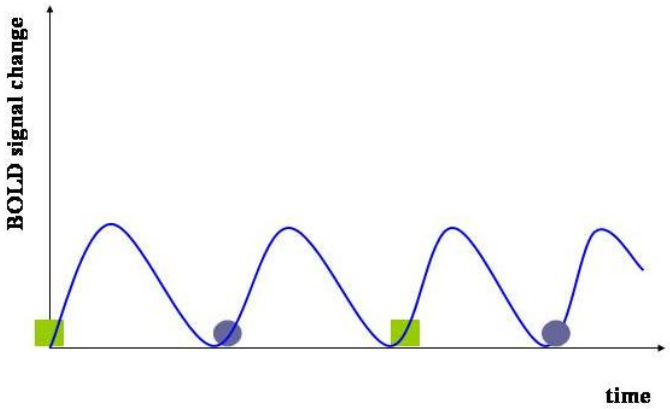


Fig 2.26: Event-related design with two conditions. Condition A in green and condition B in blue.

As already mentioned in the section of the block design; when two or more stimuli are presented in relatively rapid succession, the BOLD fMRI response increases roughly linearly (Dale & Buckner, 1997; Donaldson et al., 2001). This approximate linearity is important in event-related designs where stimuli are often presented in rapid succession. It means that the HRF for an individual stimulus can be estimated despite the overlap in HRF's for successive stimuli (Aguirre & D'Esposito, 2000).

2.2.4 FMRI analysis

The aim of an fMRI experiment is to determine which regions in the brain can be associated with the processing of a certain task. Between the datasets containing hundreds of brain volumes collected during fMRI acquisition for each subject and this final goal, are several

steps. The step where the dataset is temporally adjusted is known as slice timing correction. The steps where the dataset is spatially adjusted are spatial realignment, spatial coregistration, spatial normalization and spatial smoothing. The final step is the statistical analysis.

Slice timing correction

In an fMRI dataset each volume of the entire brain consists of a number of slices and each slice consists of a number of voxels. Generally, the different 2D slices making up a 3D volume are not all collected at the exact same time. In other words each slice covers a different time interval of the BOLD response. However, in the statistical analysis the assumption is made that the entire volume is collected at one point in time, so each voxel in a volume is assumed to represent the same moment in time. To correct for this, the individual slices of a volume must be adjusted in the temporal domain. This is done by performing a temporal correction for the differences in acquisition time between the slices. This is referred to as slice timing correction. After the slice timing correction is performed, the BOLD response starts at the same time for each voxel in each slice in a volume (Smith, 2001).

Spatial realignment

Even though subjects are usually instructed to move as little as possible inside the scanner, some head movement is unavoidable. The main result of head movements is that the same voxel does not necessarily represent the same location in the brain throughout time (Ashburner and Friston, 2000 and 2003; Brammer, 2001). The statistical analysis, however, assumes that the same voxel does represent the same location in the brain throughout time. Based on this assumption, head movements can finally appear as false fMRI activations or increase the noise in the signal which decreases the statistical power.The removal of movement effects is done by repositioning all volumes in the same time series with respect to the reference volume. This process is referred to as spatial realignment and is conducted for each subject separately. The new value of the fMRI signal for a voxel after the realignment is estimated by interpolation from the values of the fMRI signal of neighbouring voxels (Ashburner and Friston, 2003; Ashburner and Friston, 2000; Brammer, 2001).

It should be noted that realignment not only adjusts for actual head movement, but also for apparent movement. As the fMRI scanner heats up during a session it appears as though the

head drifts slightly. This is an artefact arising from the scanner and is also corrected for by realignment.

Normalisation

During a fMRI experiment, datasets are usually collected for several subjects. However, all brains differ in orientation, size and shape. To be able to make comparisons in BOLD activation for a certain task across and within subjects the voxels in the brain of each subject must represent the same anatomical location. When mapping different brains to a standard brain it is possible to compare results between different research groups. Therefore, the orientation, size and shape of the brains of individual subjects are changed to match the orientation, size and shape of a standard brain. The most commonly used standard brain is the MNI template (Tzourio-Mazoyer et al., 2002). After the normalization, the new value of the fMRI signal for a voxel is estimated by interpolation from the values of the fMRI signal of neighbouring voxels. This matching of individual brains to a standard brain is known as spatial normalization (Ashburner and Friston, 2003; Ashburner and Friston, 2000; Jenkinson, 2001).

Smoothing

Even though smoothing spatially blurs images and reduces spatial precision, it also has some positive effects. Firstly, smoothing the dataset increases the signal to noise ratio in the fMRI signal by removing the high spatial frequencies (noise). Secondly, smoothing removes small frequency differences, so comparisons across subjects are made easier.

Smoothing is generally performed by convolving the 3D volume with a 3D Gaussian kernel. In other words, each data point is multiplied by a curve in the shape of a 3D normal distribution. The shape of the 3D smoothing curve should match the spatial shape of the signal of interest, so that frequencies matching the frequencies of the 3D smoothing curve are emphasized and frequencies not matching the frequencies of the 3D smoothing curve are filtered out. The shape of the smoothing curve is defined by a normal distribution function with a Full Width Half Maximum (FWHM) of typically two or three times the voxel size (Smith, 2001).

Statistical analysis: the General Linaer Model (GLM)

To define which brain regions are significantly activated for a specific task, a statistical analysis based on the GLM is used. However, before fitting the BOLD fMRI response in a model, intensity normalization and temporal filtering have to be performed.

Intensity normalisation between different fMRI datasets is the re-scaling of the intensities to a common, predefined mean value also refered to as grand mean scaling (Kiebel & Holmes, 2003; Smith, 2001). This normalization of the intensity values is necessary to make valid comparisons over and between different fMRI datasets.

Physiological parameters such as breathing and heartbeat or scanner drift are reflected as low frequencies in the fMRI dataset and are not part of the actual signal. Using a highpass temporal filter these low frequencies can be removed or reduced, which increases the SNR (Kiebel & Holmes, 2003; Smith, 2001).

The next step, after applying intensity normalization and temporal filtering, is to fit the BOLD fMRI response on a GLM. Following basic formula is used in the GLM:

$$Y(j) = beta * x(j) + c + E(j)$$

with j indexes the volume, Y is the observed value for a voxel in volume j, beta is the slope of the linear regression line, x is the value of the predictor variable for a voxel in volume j, c is the intercept of the linear regression line and E is the error in volume j. This equation is performed on each voxel in each volume of the fMRI dataset (Kiebel et al., 2003; Friston et al., 1995a; Lange, 2000; Worsley, 2001) and can be re-formulated in terms of matrices:

$$Y = X * B + E$$

with Y is a matrix containing all the observed data with a column for each voxel and a row for each fMRI volume, X is a matrix containing the predicted data (also called design matrix) with a column for each predictor variable and a row for each fMRI volume, B is a matrix containing the slopes and intercepts (parameter matrix) and E is a matrix with the normally distributed error terms

In the design matrix the general shape of the BOLD response over time for each predictor variable (e.g. stimulus function and task performance) is modelled. However, derivatives of these predictors, such as the temporal and dispersion derivative, are often also modelled. The temporal derivative allows for variations in the onset of the BOLD response, whereas the dispersion derivative allows for variations in the width of the BOLD response. To fit the modelled BOLD response shape with time course of each voxel, the parameter matrix is estimated using lineair regression. The error matrix reflects the temporal autocorrelated, unexplained variance in the model after estimation of the parameter matrix. In the next step a t-test is used to determine for each voxel separately whether any linear combination of the parameters in the parameter matrix explain as significant amount of the variance in the BOLD fMRI dataset (Kiebel and Holmes, 2003; Friston et al., 1995a; Lange, 2000; Worsley, 2001).

Chapter 3

The role of left and right Visual Word Form Area (VWFA) in visual processing of words: an event-related fMRI study

3.1 Abstract

Recent neuroimaging studies have proposed a visual familiar supra-letter and word-level feature based recognition system in an area located lateral to the midportion of the left fusiform gyrus, also proposed as the VWFA (e.g. Cohen et al. 2000). The existence of such a region is a matter of discussion (Price and Devlin, 2003 and 2004; Vigneau et al., 2005). Vigneau and colleagues argue that the visual specialisation for words might operate through the dynamics of the interaction between the left and right VWFA, rather than rely on the regional variation of activity in the left VWFA alone. To further investigate the issue of hemispheric specialisation of the visual cortex and especially of the VWFA we conducted an event-related fMRI study. Brain activation was measured in 16 right-handed, healthy males during visual processing of words, pseudowords and false fonts. Stimuli were presented lateralized, using visual half-field technique and centrally. Determination of the Lateralization Index (LI) of the brain activation pattern, as well as effect of visual field of presentation and stimulus type were based on a Region of Interest (ROI) analysis. Our results revealed higher BOLD signal intensity change in the visual cortex contralateral to the visual field of stimulus presentation compared to the ipsilateral visual cortex reflecting the crossing of visual pathways. Further, we found that in both the left and right VWFA the BOLD signal intensity change was significant higher for visual processing of words compared to false fonts. Finally, the activation pattern of the VWFA was left lateralized, except for words initially processed in the right visual cortex. The bilateral activation of the VWFA for words presented in the left, but not in the right or central visual field, supports Vigneau's hypothesis that the superiority of word recognition in the left VWFA is the result of a reduced activity in the right VWFA under left hemispheric control.

3.2 Introduction

The human visual system is composed of multiple visual cortex areas. The primary visual area, also known as striate cortex or V1, corresponds to Brodmann Area (BA) 17 of the occipital gyrus. The extrastriate cortex, including V2, V3, V4, and V5, covers BA 18 and BA 19 (Clarke, 1990). Ungerleider and Mishkin (1982) proposed that visual processing is anatomically divided into two functionally differentiated streams: a 'ventral stream for object recognition' and a 'dorsal stream for object localization'. The ventral stream includes projections from the occipital lobe to the inferior temporal cortex, whereas the dorsal stream covers the projections from the occipital to the posterior temporoparietal cortex. As one moves from posterior to anterior through the consecutive areas of both visual streams, the stage of visual processing increases with each stage providing specific constraints on the neural encoding of the stimulus (Van Essen and Maunsell, 1983; Cohen et al., 2003). The ventral occipito-temporal cortex, at the end of the ventral stream, plays an essential role in visual form processing, including face (Kanwisher et al., 1997), object (Hanson et al., 2004) and word recognition (Cohen et al. 2000, 2002, 2003; Cohen and Dehaene, 2004; Vinckier et al., 2007). Some authors have argued for a modular organization of ventral occipital temporal cortex in which different parts are involved in the recognition of specific object categories (Spiridon and Kanwisher, 2002), but the extent to which these functions are modularly organized is a matter of discussion (Haxby et al., 2001).

Recent neuroimaging studies have proposed a visually familiar feature based word recognition system in an area located lateral to the midportion of the left fusiform gyrus, also called the VWFA (Cohen et al. 2000, 2002, 2003; Cohen and Dehaene, 2004; Vinckier et al., 2007). The left VWFA responds to words and readable pseudowords (pronounceable letterstrings) more than to letter strings or checkerboards and recent research by Vinckier suggest a posterior to anterior gradient of increased sensitivity to larger and higher-level components of words within the visual word form system. The existence of a region specialised for processing visual familiar supra-letter and word-level features has become the focus of a debate spanning both sensory modality and stimulus specificity (Price and Devlin, 2003 and 2004; Vigneau et al., 2005). Vigneau and colleagues reported a larger functional asymmetry index favouring the left hemisphere VWFA during word than non-word (non-pronounceable letter strings) reading. Based on this observation they hypothesized that the visual specialisation for words may in fact operate through the dynamics of the interaction between left and right VWFA rather than rely on the regional variation of activity in the left

VWFA alone. Support for such a dynamic interhemispheric mechanism comes from a study on perception of species-specific calls in monkeys by Poremba and colleagues (2004). These authors indeed showed that species-specific calls elicited more activation in the left superior temporal than in its right counterpart, while other types of sounds did not. However, when monkeys had been submitted to comissurectomy, this asymmetry disappeared. Poremba et al. interpreted this finding as an indication that the leftward functional asymmetry index observed in the intact monkey was the result of a reduced activity in the right superior temporal gyrus under left-hemisphere control.

In the current study, we further investigate the issue of hemispheric specialisation of the visual cortex and especially of the VWFA. A traditional, behavioural neuropsychological method to study functional cerebral specialisation in healthy subjects is based on the use of visual half-field presentation. The visual half-field presentation technique takes advantages of the crossing of the nasal optic fibres in the optic chiasma. This implies that a stimulus displayed in the right visual field (RVF) is initially projected and processed by the left hemisphere (LH), whereas a stimulus presented in the left visual field (LVF) is received and processed in the right hemisphere (RH).

To successfully manage unilateral stimulus presentation it is necessary that the participant is fixating centrally when the stimulus is presented. In order to maintain unilateral presentation the stimulus presentation should be completed before an eye movement towards the stimulus can be executed and the stimulus is fixated upon. Saccades are rapid eye movements that move the fovea towards the target stimulus (Westheimer, 1973). The mean saccadic latency ranges from 150 ms to 200 ms (Carpenter, 1988). The stimulus duration in this study was 200 ms, which has been suggested as an acceptable stimulus exposure time (Cohen et al., 2002).

When deciding where in the visual field to present the stimuli, the neuroanatomy of the visual system must be taken into consideration. As mentioned before, the nerve fibres of the primary visual system are organized in such a way that stimuli received by the temporal hemiretinae are projected to the ipsilateral hemisphere, whereas stimuli received by the nasal hemiretinae are projected to the contralateral hemisphere. However, ipsilateral and contralateral projections are not neatly divided and a certain amount of overlap occurs between the two visual fields as a result of crossover in the commissural connections in the corpus callosum (Houzel et al., 2006). There for in order to maximise the chance for unilateral stimulus presentation, it is important to present stimuli outside this region of overlap. Estimates of the size of this bilateral strip, range from 0.5° wide (Wyatt, 1978) to 3° wide (Bunt et al., 1977).

In the current study stimuli were presented at 4° from fixation. Lavidor and Ellis (2003) have suggested that, based on behavioural data, this bilateral stripe does not exist. Instead, they proposed that the fovea is vertically split with each hemi-fovea projecting to the contralateral hemisphere. However, this finding should be treated with caution and a wide range of evidence supporting bilateral projection of stimuli presented foveally is offered by Lindell and Nicholls (2003).

One potential issue when presenting stimuli unilaterally in peripheral vision is that visual acuity is highest at the fovea and decreases toward the periphery (Nazir et al., 1998, 1992). Thus stimuli presented at different distances from fixation are not perceptually equivalent. Besides, changes in peripheral acuity are not symmetrical, with nasal peripheral acuity being poorer than temporal peripheral acuity (Regan and Beverley, 1983). Thus, along with controlling the distance of the inside edge of the stimulus from central fixation, it is also important to consider how wide the stimulus is. The outside edge of a stimulus is perceived with lower visual acuity, which may have consequences for the processing of that stimulus, particularly for stimuli such as words, as initial letters are known to play an important role in enabling stimulus identification (Brysbaert et al., 1996). To counteract this lateralized bias in the word processing process we decided to use vertical stimulus presentation (Eviatar, 1999).

Apart from lateralized stimulus presentation, stimuli were also presented in the central visual field (CVF) as reference condition reflecting the standard visual field for reading. FMRI was used to study the neural networks during the visual processing of words, pseudowords (pronounceable letter strings), and false fonts (strings of Arabic signs) in an event-related design. Determination of the LI of the brain activation pattern was based on a ROI analysis. The effects of visual field of presentation and stimulus type on the BOLD response were questioned using a ROI analysis.

3.3 Methods

3.3.1 Participants

Sixteen healthy, right-handed (Edinburgh handedness inventory, Oldfield 1971) males (mean age 25.19 years, range 21-31 years) with normal or corrected-to-normal visual acuity participated in the study. Participants taking medication which could affect the central nervous system during the last six months were excluded. All participants grew up monolingual, were German native speakers, and had no knowledge of Arabic. Only the fMRI data of subjects who passed the attention task were included. Prior to participation all participants gave written consent according to the Declaration of Helsinki. Two participants were excluded due to failure in data recording, and clinical background. This study was approved by the local ethical commission.

3.3.2 Task, stimuli and fMRI Paradigm

A silent reading task with variable stimulus types (words, pseudowords and false fonts) was chosen. Words were high-imagery nouns (Fiebach and Friederici, 2004) and matched for usage frequency (Blair et al., 2002; Coney, 2005). Pseudowords, derived from real words by randomizing the letters, were pronounceable. Strings of Arabic signs were used as false fonts. To control for subjects' alertness during the experiment, without having non-language related motor activation, a second task was included by a fourth category of stimuli: animal names. The subjects were instructed to read the stimuli silently and press a button, attached around the upper leg, when the presented stimulus was an animal name. This fourth category was later not included in the SPM model. All stimuli were composed of four or five letters or signs (Whitney and Lavidor, 2004; Lindell et al., 2002; Mechelli et al., 2000) in a white font on a black background presented vertically.

Stimuli were randomly presented centrally or lateralized (4° from fixation cross) every 3 500 ms for 200 ms, followed by a 3300 ms fixation cross. The experiment consisted of three runs which were randomized between subjects. Each run counted 48 words, 48 pseudowords, 48 false fonts and 12 animal names. For each category; stimuli were equally divided over the CVF, the LVF and the RVF. Between runs the words, pseudowords and false fonts used, were the same; only the presentation field was changed. For the fourth stimulus type, animal names, stimuli were not repeated between runs.

3.3.3 Imaging Parameters

Blood oxygen level dependent (BOLD)-fMRI was performed on a 1.5 Tesla Philips Gyroscan Intera system (Philips Medical Systems, Netherlands) with standard head coil. To verify subject positioning and to plan axial (AC-PC) slice acquisition a sagital scan was obtained. An echo planar T_2*-weighted imaging sequence was acquired every 3 s during the paradigm using the following parameters: TR = 3000 ms, TE= 50 ms, $\alpha = 90°$, FOV= 256 x 256 mm^2, matrix size = 64 x 64, voxel size = 4 x 4 x 4 mm^3, 32 slices, and 203 volumes per session. Functional scanning was always preceded by 15 s of dummy scans to insure steady-state magnetization.

Due to a time difference in image acquisition frequency and stimulus presentation frequency, there is a delay between image acquisition and stimulus presentation called temporal jittering. The advantage of temporal jittering is a better detection of the BOLD response curve.

Subjects wore earplugs and the placement of foam pads around the subjects' head prohibited movement. A MRI compatible response button was attached around the upper leg of the subject easily accessible with the right hand. In this way the subject was able to response with a minimum of body movement.

3.3.4 FMRI Data Analysis

Preprocessing

Image processing was performed using SPM2, developed by the Wellcome Institue (London, UK) running on MATLAB 6.1 (The MathWorks, Natrick, USA), based on the general linear model (Friston et al., 1995 a and b). The individual subject (first level) analysis included following steps: (1) slice timing was used to correct for differences in acquisition time between slices; (2) motion correction was done by realignment of all images to the first image. Subjects whose images had more than one-voxel motion were rejected; (3) all images were normalized to a standard MNI template brain; (4) spatial smoothing using a Gaussian kernel of FWHM 8 mm; (5) modeling of the expected hemodynamic response function (hrf) and first derivative (hrf') with the appropriate event-related design (only the former function was used for statistical contrasts); (6) filtering of the time series with the value of 128 s for the cut-off period of the high-pass filter.

Group Analysis (SPM2)

The results of the individual data analysis were submitted to a random effect group (second level) analysis. To reveal BOLD activation during visual processing of false fonts, pseudowords and words; a one sample t-test was conducted for each of the following contrasts: words CVF, words LVF, words RVF, pseudowords CVF, pseudowords LVF, pseudowords RVF, false fonts CVF, false fonts LVF, and false fonts RVF. In a second part, one sample t-test were performed for the contrasts comparing lateralized with central stimulus presentation (RVF and LVF > CVF; CVF > RVF and LVF) for each stimulus category separately. Clusters were considered significant if they reached an activation threshold of $p_{FDRcorr} < .05$ (voxel-level) and $p_{corr} < .001$ (cluster-level). Automated anatomical labelling (AAL) software (Tzourio-Mazoyer et al., 2002) was used to label the peak activations.

For the VWFA [sphere as described by Cohen et al. (2002): centre x = -43 (LH) / x = 43 (RH), y = -54, z = -12 (Talairach space); diameter 5 mm] a small volume correction was accomplished. Peak activations were considered significant for the activation threshold of $p_{FDRcorr} < .05$ (voxel-level). For words presented in the LVF the threshold was lowered to $p_{uncorr} < .001$ (voxel-level).

ROI Analysis

For those regions that revealed significant peak activation in the SPM group analysis, a ROI analysis was conducted.

The ROI analysis used is based on the magnitude of signal change in a ROI defined by the weighted β values (Fernandez et al., 2001; Jansen et al., 2006). The masks used for the ROI analysis are based on the masks in Marsbar_0.38.2 which are matched to the MNI/ICBM templates (Tzourio-Mazoyer et al., 2002). For each ROI two symmetrical masks were built one for the ROI in the LH and one for its´ homologue in the RH. As for the VWFA no standard mask was available, a new mask was build based on the VWFA coordinates described by Cohen and colleagues (2002), a 5 mm sphere with centre x = -43 (LH) / x = 43 (RH), y = -54, z = -12 (Talairach space). For each region a mean maximum β value was calculated as the mean of those 5% of voxels showing the highest level of activation in the respective ROI. The threshold for inclusion in the calculation was then set at 50% of this mean maximum β value. The level of activation or signal intensity change was defined as the mean β value of all voxels exceeding the individually defined threshold.

The hemispheric lateralization can be defined by a LI which is based on the above described ROI analysis. The following formula was used to calculate the LI:

$$LI = [(AL – AR)/(AL + AR)]$$

where AL and AR refer to values of fMRI-measured activity for equal ROIs in the LH and RH hemisphere. Results range from -1 to +1. A negative value represents RH dominance, a positive value LH dominance as previously described by (Binder et al., 1996). Brain activation pattern described by a LI value with $|LI| < 0.20$ are classified as bilateral (Springer et al., 1999).

3.3.5 Statistical Analysis

All statistical data analyses were performed with SPSS software (SPSS 13.0). A repeated measures ANOVA was used to analyse the interaction between visual field and hemisphere. Comparisons between the three stimulus categories (words, pseudowords and false fonts) were performed with the Friedman-Test, a non-parametric test for several dependent variables. A following Sign-Test, a non-parametric test for two dependent variables, was used to conduct multiple comparisons to reveal which stimulus categories were significant different.

3.4 Results

3.4.1 Behavioural data

To be able to control for the participants' alertness during the experiment a semantic decision task was included by a fourth category of stimuli: animal names. The participant was instructed to press a button, attached around the upper leg, when the presented stimulus was an animal name. The stimulus category animal names had an occurrence of 12 out of 156 stimuli. For each subject and each visual field a mean accuracy score was calculated as the ratio of correct against the sum of correct, missed and false responses. Only the fMRI data of subjects who passed the attention task (mean accuracy score > 50 % for each visual field) were included. The group mean accuracy score: CVF = 73 %, S.E.M. = 4.77; RVF = 62 %, S.E.M. = 5.61; LVF = 67 %, S.E.M = 5.59.

3.4.2 Effect of visual field

The visual processing of words, pseudowords and false fonts revealed an overall bilateral activation pattern in the occipital lobe and the fusiform gyrus for all visual fields of stimulus presentation (Fig 3.1, Table 3.1, Table 3.2 and Table 3.3).

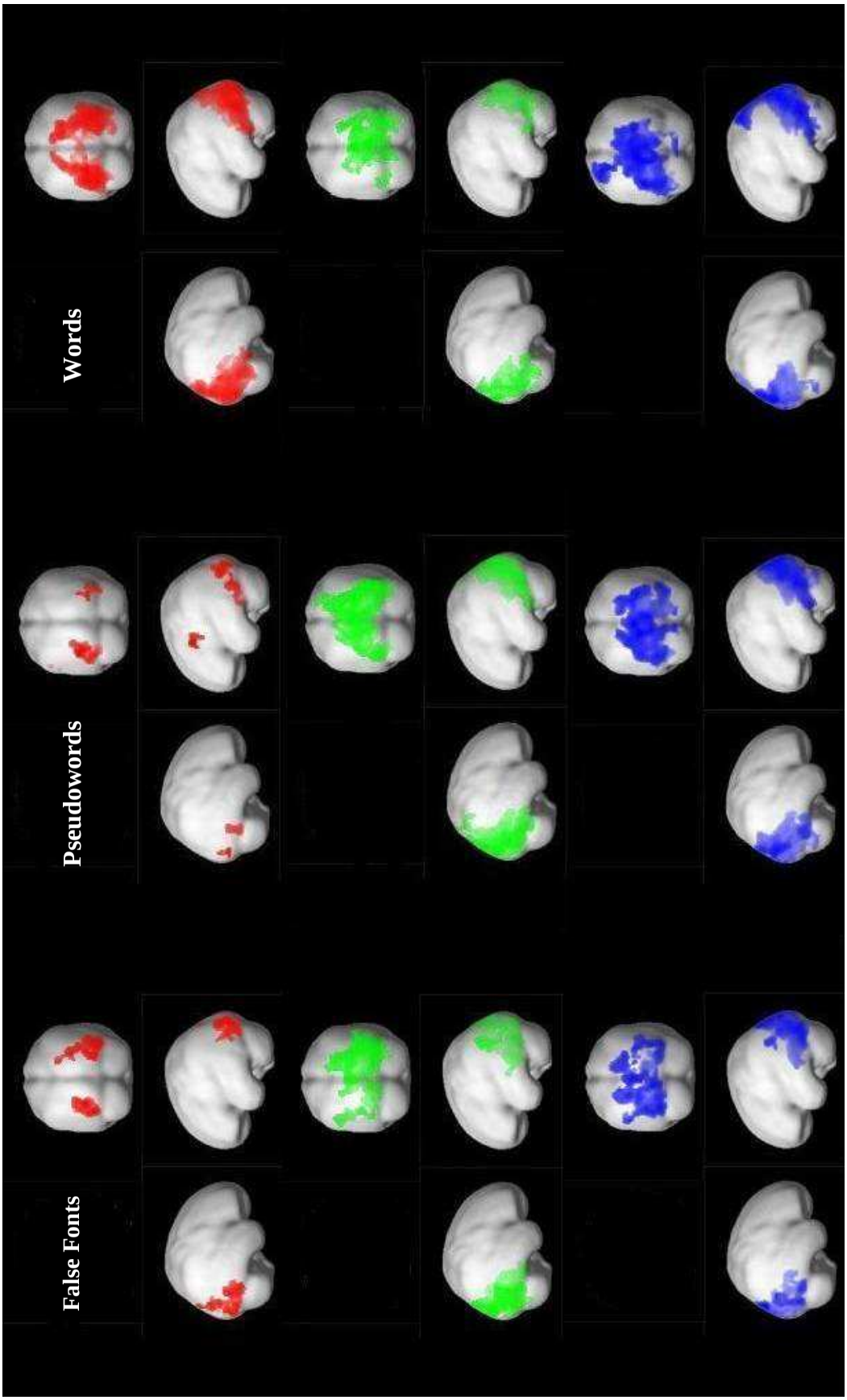


Fig 3.1: Effect of visual field (CVF = red; LVF = green; and RVF = blue) on visual processing of words, pseudowords, and false fonts. Activation is projected onto 3D anatomical template. Clusters were considered significant if they reached an activation threshold of $p_{FDRcorr} <$ .05 (voxel-level) and $p_{corr} <$ .001 (cluster-level).

Despite the bilateral activation pattern, a repeated measure ANOVA assessed a significant interaction, visual half-field x hemisphere, for the regions of the occipital gyrus, the lingual gyrus and the fusiform gyrus (see Fig 3.2 and last rows of Table 3.1, Table 3.2, and Table 3.3). For those regions, the signal intensity change was higher in the hemisphere contralateral to the visual field of stimulus presentation compared to the ipsilateral hemisphere.

The VWFA showed significant activation during the visual processing of words and pseudowords but not false fonts. Calculation of the LI of the VWFA revealed a high trend for left hemispheric predominance. One exception was the bilateral activation pattern of the VWFA during the visual processing of words presented in the LVF (Table 3.1, Table 3.2, and Table 3.3).

Comparison of visual half-field presentation with central stimulus presentation revealed a higher activation in the calcarine sulcus, cuneus and lingual gyrus for lateralized versus central stimulus presentation. In contrast, the central activation showed no increase in brain activation compared to visual half-field stimulus presentation (Table 3.4.)

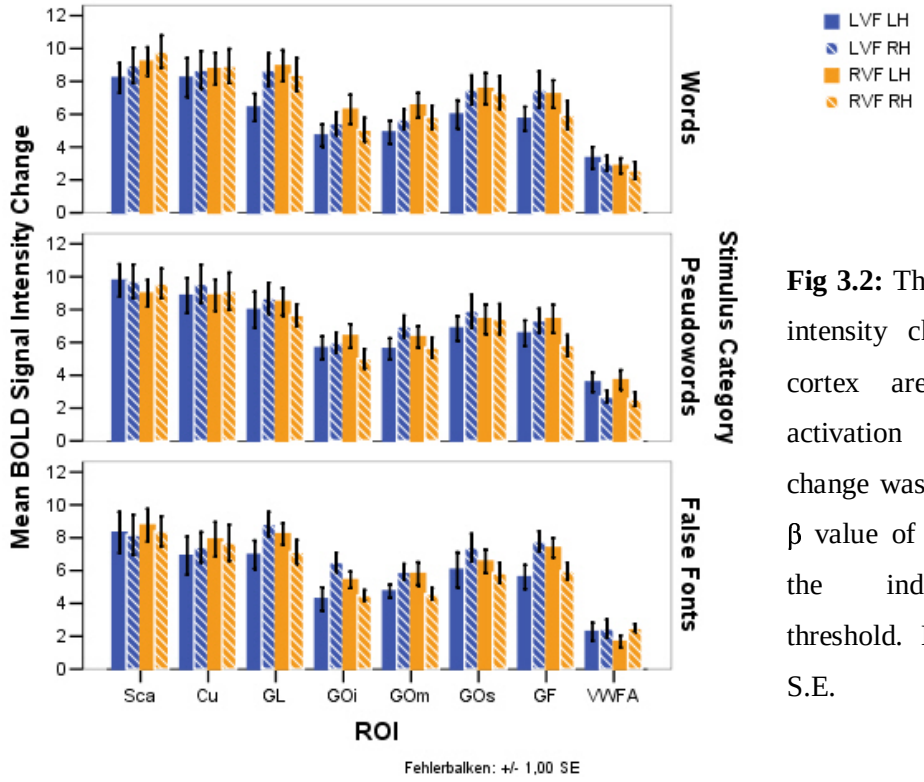


Fig 3.2: The mean BOLD signal intensity change in the visual cortex areas. The level of activation or signal intensity change was defined as the mean β value of all voxels exceeding the individually defined threshold. Error bars: +/- 1.00 S.E.

	false fonts (CVF)							false fonts (LVF)							false fonts (RVF)							
	H	BA	MNI co. x	y	z	peak activation z-value	LI	H	BA	MNI co. x	y	z	peak activation z-value	LI	H	BA	MNI co. x	y	z	peak activation z-value	LI	repeated measures ANOVA: VHF x H *p*- value
Sca	L			----------				L	17	-4	-66	16	4.10	0.01	L	17	0	-100	8	4,86	0.02	n.s.
	R			----------				R			----------				R	17	8	-82	2	3.57		
Cu	L			----------				L			----------			-0.07	L			----------				n.s.
	R			----------				R	17	18	-98	16	4.01		R			----------				
GL	L			----------			-0.07	L	18	-12	-72	-8	3.97	-0.14	L	18	-24	-80	-12	4.80	0.08	< .005
	R	19	42	-82	-16	3.53		R	18	22	-68	-10	4.71		R	18	16	-68	-6	4,16		
GOi	L	19	-34	-70	-4	4.42	-0.08	L			----------			-0.25	L	19	-40	-80	-2	4,16	0.08	< .001
	R	18	28	-96	-6	3,99		R	19	40	-84	0	4.37		R	19	30	-84	-14	3.74		
GOm	L	19	-34	-78	0	4.39	0.01	L	18	-40	-84	2	3,84	-0.11	L	19	-40	-74	8	3.73	0.10	< .005
	R	19	36	-88	22	3.86		R	18	40	-84	4	4.24		R	19	38	-82	16	3,51		
GOs	L			----------			0.01	L			----------			-0.14	L	19	-22	-84	26	3.56	0.05	< .05
	R	19	24	-90	34	4.09		R	19	26	-88	38	4.95		R			----------				
GF	L			----------			0.00	L			----------			-0.17	L	19	-24	-64	-14	4.70	0.11	< .005
	R	19	44	-68	-16	4.39		R	19	36	-64	-16	4.78		R	19	42	-64	-18	4.74		
VWFA	L			----------				L			----------				L			----------				n.s.
	R			----------				R			----------				R			----------				

Table 3.1: Brain regions identified by group analysis (SPM2) for visual processing of false fonts presented in the CVF, LVF and RVF (significance threshold: voxel-level $p_{FDR\text{-}corr} < .05$, cluster-level $p_{corr} < .001$). Peak activations in the VWFA were identified using a small volume correction for a 5 mm sphere with centre x = -43 (LH) / x = 43 (RH), y = -54, z = -12 (Talairach space). Peak activations in the VWFA were considered significant for the activation threshold of $p_{FDRcorr} < .05$ (voxel-level). H = hemisphere, L = LH and R = RH.

pseudowords (CVF)								pseudowords (LVF)								pseudowords (RVF)								
	H	BA	MNI co. x	y	z	peak activation z-value	LI		H	BA	MNI co. x	y	z	peak activation z-value	LI		H	BA	MNI co. x	y	z	peak activation z-value	LI	repeated measures ANOVA: VHF x H *p*- value
Sca	L			----------				Sca	L			----------			0.01	Sca	L	18	-8	-92	-6	4.75	-0.03	< .05
	R			----------					R	17	18	-68	8	4.22			R	17	8	-80	6	4.74		
Cu	L			----------				Cu	L	18	0	-94	16	3.90	-0.02	Cu	L			----------				n.s.
	R			----------					R	19	14	-82	36	4.05			R			----------				
GL	L			----------				GL	L	18	-18	-72	2	4.66	-0.05	GL	L	18	-12	-68	-6	5.29	0.04	= .058
	R			----------					R	18	10	-88	-6	3.85			R	18	12	-66	-6	4.99		
GOi	L	19	-50	-70	-16	3.58	0.01	GOi	L			----------			-0.05	GOi	L			----------				< .005
	R	19	36	-88	-8	3.84			R	19	44	-68	-14	5.17			R			----------				
GOm	L	19	-40	-82	2	4.59	0.01	GOm	L	19	-38	-82	0	3.91	-0.11	GOm	L	19	-42	-76	8	4.80	0.05	< .005
	R	18	36	-92	2	3.50			R			----------					R	19	36	-84	16	4.34		
GOs	L			----------				GOs	L	17	-12	-92	2	4.23	-0.05	GOs	L	18	-16	-90	12	4.24	0.01	n.s.
	R			----------					R	19	24	-88	40	4.28			R	19	24	-86	30	4.04		
GF	L	37	-36	-44	-22	4.22	0.09	GF	L	37	-36	-44	-24	4.28	-0.06	GF	L	19	-34	-70	-12	4.55	0.11	< .01
	R			----------					R	19	36	-62	-16	4.81			R	19	24	-62	-10	4.07		
VWFA	L		-42	-54	-18	3.74	0.08	VWFA	L		-44	-54	-16	4.12	0.14	VWFA	L		-48	-48	-20	3.74	0.11	n.s.
	R			----------					R		44	-56	-20	3.64			R		44	-56	-20	2.92		

Table 3.2: Brain regions identified by group analysis (SPM2) for visual processing of pseudowprds presented in the CVF, LVF and RVF (significance threshold: voxel-level $p_{FDR\text{-}corr} < .05$, cluster-level $p_{corr} < .001$). Peak activations in the VWFA were identified using a small volume correction for a 5 mm sphere with centre x = -43 (LH) / x = 43 (RH), y = -54, z = -12 (Talairach space). Peak activations in the VWFA were considered significant for the activation threshold of $p_{FDRcorr} < .05$ (voxel-level). H = hemisphere, L = LH and R = RH.

words (CVF)								words (LVF)								words (RVF)								
	H	BA	MNI co. x	y	z	peak activation z-value	LI		H	BA	MNI co. x	y	z	peak activation z-value	LI		H	BA	MNI co. x	y	z	peak activation z-value	LI	repeated measures ANOVA: VHF x H *p*- value
Sca	L	19	-24	-66	8	3.68	-0.06	Sca	L	18	-2	-86	0	4.24	-0.03	Sca	L	18	-2	-90	14	4.43	-0.03	n.s.
	R	17	12	-74	14	3.03			R	17	6	-70	8	3.65			R	19	28	-60	10	4.41		
Cu	L			----------				Cu	L	18	2	-94	16	4.07	-0.05	Cu	L	19	-8	-82	16	4.39	0.00	n.s.
	R			----------					R			----------					R			----------				
GL	L	18	-28	-92	-12	4.03	-0.09	GL	L			----------			-0.16	GL	L	19	-20	-60	-10	4.98	0.03	< .005
	R	19	24	-92	-12	4.11			R	19	22	-62	-6	4.80			R	18	12	-64	-4	4.01		
GOi	L	19	-42	-82	-2	5.17	0.00	GOi	L			----------			-0.10	GOi	L	19	-38	-72	-10	4.86	0.10	< .001
	R	19	42	-72	-2	4.21			R	18	32	-84	-10	4.03			R			----------				
GOm	L	18	-30	-96	2	5.14	-0.02	GOm	L	19	-30	-72	22	3.66	-0.10	GOm	L	19	-42	-78	2	4.62	0.06	= .054
	R	19	26	-82	16	5.13			R	19	34	-80	14	3.65			R			----------				
GOs	L	19	-22	-82	32	4.03	-0.05	GOs	L			----------			-0.13	GOs	L	18	-14	-90	14	4.09	0.03	< .005
	R	19	22	-86	32	4.54			R	18	22	-94	10	3.84			R	19	26	-88	36	3.81		
GF	L	37	-36	-56	-16	4.50	-0.03	GF	L			----------			-0.14	GF	L	37	-36	-54	-12	4.60	0.11	< .001
	R	37	34	-40	-20	3.64			R	37	36	-44	-22	3.93			R			----------				
VWFA	L		-44	-56	-16	4.30	0.11	VWFA	L		-44	-56	-20	2.82	-0.02	VWFA	L		-42	-54	-18	3.23	0.12	n.s.
	R		42	-54	-18	3.70			R		-44	-56	16	3.31			R			----------				

Table 3.3: Brain regions identified by group analysis (SPM2) for visual processing of words presented in the CVF, LVF and RVF (significance threshold: voxel-level $p_{FDR\text{-}corr} < .05$, cluster-level $p_{corr} < .001$). Peak activations in the VWFA were identified using a small volume correction for a 5 mm sphere with centre x = -43 (LH) / x = 43 (RH), y = -54, z = -12 (Talairach space). Peak activations in the VWFA were considered significant for the activation threshold of $p_{FDRcorr} < .05$ (voxel-level) and for presentation in the LVF the threshold was lowered to $p_{uncorr} < .001$ (voxel-level). H = hemisphere, L = LH and R = RH.

words							**pseudowords**							**false fonts**						
			MNI co.			peak activation				MNI co.			peak activation				MNI co.			peak activation
	H	BA	x	y	z	z-value		H	BA	x	y	z	z-value		H	BA	x	y	z	z-value
LVF and RVF > CVF							*LVF and RVF > CVF*							*LVF and RVF > CVF*						
Sca	L	17	-2	-92	6	4.72	Sca	L	17	-8	-82	14	5.41	Sca	L	17	-8	-92	-4	5.55
	R	17	10	-82	2	4.15		R	17	8	-86	8	4.69		R	18	0	-90	12	
GL	L	18	-12	-78	2	4.32	Cu	R	18	18	-96	16	4.20	GL	L	17	10	-78	4	4.50
															R	18	-14	-80	-8	4.01
							GL	L	19	18	-50	0	4.47							
								R	19	-20	-56	-2	4.01							
CVF > LVF and RVF							*CVF > LVF and RVF*							*CVF > LVF and RVF*						
no significant activations							no significant activations							no significant activations						

Table 3.4: Brain regions identified by group analysis (SPM2) for the contrasts comparing visual half-field presentation with central visual field presentation (significance threshold:voxel-level $p_{FDR\text{-}corr} < .05$, cluster-level $p_{corr} < .001$). H = hemisphere, L = LH and R = RH.

3.4.3 Effect of stimulus type

To examine if the signal intensity change in a ROI depends on the stimulus type a Friedman-test was performed. The Friedman-Test is a non-parametric test for several dependent variables. A following Sign-Test, a non-parametric test for two dependent variables, was used to conduct multiple comparisons to reveal which stimulus categories were significant different. For LVF, the BOLD signal intensity change value of the right fusiform gyrus was significant higher for false fonts (mean BOLD signal intensity change = 7.78, SEM = 0.62) compared to words (mean BOLD signal intensity change = 7.51, SEM = 1.09) (Friedman-Test $\chi^2 = 6.14$, $p < .05$; Sign-Test $p < .05$). In contrast, the right VWFA (LVF), which is a part of the fusiform gyrus, showed higher activations for words (mean BOLD signal intensity change = 2.77, SEM = 0.43) versus false fonts (mean BOLD signal intensity change = 2.43, SEM = 0.43) (Friedman-Test $\chi^2 = 1.08$, p = n.s.). For RVF, a significant difference in activation was found for the left VWFA during visual processing of words (mean BOLD signal intensity change = 3.02, SEM = 0.48) and false fonts (mean = 1.51 SEM = 0.32) (Friedman-Test $\chi^2 = 10.31$, $p < .01$; Sign-Test $p < .001$).

3.5 Discussion

When considering the BOLD response during the visual processing of words, pseudowords and false fonts, we found a higher signal change in the hemisphere contralateral to the visual field of stimulus presentation compared to the ipsilateral hemisphere. This interaction was found for most regions of the visual cortex. This finding is consistent with the generality of crossed visual input (Marzi, 1986). That no such interaction was found for the calcarine sulcus and the cuneus is probably due to the fact that even though these two regions are anatomically separately situated, on a slice they lay adjacent to each other. To be able to separate left and right hemispherical activations in those two regions it might be necessary to use both a higher image resolution, and a smaller smoothing Kernel as done in this study, and to flatten both areas before analyzing (Tootell et al., 1998, Engel et al., 1997).

In contrast, for the VWFA a tendency for LH predominance was assessed during the visual processing of words and pseudowords. One exception was the bilateral activation pattern of the VWFA for the visual processing of words presented in the LVF. However, in both right VWFA (LVF) and left VWFA (RVF) the signal intensity change was higher for words versus false fonts. Ben-Shachar et al. (2007) also reported a higher sensitivity for words than false fonts or line drawings in left and right posterior occipito-temporal sulcus (VWFA). Some behavioural studies assume that presentation of words in a non-standard visual format (e.g. vertical) impedes the recognition of visually familiar supra-letter and word-level features, changing the processing strategy into letter-by-letter reading (Lindell et al., 2002; Chiarello, 1988). In the case of a letter-by-letter reading strategy, no specific activation of the left VWFA during word compared to pseudoword reading would be expected. Similarly, several other studies using horizontal stimulus presentation have failed to uncover significant differences between the visual processing of words and pseudowords (Cohen et al., 2003; Vigneau et al., 2005). These facts have been interpreted as an extention of the left VWFA specificity for all stimuli containing letters or supra letter features.

The only exclusion of a trend towards LH predominance of the VWFA activation pattern was during word processing presented in the LVF. Words presented in the LVF are initially processed in the right visual cortex and showed a bilateral activation pattern of the VWFA. These findings support the hypothesis of Vigneau and colleagues (2005) that the visual specialisation for words in the left VWFA relies on interhemispheric interaction between the left and right VWFA instead of relying on the regional variation of activity in the left VWFA

alone. Our data are congruent with the suggestion that the LH predominance for word recognition is the result of a reduced activity in the right VWFA controlled by the LH. The fact that for processing pseudowords this effect was absent, points to the capability of at least the right VWFA to distinguish between pseudowords and words, even in the case of vertical presentation.

Even though we found a visual field x hemisphere interaction during processing of lateralized presented stimuli, determination of the LI revealed bilateral activation pattern for the visual cortex, independent of the visual field of presentation. A number of anatomical and electrophysiological studies have revealed that callosal connections are not restricted to the vertical midline representation (bilateral stripe). In rodents, callosal connections are densely packed along the border between areas 17 and 18, a region that represents the vertical midline. Additionally the entire mediolateral extent of the rat striate cortex (area 17), representing the peripheral visual field, contains numerous callosal cells and terminals. In the macaque monkey it has been caculated that neural activity takes 11 msec to pass from V1 to V4 and 12 msec to pass from V1 to MT (V5) (Maunsell and Schiller, 1984). By adding to the above values the time necessary for the conduction along callosal fibres (1-2 msec), Marzi (1986) came up with a interhemispheric transmission time of about 15 msec. Thus, although visual information is initially received in the contralateral hemisphere, the BOLD response, measured by fMRI, is too slow (about 5 sec) to assess only the contralateral activation in the occipital gyrus after lateralized stimulus presentation.

Within the visual cortex the primary visual cortex is highly retinotopically organized (Tootell et al., 1998, Engel et al., 1997). In higher visual areas the receptive fields become larger and bilateral so that retinotopy decreases. The absence of activation for CVF in BA 17 and BA 18 might be due to the presence of the fixation cross in the baseline. As the fixation cross is presented centrally, the corresponding neurons in border area 17/18 are activated. Central presentation of other stimuli, activating the same neurons of the visual cortex, would appear not to further increase activation compared to the fixation cross. In contrast, stimulus presentation in the left or right visual field activates other sets of neurons.

In conclusion, our findings of higher BOLD signal intensity change in the hemisphere contralateral to the visual field of stimulus presentation compared to the ipsilateral hemisphere reflect the generality of crossed visual input. Further, we found that in both the left and right VWFA the BOLD signal intensity change was highest for visual processing of words compared to false fonts. Finally, the activation pattern of the VWFA was left

lateralized, except for words initially processed in the right visual cortex. The bilateral activation of the VWFA for words presented in the LVF but not in the RVF or CVF, suggests that the superiority of the left VWFA for recognition words is the result of a reduced activity in the right VWFA under left hemispheric control.

Chapter 4

Processing of linguistic information received in the “wrong” hemisphere: an event-related fMRI study

4.1 Abstract

The apparently symmetrical cerebral hemispheres of the human brain are functionally specialised, e.g. language processing is mainly organized in the left hemisphere (LH). The current event-related fMRI study attempted to identify how linguistic information is processed in the subdominant, right hemisphere (RH) by using the visual half-field technique and central presentation as reference. The advantage of the visual half-field technique is that the information initially arrives selectively in the RH or LH. Brain activation was measured in 16 right-handed, healthy males during phonological and semantic processing. The spatial extent of activation as well as the lateralization index (LI) was defined based on region of interests (ROI) analysis method represented by Jansen et al. (2006). Analysis of the data revealed, independent of the field of stimulus presentation, left hemispheric predominance during phonological processing, and a bilateral pattern during semantic processing. However, the spatial extent of activation did not differ subject to the field of stimulus presentation during neither phonological nor semantic processing. Our results suggest that linguistic information received in the subdominant RH, is interhemispheric transferred to the LH for phonological processing. Semantic processing in contrast occurs in the specialised and in the non-specialised hemisphere.

4.2 Introduction

The human brain is characterised by two apparently symmetrical cerebral hemispheres. However, the functions attributed to each half of the brain are very distinct. A relative specialisation of the LH for language processing has been recognised since the late 19th century. Based on the data from aphasic patients with brain lesions a "classical model" of language organization was popularized. Generally this model emphasized the role of three cerebral regions within the LH: Broca's area (Broca, 1861) in the left inferior frontal lobe, for planning and executing speech; Wernickes' area (Wernicke, 1874) in the left posterior superior temporal region, for the analysis and identification of speech; and the angular gyrus described by Dejerine (1891, 1892), for orthographic to phonological decoding during reading (Binder et al., 1997; Nevill and Bavelier, 1998). In 1874, Jackson proposed an alternative concept of functional neuroanatomy of language which included an important role of the RH. According to Jackson, the RH plays a role in the most automatic use of words, whereas in the LH the automatic use of words merges into voluntary use of words into speech.

Subsequently, a variety of methods have been employed to study hemispheric specialisation for language. Patients whose corpus callosum had been resected to prevent the spread of epileptic seizures from one hemisphere to the other allowed researchers to test each hemisphere in isolation. Studies on patients with brain damage restricted to one hemisphere gave insight into which language function the lesioned region was responsible for. In the past, intracarotoid amobarbital anaesthesia, also known as the Wada test, was a frequently applied invasive method to define the hemispheric language dominance prior to epileptic surgery (Wada and Rasmussen, 1960). The problem with patient studies is that one must be attentive to the fact that following brain damage a reorganisation of the brain might take place. Thus, the information from these studies can not, without restrictions, be applied on the scheme of language processing in healthy individuals. To study language organisation in the healthy population more modern, non-invasive techniques such as functional transcranial Doppler sonography and functional magnetic resonance imaging (fMRI) can be employed. The findings of these non-invasive techniques are congruent with what is known on the basis of WADA tests and the neuropsychological literature of brain lesions (Knecht et al., 1998; Binder et al., 1996).

Nevertheless most laterality research has been performed on a behavioural level, using techniques such as dichotic listening or visual half-field presentation. During a dichotic

listening task, stimuli, most commonly consonant-vowel syllables or monosyllabic words, are presented simultaneously to the participant via ear phones and the subject has to report what he/she has heard. Although there is a bilateral projection of auditory information to the cortex, the contralateral projections from each ear override ipsilateral projections, so that the left ear has better communication with the RH, whereas the right ear has preferential acces to the LH (Kimura, 1967). The visual half-field technique involves the presentation of stimuli in the left or right visual field (LVF or RVF) for a very short time (about 200 ms). This duration is chosen to minimize the possibility of saccadic eye movements. During the presentation of lateralized stimuli, the gaze of the participants is fixated on a centrally presented fixation cross. This technique takes advantage of the anatomy of the visual pathway as the temporal hemiretinae project ipsilateral, while the nasal hemiretinae project contralateral. Thus, stimuli presented in the LVF or RVF are initially processed in the contralateral hemisphere (Bourne, 2006). The processing capability of each hemisphere is described in terms of reaction times and/or numbers of errors in response to stimuli presented in the contralateral visual field or ear. The prediction in these behavioural studies is that individuals with LH language dominance will show a RVF advantage for a visual half-field task and a right ear advantage for a dichotic listening task. People with RH language dominance will show the reverse advantage.

In the current fMRI study, we investigated the hypothesis for information processing in the non-specialised hemisphere proposed by Hunter and Brysbaert (2008). They suggested that information arriving in the subdominant hemisphere either requires interhemispheric transfer to reach the dominant hemisphere or is processed more slowly by the less specialised hemisphere. We have examined this hypothesis for the case of linguistic processing.

Nowadays, neuroimaging offers not only the opportunity to define which regions are involved, but also how language processing is accomplished. In the broadest sense, language processing entails different components such as the analysis of word forms (orthography), the analysis of word pronunciation (phonology), the analysis of word meaning (semantics), the analysis of sentences (syntax) and in most cases also sensory and motor components (Fiez and Petersen, 1998; Small and Burton, 2002).

In our study we selected two components of language processing namely phonology and semantics. The brain activation pattern associated with phonology was assessed by subtracting the BOLD response during reading of pseudowords (pronounceable letter strings) with the BOLD response during reading of false fonts. Calculation of the BOLD reponse

during reading of words versus the BOLD response during the reading of pseudowords, revealed the brain activation pattern for semantic processing. The stimuli: words, pseudowords and false fonts were presented at random in the central visual field (CVF), RVF and LVF using an event-related design. CVF stimulus presentation was included as reference condition reflecting the standard visual field for reading. Based on the results of the substraction method we conducted a ROI analysis to define the LI and spatial extent of activation as described by Jansen et al. (2006). The effect of visual field of stimulus presentation on the BOLD response was examined by a ROI analysis.

4.3 Methods

4.3.1 Participants

Sixteen healthy, right-handed (Edinburgh handedness inventory, Oldfield 1971) males (mean age 25.19 years, range 21-31 years) with normal or corrected-to-normal visual acuity participated in the study. Participants taking medication which could affect the central nervous system during the last six months were excluded. All participants grew up monolingual, were German native speakers, and had no knowledge of Arabic. Only the fMRI data of subjects who passed the attention task were included. Prior to participation all participants gave written consent according to the Declaration of Helsinki. Two participants were excluded due to failure in data recording, and clinical background. This study was approved by the local ethical commission.

4.3.2 Task, Stimuli and fMRI Paradigm

A silent reading task with variable stimulus types (words, pseudowords and false fonts) was chosen. Words were high-imagery nouns (Fiebach and Friederici, 2004) and matched for usage frequency (Blair et al., 2002; Coney, 2005). Pseudowords, derived from real words by randomizing the letters, were pronounceable. Strings of Arabic signs were used as false fonts. To control for subjects' alertness during the experiment, without having non-language related motor activation, a semantic decision task was included by a fourth category of stimuli: animal names. The subjects were instructed to read the stimuli silently and press a button, attached around the upper leg, when the presented stimulus was an animal name. This fourth category was later not included in the SPM model. All stimuli were composed of four or five letters or signs (Whitney and Lavidor, 2004; Lindell et al., 2002; Mechelli et al., 2000) in a white font on a black background presented vertically.

Stimuli were randomly presented centrally or lateralized (4° from fixation cross) every 3500 ms for 200 ms, followed by a 3300 ms fixation cross. The experiment consisted of three runs which were randomized between subjects. Each run counted 48 words, 48 pseudowords, 48 false fonts and 12 animal names. For each category; stimuli were equally divided over the CVF, LVF and RVF. Between runs the words, pseudowords and false fonts used, were the same; only the presentation field was changed. For the fourth stimulus type, animal names, stimuli were not repeated between runs.

4.3.3 Imaging Parameters

Blood oxygen level dependent (BOLD)-fMRI was performed on a 1.5 Tesla Philips Gyroscan Intera system (Philips Medical Systems, Netherlands) with standard head coil. To verify subject positioning and to plan axial (AC-PC) slice acquisition a sagital scan was obtained. An echo planar T_2*-weighted imaging sequence was acquired every 3 s during the paradigm using the following parameters: TR = 3000 ms, TE = 50 ms, $\alpha = 90°$, FOV = 256 x 256 mm^2, matrix size = 64 x 64, voxel size = 4 x 4 x 4 mm^3, 32 slices, and 203 volumes per session. Functional scanning was always preceded by 15 s of dummy scans to insure steady-state magnetization.

Due to a time difference in image acquisition frequency and stimulus presentation frequency, there is a delay between image acquisition and stimulus presentation called temporal jittering. The advantage of temporal jittering is a better detection of the BOLD response curve.

Subjects wore earplugs and the placement of foam pads around the subjects´ head prohibited movement. A MRI compatible response button was attached around the upper leg of the subject easily accessible with the right hand. In this way the subject was able to response with a minimum of body movement.

4.3.4 FMRI Data Analysis

Preprocessing

Image processing was performed using SPM2, developed by the Wellcome Institue (London, UK) running on MATLAB 6.1 (The MathWorks, Natrick, USA), based on the general linear model (Friston et al. 1995a and b). The individual subject (first level) analysis included following steps: (1) slice timing was used to correct for differences in acquisition time between slices; (2) motion correction was done by realignment of all images to the first image. Subjects whose images had more than one-voxel motion were rejected; (3) all images were normalized to a standard MNI template brain; (4) spatial smoothing using a Gaussian kernel of FWHM 8 mm; (5) modeling of the expected hemodynamic response function (hrf) and first derivative (hrf') with the appropriate event-related design (only the former function was used for statistical contrasts); (6) filtering of the time series with the value of 128 s for the cut-off period of the high-pass filter.

Group Analysis (SPM2)

The results of the individual data analysis were submitted to a random effect group (second level) analysis. Following tests were conducted for the three visual fields of stimulus presentation (CVF, RVF LVF): (1) one sample t-tests to reveal BOLD activation during semantic processing (words > pseudowords); (2) one sample t-tests showing phonologic (pseudowords > false fonts) related BOLD activation. Clusters were considered significant if they reached an activation threshold of $p_{uncorr} < .001$ (voxel-level) and $p_{corr} < .05$ (cluster-level). In a second step, a lower threshold for semantic processing was included (voxel-level $p_{uncorr} < .001$; cluster-size < 20 voxel). Automated anatomical labelling (AAL) software (Tzourio-Mazoyer et al., 2002) was used to label the peak activations.

ROI Analysis:

Lateralization Index and Spatial Extent of Activation

Based on the results of the group analysis (SPM2), the ROIs were selected. A ROI analysis was conducted to define the LI and spatial extent of activation (or number of activated voxels) in these ROIs.

To calculate a LI on the basis of fMRI data various methods have been introduced. Roughly they can be divided into two categories. Either LI calculation is based on the extent of the activated brain region (number of active voxels in a ROI) (Binder et al., 1996; Knecht et al., 2003) or on the magnitude of the fMRI signal change in a ROI (Adcock et al., 2003; Fernandez et al. 2001). An overall problem although is the robustness and reproducibility of LI calculation. Jansen et al. (2006) evaluated diverse methods on those two parameters and found that the lateralization of a cognitive function was best described by thresholded signal intensity changes where the activity measure was based on signal intensity changes in those voxels in a ROI that exceeded a predefined activation level. On basis of the high reproducible and robust character of Jansen's method and the possibility to decrease the influence of eventual noise, we decided not only to use this method for LI determination, but also to define spatial extent of activation in a ROI.

Thus, the LI was calculated as described by Fernandez et al. (2001) and Jansen et al. (2006) based on the magnitude of signal change in a ROI defined by the weighted β values. A first step was to accomplish two masks for each selected ROI. The masks used for the ROI

analysis are based on the masks in Marsbar_0.38.2 which are matched to the MNI/ICBM templates (Tzourio-Mazoyer et al., 2002). For each ROI two symmetrical masks were built one for the ROI in the LH and one for its´ homologue in the RH. For each region a mean maximum β value was calculated as the mean of those 5% of voxels showing the highest level of activation in the respective ROI. The threshold for inclusion in the calculation was then set at 50% of this mean maximum β value. The level of activation or signal intensity change was defined as the mean β value of all voxels exceeding the individually defined threshold and the volume of activation or spatial extent was calculated as the number of these voxels.

The hemispheric lateralization can be defined by a LI which is based on the above described ROI analysis. The following formula was used to calculate the LI:

$$LI = [(AL - AR)/(AL + AR)]$$

where AL and AR refer to values of fMRI-measured activity for equal ROIs in the LH and RH hemisphere. Results range from -1 to +1. A negative value represents RH dominance, a positive value LH dominance as previously described by (Binder et al., 1996). Brain activation pattern described by a LI value with $|LI| < 0.20$ are classified as bilateral (Springer et al., 1999).

4.3.5 Statistical Analysis

Statistical data analysis was performed with SPSS software (SPSS 13.0). A repeated measures ANOVA was used to analyse the interaction between visual field of stimulus presentation and hemisphere. Comparisons between the three visual fields (CVF, LVF and RVF) were performed with the Friedman-Test, a non-parametric test for several dependent variables. A following Sign-Test, a non-parametric test for two dependent variables, was used to conduct multiple comparisons to reveal which stimulus presentation fields caused significant differences in LI value or spatial extent of activation. In case the data were restricted to two out of three visual fields a Wilcoxon Signed Rank Test, a non-parametric test for two dependent samples was conducted.

4.4 Results

4.4.1 Behavioural data

To be able to control for the participants' alertness during the experiment a semantic decision task was included by a fourth category of stimuli: animal names. The participants were instructed to press a button, attached around the upper leg, when the presented stimulus was an animal name. The stimulus category animal names had an occurrence of 12 out of 156 stimuli. For each subject and each visual field (VF) a mean accuracy score was calculated as the ratio of correct against the sum of correct, missed and false responses. Only the fMRI data of subjects who passed the attention task (mean accuracy score > 50 % for each visual field) were included. The group mean accuracy score: CVF = 73 %, S.E.M. = 4.77; RVF = 62 %, S.E.M. = 5.61; LVF = 67 %, S.E.M = 5.59. Accomplishment of the Friedman-Test, a non-parametric test for several dependent variables revealed no significant difference in performance between the visual fields of presentation ($\chi^2 = 3.17$, n.s.).

4.4.2 FMRI Group Analysis

Phonological processing (Fig 4.1 and Table 4.1) produced a widespread and robust respons in the inferior frontal gyrus (pars triangularis and pars opercularis), the precentral gyrus, super motor area and insula. Activation in the parietal lobule was restricted to lateral stimulus presentation. For RVF presentation a BOLD signal increase was also observed in the fusiform gyrus. The BOLD activations were also found in the occipital regions: lingual gyrus, cuneus and calcarine sulcus.

The network associated with the processing of semantics was smaller for lateral, especially LVF, versus central stimulus presentation (Fig 4.2 and Table 4.2). For LVF presentation, a BOLD signal increase was located frontal in the middle frontal gyrus and inferior frontal gyrus pars orbitalis, and in the inferior parietal lobule. Lateralized presentation in the RVF included also activation in the middle frontal gyrus and the inferior parietal lobule. Further signal increases were found in the middle temporal gyrus, precuneus, middle and anterior cingulated cortex. CVF presentation activated a network of regions including the middle and superior frontal gyrus, the inferior frontal gyrus pars orbitalis, the inferior and middle temporal gyrus, fusiform gyrus and inferior parietal lobule. Further activations were found in the precuneus, middle and anterior cingulated cortex and the middle occipital gyrus.

The BOLD activations in the occipital regions: middle occipital, lingual gyrus, cuneus and calcarine sulcus were excluded from further analysis as these regions are competent for visual but not specific for phonological or semantic processing (Indefrey et al., 1997).

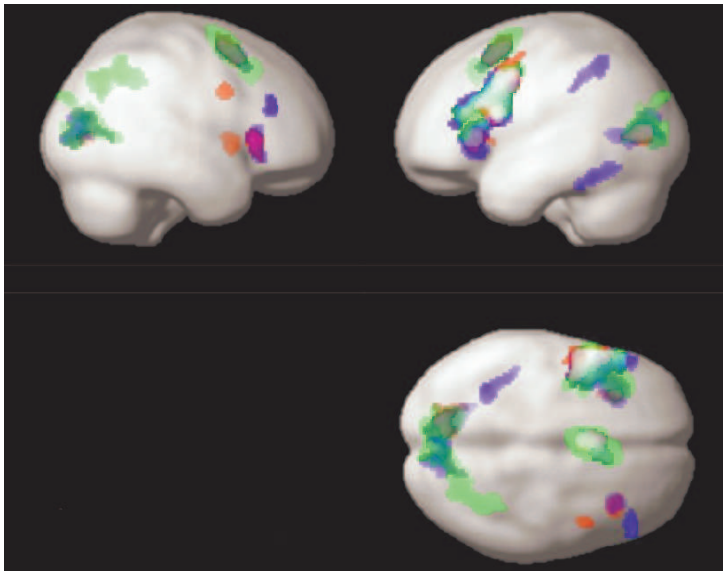


Fig 4.1: Phonological processing (CVF = red; LVF = green; and RVF = blue). Activation is projected onto 3D anatomical template. Clusters were considered significant if they reached an activation threshold of $p_{uncorr} < .001$ (voxel-level) and $p_{corr} < .05$ (cluster-level).

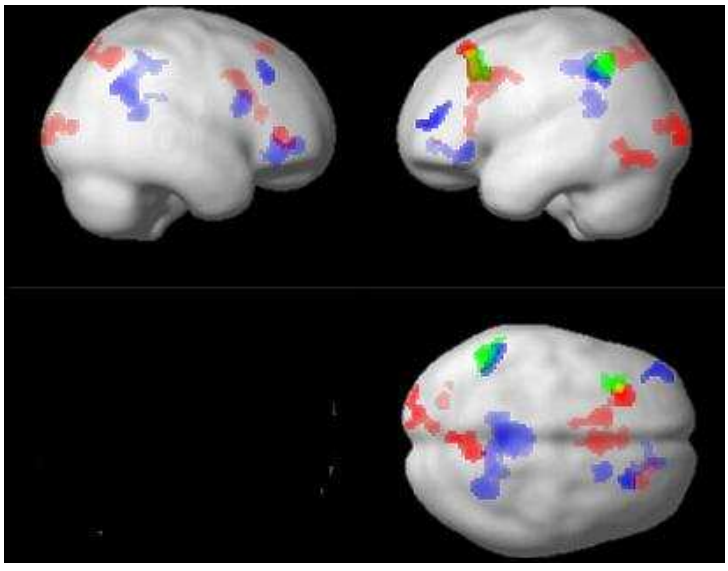


Fig 4.2: Semantic processing (CVF = red; LVF = green; and RVF = blue). Activation is projected onto 3D anatomical template. Clusters were considered significant if they reached an activation threshold of $p_{uncorr} < .001$ (voxel-level) and $p_{corr} < .05$ (cluster-level).

	pseudowords > fasle fonts (CVF)						pseudowords > false fonts (LVF)						pseudowords > false fonts (RVF)						
		MNI co.			peak activation	LI		MNI co.			peak activation	LI		MNI co.			peak activation	LI	repeated measures ANOVA: VHF x H
	H	x	y	z	z-value		H	x	y	z	z-value		H	x	y	z	z-value		*p*- value
GFi pars opercularis	L	-56	10	18	4.43	0.18	L	-38	6	20	4.64	0.24	L	-42	8	26	4.23	0.21	n.s.
	R	----------					R	----------					R	----------					
GFi pars triangularis	L	----------					L	-38	26	16	4.03	0.19	L	-40	14	28	4.21	0.18	n.s.
	R	----------					R	----------					R	54	34	28	3.37		
GPrC	L	-48	4	40	4.16	0.13	L	-48	8	36	4.81	0.19	L	-46	8	34	4.68	0.23	n.s.
	R	----------					R	----------					R	----------					
INS	L	----------				-0.10	L	-28	24	4	3.68	0.02	L	-28	24	-2	4.79	0.03	n.s.
	R	38	22	4	3.98		R	34	28	2	4.12		R	36	24	4	4.09		
SMA	L	-4	10	58	4.07	0.04	L	-4	2	66	4.98	0.03	L	-6	8	54	4.36	0.04	n.s.
	R	----------					R						R	----------					
GF	L	----------					L	----------					L	-44	-58	-16	3.62	0.06	n.s.
	R	----------					R	----------					R	----------					
LPi	L	----------					L	-28	-48	42	4.39	0.12	L	-32	-52	48	4.07	0.16	n.s.
	R	----------					R	38	-44	36	3.61		R	----------					
GL	L	-20	-78	8	4.04		L	----------					L	----------					
	R	----------					R	----------					R	----------					
Cu	L	----------					L	----------					L	0	-80	16	4.05		
	R	----------					R	----------					R	----------					
Sca	L	-10	-78	2	3.85		L	-8	-80	6	4.22		L	-14	-76	8	4.02		
	R	----------					R	----------					R	6	-80	8	3.74		

Table 4.1: Brain regions identified by group analysis (SPM2) for phonological processing. Stimuli were presented in the CVF, LVF and RVF (significance threshold: voxel-level $p_{uncorr} < .001$; cluster-level $p_{corr} < .05$). H = hemisphere, L = LH and R = RH.

words > pseudowords (CVF)							**words > pseudowords (LVF)**							**words > pseudowords (RVF)**							
		MNI co.			peak activation	LI			MNI co.			peak activation	LI			MNI co.			peak activation	LI	repeated measures ANOVA: VHF x H
	H	x	y	z	z-value			H	x	y	z	z-value			H	x	y	z	z-value		*p*- value
GFm	L	-30	26	42	4.02	0.03	GFm	L	-34	22	42	4.17	-0.07	GFm	L	-30	38	18	3.43	0.03	n.s.
	R	16	46	-4	4.27			R			----------				R	24	32	38	3.66		
GFs	L	-16	16	38	4.27	-0.02	GFs	L			----------			GFs	L			----------			
	R	26	38	4	4.27			R			----------				R			----------			
GFi pars	L	*-32*	*34*	*-6*	*2.80*	-0.09	GFi pars	*L*	*-20*	*32*	*-4*	*3.62*	-0.06	GFi pars	L			----------			n.s.
orbitalis	R			----------			orbitalis	R			----------			orbitalis	R			----------			
GTi	L	*-40*	*8*	*-36*	*2.99*	-0.02	GTi	L			----------			GTi	L			----------			
	R			----------				R			----------				R			----------			
GTm	L			----------		0.06	GTm	L			----------			GTm	L			----------		0.00	n.s.
	R	*44*	*-52*	*6*	*4.08*			R			----------				R	*38*	*-62*	*8*	*2.96*		
GF	L	-26	-72	-10	3.37	-0.02	GF	L			----------			GF	L			----------			
	R	*28*	*-78*	*-12*	*2.97*			R			----------				R			----------			
LPi	L	*40*	*-54*	*32*	*3.25*	0.07	LPi	L	-52	-54	44	4.12	0.07	LPi	L	-54	-48	38	3.59	0.06	n.s.
	R			----------				R			----------				R			----------			
PCu	L			----------		-0.04	PCu	L			----------			PCu	L	-12	-48	18	3.81	-0.02	n.s.
	R	8	-64	48	4.69			R			----------				R			----------			
MCC	L	-16	16	38	4.27	-0.01	MCC	L			----------			MCC	L	-6	-44	44	4.86	-0.05	n.s.
	R	4	12	38	3.93			R			----------				R			----------			
ACC	L	0	18	28	3.13	0.00	ACC	L			----------			ACC	L	*-8*	*30*	*16*	*3.10*	0.01	n.s.
	R			----------				R			----------				R			----------			
GOm	L	-18	-96	8	3.74		GOm	L			----------			GOm	L			----------			
	R							R			----------				R			----------			

Table 4.2: Brain regions identified by group analysis (SPM2) for semantic processing. Stimuli were presented in the CVF, LVF and RVF (significance threshold: voxel-level $p_{uncorr} < .001$; cluster-level $p_{corr} < .05$; and Italic print significance threshold: voxel-level $p_{uncorr} < .001$; cluster-size of 20 voxel). H = hemisphere, L = LH and R = RH.

4.4.3 LI and Spatial Extent of Activation

The LI values are presented in Table 4.1 and Table 4.2. Phonological processing was associated with predominant leftward activation of the precentral gyrus, the inferior frontal gyrus pars triangularis and pars opercularis. Insula and super motor area activation were bilateral. The temporo-parietal activation pattern was bilateral with a tendency for LH predominance.The BOLD response during semantic processing displayed an overall bilateral activation pattern.

Based on these anatomical features of the visual pathway, we performed a repeated measures ANOVA to detect a visual field x hemisphere interaction with higher BOLD signal intensity change in the contralateral versus the ipsilateral hemisphere. The results of the repeated measures ANOVA revealed no significant visual field x hemisphere interaction for any ROI (Table 4.1 and Tabel 4.2).

The effect of the visual field (CVF, LVF and/or RVF) on the LI value or spatial extent of activation was assessed conducting a Wilcoxon Signed Rank Test, a non-parametric test for two dependent samples, or a Friedman-Test, a non-parametric test for several dependent variables. In case a Friedman-Test was calculated a following Sign-Test, a non-parametric test for two dependent variables, was used to conduct multiple comparisons to reveal for which visual fields the values were significant different. For all ROIs the LI values and the spatial extent of activation did not differ subject to the field of stimulus presentation during neither phonological nor semantic processing (Table 4.1, Tabel 4.2, Fig 4.3 and Fig 4.4).

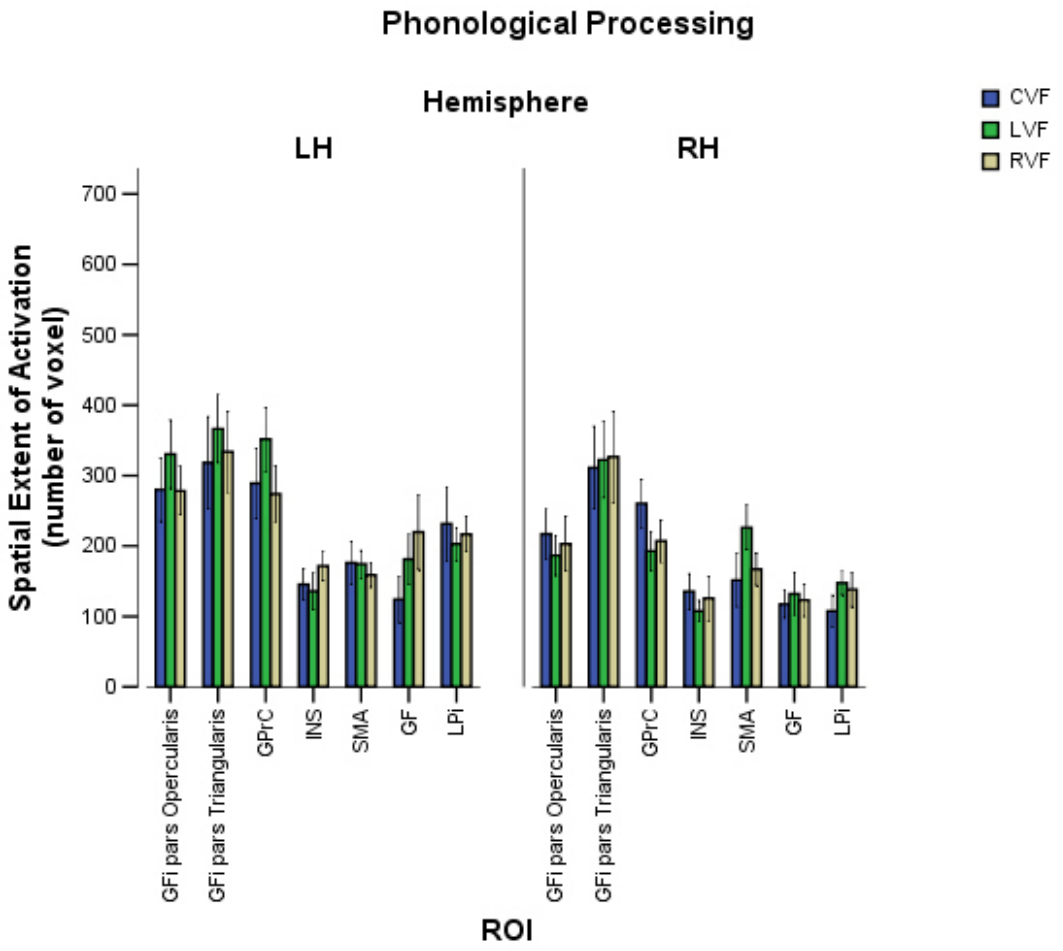


Fig 4.3: Spatial extent of activation during phonological processing for stimulus presentation in the CVF, LVF and RVF. Error bars: +/- 1.00 S.E.

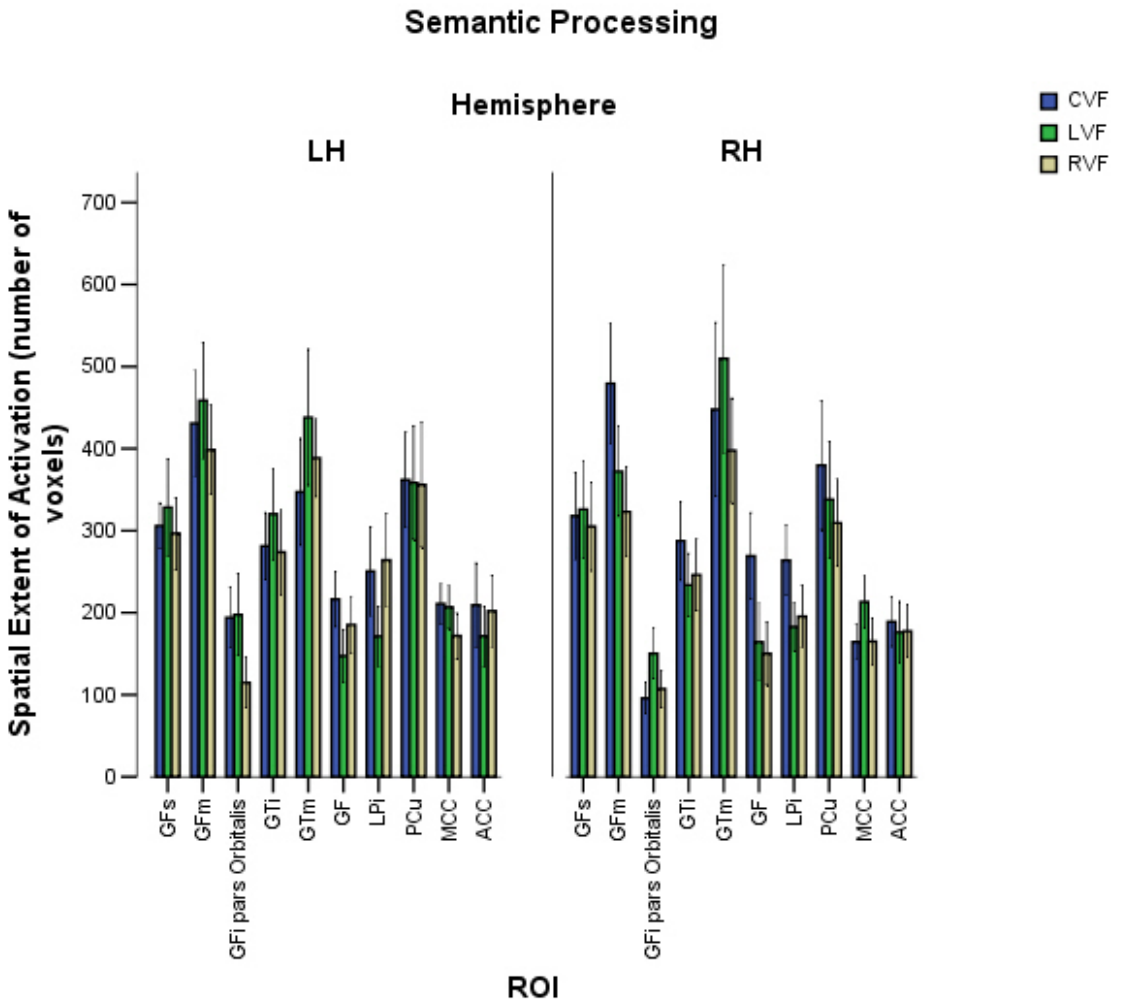


Fig 4.4: Spatial extent of activation during semantic processing for stimulus presentation in the CVF, LVF and RVF. Error bars: +/- 1.00 S.E.

4.5 Discussion

Our results suggest that linguistic information received in the subdominant RH, is interhemispheric transferred to the LH for phonological processing. Semantic processing in contrast occurs in the specialised and in the non-specialised hemisphere.

By employing a visual half-field technique the visual information is initially selectively received and processed in the right or left visual cortex (Bourne, 2006). In an earlier study on visual processing of false fonts, pseudowords and words we effectively assessed a higher BOLD signal intensity change in the visual cortex contralateral to the visual field of stimulus presentation. However, the activation pattern related to phonology or semantics in the current study did not reveal a visual field x hemisphere interaction, supporting the idea of hemispheric specialisation for both processes.

Indeed, assessment of LI values revealed, during phonological processing left lateralization in the frontal region including the inferior frontal gyrus pars opercularis and pars triangularis, and precentral gyrus. Also other research involving phonological processing has implicated the inferior frontal region and adjacent areas (Shaywitz et al., 1995; Xu et al., 2001). As the left lateralization of the frontal region is stable and independent of the visual field of stimulus presentation our data suggest that this LH dominance is the result of interhemispheric transfer of information. This implies that linguistic information received in the RH is transferred to the LH to enable phonological processing. Semantic processing activated, for all three visual fields, a bilateral pattern. In accordance with Hunter and Brysbaerts' hypothesis (2008), the observed activation pattern might be the result of both processing in the specialised and slower, non-specialised hemisphere. A bilateral activation pattern for semantic processing has been reported before (Kiehl et al., 1999). Otherwise, it can not be excluded that the processing of the semantic task used in this study is not hemispherical lateralized. The absence of a visual field x hemisphere interaction in that case, might be due to the fact that the effect of stimulus presentation becomes smaller as the information progresses gradually from posterior to anterior in the brain.

An increase in activation of a region can be marked by a rise in signal intensity, but also in a growth of spatial extent of the BOLD response. No effect of visual field on spatial extent of the activation during both semantics and phonology was assessed.

Remarkably the number of regions identified as being part of the semantic network was reduced when the linguistic information was first received in the non-specialised RH. Possible explanations are that information is lost in the case of interhemispheric transfer; or that

linguistic information is not entirely processed as the RH network is not as developed as the LH language network. Even though, the performance scores are not directly associated with the discussed activation pattern, they showed no significant visual field effect. This implies that neither information is lost, nor incompletely processed. Instead, the restricted semantic network for LVF stimulus presentation is probably due to a large individual variability as the SPM2 group analysis only represents those regions which are activated in each subject.

The language processes investigated in the current study emphasized analysis of the pronounciation of written words (phonology) and retrieval of word meaning (semantics). The inferior frontal gyrus is involved in both processing steps. Previous studies (Poldrack et al., 1999; Fiez, 1997) have shown that this region is functionally segregated; pars orbitalis is suggested to be involved in semantic processing whereas pars opercularis and pars triangularis are related to phonological processing. Other studies (Roskies et al., 2001; Zatorre et al., 1992) suggest that the sub-regions, pars opercularis and pars triangularis of the inferior frontal gyrus, are differently involved in semantic (pars triangularis) and phonological processing (pars opercularis). We did not obtain this functional isolation between pars triangularis and pars opercularis for the employed tasks. The inferior frontal region is believed to be involved in short-term memory (Grensbach and Kaschak, 2003). Activation of futher frontal areas: precentral gyrus, insula and supper motor area have been reported as being implicated amongst others in producing verbal and non-verbal motor responses to tasks, and in the maintenance of phonological representations (Hinke et al., 1993). Extensive left frontal activation including the anterior cingulated cortex during language processing has been previously reported (Binder et al., 1997; Price et al., 1996a). Studies of patients with Broca´s aphasia have demonstrated that the characteristic linguistic deficits are associated with lesions usually involving the inferior frontal gyrus, middle frontal gyrus, insula, pre-and postcentral gyri, or anterior parietal areas (Mohr, 1976; Mohr et al. 1978). Processing of pseudowords, in contrast to words, tends to elicit greater activations in the left inferior frontal gyrus (Mechelli et al., 2003). A conceivable explanation is that pseudowords activate semantic representations more strongly than real words because a more prolonged search for the missing representation occurs (Price et al., 1996a). This hypothesis might also be applied on our data as the left inferior frontal gyrus pars triangularis and pars opercularis, and adjacent regions were significant activated during phonological (reading pseudowords > reading false fonts) but not semantic processing (reading words > reading pseudowords). The fusiform gyrus and the inferior parietal lobule, in particular the angular gyrus, are classically involved in early visual processing of words and letter strings (Grensbach and Kaschak, 2003). The middle and

superior frontal gyrus showed activation during semantic, but not phonological processing. This finding is consistent with other studies reporting involvement of these regions in e.g. semantic decision tasks and semantic memory tasks (Frost et al., 1999). Functional activation of the precuneus, and middle cingulate cortex during semantic processing was also found during a semantic decision task contrasted with a tone task (Binder et al., 1997). Binder and colleagues hypothesized that as much of this region probably coincides with retrosplenial cortex (Vogt, 1976), which has connections with hippocampus, parahippocampus (Mufson and Pandya, 1984; Suzuki and Amaral, 1994), and anterolaterodorsal thalamus (Sripanidkulchai and Wyss, 1986), it might be involved in memory functions. However, LH lesions in this general region reportedly cause a verbal amnestic syndrome (Valenstein et al., 1987; Rudge and Warrington, 1991). Retrosplenial activation may therefore be related to memory encoding processes that accompanied performance of the semantic task.

First, our results suggest that linguistic information, initially received in the right, non-specialised hemisphere, is one hand hand transferred to the left specialised hemisphere but on the other hand also processed in the RH. The network of regions associated with semantic processing, in case of LVF stimulus presentation, revealed a large individual variability.

Chapter 5

Menstrual cycle-dependent progesterone fluctuation affects a semantic network involving both hemispheres: an event-related fMRI study

5.1 Abstract

About 95% of right-handed men have a left hemispheric specialisation for language. In contrast, data on language organisation in women are ambiguous. Some studies report a left hemispheric predominance, whereas others mention bilateral language organization. It is supposed that this ambivalent picture might be associated with changes in gonadal steroid levels in blood during the menstrual cycle. However, gonadal steroid effects are complex and their role in functional cerebral lateralization is still open to discussion. To investigate changes in language organisation during the menstrual cycle, we conducted an event-related fMRI study during semantic and phonological processing. A group of fourteen healthy, right-handed, naturally cycling women was measured twice, once during the menstrual and once during the midluteal phase of the cycle. Data analysis revealed that during semantic processing, salivary progesterone levels correlated positively with brain activity of the left superior frontal gyrus, left middle and inferior occipital gyri and bilateral fusiform gyrus. For the left superior frontal gyrus the midluteal phase was associated with an increase in volume of activation. In contrast, the brain activation pattern for phonological processing did not change significantly across the menstrual cycle. In conclusion, the effect of serum progesterone levels on brain activity is task and region specific.

5.2 Introduction

The left hemisphere (LH) is functionally specialised for language processing in the majority (about 95%) of right-handed men. A much debated issue however is how language is organized in women. The findings of functional neuroimaging studies on this topic are rather ambiguous.

Frost and colleagues (1999) observed in both sexes a strong left lateralization in the activation pattern during a semantic decision task. There results were based on a whole brain voxelwise comparison and a ROI analysis using both the spatial extent (number of activated voxels) and magnitude of activation. Also Halari et al. (2006) did not find sex differences in brain activation pattern during a verbal fluency task (cluster-analysis). Shaywitz et al. (1995) reported sex differences in the pattern of activation during a phonological (rhyme judgment) task. A ROI analysis based on the extent of activation revealed that brain activation in males was lateralized to left inferior frontal gyrus; females had a more diffuse activation pattern that involved both the left and right inferior frontal gyrus. A PET study (Jaeger et al., 1998), using both reading tasks and language production tasks, reported LH dominance for the reading task in both sexes. However for the language production tasks the data suggested a greater degree of left lateralization for men compared to women. An fMRI study by Vikingstad et al. (2000) examined the pattern of lateralization during two language paradigms: silent picture naming and silent verb generation by calculating a Lateralisation Index (LI) based on the spatial extent of activated tissue in each gyrus. They found in males language to be left lateralized, whereas in women, approximately half had left lateralization and the other half had bilateral language representation.

It is supposed that this ambivalent picture of language organisation in women might be associated with changes in gonadal steroid levels in blood during the menstrual cycle. Concentrations of gonadal steroid hormones fluctuate with low levels at the menses and high levels during the follicle and luteal phase. Behavioural studies using visual half-field presentation to study functional lateralisation in women have provided a somewhat confusing picture. Heister et al. (1989) tested the same women during four different cycle phases (menstruation, follicular phase, luteal phase and the premenstrual phase) using a lexical decision task (left hemispheric task) as well as a figural comparison task (right hemispheric task). For the lexical decision task no change in reaction time throughout the menstrual cycle was observed. The asymmetry in reaction time for the figural comparison task decreased from

a right hemisphere (RH) superiority during menstruation to bilateralism during the premenstrual phase. Using the same stimulus paradigm and tasks, Rode et al. (1995) confirmed the results observed by Heister et al. (1989). In contrast, Hausmann and Güntürkün (2000) and Hausmann et al. (2002) measured corrected responses instead of reaction times. Results revealed for all tasks (lexical decision task, figural comparison task and face discrimination task) a decrease in lateralisation during the midluteal phase compared with menstruation. Related to their findings, Hausmann and Güntürkün (2000) proposed the progesterone-mediated interhemispheric decoupling hypothesis. This hypothesis suggests that progesterone attenuates the excitatory response of neurons to glutamate and augments the inhibitory response to γ-aminobutyric acid (GABA). Cortico-cortical transmission is mainly based on a feedforward inhibition circuit in which the glutamergic excitatory postsynaptic potential (EPSP) is mediated by a GABAergic inhibitory postsynaptic potential (IPSP) (Conti and Manzoni, 1994). The effect of a rise in progesterone would result in a decrease in cortico-cortical transmission (inhibition) or functional hemispheric decoupling and thus to a temporal reduction in functional asymmetry.

Compared to behavioural techniques functional imaging is able to define the independent contribution of each hemisphere. An fMRI study by Veltman et al. (2000) used two different tasks: a rhyming decision task and a single word reading task. They did not observe an interaction between cycle phase (menses and midluteal phase) and language related activations. Dietrich et al. (2001) using a finger opposition, a word stem completation task and a mental rotation task found an overall increase in spatial extent at ovulation (high plasma oestrogen), but no changes in cortical activation pattern or lateralization. A bilateral increase in spatial extent was also found during the midluteal phase for a semantic decision task in the superior temporal gyrus and the medial wall of the superior frontal gyrus (Fernandez et al., 2003). The activity in both regions also correlated with progesterone serum levels.

When comparing the data of different studies on language processing in women there are two main points to be considered. Firstly, different methods are used to define the pattern of lateralization both in behavioural and function neuroimaging studies. A general problem although is the robustness and reproducibility of the methods used. Most fMRI studies calculate a LI which is based on the extent of the activated brain region (number of active voxels in a region of interest (ROI)) (Binder et al., 1996; Knecht et al., 2003) or on the magnitude of the fMRI signal change in a ROI (Adcock et al., 2003; Fernandez et al. 2001). Jansen et al. (2006) evaluated diverse methods on those two parameters and found that the

lateralization of a cognitive function was best described by individual thresholded signal intensity changes where the activity measure was based on signal intensity changes in those voxels in a ROI that exceeded a predefined activation level.

Second, high rates of anovulation (Vuorento and Huhtaniemi, 1992; Vuorenti et al, 1989), as well as lower progesterone profiles (Ellison et al., 1987) in young adults are often reported. So, if the gonadal steroid levels play a role in the lateralization pattern it is necessary to determine their exact concentration in blood or saliva to define the menstrual cycle phase.

The aim of the following fMRI study was to test the progesterone-mediated interhemispheric decoupling hypothesis (Hausmann and Güntürkün, 2000) for language lateralization. In line with this hypothesis an increased participation of the non-dominant, RH during language processing was expected for the midluteal phase. As a consequence a more bilateral activation pattern during the midluteal phase compared to the menstrual phase was expected.

Here 14 right-handed women were investigated during different phases of the menstrual cycle on a 1.5 T scanner using a silent reading task. Women were scanned twice once during menstruation and once during the midluteal phase, progesterone concentrations were assed in saliva samples. We decided to use a visual-half field presentation paradigm in combination with central visual field (CVF) presentation as reference condition representing the standard visual field for reading. As stimuli words, pseudowords (letter strings which can be pronounced) and false fonts were chosen. Using a subtraction method we were able to isolate brain activation for semantic as well as phonological processing, which are both components of language processing. Based on these results we conducted a ROI analysis to define the LI and the spatial extent of the activated regions as described by Jansen et al. (2006). Data of the midluteal phase were compared with those of the menstrual phase. We also a conducted a regression analysis to directly correlate BOLD activations with progesterone levels in saliva.

5.3 Methods

5.3.1 Participants

A total of fourteen, right-handed (Edinburgh handedness inventory, Oldfield 1971) females (mean age = 23.43 years; range 20-28 years) with normal or corrected-to-normal visual acuity enrolled in the study after having given written consent according to the Declaration of Helsinki. All women had a regular menstrual cycle (mean length = 28.20 days; range 26-30 days) and had not used, during the last 6 months, oral contraceptives or hormonal replacements. Participants taking medication which could affect the central nervous system during the last six months were excluded, as well as subjects smoking more than 5 cigarettes a day (Windham et al., 1999 and 2005). All participants grew up monolingual, were German native speakers, and had no knowledge of Arabic. Eight out of the group of fourteen women (mean age = 24.88 years; range 21-28 years and mean menstrual cycle length = 28.11 days; range 26-30 days) successfully completed both scan terms with menstrual (mean day = 3.33; range day 1-5) and midluteal phase (mean day = 20.78; range day 20-22) verified by saliva progesterone levels. This study was approved by the local ethical commission.

5.3.2 Saliva Analysis

Prior to the experimental session, women were informed about the general procedure and data were collected about their individual menstrual cycles in order to plan the dates of the experimental sessions. Half of the women had their first session during the menstrual phase, the other half during the midluteal phase. Salivary progesterone levels were assessed by luminescence immunoassay (LIA) to evaluate the menstrual cycle phase. The measurement of steroid levels in saliva is a valid and non-invasive method (Riad-Fahmy et al., 1982 and 1983). Participants were instructed not to eat and to drink only tap water from three hours prior to the start of the session. During the last 30 min also brushing teeth, as well as eating chewing gum were forbidden. These measures were taken into account to prohibit contamination of saliva. During each session a saliva sample was collected every 30-40 minutes, with a total of 3 samples over the whole session. Progesterone is secreted by the corpus luteum into the blood in a pulsatile manner (every 90 min) in the midluteal phase (Filicori et al 1984; Soules et al., 1988). By sampling every half hour we were able to cover eventual pulse depending fluctuations in progesterone concentration. Even though blood

progesterone has to cross the blood saliva barrier a parallelism between plasma and saliva progesterone concentration was found (Delfs et al., 1994). After collection each sample was stored at -20° untill all samples had been collected.

5.3.3 State of Mood

To be able to take into account eventual changes in mood state between both sessions a German mood questionnaire, Mehrdimensionaler Befindlichkeitsfragenbogen (MDBF) (Steyer et al., 1994), was filled out. The MDBF questionnaire evaluates the actual temper by three bipolar dimensions: good temper - bad temper (GS), alertness – tiredness (WM), and tranquilness – restlessness (RU). For each of the three bipolar dimensions the minimum possible score is 4 and the maximum possible score is 20. The MBDF has two short forms, so every subject had two different questionnaires for each session. The order of the short forms was randomized between subjects and between sessions.

5.3.4 Task, Stimuli and fMRI Paradigm

A silent reading task with variable stimulus types (words, pseudowords and false fonts) was chosen. Words were high-imagery nouns (Fiebach and Friederici, 2004) and matched for usage frequency (Blair et al., 2002; Coney, 2005). Pseudowords, derived from real words by randomizing the letters, were pronounceable. Strings of arabic signs were used as false fonts. To control for subjects' alertness during the experiment, without having non-language related motor activation, a semantic decision task was included by a fourth category of stimuli: animal names. The subjects were instructed to read the stimuli silently and press the MRI compatible response button, fixated on the upper leg, when the presented stimulus was an animal name. This fourth category was not included in the SPM model. All stimuli were composed of four or five letters or signs (Whitney and Lavidor, 2004; Lindell et al., 2002; Mechelli et al., 2000) in a white font on a black background and presented vertically.

Stimuli were randomly presented centrally or lateralized (4° from fixation cross) every 3500 ms for 200 ms, followed by a 3300 ms fixation cross. The experiment consisted of three runs which were randomized between subjects. Each run counted 48 words, 48 pseudowords, 48 false fonts and 12 animal names. For each category, stimuli were equally divided over the CVF, left visual fields (LVF) and right visual field (RVF). Between runs the words,

pseudowords and false fonts used, were the same; only the presentation field was changed. For the fourth stimulus type, animal names, stimuli were not repeated between runs. Two different versions of the experiments were made and randomized between subjects and between sessions.

5.3.5 Imaging Parameters

Blood oxygen level dependent (BOLD)-fMRI was performed on a 1.5 Tesla Philips Gyroscan Intera system (Philips Medical Systems, Netherlands) with standard head coil. To verify subject positioning and to plan axial (AC-PC) slice acquisition a sagital scan was obtained. An echo planar T_2*-weighted imaging sequence was acquired every 3 s during the paradigm using the following parameters: TR = 3000 ms, TE = 50 ms, $\alpha = 90°$, FOV = 256 x 256 mm^2, matrix size = 64 x 64, voxel size = 4 x 4 x 4 mm^3, 32 slices, and 203 volumes per session. Functional scanning was always preceded by 15 s of dummy scans to insure steady-state magnetization.

Due to a time difference in image acquisition frequency and stimulus presentation frequency, there is a delay between image acquisition and stimulus presentation called temporal jittering. The advantage of temporal jittering is a better detection of the BOLD response curve.

Subjects wore earplugs and the placement of foam pads around the subjects´ head prohibited movement. An MRI compatible response button was attached around the upper leg of the subject easily accessible with the right hand. In this way the subject was able to response with a minimum of body movement.

5.3.6 FMRI Data Analysis:

Preprocessing

Image processing was performed using SPM2, developed by the Wellcome Institue (London, UK) running on MATLAB 6.1 (The MathWorks, Natrick, USA), based on the general linear model (Friston et al. 1995a and b). The individual subject (first level) analysis included following steps; (1) slice timing was used to correct for differences in acquisition time between slices; (2) motion correction was done by realignment of all images to the first image. Subjects whose images had more than one-voxel motion were rejected; (3) all images

were normalized to a standard MNI template brain; (4) spatial smoothing using a Gaussian kernel of FWHM 8 mm; (5) modelling of the expected hemodynamic response function (hrf) and first derivative (hrf') with the appropriate event-related design (only the former function was used for statistical contrasts); (6) filtering of the time series with the value of 128 s for the cut-off period of the high-pass filter.

Group Analysis (SPM2)

The results of the individual data analysis were submitted to a random effect group (second level) analysis. The following tests were conducted for the three visual fields of stimulus presentation (CVF, RVF LVF) and both menstrual cycle phases: (1) one sample t-tests to reveal BOLD activation during semantic processing (words > pseudowords); (2) one sample t-tests showing phonologic (pseudowords > false fonts) related BOLD activation. To compare the processing of semantics (3) and phonology (4) between the menstrual and midluteal phase paired t-tests were conducted. Finally, regression analyses was proceeded to discover progesterone correlated activation for semantic processing (5) and phonological processing (6). The paired t-tests as well as the regression analyses were calculated for the three visual fields separately.

Clusters were considered significant if they reached an activation threshold of $p_{uncorr} < .001$ (voxel-level) and $p_{corr} < .05$ (cluster-level). For semantic processing (one sample t-test) the threshold was $p_{uncorr} < .001$ (voxel-level) and cluster-size of 20 voxels. In a second step the threshold for semantic processing was lowered: $p_{uncorr} < .005$ (voxel-level) and cluster-size of 20 voxels. Automated anatomical labelling (AAL) software (Tzourio-Mazoyer et al., 2002) was used to label the peak activation of the cluster analysis.

ROI Analysis: Lateralization Index and Spatial Extent of Activation

The ROI analysis used is based on the magnitude of signal change in a ROI defined by the weighted β values (Fernandez et al., 2001; Jansen et al., 2006). The masks used for the ROI analysis are based on the masks in Marsbar_0.38.2 which are matched to the MNI/ICBM templates (Tzourio-Mazoyer et al., 2002). For each ROI two symmetrical masks were built one for the ROI in LH and one for its´ homologue in the RH. For each region a mean maximum β value was calculated as the mean of those 5% of voxels showing the highest level

of activation in the respective ROI. The threshold for inclusion in the calculation was then set at 50% of this mean maximum β value. The level of activation or signal intensity change was defined as the mean β value of all voxels exceeding the individually defined threshold and the volume of activation or spatial extent was calculated as the number of these voxels.

The hemispheric lateralization can be defined by a LI which is based on the above described ROI analysis. The following formula was used to calculate the LI:

$$LI = [(AL – AR)/(AL + AR)]$$

where AL and AR refer to values of fMRI-measured activity for equal ROIs in the LH and RH hemisphere. Results range from -1 to +1. A negative value represents RH dominance, a positive value LH dominance as previously described by (Binder et al., 1996). Brain activation pattern described by a LI value with $|LI| < 0.20$ are classified as bilateral (Springer et al., 1999).

5.3.7 Statistical Analysis

All statistical data analyses were performed with SPSS software (SPSS 13.0). Comparisons between the two menstrual cycle phases were performed with the Wilcoxon Signed Rank Test a non-parametric test for two dependent samples. The non-parametric Spearman Rank correlation was used to analyse possible correlations between salivary progesterone levels and behavioural performance (accuracy scores) and MDBF scores.

5.4 Results

5.4.1 Blood Progesterone Concentration

Fourteen healthy, normally cycling women completed two sessions. Six women were excluded because their progesterone levels were low in both sessions without the expected rise in concentration during the midluteal phase. High rates of anovulation (Vuorento and Huhtaniemi, 1992; Vuorenti et al, 1989), as well as lower progesterone profiles (Ellison et al., 1987) in young adults are often reported. The mean concentration of salivary progesterone of the remaining eight women was 29.38 (S.E.M. = 8.30) pg/ml during the menstrual phase and 326.03 (S.E.M. = 41.67) pg/ml in the midluteal phase. A non-parametric Wilcoxon Signed-Rank Test revealed a significant difference in mean progesterone concentration ($Z = -2.52$, $p < .05$) between both phases.

5.4.2 Behavioural Performance

For each subject and each VF an accuracy score was calculated as the ratio of correct against the sum of correct, missed and false responses (Table 5.1).

	Menstrual Phase		**Midluteal phase**	
VF	Mean (%)	S.E.M	Mean (%)	S.E.M.
CVF	76.36	5.05	82.53	3.61
RVF	69.81	6.36	68.91	7.56
LVF	66.39	9.11	75.40	5.03

Table 5.1: Behavioural performance (mean accuracy scores) during the menstrual and midluteal phase. A non-parametric Wilcoxon Signed-Rank Test revealed no difference in behavioural performance between both phases for CVF ($Z = -.94$, n.s.), RVF ($Z = -.14$, n.s.) and LVF ($Z = -.85$, n.s.).

To investigate the subjects´ performances across the menstrual cycle a non-parametric Wilcoxon Signed-Rank Test was performed for each VF separately. No difference in accuracy score was found between menses an midluteal phase for CVF ($Z = -.94$, n.s.), RVF ($Z = -.14$, n.s.) and LVF ($Z = -.85$, n.s.). The Spearman Rank correlation test did not reveal a significant

correlation between salivary progesterone levels and accuracy scores of the different VFs (CVF: r = .13, n.s.; RVF: r = .15, n.s. and LVF: r = .20, n.s). Hence, differences in imaging results between midluteal phase and menses cannot be attributed to differences in performance.

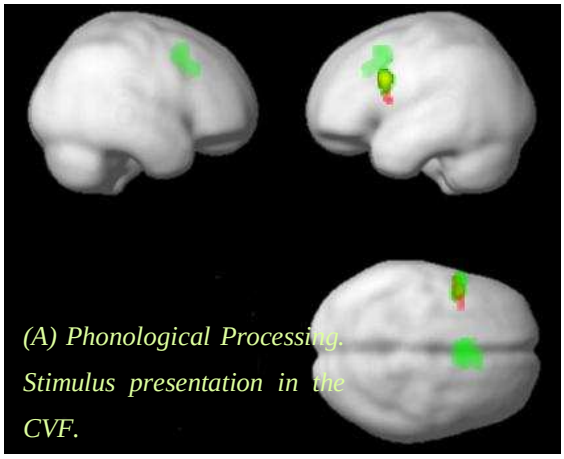
5.4.3 State of Mood

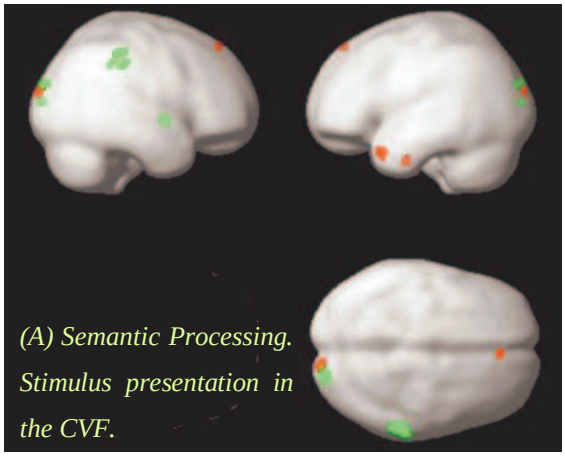
To investigate mood changes across the menstrual cycle a non-parametric Wilcoxon Signed-Rank test was used to compare MDBF scores for each bipolar dimension between menstrual and midluteal phases (Table 5.2). Significantly higher MDBF scores were found for the midluteal versus the menstrual phase for following bipolar dimensions: GS (Z = -2.20, $p < .05$) and WM (Z = -2.05, $p < .05$). For the bipolar dimension RU (Z = -.94, n.s.) no such difference was found (Table 5.2). Using the Spearman Rank correlation test, a positive correlation was detected between salivary progesterone levels and MDBF scores of the bipolar dimension WM (r = .49, $p < .05$). No further correlations between salivary progesterone level and MDBF scores were observed (GS: r = .20, n.s.; RU: r = .31, n.s.). Neither did we find any correlation between MDBF scores of the bipolar dimensions GS and WM and behavioural accuracy scores of the different visual fields: RVF (GS: r = .12, n.s.; WM: r = .26, n.s.; RU: r = -.17 ,n.s.), CVF (GS: r = -.10, n.s.; WM: r = .29, n.s.; RU: r = -.32 , n.s.) and LVF (GS: r = .21, n.s.; WM: r = .12, n.s.; RU: r = .01 , n.s.).

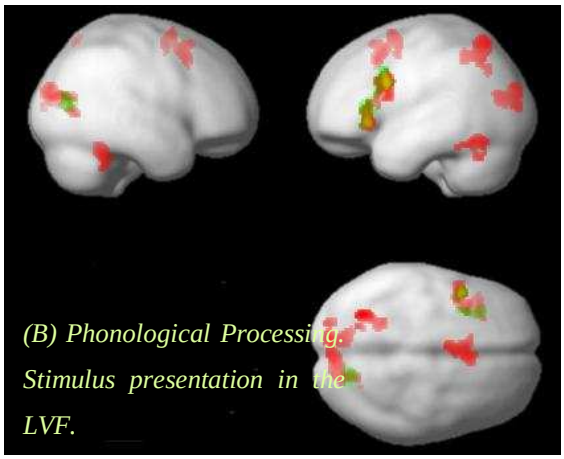
	Menstrual Phase		**Midluteal Phase**	
Bipolar dimension	Mean	S.E.M.	Mean	S.E.M.
good temper - bad temper (GS)	15.38	0.93	16.13	0.99
alertness - tiredness (WM)	12.13	0.61	14.25	1.39
tranquilness - restlessness (RU)	14.38	0.75	14.25	1.29

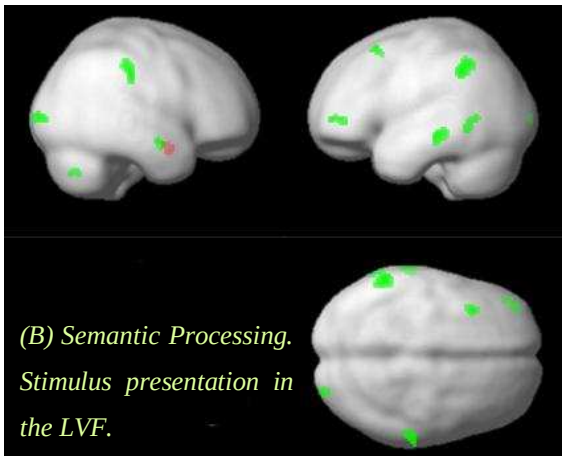
Table 5.2: MDBF scores. Using a non-parametric Wilcoxon Signed-Rank test significant higher MDBF scores were found for the midluteal phase versus the menses for following bipolar dimensions: GS (Z = -2.20, $p < .05$) and WM (Z = -2.05, $p < .05$). For the bipolar dimension RU (Z = -.94, n.s.) no such difference was found.

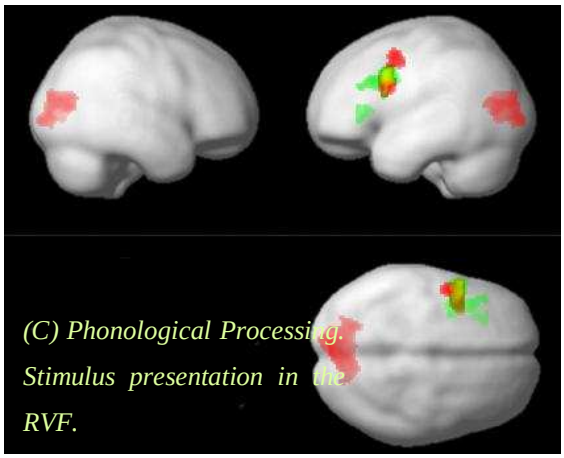
5.4.4 FMRI Results











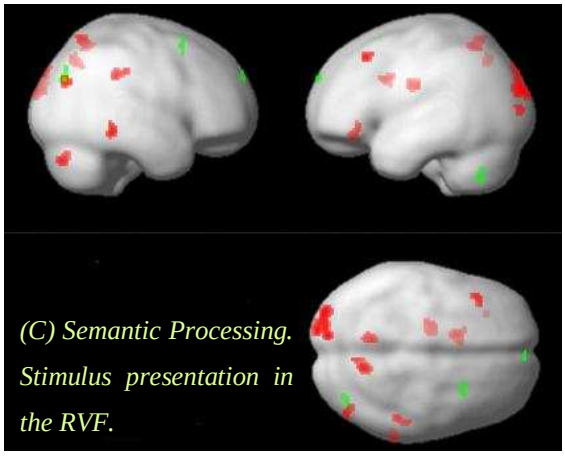


Fig 5.1 (left) and Fig 5.2 (right): Phonological processing (left) and semantic processing (right) (menstrual phase = red; midluteal phase = green). Activation is projected onto 3D anatomical template. Activations were considered significant if they reached an activation threshold of p_{uncorr} < .001 (voxel-level) and p_{corr} < .05 (cluster-level). For semantic processing the significance threshold was: p_{uncorr} < .001 (voxel-level) and cluster-size of 20 voxels (cluster-level).

The one sample t-tests revealed for phonological processing significantly increased activation in both the inferior frontal gyrus and the precentral gyrus. To a smaller extent activation was found in the middle and superior frontal gyrus, super motor area, insula and middle cingulate cortex. The peak activation of the majority of clusters was situated in the LH, independent of the stimulus presentation field (Fig 5.1 and Table 5.3).

During semantic processing, activations were mainly found in the frontal lobe: superior, middle and inferior (pars orbitalis and pars triangularis) gyrus; temporal lobe: inferior, middle and superior temporal gyrus, fusiform gyrus; parietal lobe: inferior parietal lobule and precuneus; and cingulated cortex. For semantic processing the clusters were located in the LH, RH or bilaterally (Fig 5.2 and Table 5.4).

Some occipital activation was also observed during the processing of phonology and semantics. As these regions are competent for visual but not specific for phonologival or semantic processing they were excluded from further analysis (Indefrey et al., 1997).

Paired t-tests were conducted to test for significant differences in activation between menstrual and midluteal phase. No significant differences in activation between menses and midluteal phase were found.

Menstrual Phase							Miduteal Phase						
	H	MNI co. x	y	z	peak activation z-value	LI		H	MNI co. x	y	z	peak activation z-value	LI
pseudowords > fasle fonts (CVF)							*pseudowords > fasle fonts (CVF)*						
GFi pars opercularis	L	-44	8	28	4.32	0.15	GFi pars opercularis	L	-44	10	26	4.95	0.15
GFi pars triangularis	L	-38	13	28	3.90	0.06	GPrC	L	-46	8	42	3.27	0.25
							SMA	L	-4	14	50	4.65	-0.07
							MCC	R	6	16	40	4.57	-0.02
							Sca	R	16	-66	8	4.05	
pseudowords > false fonts (LVF)							*pseudowords > false fonts (LVF)*						
GFs	L	-12	18	44	4.19	0.00	GFm	L	-46	12	36	4.02	0.17
GFi pars orbitalis	L	-38	24	-4	3.92	0.02	GFi pars opercularis	L	-46	10	28	3.79	0.17
GFi pars opercularis	L	-34	14	20	4.63	0.07	GFi pars triangularis	L	-32	16	22	4.49	0.12
GFi pars triangularis	L	-38	18	28	3.56	0.14	INS	L	-30	28	6	4.41	0.04
INS	L	-26	28	6	3.87	0.00	GOs	R	16	-74	8	4.11	
SMA	L	-4	14	46	3.98	-0.08	Sca	R	22	-78	18	3.36	
	R	4	16	46	4.01								
GTi	L	-38	-8	-28	4.12	0.27							
GF	L	-46	-62	-20	3.60	0.12							
MCC	R	12	4	28	3.78	-0.08							
GOs	L	-20	-68	38	3.92								
	R	18	-80	18	4.03								
GOm	L	-24	-90	8	4.07								
Cu	L	-10	-90	24	4.06								
pseudowords > false fonts (RVF)							*pseudowords > false fonts (RVF)*						
GFi pars opercularis	L	-48	8	26	4.35	0.11	GFi pars opercularis	L	-46	30	24	3.40	0.18
GFi pars triangularis	L	-36	10	24	4.00	0.01	GFi pars triangularis	L	-38	20	30	4.98	0.14
GPrC	L	-50	-2	44	3.86	0.19	GPrC	L	-48	10	36	5.05	0.20
GOs	L	-12	-90	4	4.88		INS	L	-26	30	2	4.23	0.04
Sca	L	-12	-96	-2	4.46								

Table 5.3: Brain regions identified by group analysis (SPM2) for phonological processing (CVF, LVF, and RVF) during the menstrual phase and midlutueal phase (significance threshold: p_{uncorr} < .001 (voxel-level) and p_{corr} < .05 voxel (cluster-level). H = hemisphere, L = LH and R = RH.

Menstrual Phase							Midluteal Phase						
		MNI co.			peak activation	LI			MNI co.			peak activation	LI
	H	x	y	z	z-value			H	x	y	z	z-value	
words > pseudowords (CVF)							*words > pseudowords (CVF)*						
GFm	L	-44	30	42	3.67	-0.01	INS	*L*	*-42*	*-4*	*-2*	*3.03*	-0.03
GFs	L	-28	42	38	3.29	0.02	GTs	*L*	*-50*	*2*	*-6*	*3.56*	-0.10
	R	4	42	52	3.29			*R*	*44*	*-12*	*-4*	*3.00*	
GTi	L	-42	-6	-36	3.64	-0.02	GF	*R*	*36*	*-54*	*-18*	*3.07*	0.01
GTm	L	-48	14	-30	4.75	-0.07	LPi	R	60	-34	48	4.53	-0.06
GF	*L*	*-34*	*-42*	*-12*	*3.49*	-0.11	Cu	R	18	-96	8	3.94	
LPi	*L*	*-42*	*-46*	*32*	*3.29*	-0.02	GOs	R	22	-96	26	3.87	
PCu	*L*	*-10*	*-60*	*56*	*3.34*	-0.02							
MCC	L	-8	-10	44	3.75	-0.06							
	R	*24*	*-46*	*34*	*3.29*								
Cu	R	12	-96	20	4.57								
words > pseudowords (LVF)							*words > pseudowords (LVF)*						
GFm	*R*	*30*	*12*	*50*	*3.57*	0.01	GFm	L	-38	50	2	3.92	0.05
GTm	*R*	*70*	*-40*	*2*	*3.73*	-0.03	GFs	*L*	*-16*	*58*	*-8*	*3.52*	0.05
PHi	R	12	4	-20	3.70	0.02	GFi pars orbitalis	*L*	*-40*	*42*	*-12*	*3.45*	0.07
							INS	*L*	*-36*	*-18*	*14*	*3.22*	0.05
							GTi	*L*	*-38*	*14*	*-40*	*2.92*	0.13
								R	*56*	*-28*	*-16*	*2.87*	
							GTm	L	-68	-28	-10	4.78	0.02
								R	56	-6	16	4.83	
							GTs	*R*	*70*	*-26*	*8*	*3.12*	-0.06
							LPi	L	-60	-48	38	4.16	0.09
								R	66	-26	34	3.67	
							PCu	*L*	*-8*	*-76*	*44*	*3.25*	-0.04
							GOm	R	28	-96	4	4.08	
words > pseudowords (RVF)							*words > pseudowords (RVF)*						
GFm	L	-26	36	-14	3.80	-0.05	GFm	R	32	14	54	3.57	-0.01
	R	*36*	*34*	*26*	*3.94*		GFs	*L*	*-18*	*20*	*34*	*3.63*	-0.06
GFs	*R*	*20*	*36*	*38*	*3.81*	-0.03		R	4	62	32	4.66	
GFi pars orbitalis	L	-32	30	-10	3.49	-0.05	SMA	*R*	*14*	*-2*	*58*	*3.59*	-0.06
GFi pars triangularis	*L*	*-36*	*30*	*12*	*3.49*	-0.05	GTi	*L*	*-50*	*-8*	*-30*	*3.28*	-0.05
GTm	R	64	-40	-12	3.73	-0.01	GTm	*L*	*-56*	*2*	*-34*	*3.08*	0.02
GTs	*L*	*-64*	*-52*	*18*	*3.52*	-0.02	LPi	*L*	*-44*	*-50*	*30*	*3.56*	0.02
GF	*L*	*-30*	*-80*	*-14*	*3.08*	-0.11		*R*	*34*	*-58*	*52*	*3.51*	
LPi	R	50	-38	32	4.27	-0.04	PCu	*R*	*24*	*-52*	*20*	*3.42*	0.00
PCu	L	-10	-56	54	3.49	-0.07	GOm	R	38	-76	30	3.34	
	R	14	-62	60	4.42								
MCC	L	-14	8	30	4.53	0.02							
ACC	*L*	*2*	*18*	*14*	*3.07*	0.04							
	R	*8*	*30*	*0*	*3.35*								
GOs	L	-14	-92	34	3.92								
GOm	L	-32	-92	20	3.53								
	R	50	-76	26	3.68								

Table 5.4: Brain regions identified by group analysis (SPM2) for semantic processing (CVF, LVF, and RVF) during the menstrual phase and midlutueal phase (significance threshold: $p_{uncorr} < .001$ (voxel-level) and cluster-size of 20 voxel (cluster-level); and Italic print significance threshold: voxel-level $p_{uncorr} < .005$; cluster-size of 20 voxel. H = hemisphere, L = LH and R = RH.

Correlation of progesterone levels during the menstrual cycle with the BOLD activation revealed that, during semantic processing with stimulus presentation in the LVF, brain activity in the left superior frontal gyrus, left middle and inferior occipital gyri and bilateral fusiform gyrus correlated with progesterone concentrations in saliva (Fig 5.3 and Table 5.5). During phonological processing no brain activation was significant correlated with progesterone levels.

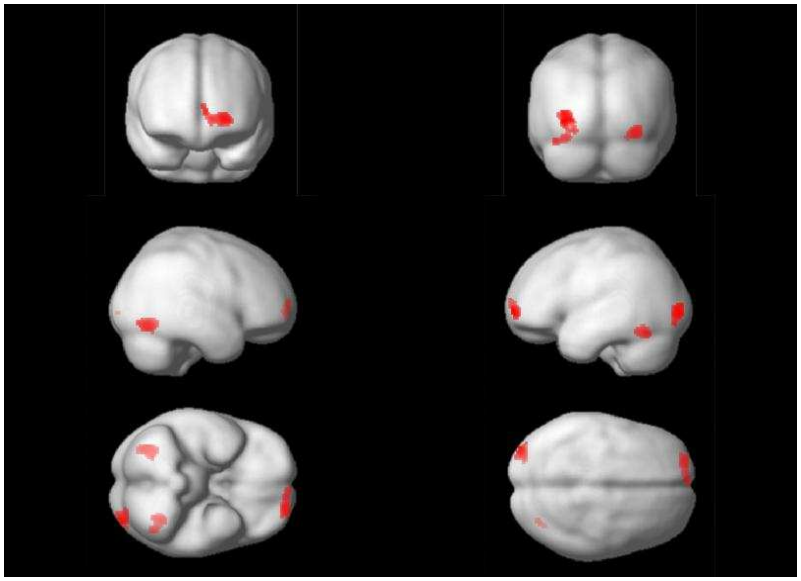


Fig 5.3: Brain activation positively correlated with progesterone saliva level for the processing of semantics (LVF). Activation is projected onto 3D anatomical template. Activations were considered significant if they reached an activation threshold of p_{uncorr} < .001 (voxel-level) and p_{corr} < .05 (cluster-level).

	H	MNI co. x	y	z	peak activation z-value		H	MNI co. x	y	z	peak activation z-value
words > pseudowords (CVF)						*pseudowords > false fonts (CVF)*					
no significant activations						no significant activations					
words > pseudowords (LVF)						*pseudowords > false fonts (LVF)*					
GFs	L	-24	62	-2	4.38	no significant activations					
GF	L	-32	-58	-18	3.96						
	R	34	-70	-14	4.33						
GOm	L	-34	-92	-4	4.86						
GOi	L	-24	-90	-12	3.45						
words > pseudowords (RVF)						*pseudowords > false fonts (RVF)*					
no significant activations						no significant activations					

Table 5.5: Brain activations possitively correlated with progesterone saliva level for semantic processing (LVF). Activations were considered significant if they reached an activation threshold of p_{uncorr} < .001 (voxel-level) and p_{corr} < .05 (cluster-level). H = hemisphere, L = LH and R = RH.

ROI Analysis:

LI

Calculation of the LI was based on the signal intensity change in a ROI. The selection of the ROIs was based on the results of the group analysis (Table 5.2 and Table 5.3).

A non-parametric Wilcoxon Signed-Rank test was performed to define an eventual shift in LI between both cycle phases. No such a difference was found for any of the regions during neither the processing of semantics, or phonology.

Spatial Extent of Activation

The spatial extent of activation was defined, as for the LI calculation, for those regions which were significantly activated in the group analysis (SPM2).

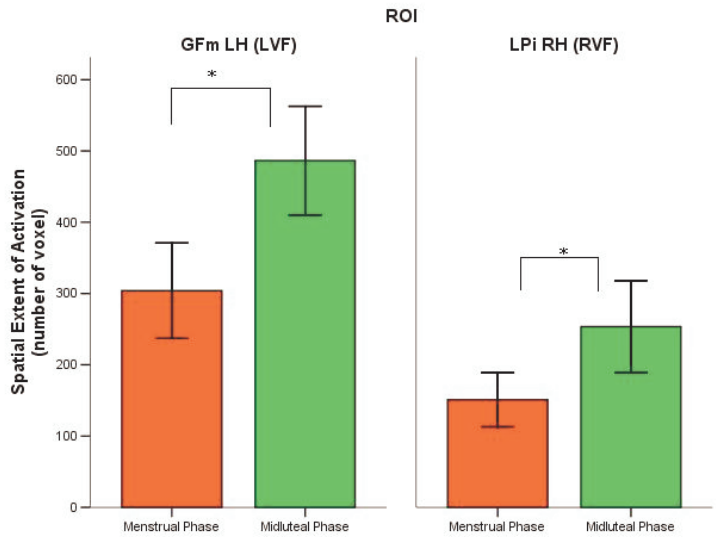


Fig 5.6: The spatial extent of activation in the left middle frontal gyrus (LVF) and right inferior parietal lobule (RVF) was significant larger during the midluteal phase (green) compared to the menstrual phase (red). Error bars: ± 1.00 S.E.

To explore changes in the spatial extent of activation between the two cycle phases a non-parametric Wilcoxon Signed-Rank test was calculated. No significant difference in volume of activation was found between both phases for phonological processing. In contrast, for semantic processing a significant difference in the spatial extent of activation was found (Fig 5.6). For the frontal lobe (LVF left GFm: $Z = -2.31$, $p < .05$) and the parietal lobe (RVF right LPi: $Z = -2.24$, $p < .05$) the volume of voxels significantly activated was larger during the midluteal than the menstrual phase

5.5 Discussion

The present study demonstrates that the effect of fluctuations in the progesterone level during the menstrual cycle on brain activity is task and region dependent. Brain activation was defined by both signal intensity change and the spatial extent of activation. Based on the progesterone-mediated interhemispheric decoupling hypothesis we expected for language processing, an increase in brain activity of the non-dominant RH when comparing the data of the midluteal (high serum progesterone levels) with the menstrual phase (low serum progesterone levels). Interestingly, however, our data did reveal a progesterone dependent rise in brain activation concerned regions in both hemispheres. Fernandez et al (2003) also reported a correlation of serum progesterone with bilateral brain activity for a semantic decision task.

The concentration of the gonadal steroid hormone progesterone fluctuates during the menstrual cycle with low levels during menstrual phase and peak level at the midluteal phase. Progesterone which is formed mainly peripherally by the corpus luteum, can because of its lipophilic nature cross the blood brain barrier (Hu et al., 1987). In the brain, progesterone can be reduced to the neuroactive steroids 3α-hydroxy-5α-pregnan-20-one (allopregnanolone) and/or 3α-hydroxy-5β-pregnan-20-one (pregnanolone) by the 3α-hydroxysteroid oxidoreductase (Rupprecht, 1997). Both pregnanolone and allopregnanolone modulate neuronal excitability as established positive allosteric modulators of the γ-aminobutyric acid type A ($GABA_A$) receptor, by increasing the frequency and/or duration of openings of the $GABA_A$-gated chloride channel (Lambert et al. 2003; Rupprecht 2003). Moreover, Woolley et al. (1992 and 1996) reported cycle-dependent synaptogenesis in rodents. Estrogen not only increases the density of presynaptic, excitatory, glutamergic terminals on dendrites of pyramidal neurons, but also converts some presynaptic terminals that innervated only a single spine into terminals innervating multiple spines. Such modulating effects on neurotransmission and/or synaptogenesis may cause changes in brain activation during the menstrual cycle.

Comparison of the activation patterns during both semantic and phonological processing revealed that there was no recruitment of new regions at the different time points in the menstrual cycle. Instead, the correlation of the saliva progesterone values with the fMRI data showed that, for the semantic processing, BOLD activity in the left superior frontal gyrus, left middle and inferior occipital gyrus and bilateral fusiform gyrus is positively correlated with progesterone concentrations. The left superior frontal gyrus the midluteal phase was

associated with an increase in volume of activation. The fact that this network was found for LVF but neither for RVF nor CVF stimulus presentation, might imply that it is under left hemispheric control. In contrast, the brain activation pattern for phonological processing was invariable across the menstrual cycle.

The BOLD response is an indirect measure of neuronal activity depending on differences in magnetic susceptibility between oxyhaemoglobin and deoxyhaemoglobin. An increase in neuronal activity causes a local change in the ratio of oxy- and deoxygenated blood which results in a rise in BOLD signal (Ogawa et al., 1990). The question that comes up is whether the progesterone related increase in brain activation reflects true alterations in neural activity or indicates a change in cerebrovascular reactivity or/and cerebral blood flow. Both in this study as in other studies (Binder et al., 1997) it is shown that semantic processing activates a network including regions in the frontal lobe, temporo-parietal lobe as well as parts of the cingulum (see also chapter 4). The fact that significant changes were seen in some but not all portions of this network points out that the effects may not be due to a widespread phenomenon such as vascular tone or cerebral blood flow. However, changes in cerebral blood flow over the course of the menstrual cycle are known to be linked to estrogen rather than progesterone levels (Brackley et al., 1999; Krejza et al., 2004). Decreases in cerebrovascular resistance are correlated with increasing estrogen concentrations at the end of the follicular phase. Estrogen also enhances the production or sensitivity to vasodilatory factors (Ospina et al., 2003).

The cycle-dependent changes in brain activation during semantic processing were found for stimulus presentation in the LVF. These findings are in line with the progesterone mediated hemispheric decoupling hypothesis, as language processing is predominantly organized in the left hemisphere and following the hypothesis progesterone is expected to affect the non-dominant hemisphere. The associated BOLD activations where in contrast not limited to the RH which suggests that the effect of fluctuating progesterone levels is firstly not limited to a single hemisphere, and secondly the effect of progesterone affects interconnected networks of brain regions.

For phonological processing neither changes in brain activation pattern nor specific progesterone correlated activation where found across the menstrual cycle. An explanation for the lack of cycle dependent changes could lie not in the absence of an average change, but rather in the existence of high variability in the activated network during phonological processing between subjects. Weekes et al. (1999) suggested that the presence of

phonological processing in the RH depends on the available resources and the strategies used, which are subject to individual differences.

Hausmann and Güntürkün (2000) based their progesterone-mediated hemispheric decoupling hypothesis on an increase in performance of the subdominant hemisphere related to high serum progesterone levels. The behavioural performance data of for the semantic decision task revealed no significant change in performance when comparing the menstrual to the midluteal phase. Even though the significance level was not reached, behavioural accuracy increased for CVF but especially for LVF stimulus presentation which is in accordance with the hypothesis of Hausmann and Güntürkün (2000).

Cycle-related fluctuation in progesterone plasma levels seems to be associated with mood changes. For the bipolar dimensions WM and GS we found significantly higher scores during the midluteal phase versus the menses, whereas MDBF WM scores were positively correlated with salivary progesterone levels. These results are in accordance with a study of Meaden et al. (2005). Meaden and colleagues studied a sample of 900 women and found that the majority of these women experienced physiological, social, emotional and cognitive distress varying with the menstrual cycle. During the week prior to menses symptoms increased, with a peak on the first day of menses, and dropping of by the sixth day of the menstrual cycle. In our study changes in mood across the cycle did not influence behavioural performance.

In conclusion, the results of the presented study indicate that gonadal steroid levels during the menstrual affects semantic, but not phonological processing. However, the progesterone correlated network includes regions in both hemispheres, and might be under left hemispheric control

Chapter 6

General discussion

This work presents event-related fMRI studies on different components of language processing after presentation of linguistic stimuli in the RVF, LVF, and CVF. Fluctuating progesterone levels during the menstrual cycle were included as additional factor for female participants.

Firstly, we investigated the visual processing of different linguistic stimuli received initially in the left, right or both visual cortices. Consistent with the generality of crossed visual input (Bourne, 2006), we found, for lateral stimulus presentation, a higher BOLD response in most visual areas contralateral to the visual field of presentation compared to the ipsilateral regions. For the primary visual areas such as the calcarine sulcus and cuneus this effect was not found, which can be ascribed to the spatial limitations of the used fMRI data acquisition parameters and data analysis. In general this finding suggests that, for visual processing, there is no "prefered" hemisphere. Some studies (Petersen et al, 1990) reported a specialisation of the left middle occipital gyrus for words and pseudowords versus false fonts on observation that could not be supported by our data.

Even though the fusiform gyrus revealed no hemispheric specialisation for visual processing, the VWFA, which is part of this region, did. A trend for left hemispheric predominance was observed for the processing of words, and pseudowords. An exception was visual processing of words presented in the left visual field that resulted in a bilateral activation pattern of the VWFA. Thus, not only the left VWFA, as previously reported (Cohen et al., 2000), but also the right VWFA is sensitive to recognition of visual word-level features. In addition, the absence of activation in the right VWFA for CVF and RVF stimulus presentation supports Vingneau's hypothesis (Vigneau et al., 2005) that the visual specialisation for words operates through the dynamics of the interaction between the left and right VWFA. Within this framework, the superiority of the left VWFA is the result of a reduced activity in the right VWFA under left hemispheric control.

Language processing not only includes the initial visual processing of linguistic stimuli, but also the processing of phonology (analysis of the pronunciation of words) and semantics (analysis of the meaning of words). In a second step, we explored phonological and semantic processing of linguistic stimuli initially received in the left, right or both visual cortices. Independent of the visual field of stimulus presentation field, the data revealed, during phonological processing, a predominantly left hemispheric network of activated regions. The activation pattern during semantic processing was, independent of the visual field stimulated, bilateral. Other studies (Shaywitz et al., 1995; Kiehl et al., 1999), using only CVF stimulus

presentation, reported activation pattern congruent with ours. Hunter and Brysbaert (2008) proposed a hypothesis for information processing in the non-specialised hemisphere. They suggested that information arriving in the subdominant hemisphere either requires interhemispheric transfer to reach the dominant hemisphere or is processed more slowly by the less specialised hemisphere. Application of this hypothesis to our results suggests interhemispheric transfer of information from the right to left hemisphere during phonological processing. The interpretation of the bilateral pattern during semantic processing is not so well-defined. Probably, it reflects processing in both hemispheres without the presence of a distinct hemispheric specialisation for the semantic task used. Remarkably, there was a reduced network activated during semantic processing for stimulus presentation in the LVF. This reduction did not affect behavioural performance. Instead, it reflects a large inter-individual variability in networks used for this task.

In contrast to men, language organisation in women is ambiguous. To address this, we assessed the effect of changes in hormone levels during the menstrual cycle on the processing of phonology and semantics in both hemispheres. Hausmann and Güntürkün (2000) proposed, in this context, that a rise in progesterone would result in a decrease in cortico-cortical transmission. Instead, our data revealed, during semantic processing, a network of regions, covering both hemispheres, whose signal intensity change was correlated with salivary progesterone levels during the female cycle. Fernandez and colleagues also reported a correlation of serum progesterone with bilateral brain activity for a semantic decision task. This network was found for LVF, but neither RVF nor CVF stimulus presentation, which might imply that it is under left hemispheric control. In contrast, the brain activation pattern for phonological processing did not change significantly throughout the menstrual cycle.

It has been proposed that language is more strongly lateralized in men than in women (Kansaku and Kitazawa, 2001). Functional neuroimaging studies reported sex differences in the inferior frontal gyrus during a rhyme judgement task (Shaywitz et al., 1995) and during generation of past tenses of verbs (Jaeger et al., 1998). On the other hand, no sex differences were found during a verb generation task (Buckner et al., 1995) or a semantic judgement task (Frost et al., 1999). Additional analyses (see addendum) of our data for sex differences showed that for neither men nor women in the menstrual or midluteal phase the LI of activation pattern, during the processing of phonology and semantics, was affected by the field of stimulus presentation. Comparison of the LI values revealed, for phonological processing, a trend to a more right lateralized activation pattern in the inferior frontal gyrus

for women during the menstrual phase compared to men. The LI of the activation during semantic processing did not differ with sex. Other fMRI studies reported sex differences in brain activation during language processing. Shaywitz et al. (1995) also found, for a phonological task, that brain activation in men was lateralized to left inferior frontal gyrus, whereas women had a more diffuse activation pattern that involved both the left and right inferior frontal gyrus. An fMRI study by Vikingstad and colleaques (2000) showed for language processing in men a left lateralized activation pattern. Women in contrast, had approximately half left lateralization and the other half bilateral language representation. Neither study, however, controlled for differences in plasma hormone level.

In summary, the results of the different event-related fMRI studies revealed for the tasks used no hemispherical specialisation for visual processing of linguistic stimuli. In the VWFA, at the end of the visual processing stream, a left hemispheric specialisation for the processing of word-level features occurred. Suggesting that this left hemispheric predominance is the result of a reduced activity in the right VWFA under left hemispheric control. The processing of phonology and semantics was independent of the field of stimulus presentation. Phonological processing was mainly observed in the LH probably due to interhemispheric transfer of information from the right to left hemisphere. The bilateral pattern during the processing of semantics might reflect processing in both hemispheres without the presence of a distinct hemispheric specialisation for the semantic task used. A trend for a stronger left lateralization during phonological processing was assessed in men compared to women in the menstrual phase. Further investigation on women revealed a progesterone-correlated semantic network covering both hemispheres. In addition, this network might be under left hemispheric control.

The novelty of the performed studies is the combination of fMRI and the presentation of stimuli in different visual fields. Visual half-field presentation allows us to study the specialised and non-specialised hemisphere, but gives also an idea on how both might interact. In contrast to the “classic” behavioural outcomes of visual half-field presentation, studying the BOLD response with fMRI allows us to directly measure processing in each hemisphere. In addition, we were able to identify a network of brain regions whose activation was correlated with progesterone concentrations during the menstrual cycle. It would be interesting to extend this work to a predominantly right hemispheric task such as a visuo-spatial task.

The presented work contributes to the general brain asymmetry research and might be of particular relevance in the framework of revalidation therapies after e.g. brain infarcts.

Furthermore we showed that steroid hormone levels during the menstrual cycle is a factor which should be considered when performing studies in female participants.

References

Aboitiz, F., Scheibel, A. B., Fisher, R. S., and Zaidel, E., 1992. Individual differences in brain asymmetries and fiber composition in the human corpus callosum. Brain Research, 598, 154-161.

Adcock, J.E., Wise, R.G., Oxbury, J.M., Oxbury, S.M., and Matthews, P.M., 2003. Quantitative fMRI assessment of the differences in lateralization of language-related brain activation in patients with temporal lobe epilepsy. NeuroImage 18, 423-438.

Aguirre, G.K., and D'Esposito, M., 2000. Experimental design for brain fMRI. In: Moonen, C.T.W., Bandettini, P.A. (Eds.), Functional MRI, Springer-Verlag Berlin, Heidelberg, pp. 369-380.

Annett, M., 1972. The distribution of manual asymmetry, Br J Psychol 63, 343– 358.

Annett, M., 1999. Handedness and lexical skills in undergraduates, Cortex 35, 357– 372.

Allen, W.M., 1935. The isolation of crystalline progestin. Science 82, 89-93.

Allen, W.M., 1970. Progesterone: how did the name originate? South Med J. 63, 1151-1155.

Ashburner, J., and Friston, K.J., 2003. Rigid body registration. In: Frackowiak, R.S.J., Friston, K.J., Frith, C., Dolan, R., Price, C.J., Zeki, S., Ashburner, J., Penny, W.D. (Eds.), Human brain function, 2nd ed. Academic Press, San Diego.

Ashburner, J., and Friston, K.J., 2000. Image registration. In: Moonen, C.T.W., Bandettini, P.A. (Eds.), Functional MRI, Springer-Verlag Berlin, Heidelberg, pp. 285-299.

Bandettini, P.A., and Cox, R.W., 1998. Contrast in single trial fMRI: interstimulus interval dependency and comparison with blocked strategies. In: Proc ISMRM 6th Annual Meeting Sydney, pp. 161.

Bandettini, P.A., 2000. The temporal resolution of functional MR. In: Moonen, C.T.W., Bandettini, P.A. (Eds.), Functional MRI, Springer-Verlag Berlin, Heidelberg, pp. 205-220.

Banich, M. T, and Belger, A., 1990. Interhemispheric interaction: How do the hemispheres divide and conquer a task. Cortex 26, 77-94.

Banich, M.T., 1998. The missing link: the role of interhemispheric interaction in attentional processing. Brain Cogn 36,128 –157.

Barnard, E.A., Skolnick, P., Olsen, R.W., Mohler, H., Sieghart, W., Biggio, G., Braestrup, C., Bateson, A.N., and Langer, S.Z., 1998. International Union of Pharmacology. XV. Subtypes of gamma-aminobutyric acidA receptors: classification on the basis of subunit structure and receptor function. Pharmacol Rev. 50, 291-313.

Barnett, K.J., and Kirk, I.J., 2005. Lack of asymmetrical transfer for linguistic stimuli in schizophrenia: an ERP study. Clin Neurophysiol 116, 1019 –1027.

Baulieu, E.E., 1991. Neurosteroids: a new function in the brain. Biol Cell 71, 3-10.

Baulieu, E.E., 1998. Neurosteroids: a novel function of the brain. Psychoneuroendocrinology 23, 963-987.

Baynes, K., Tramo, M.J., and Gazzaniga, M.S., 1992. Reading with a limited lexicon in the right hemisphere of a callosotomy patient. Neuropsychologia 30, 187-200.

Belger, A., Banich, M.T., 1998. Costs and benefits of integrating information between the cerebral hemispheres: a computational perspective. Neuropsychology12, 380 –398.

Ben-Shachar, M., Dougherty, R.F., Deutsch, G.K., and Wandell, B.A., 2007. Contour and word form processing in human ventral occipito-temporal cortex. Cerebral Cortex 17, 1604-11.

Binder, J.R., Rao, S.M., Hammeke, T.A., Frost, J.A., Bandettini, P.A., Jesmanowicz, A., and Hyde, J.S., 1995. Lateralized human brain language systems demonstrated by task subtraction functional magnetic resonance imaging. Arch Neurol 52, 593-601.

Binder, J.R., Swanson, S.J., Hammeke, T.A., Morris, G.L., Mueller, W.M., Fischer, M., Benbadis, S., Frost, J.A., Rao, S.M., and Haughton, V.M., 1996. Determination of language dominance using functional MRI: a comparison with the Wada test. Neurology 46, 978-984.

Binder, J.R., Frost, J.A., Hammeke, T.A., Cox, R.W., Rao, S.M., and Prieto, T., 1997. Human brain language areas identified by functional magnetic resonance imaging. J Neurosci 17, 353-362.

Binder, J.R., and Price, C.J., 2001. Functional neuroimaging of language. In: Cabeza, R., Kingstone, A. (Eds) Handbook of Functional Neuroimaging of Cognition, MA: MIT Press, Cambridge, pp. 187–251.

Bisazza, A., Rogers, L.J., and Vallortigara G., 1998. The origins of cerebral asymmetry: a review of evidence of behavioural and brain lateralization in fishes, reptiles and amphibians, Neurosci Biobehav Rev 22, 411 – 426.

Bitran, D., Shiekh, M., and McLeod, M., 1995. Anxiolytic effect of progesterone is mediated by the neurosteroid allopregnanolone at brain GABAA receptors. J Neuroendocrinol 7, 171-177.

Blair, I.V., Urland, G.R., and Ma, J.E., 2002. Using Internet search engines to estimate word frequency. Behav Res Methods Instrum Comput 34, 286-290.

Bookheimer, S.Y., Zeffiro, T.A., Blaxton, T., Gaillard, W., and Theodore, W., 1995. Regional cerebral blood flow during object naming and word reading. Human Brain Mapping 3, 93-106.

Bourne, V. J., 2006. The divided visual field paradigm: Methodological considerations. Laterality 11(4), 373–393.

Brackley, K.J., Ramsay, M.M., Broughton, P.F., and Rubin, P.C., 1999. The effect of the menstrual cycle on human cerebral blood flow: studies using Doppler ultrasound. Ultrasound Obstet Gynecol. 14, 52-57.

Brammer, M.J., 2001. Head motion and its correction. In: Jezzard, P., Matthews, P.M., Smith, S.M (Eds.), Functional MRI: An introduction to Methods. Oxford University Press Inc., New York, pp. 243-250.

Brodal, A., 1981. Neurological anatomy (3 Ausgabe). New York: Oxford University Press.

Broca, P., 1861. Perte de la parolle, ramolissement chronique et destruction partielle du lobe antérieur guche du cerveaux. Bulletin de la Société d' Anthropologie de Paris 2, 235-238.

Bryden, M.P., Hecaen, H., and DeAgostini, M., 1983. Patterns of cerebral organization. Brain Lang 20, 249-262.

Brysbaert, M., 1996. The right visual field advantage and the optimal viewing position effect: On the relation between foveal and and parafoveal word cognition. Neuropsychology 10, 385-395.

Buchanan, T.W., al'Absi, M., and Lovallo, W.R., 1999. Cortisol fluctuates with increases and decreases in negative affect. Psychoneuroendocrinology 24, 227-241.

Bunt, A.H., Minckler, D.S., and Johanson, G.W., 1977. Demonstration of bilateral projection of the central retina of the monkey with horseradish peroxidase neuronography. J Comp Neurol 171, 619-630.

Bures, J., Buresova, O., 1960. The use of Leao's spreading depression in the study of interhemispheric transfer of memory traces. J Comp Physiol Psychol 53, 558 –563.

Butenandt, A., and Westphal U., 1934. "Zur Isolierung und Charakterisierung des Corpusluteum-Hormons". Berichte Deutsche chemische Gesellschaft 67, 1440–1442.

Carpenter, R.H.S., 1988. Movements of the eyes. London: Pion.

Chen, W., and Ogawa, S., 2000. Principles of functional MRI. In: Moonen, C.T.W., Bandettini, P.A. (Eds.), Functional MRI, Springer-Verlag Berlin, Heidelberg, pp. 103-114.

Chiarello, C. and Church, K.L., 1986. Lexical judgments after right- or left-hemisphere injury. Neuropsychologia 24, 623-630.

Chiarello, C., 1988. More on words, hemifields, and hemispheres: a reply to Schwartz and Kirsner. Brain Cogn 7, 394-401.

Clarke, S., and Miklossy, J., 1990. Occipital cortex in man: organization of callosal connections, related myelo- and cytoarchitecture, and putative boundaries of functional visual areas. The Journal of Comparative Neurology 298, 188-214.

Code, C., 1997. Can the right hemisphere speak? Brain Lang. 57, 38-59.

Cohen, L., Dehaene, S., Naccache, L., Lehericy, S., Dehaene-Lambertz, G., Henaff, M.A., and Michel, F., 2000. The visual word form area: spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. Brain 123(2), 291-307.

Cohen, L., Lehericy, S., Chochon, F., Lemer, C., Rivaud, S., and Dehaene, S., 2002. Language-specific tuning of visual cortex? Functional properties of the Visual Word Form Area. Brain 125, 1054-1069.

Cohen, L., Martinaud, O., Lemer, C., Lehericy, S., Samson, Y., Obadia, M., Slachevsky, A., and Dehaene, S., 2003. Visual word recognition in the left and right hemispheres: anatomical and functional correlates of peripheral alexias. Cereb Cortex 13, 1313-1333.

Cohen, L. and Dehaene, S., 2004. Specialization within the ventral stream: the case for the visual word form area. Neuroimage 22, 466-476.

Compton, R.J., Costello, C., and Diepold, J., 2004. Interhemispheric integration during the menstrual cycle: failure to confirm progesterone-mediated interhemispheric decoupling. Neuropsychologia 42(11), 1496-503.

Coney, J., 2005. Word frequency and the lateralization of lexical processes. Neuropsychologia 43, 142-148.

Conti, F. and Manzoni, T., 1994. The neurotransmitters and postsynaptic actions of callosally projecting neurons. Behav Brain Res 64, 37-53.

Corballis, M.C., 1998. Cerebral asymmetry: motoring on, TICS 2, 152– 157.

Corballis, M.C., 2003. From mouth to hand: gesture, speech, and the evolution of right-handedness, Behav Brain Sci 26 (2), 199-208.

Coren, S. and Halpern, D.F., 1991. Left-handedness: a marker for decreased survival fitness. Psychol Bull 109, 90-106.

Cowell, P.E., Allen, L.S., Zalatimo, N.S., and Denenberg, V.H., 1992. A developmental study of sex and age interactions in the human corpus callosum. Developmental Brain Research 66, 187-192.

Cox, I.H., Roberts, T.P.L, and Moseley, M.E., 1994. Principles and Techniques in Neuroimaging. In: Kucharczyk, J., Moseley, M., Barkovich, A.J. (Eds.), Magnetic Resonance Neuroimaging. CRC Press, Florida, pp. 2-102.

Craik, F., and Lockhart, R., 1972. Levels of processing: A framework for memory research. Journal of Verbal Learning & Verbal Behavior 11, 671-684.

Dale, A.M., and Buckner, R.L., 1997. Selective averaging of rapidly presented individual trials using fMRI. Human Brain Mapping 5, 329-340.

Damasio, H., Grabowski, T.J., Tranel, D., Hichwa, R.D., and Damasio, A.R., 1996. A neural basis for lexical retrieval. Nature 380, 499-505.

Dehaene, S., Naccache, L., Cohen, L., Bihan, D.L., Mangin, J.F., Poline, J.B., and Riviere, D., 2001. Cerebral mechanisms of word masking and unconscious repetition priming. Nat Neurosci 4, 752-758.

Dehaene, S., Le Clec'H, G., Poline, J.B., Le Bihan, D., and Cohen, L., 2002. The visual word form area: a prelexical representation of visual words in the fusiform gyrus. Neuroreport 13, 321-325.

Dehaene, S., Jobert, A., Naccache, L., Ciuciu, P., Poline, J.B., Le Bihan, D., and Cohen, L., 2004. Letter binding and invariant recognition of masked words: behavioral and neuroimaging evidence. Psychol Sci 15, 307-313.

Dejerine, J., 1891. Sur un cas de cecite verbale avec agraphie, suivie d' autopsie. Mémoires de la Société Biologique 3, 197-201.

Dejerine, J., 1892. Contribution a l' étude anatomoclinique et clinique des differentes varietes de cecite verbal. Compte Rendu Hebdomadaire des Séances et Mémoires de la Société de Biologie 4, 61-90.

Delfs, T.M., Klein, S., Fottrell, P., Naether, O.G., Leidenberger, F.A.,and Zimmermann, R.C., 1994. 24-hour profiles of salivary progesterone. Fertil Steril, 62 (5), 960-966.

Demb, J.B., Desmond, J.E., Wagner, A.D., Vaidya, C.J., Glover, G.H., and Gabrieli, J.D., 1995. Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process specificity. J Neurosci 15, 5870-5878.

Demonet, J.F., Price, C., Wise, R., and Frackowiak, R.S., 1994. Differential activation of right and left posterior sylvian regions by semantic and phonological tasks: a positron-emission tomography study in normal human subjects. Neurosci Lett 182, 25-28.

Demonet, J.F., Chollet, F., Ramsay, S., Cardebat, D., Nespoulous, J.L., Wise, R., Rascol, A., and Frackowiak, R., 1992. The anatomy of phonological and semantic processing in normal subjects. Brain 115 (6), 1753-1768.

Detre, J.A., and Wang, J., 2002. Technical aspects and utility of fMRI using BOLD and ASL. Clinical Neurophysiology 113, 621-634.

Dighe, K.K., and Hunter, W.M., 1974. A solid-phase radioimmunoassay for plasma progesterone. Biochem J 143 (1), 219–231.

Dietrich, T., Krings, T., Neulen, J., Willmes, K., Erberich, S., Thron, A., and Sturm, W., 2001. Effects of blood estrogen level on cortical activation patterns during cognitive activation as measured by functional MRI. NeuroImage 13, 425-432.

Do-Rego, J.L., Mensah-Nyagan, G.A., Beaujean, D., Vaudry, D., Sieghart, W., Luu-The, V., Pelletier, G., and Vaudry, H., 2000. gamma-Aminobutyric acid, acting through gamma -aminobutyric acid type A receptors, inhibits the biosynthesis of neurosteroids in the frog hypothalamus. Proc Natl Acad Sci USA 97, 13925-13930.

Dorit, R.L., Walker, W.F., and Barnes, R.D., 1991. Zoology, Saunders College Publishing, Holt, Rinehart and Winston, Inc., Orlando, Florida.

Donaldson, D.L., Buckner, R.L., 2001. Effective paradigm design. In: Jezzard, P., Matthews, P.M., Smith, S.M (Eds.), Functional MRI: An introduction to Methods. Oxford University Press Inc., New York, pp. 177-195.

Dubrovsky, B.O., 2005. Steroids, neuroactive steroids and neurosteroids in psychopathology. Prog Neuropsychopharmacol Biol Psychiatry 29, 169-192.

Ellison, P.T., Lager, C., Calfee, J., 1987. Low profiles of salivary progesterone among college undergraduate women. J Adolesc Health Care 8, 204-207.

Engel, S.A., Glover, G.H., and Wandell, B.A., 1997. Retinotopic organization in human visual cortex and the spatial precision of functional MRI. Cereb Cortex 7, 181-192.

Epperson, C.N., Haga, K., Mason, G.F., Sellers, E., Gueorguieva, R., Zhang, W., Weiss, E., Rothman, D.L., and Krystal, J.H., 2002. Cortical gamma-aminobutyric acid levels across the menstrual cycle in healthy women and those with premenstrual dysphoric disorder: a proton magnetic resonance spectroscopy study. Arch Gen Psychiatry 59, 851-858.

Eviatar, Z., 1999. Cross-language tests of hemispheric strategies in reading nonwords. Neuropsychology 13, 498-515.

Fedio, P., August, A., Patronas, N., Sato, S., and Kufta, C., 1997. Semantic, phonological, and perceptual changes following left and right intracarotid injection (Wada) with a low amytal dosage. Brain Cogn 33, 98-117.

Fernandes, M.A. and Smith, M.L., 2000. Comparing the Fused Dichotic Words Test and the Intracarotid Amobarbital Procedure in children with epilepsy. Neuropsychologia 38, 1216-1228.

Fernandes, M.A., Smith, M.L., Logan, W., Crawley, A., McAndrews, M.P., 2006. Comparing language lateralization determined by dichotic listening and fMRI activation in frontal and temporal lobes in children with epilepsy. Brain Lang 96 (1), 106-14.

Fernandez, G., de Greiff, A., von Oertzen, J., Reuber, M., Lun, S., Klaver, P., Ruhlmann, J., Reul, J., and Elger, C.E., 2001. Language mapping in less than 15 minutes: real-time functional MRI during routine clinical investigation. NeuroImage 14, 585-594.

Fernandez, G., Weis, S., Stoffel-Wagner, B., Tendolkar, I., Reuber, M., Beyenburg, S., Klaver, P., Fell, J., de Greiff, A., Ruhlmann, J., Reul, J., Elger, C.E., 2003. Menstrual

cycle-dependent neural plasticity in the adult human brain is hormone, task, and region specific. J Neurosci 23, 3790-3795.

Fiebach, C.J., Friederici, A.D., 2004. Processing concrete words: fMRI evidence against a specific right-hemisphere involvement. Neuropsychologia 42, 62-70.

Fiez, J.A., 1997. Phonology, semantics, and the role of the left inferior prefrontal cortex. Hum Brain Mapp 5, 79-83.

Fiez, J.A. and Petersen, S.E., 1998. Neuroimaging studies of word reading. Proc Natl Acad Sci USA 95, 914-921.

Filicori, M., Butler, J.P., Crowley, W.F., Jr., 1984. Neuroendocrine regulation of the corpus luteum in the human. Evidence for pulsatile progesterone secretion. J Clin Invest 73, 1638-1647.

Fink, G.R., Driver, J., Rorden, C., Baldeweg, T., and Dolan, R.J., 2000. Neural consequences of competing stimuli in both visual hemifields: a physiological basis for visual extinction. Ann Neurol 47, 440–446.

Flannery, K.A., Liederman, J., Daly, L., and Schultz, J., 2000. Male prevalence for reading disability is found in a large sample of black and white children free from ascertainment bias. J Int Neuropsychol Soc 6, 433-442.

Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.P., Frith, C.D., Frackowiak, R.S.J., 1995a. Statistical parametric maps in functional imaging: A general linear approach. Human Brain Mapping 2, 189-210.

Friston, K.J., Frith, C.D., Frackowiak, R.S., Turner, R., 1995b. Characterizing dynamic brain responses with fMRI: a multivariate approach. NeuroImage 2, 166-172.

Fritschy, J.M. and Brunig, I., 2003. Formation and plasticity of GABAergic synapses: physiological mechanisms and pathophysiological implications. Pharmacol Ther 98, 299-323.

Frost, J.A., Binder, J.R., Springer, J.A., Hammeke, T.A., Bellgowan, P.S., Rao, S.M., and Cox, R.W., 1999. Language processing is strongly left lateralized in both sexes. Evidence from functional MRI. Brain 122 (2), 199-208.

Fujimaki, N., Miyauchi, S., Putz, B., Sasaki, Y., Takino, R., Sakai, K., and Tamada, T., 1999. Functional magnetic resonance imaging of neural activity related to orthographic, phonological, and lexico-semantic judgments of visually presented characters and words. Hum Brain Mapp 8, 44-59.

Galaburda, A.M., Corsiglia, J., Rosen, G.D., and Sherman, G.F., 1987. Planum temporale asymmetry, reappraisal since Geschwind and Levitsky. Neuropsychologia 25, 853–868.

Gazzaniga, M.S., 2000. Cerebral specialization and interhemispheric communication: does the corpus callosum enable the human condition? Brain 123 (7), 1293-1326.

Geschwind, N. and Galaburda, A.M., 1985. Cerebral lateralization. Biological mechanisms, associations, and pathology: I. A hypothesis and a program for research. Arch Neurol 42, 428-459.

Geschwind, N. and Levitsky, W., 1968. Human brain: left-right asymmetries in temporal speech region. Science 161, 186-187.

Goldstein, E.B., 1997. Wahrnehmungspsychologie: Eine Einführung. Heidelberg.

Graham, J.D. and Clarke, C.L., 1997. Physiological action of progesterone in target tissues. Endocr Rev 18, 502-519.

Greener, M., 2003. Steroid actions get a rewrite. Scientist 17, 32.

Grensbacher, M.A., and Kaschak, M.P., 2003. Neuroimaging studies of language production and comprehension. Annu Rev Psychol 54, 91-114.

Grimshaw, G.M., Bryden, M.P., and Finegan, J.-A.K., 1995. Relations between prenatal testosterone and cerebral lateralization in children, Neuropsychology 9, 68–79.

Gur, R.C., Alsop, D., Glahn, D., Petty, R., Swanson, C.L., Maldjian, J.A., Turetsky, B.I., Detre, J.A., Gee, J., and Gur, R.E., 2000. An fMRI study of sex differences in regional activation to a verbal and a spatial task. Brain Lang 74, 157-170.

Hättig, H.,2004. Entwicklung und Erprobung eines dichotischen Hörtests zur Erfassung der Sprachdominanz bei epilepsiechirurgischen Kandidaten (PhD Thesis).

Halari, R., Sharma, T., Hines, M., Andrew, C., Simmons, A., and Kumari, V., 2006. Comparable fMRI activity with differential behavioural performance on mental rotation and overt verbal fluency tasks in healthy men and women. Exp Brain Res 169, 1-14.

Hanson, S.J., Matsuka, T., and Haxby, J.V., 2004. Combinatorial codes in ventral temporal lobe for object recognition: Haxby (2001) revisited: is there a “face” area? Neuroimage 23, 156-166.

Harrington, A., 1987. Medicine, mind and the double brain: A study in nineteenth-century thought. Princeton, N.J: Princeton University Press.

Hartmann, M., and Wettstein, A., 1934. "Ein krystallisiertes Hormon aus Corpus luteum". Helvetica Chimica Acta 17, 878–882.

Hausmann, M. and Gunturkun, O., 2000. Steroid fluctuations modify functional cerebral asymmetries: the hypothesis of progesterone-mediated interhemispheric decoupling. Neuropsychologia 38, 1362-1374.

Hausmann, M., Becker, C., Gather, U., and Gunturkun, O., 2002. Functional cerebral asymmetries during the menstrual cycle: a cross-sectional and longitudinal analysis. Neuropsychologia 40, 808-816.

Hausmann, M., Tegenthoff, M., Sänger, J., Janssen, F., Güntürkün, O., and Schwenkreis, P., 2006. Transcallosal inhibition across the menstrual cycle: a TMS study. Clin Neurophysiol 117 (1), 26-32.

Haxby, J.V., Gobbini, M.I., Furey, M.L., Ishai, A., Schouten, J.L., and Pietrini, P., 2001. Distributed and overlapping representations of faces and objects in ventral temporal cortex. Science 293, 2425-2430.

Hecaen, H., De Agostini, M., and Monzon-Montes, A., 1981. Cerebral organization in left-handers. Brain Lang 12, 261-284.

Hedreen, J.C., and Yin, T.C.T., 1981. Homotopic and heterotopic callosal afferents of caudal inferior parietal lobule in Macaco mulatto.Journal of Comparative Neurology 197, 605-621.

Heeger, D.J., and Ress, D., 2002. What does fMRI tell us about neuronal activity? Nature Reviews Neuroscience 3, 142-151.

Heister, G., Landis, T., Regard, M., and Schroeder-Heister, P., 1989. Shift of functional cerebral asymmetry during the menstrual cycle. Neuropsychologia 27, 871-880.

Hinke, R.M., Hu, X., Stillman, A.E., Kim, S.G., Merkle, H., Salmi, R., and Ugurbil, K., 1993. Functional magnetic resonance imaging of Broca's area during internal speech. Neuroreport 4, 675-678.

Hoptman, M.J., and Davidson, R. J., 1994. How and Why Do the Two Cerebral Hemispheres Interact? Psychological Bulletin 116 (2), 195-219.

Houzel, J.C., Carvalho, M.L., and Lent, R., 2002. Interhemispheric connections between primary visual areas: beyond the midline rule. Braz J Med Biol Res 35, 1441-1453.

Hu, Z.Y., Bourreau, E., Jung-Testas, I., Robel, P., and Baulieu, E.E., 1987. Neurosteroids: oligodendrocyte mitochondria convert cholesterol to pregnenolone. Proc Natl Acad Sci USA 84, 8215-8219.

Hund-Georgiadis, M., Lex, U., Friederici, A.D., and von Cramon, D.Y., 2002. Non-invasive regime for language lateralization in right- and left-handers by means of functional MRI and dichotic listening. Exp Brain Res 145, 166-176.

Hunter, Z.R., and Brysbaert, M., 2008. Visual half-field experiments are a good measure of cerebral dominance if used properly: Evidence from fMRI. Neuropsychologia 46, 316-325.

Indefrey, P., Kleinschmidt, A., Merboldt, K.D., Kruger, G., Brown, C., Hagoort, P., and Frahm, J., 1997. Equivalent responses to lexical and nonlexical visual stimuli in occipital cortex: a functional magnetic resonance imaging study. NeuroImage 5, 78-81.

Jackson, J.H., 1958. Evolution and dissolution of the nervous system. In: Taylor, J. (Ed.), Selected writings of John Hughings Jackson (Vol.2, pp. 45-75). New York: Basic Books. (Original work published 1884).

Jackson, J.H., 1874. On the nature of the duality of the brain. Medical Press and Circular, New Ser 17: 19-21, 41-44, 63-66. (Reprinted in Brain 38, 80-103, 1915).

Jaeger, J.J., Lockwood, A.H., Van, V.R., Jr., Kemmerer, D.L., Murphy, B.W., and Wack, D.S., 1998. Sex differences in brain regions activated by grammatical and reading tasks. Neuroreport 9, 2803-2807.

Jansen, A., Menke, R., Sommer, J., Forster, A.F., Bruchmann, S., Hempleman, J., Weber, B., and Knecht, S., 2006. The assessment of hemispheric lateralization in functional MRI—robustness and reproducibility. Neuroimage 33, 204-217.

Jenkinson, M., 2001. Registration, atlases and cortical flattening. In: Jezzard, P., Matthews, P.M., Smith, S.M (Eds.), Functional MRI: An introduction to Methods. Oxford University Press Inc., New York, pp. 271-293.

Jobard, G., Crivello, F., and Tzourio-Mazoyer, N., 2003. Evaluation of the dual route theory of reading: a metanalysis of 35 neuroimaging studies. NeuroImage 20, 693-712.

Johnson, M.K, Nolde, S.F., Mather M., Kounios, J., Schacter, D.L., Curran, T., 1997. The similarity of brain activaity associated with true and false recognition memory depends on test format. Psychol Sci 8, 250-257.

Josephs, O., Turner, R., and Friston, K. 1997. Event-related fMRI. Human Brain Mapping 5, 1-7.

Josse, G., Mazoyer, B., Crivello, F., and Tzourio-Mazoyer, N., 2003. Left planum temporale: an anatomical marker of left hemispheric specialization for language comprehension. Brain Res Cogn Brain Res 18 (1), 1-14.

Kansaku, K. and Kitazawa, S., 2001. Imaging studies on sex differences in the lateralization of language. Neurosci Res 41, 333-337.

Kanwisher, N., McDermott, J., and Chun, M.M., 1997. The fusiform face area: a module in human extrastriate cortex specialised for face perception. J Neurosci 17, 4302-4311.

Kapur, S., Rose,R., Liddle, P.F., Zipursky, R.B., Brown, G.M., Stuss, D., Houle, S., and Tulving, E., 1994. The role of the left prefrontal cortex in verbal processing: semantic processing or willed action? Neuroreport 5, 2193-2196.

Kastner, P., Krust, A., Turcotte, B., Stropp, U., Tora, L., Gronemeyer, H., and Chambon, P., 1990. Two distinct estrogen-regulated promoters generate transcripts encoding the two functionally different human progesterone receptor forms A and B. EMBO J 9, 1603-1614.

Kiebel, S.J., Holmes, A.P., 2003. The general linear model. In: Frackowiak, R.S.J., Friston, K.J., Frith, C., Dolan, R., Price, C.J., Zeki, S., Ashburner, J., Penny, W.D. (Eds.), Human brain function, 2nd ed. Academic Press, San Diego.

Kiehl, K.A., Liddle, P.F., Smith, A.M., Mendrek, A., Forster, B.B., Hare, R.D., 1999. Neural pathways involved in the processing of concrete and abstract words. Hum Brain Mapp 7, 225-233.

Kimura, D., 1967. Functional asymmetry of the brain in DL. Cortex 3, 163-168.

Kimura, D., 1983. Speech representation in an unbiased sample of left-handers. Hum Neurobiol 2, 147-154.

Kinsbourne, M., 1970. The cerebral basis of lateral asymmetries of attention. Acta Psychol 33, 193–201.

Knecht, S., Deppe, M., Ebner, A., Henningsen, H., Huber, T., Jokeit, H., et al., 1998. Noninvasive determination of language lateralization by functional transcranial Doppler sonography: A comparison with theWada test. Stroke 29 (1), 82–86.

Knecht, S., Drager, B., Deppe, M., Bobe, L., Lohmann, H., Floel, A., Ringelstein, E.B., and Henningsen, H., 2000. Handedness and hemispheric language dominance in healthy humans. Brain 123 (12), 2512-2518.

Knecht, S., Jansen, A., Frank, A., van Randenborgh, J., Sommer, J., Kanowski, M., and Heinze, H.J., 2003. How atypical is atypical language dominance? NeuroImage 18, 917-927.

Krejza, J., Mariak, Z., Nowacka, A., Melhem, E.R., and Babikian, V.L., 2004. Influence of 17-beta-estradiol on cerebrovascular impedance during menstrual cycle in women. J Neurol Sci 221, 61-67.

Lambert, J.J., Belelli, D., Peden, D.R., Vardy, A.W., and Peters, J.A., 2003. Neurosteroid modulation of GABAA receptors. Prog Neurobiol 71, 67-80.

LaMantia, A.-S., and Rakic, P., 1990. Axon overproduction and elimination in the corpus callosum of the developing rhesus monkey. Journal of Neuroscience 10, 2156-2175.

Lange, N., 2000. Statistical procedures for functional MRI. In: Moonen, C.T.W., Bandettini, P.A. (Eds.), Functional MRI, Springer-Verlag Berlin, Heidelberg, pp. 301-335.

Lavidor, M. and Ellis, A.W., 2003. Interhemispheric integration of letter stimuli presented foveally or extra-foveally. Cortex 39, 69-83.

Levy, J., 1985. Interhemispheric collaboration: Single-mindedness in the asymmetric brain. In: Best, C. T. (Ed.), Hemispheric function and collaboration in the child. CA: Academic Press, San Diego, pp. 11-31.

Lindell, A.K., Nicholls, M.E., and Castles, A.E., 2002. The effect of word length on hemispheric word recognition: evidence from unilateral and bilateral-redundant presentations. Brain Cogn 48, 447-452.

Lindell, A.K. and Nicholls, M.E., 2003. Cortical representation of the fovea: implications for visual half-field research. Cortex 39, 111-117.

Marzi, C.A., 1986. Transfer of visual information after unilateral input to the brain. Brain Cogn 5, 163-173.

Marzi, C. A., Bisiacchi, P., and Nicoletti, R., 1991. Is interhemispheric transfer of visuomotor information asymmetric? Evidence from a meta-analysis. Neuropsychologia 29, 1163-1177.

Maunsell, J.H.R., and Schiller, P.H., 1984. Evidence for the segregation of parvo- and magnocellular channels in the visual cortex of the macaque monkey. Neuroscience Abstracts 10, 520.

Maurer, U., Brem, S., Kranz, F., Bucher, K., Benz, R., Halder, P., Steinhausen, H.C., and Brandeis, D., 2006. Coarse neural tuning for print peaks when children learn to read. NeuroImage 33, 749-758.

McGuire, P.K., Silbersweig, D.A., Murray, R.M., David, A.S., Frackowiak, R.S., and Frith, C.D., 1996. Functional anatomy of inner speech and auditory verbal imagery. Psychol Med 26, 29-38.

Mechelli, A., Humphreys, G.W., Mayall, K., Olson, A., and Price, C.J., 2000. Differential effects of word length and visual contrast in the fusiform and lingual gyri during reading. Proc Biol Sci 267, 1909-1913.

Mechelli, A., Gorno-Tempini, M.L., and Price, C.J., 2003. Neuroimaging studies of word and pseudoword reading: consistencies, inconsistencies, and limitations. J Cogn Neurosci 15, 260-271.

Meyer, B.U., Roricht, S., Grafin von Einsiedel, H., Kruggel, F., and Weindl, A., 1995. Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. Brain 118, 429–440.

Mohr, J.P., 1976. Broca's area and Broca's aphasia. Whitaker, H., Whitaker, H. (Eds), Studies in neurolinguistics, New York: Academic, pp 201–236.

Mohr, J.P., Pessin, M.S., Finkelstein, S., Funkenstein, H.H., Duncan, G.W., and Davis, K.R., 1978. Broca aphasia: pathologic and clinical. Neurology 28, 311–324.

Mufson, E.J., and Pandya, D.N., 1984. Some observations on the course and composition of the cingulum bundle in the rhesus monkey. J Comp Neurol 225, 31– 43.

Muray, J.L., 1998. Natural Progesterone: What Role in Women's Health. WOMEN'S HEALTH in Primary Care, 1(8), 671-687.

Musso, M., Weiller, C., Kiebel, S., Muller, S.P., Bulau, P., and Rijntjes, M., 1999. Training-induced brain plasticity in aphasia. Brain 122 (9), 1781-1790.

Muter, V., Taylor, S., and Vargha-Khadem, F., 1997. A longitudinal study of early intellectual development in hemiplegic children. Neuropsychologia 35, 289-298.

Nazir, T.A., Heller, D., and Sussmann, C., 1992. Letter visibility and word recognition: the optimal viewing position in printed words. Percept Psychophys 52, 315-328

Nazir, T.A., Jacobs, A.M., and O'Regan, J.K., 1998. Letter legibility and visual word recognition. Mem Cognit 26, 810-821.

Neville, H.J. and Bavelier, D., 1998. Neural organization and plasticity of language. Curr Opin Neurobiol 8, 254-258.

Ogawa, S., Lee, T.M., Kay, A.R., and Tank, D.W., 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc. Natl. Acad. Sci. USA 87, 9868-9872.

Oldfield, R.C., 1971. The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia 9, 97-113.

Ospina, J.A., Duckles, S.P., and Krause, D.N., 2003. 17beta-estradiol decreases vascular tone in cerebral arteries by shifting COX-dependent vasoconstriction to vasodilation. Am J Physiol Heart Circ Physiol. 285, H241-H250.

Pandya, D. N., and Seltzer, B., 1986. The topography of commissural fibers. In: Lepore F., Ptito M., and Jasper H. H. (Eds.). Two hemispheres—One brain: Functions of the corpus callosum. New York: Alan R. Liss., pp. 47-73.

Paul, S.M. and Purdy, R.H., 1992. Neuroactive steroids. FASEB J. 6, 2311-2322.

Paulesu, E., Frith, C.D., and Frackowiak, R.S., 1993. The neural correlates of the verbal component of working memory. Nature 362, 342-345.

Pell, M.D., 1999. The temporal organization of affective and non-affective speech in patients with right-hemisphere infarcts. Cortex 35, 455-477.

Pell, M.D., 2006. Cerebral mechanisms for understanding emotional prosody in speech. Brain Lang 96, 221-234.

Petersen, S.E., Fox, P.T., Posner, M.I., Mintun, M., and Raichle, M.E., 1988. Positron emission tomographic studies of the cortical anatomy of single-word processing. Nature 331, 585-589.

Petersen, S.E., Fox, P.T., Snyder, A.Z., and Raichle, M.E., 1990. Activation of extrastriate and frontal cortical areas by visual words and word-like stimuli. Science 249, 1041-1044.

Poffenberger, A.T., (1912). Reaction time to retinal stimulation with special reference to the time lost in conduction through nerve centers. Archives of Psychology 21, 1-73.

Poldrack, R.A., Wagner, A.D., Prull, M.W., Desmond, J.E., Glover, G.H., and Gabrieli, J.D., 1999. Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. NeuroImage 10, 15-35.

Polk, T.A. and Farah, M.J., 2002. Functional MRI evidence for an abstract, not perceptual, word-form area. J Exp Psychol Gen 131, 65-72.

Porac, C., Searleman, A., 2002. The effects of hand preference side and hand preference switch history on measures of psychological and physical well-being and cognitive performance in a sample of older adult right and left-handers, Neuropsychologia 40, 2074– 2083.

Poremba, A., Malloy, M., Saunders, R.C., Carson, R.E., Herscovitch, P., and Mishkin, M., 2004. Species-specific calls evoke asymmetric activity in the monkey's temporal poles. Nature 427, 448-451.

Posner, M.I., Petersen, S.E., Fox, P.T., and Raichle, M.E., 1988. Localization of cognitive operations in the human brain. Science 240, 1627-1631.

Previc, F.H., 1991. A general theory concerning the prenatal origins of cerebral lateralization in humans, Psychol Rev 98, 299– 334.

Price, C.J., Wise, R.J., Watson, J.D., Patterson, K., Howard, D., and Frackowiak, R.S., 1994. Brain activity during reading. The effects of exposure duration and task. Brain 117 (6), 1255-1269.

Price, C.J., Wise, R.J., and Frackowiak, R.S., 1996a. Demonstrating the implicit processing of visually presented words and pseudowords. Cereb Cortex 6, 62-70.

Price, C.J., Wise, R.J., Warburton, E.A., Moore, C.J., Howard, D., Patterson, K., Frackowiak, R.S., and Friston, K.J., 1996b. Hearing and saying. The functional neuro-anatomy of auditory word processing. Brain 119 (3), 919-31.

Price, C.J., Moore, C.J., Humphreys, G.W., and Wise, R.J.S., 1997. Segregating semantic from phonological processes during reading. J Cogn Neurosci 9, 727–733.

Price, C.J., 2000. The anatomy of language: contributions from functional neuroimaging. J Anat 197 (3), 335-359.

Price, C.J. and Devlin, J.T., 2003. The myth of the visual word form area. NeuroImage 19, 473-481.

Price, C.J. and Devlin, J.T., 2004. The pro and cons of labelling a left occipitotemporal region: "the visual word form area". NeuroImage 22, 477-479.

Puce, A., Allison, T., Asgari, M., Gore, J.C., and McCarthy, G., 1996. Differential sensitivity of human visual cortex to faces, letterstrings, and textures: a functional magnetic resonance imaging study. J Neurosci 16, 5205-5215.

Pugh, K.R., Shaywitz, B.A., Shaywitz, S.E., Constable, R.T., Skudlarski, P., Fulbright, R.K., Bronen, R.A., Shankweiler, D.P., Katz, L., Fletcher, J.M., and Gore, J.C., 1996. Cerebral organization of component processes in reading. Brain 119 (4), 1221-1238.

Pujol, J., Torres, L., Deus, J., Cardoner, N., Pifarre, J., Capdevila, A., and Vallejo, J., 1999. Functional magnetic resonance imaging study of frontal lobe activation during word generation in obsessive-compulsive disorder. Biol Psychiatry 45, 891-897.

Rakic, P., and Yakovlev, P.I., 1968. Development of the corpus callosum and cavum septi in man. Journal of Comparative Neurology 132, 45-72.

Rapcsak, S.Z., Beeson, P.M., and Rubens, A.B., 1991. Writing with the right hemisphere. Brain Lang 41, 510-530.

Rapcsak, S.Z., Polster, M.R., Comer, J.F., and Rubens, A.B., 1994. False recognition and misidentification of faces following right hemisphere damage. Cortex 30, 565-583.

Rasmussen, T., and Milner, B., 1975. Clinical and surgical studies of the cerebral speech areas in man. In: Zülch, K.R., Creutzfeldt, O., Galbraith, G.C. (Eds) Cerebral localization. Springer, New York Berlin Heidelberg, pp 238–257

Rasmussen, T. and Milner, B., 1977. The role of early left-brain injury in determining lateralization of cerebral speech functions. Ann N Y Acad Sci 299, 355-369.

Regan, D. and Beverley, K.I., 1983. Visual fields described by contrast sensitivity, by acuity, and by relative sensitivity to different orientations. Invest Ophthalmol Vis Sci 24, 754-759.

Riad-Fahmy, D., Read, G.F., Walker, R.F., and Griffiths, K., 1982. Steroids in saliva for assessing endocrine function. Endocr Rev 3, 367-395.

Riad-Fahmy, D., Read, G.F., and Walker, R.F., 1983. Salivary steroid assays for assessing variation in endocrine activity. J Steroid Biochem 19, 265-272.

Rinck, P.A., 2001. Magnetic Resonance in Medicine: The Basic Textbook of the European Magnetic Resonance Forum, 4th ed. EMRF Foundation, Minusio, Switzerland.

Rode, C., Wagner, M., and Gunturkun, O., 1995. Menstrual cycle affects functional cerebral asymmetries. Neuropsychologia 33, 855-865.

Rosen, R.R., Belliveau, J.W., Aronen, H.J., Hamberg, L.M., Kwong, K.K., and Fordham, J.A., 1994. Functional Neuroimaging. In: Kucharczyk, J., Moseley, M., Barkovich, A.J. (Eds.), Magnetic Resonance Neuroimaging. CRC Press Inc., Florida, pp. 141-166.

Roskies, A.L., Fiez, J.A., Balota, D.A., Raichle, M.E., and Petersen, S.E., 2001. Task-dependent modulation of regions in the left inferior frontal cortex during semantic processing. J Cogn Neurosci 13, 829-843.

Rossi, G.F., Corletto, F., Gentilomo, A., and Rosadini, G., 1967. [Attempted interpretation on a neurophysiological basis of the mechanisms of the production of bilateral and synchronous discharges]. Neurochirurgie 13, 547-556.

Rudge, P., and Warrington, E.K., 1991. Selective impairment of memory and visual perception in splenial tumours. Brain 114, 349 –360.

Rumsey, J.M., Horwitz, B., Donohue, B.C., Nace, K., Maisog, J.M., and Andreason, P., 1997. Phonological and orthographic components of word recognition. A PET-rCBF study. Brain 120 (5), 739-759.

Rupprecht, R., 1997. The neuropsychopharmacological potential of neuroactive steroids. J Psychiatr Res 31, 297-314.

Rupprecht, R., 2003. Neuroactive steroids: mechanisms of action and neuropsycho-pharmacological properties. Psychoneuroendocrinology 28, 139-168.

Ryding, E., Bradvik, B., and Ingvar, D.H., 1987. Changes of regional cerebral blood flow measured simultaneously in the right and left hemisphere during automatic speech and humming. Brain. 110 (5), 1345-1358.

Schumacher, M., Akwa, Y., Guennoun, R., Robert, F., Labombarda, F., Desarnaud, F., Robel, P., De Nicola, A.F., and Baulieu, E.E., 2000. Steroid synthesis and metabolism in the nervous system: trophic and protective effects. J Neurocytol 29, 307-326.

Schumacher, M., Guennoun, R., Mercier, G., Desarnaud, F., Lacor, P., Benavides, J., Ferzaz, B., Robert, F., and Baulieu, E.E., 2001. Progesterone synthesis and myelin formation in peripheral nerves. Brain Res Brain Res Rev 37, 343-359.

Schwartz, T.H., Ojemann, G.A., Haglund, M.M., and Lettich, E., 1996. Cerebral lateralization of neuronal activity during naming, reading and line-matching. Brain Res Cogn Brain Res 4, 263-273.

Selye, H., 1941. Anesthetic effects of steroid hormones. Proc Soc Exp Biol Med 46, 116–121.

Selye, H., 1942. The antagonism between anesthetic steroid hormones and pentamethylentetrazol (metrazol). J Lab Clin Med 27, 1051–1053.

Shaywitz, B.A., Shaywitz, S.E., Pugh, K.R., Constable, R.T., Skudlarski, P., Fulbright, R.K., Bronen, R.A., Fletcher, J.M., Shankweiler, D.P., and Katz, L., 1995. Sex differences in the functional organization of the brain for language. Nature 373, 607-609.

Shaywitz, B.A., Shaywitz, S.E., Pugh, K.R., Mencl, W.E., Fulbright, R.K., Skudlarski, P., Constable, R.T., Marchione, K.E., Fletcher, J.M., Lyon, G.R., and Gore, J.C., 2002. Disruption of posterior brain systems for reading in children with developmental dyslexia. Biol Psychiatry 52, 101-110.

Sieghart, W. and Sperk, G., 2002. Subunit composition, distribution and function of GABA(A) receptor subtypes. Curr Top Med Chem 2, 795-816.

Silbernagl, S. and Despopoulos, A., 2001. Atlas van de fysiologie. SESAM/HB uitgevers, Baarn, Nederland

Slotta, K.H., Ruschig, H., and Fels, E., 1934. Reindarstellung der Hormone aus dem Corpus luteum. Berichte Deutsche chemische Gesellschaft 67,1270–1273.

Small, S.L., Noll, D.C., Perfetti, C.A., Hlustik, P., Wellington, R., and Schneider, W., 1996. Localizing the lexicon for reading aloud: replication of a PET study using fMRI. Neuroreport 7, 961-965.

Small, S.L. and Burton, M.W., 2002. Functional magnetic resonance imaging studies of language. Curr Neurol Neurosci Rep 2, 505-510.

Smidt, R. F., and Thews, G., 1990. Physiologie des Menschen. 24 the edition Springer Verlag Berlin.

Smith, S.M., 2001. Preparing fMRI data for statistical analysis. In: Jezzard, P., Matthews, P.M., Smith, S.M (Eds.), Functional MRI: An introduction to Methods. Oxford University Press Inc., New York, pp. 229-241.

Smith, S.S., Waterhouse, B.D., Chapin, J.K., and Woodward, D.J., 1987a. Progesterone alters GABA and glutamate responsiveness: a possible mechanism for its anxiolytic action. Brain Res Bull 6; 400(2), 353-9.

Smith, S.S., Waterhouse, B.D., and Woodward, D.J., 1987b. Locally applied progesterone metabolites alter neuronal responsiveness in the cerebellum. Brain Res Bull 18 (6), 739-47.

Smith, S.S., 1991. Progesterone administration attenuates excitatory amino acid responses of cerebellar Purkinje cells. Neuroscience 42 (2), 309-20.

Smith, S.S. and Woolley, C.S., 2004. Cellular and molecular effects of steroid hormones on CNS excitability. Cleve Clin J Med. 71 (2), 4-10.

Sommer, I.E., Ramsey, N.F., Mandl, R.C., and Kahn, R.S., 2002. Language lateralization in monozygotic twin pairs concordant and discordant for handedness, Brain 125, 2710–2718.

Sommer, I.E., Ramsey, N.F., Mandl, R.C., van Oel, C.J., and Kahn, R.S, 2004. Language activation in monozygotic twins discordant for schizophrenia. Br J Psychiatry 184,128-35.

Soules, M.R., Clifton, D.K., Steiner, R.A., Cohen, N.L.,and Bremner, W.J., 1988. The corpus luteum: determinants of progesterone secretion in the normal menstrual cycle. Obstet Gynecol 71, 659-666.

Spence, J.E., 1997. Anovulation and monophasic cycles. Ann N Y Acad Sci 816, 173-176.

Spiridon, M. and Kanwisher, N., 2002. How distributed is visual category information in human occipito-temporal cortex? An fMRI study. Neuron 35, 1157-1165.

Springer, J.A., Binder, J.R., Hammeke, T.A., Swanson, S.J., Frost, J.A., Bellgowan, P.S., Brewer, C.C., Perry, H.M., Morris, G.L., and Mueller, W.M., 1999. Language dominance in neurologically normal and epilepsy subjects: a functional MRI study. Brain 122 (11), 2033-2046.

Sripanidkulchai, K., and Wyss, J.M., 1986. Thalamic projections to retrosplenial cortex in the rat. J Comp Neurol 254,143–165.

Staudt, M., Lidzba, K., Grodd, W., Wildgruber, D., Erb, M., and Krageloh-Mann, I., 2002. Right-hemispheric organization of language following early left-sided brain lesions: functional MRI topography. NeuroImage 16, 954-967.

Stephan, K.E, Marshall, J.C. , Penny, W.D., Friston, K.J., and Fink, G.R., 2007. Interhemispheric Integration of Visual Processing during Task-Driven Lateralization. The Journal of Neuroscience, 27(13), 3512–3522.

Steyer, R., Schwenkmezger, P., Notz, P., and Eid, M., 1997. Der Mehrdimensionale Befindlichkeitsfragebogen (MDBF). Handanweisung. Göttingen: Hogrefe.

Strauss, E., Gaddes, W.H., and Wada, J., 1987. Performance on a free-recall verbal dichotic listening task and cerebral dominance determined by the carotid amytal test. Neuropsychologia 25, 747-753.

Suzuki, W.A., and Amaral, D.G., 1994. Perirhinal and parahippocampal cortices of the macaque monkey: cortical afferents. J Comp Neurol 350, 497–533.

Szaflarski, J.P., Binder, J.R., Possing, E.T., McKiernan, K.A., Ward, B.D., and Hammeke, T.A., 2002. Language lateralization in left-handed and ambidextrous people: fMRI data. Neurology 59, 238-244.

Tootell, R.B., Mendola, J.D., Hadjikhani, N.K., Liu, A.K., and Dale, A.M., 1998. The representation of the ipsilateral visual field in human cerebral cortex. Proc Natl Acad Sci USA 95, 818-824.

Toyama, K., Matsunami, K., Ohno, T., and Tokahiki, S., 1974. An intracellular study of neuronal organization in the visual cortex. Exp Brain Res 21, 45-66.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., and Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15, 273-289.

Ungerleider, L.G. and Mishkin, M., 1982. Two cortical visual systems. D.J.Ingle and M.A.Goodale (Eds.), Analysis of Visual Behavior. MIT Press, Cambridge, Massachusetts, pp. 549-585.

Valenstein, E., Bowers, D., Verfaellie, M., Heilman, K.M., Day, A., and Watson, R.T., 1987. Retrosplenial amnesia. Brain 110, 1631–1646.

Van Essen, D.C., and Maunsell, J.H.R., 1983. Hierarchical organization and functional streams in the visual cortex. Trends in NeuroSciences 6, 370-375.

Vargha-Khadem, F., O'Gorman, A.M., and Watters, G.V., 1985. Aphasia and handedness in relation to hemispheric side, age at injury and severity of cerebral lesion during childhood. Brain 108 (3), 677-696.

Veltman, D.J., Friston, K.J., Sanders, G., and Price, C.J., 2000. Regionally specific sensitivity differences in fMRI and PET: where do they come from? NeuroImage 11, 575-588.

Vigneau, M., Jobard, G., Mazoyer, B., and Tzourio-Mazoyer, N., 2005. Word and non-word reading: what role for the Visual Word Form Area? Neuroimage 27, 694-705.

Vikingstad, E.M., George, K.P., Johnson, A.F., and Cao, Y., 2000. Cortical language lateralization in right handed normal subjects using functional magnetic resonance imaging. J Neurol Sci 175, 17-27.

Vinckier, F., Dehaene, S., Jobert, A., Dubus, J.P., Sigman, M., and Cohen, L., 2007. Hierarchical coding of letter strings in the ventral stream: dissecting the inner organization of the visual word-form system. Neuron 55, 143-156.

Voets, N.L., 2005. Distinct right frontal lobe activation in language processing following left hemisphere injury. Brain, 1-13.

Vogt, B.A., 1976. Retrosplenial cortex in the rhesus monkey: a cytoarchitectonic and Golgi study. J Comp Neurol 169, 63–97.

Vuorento, T., Lahti, A., Hovatta, O., and Huhtaniemi, I., 1989. Daily measurements of salivary progesterone reveal a high rate of anovulation in healthy students. Scand J Clin Lab Invest 49, 395-401.

Vuorento, T., Huhtaniemi, I., 1992. Daily levels of salivary progesterone during menstrual cycle in adolescent girls. Fertil Steril 58, 685-690.

Wada, J., and Rasmussen, T., 1960. Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance. Journal of Neurosurgery 17, 266–282.

Wahler-Luck, M., Schutz, T., and Kretschmann, H.J., 1991. A new anatomical representation of the human visual pathways. Graefes Arch Clin Exp Ophthalmol 229, 201-205.

Wassermann, E.M., Fuhr, P., Cohen, L.G., and Hallett, M., 1991. Effects of transcranial magnetic stimulation on ipsilateral muscles. Neurology 41, 1795.

Weekes, N.Y., Capetillo-Cunliffe, L., Iacoboni, M., and Zaidel, E., 1999. Individual differences in the hemispheric specialization of dual routes variables. Brain and Language 67, 110-133.

Weisskoff, R.M., 2000. Basic theoretical models of BOLD signal change. In: Moonen, C.T.W., Bandettini, P.A. (Eds.), Functional MRI, Springer-Verlag Berlin, Heidelberg, pp. 115-124.

Weissman, D.H., Banich, M.T., 2000. The cerebral hemispheres cooperate to perform complex but not simple tasks. Neuropsychology 14, 41–59.

Wernicke, C., 1874. Der aphasische Symptomenkomplex. Cohen and Weigert, Breslau.

Westheimer, G., 1973. Saccadic eye movements. V. Zickmund (Ed.), The oculomotor system and brain functions. Sevenoaks, UK, Butterworth, pp. 59-77.

Whitney, C., and Lavidor, M., 2004. Why word length only matters in the left visual field. Neuropsychologia 42, 1680-1688.

Wierman, M.E., 2007. Sex steroid effects at target tissues: mechanisms of action. Adv Physiol Educ 31, 26-33.

Windham, G.C., Elkin, E.P., Swan, S.H., Waller, K.O., and Fenster, L., 1999. Cigarette smoking and effects on menstrual function. Obstet Gynecol 93, 59-65.

Windham, G.C., Mitchell, P., Anderson, M., and Lasley, B.L., 2005. Cigarette smoking and effects on hormone function in premenopausal women. Environ Health Perspect 113, 1285-1290.

Wise, R.J., Scott, S.K., Blank, S.C., Mummery, C.J., Murphy, K., and Warburton, E.A., 2001. Separate neural subsystems within 'Wernicke's area'. Brain 124, 83-95.

Woolley, C.S., Wenzel, H.J., and Schwartzkroin, P.A., 1996. Estradiol increases the frequency of multiple synapse boutons in the hippocampal CA1 region of the adult female rat. J Comp Neurol 373, 108-117.

Woolley, C.S. and McEwen, B.S., 1992. Estradiol mediates fluctuation in hippocampal synapse density during the estrous cycle in the adult rat. J Neurosci. 12, 2549-2554.

Worsley, K.J., 2001. Statistical analysis of activation images. Jezzard, P., Matthews, P.M., Smith, S.M (Eds.), Functional MRI: An introduction to Methods. Oxford University Press Inc., New York, pp. 251-270.

Wyatt, H.J., 1978. Nasotemporal overlap and visual field sparing. Invest Ophthalmol Vis Sci 17, 1128-1130.

Xu, B., Grafman, J., Gaillard, W.D., Ishii, K., Vega-Bermudez, F., et al., 2001. Conjoint and extended neural networks for the computation of speech codes: the neural basis of selective impairment in reading words and pseudowords. Cereb Cortex 11, 267–277.

Yakovlev, P.I., and Lecours, A.R., 1967. The myelogenetic cycles of regional maturation of the brain. In Minkowski, A. (Ed.), Regional development of the brain in early life. Philadelphia: F. A. Davis, pp. 3-65.

Zaidel, E., 1978. Concepts of cerebral dominance. In: Buser, P., Rougeul-Buser, A. (eds) Cerebral correlates of conscious experience. Elsevier, Amsterdam, pp 263–284

Zaidel, E. and Peters, A.M., 1981. Phonological encoding and ideographic reading by the disconnected right hemisphere: two case studies. Brain Lan. 14, 205-234.

Zarahn, E., Aguirre, G., D'Esposito, M., 1997. A trial-based experimental design for fMRI. NeuroImage 6, 122-138.

Zatorre, R.J., Evans, A.C., Meyer, E., and Gjedde, A., 1992. Lateralization of phonetic and pitch discrimination in speech processing. Science 256, 846-849.

Zatorre, R.J., Meyer, E., Gjedde, A., and Evans, A.C., 1996. PET studies of phonetic processing of speech: review, replication, and reanalysis. Cereb Cortex 6, 21-30.

Zatorre, R.J., Belin, P., and Penhune, V.B., 2002. Structure and function of auditory cortex: music and speech. Trends Cogn Sci 6, 37-46.

Zilles, K., Armstrong, E., Moser, K.H., Schleicher, A., and Stephan, H., 1989. Gyrification in the cerebral cortex of primates. Brain Behav Evol 34, 143-150.

Addendum

Menstrual Phase														
	H	MNI co. x	y	z	peak activation z-value	LI		H	MNI co. x	y	z	peak activation z-value	LI	repeated measures ANOVA: VHF x H *p*- value
pseudowords > false fonts (LVF)							*pseudowords > false fonts (RVF)*							
GFs	L	-12	18	44	4.19	0.00	GFs	L			-----			
	R			-----				R			-----			
GFi pars orbitalis	L	-38	24	-4	3.92	0.02	GFi pars orbitalis	L			-----			
	R			-----				R			-----			
GFi pars opercularis	L	-34	14	20	4.63	0.07	GFi pars opercularis	L	-48	8	26	4.35	0.11	n.s.
	R			-----				R			-----			
GFi pars triangularis	L	-38	18	28	3.56	0.14	GFi pars triangularis	L	-36	10	24	4.00	0.01	n.s.
	R			-----				R			-----			
GPrC	L						GPrC	L	-50	-2	44	3.86	0.19	
	R							R			-----			
INS	L	-26	28	6	3.87	0.00	INS	L			-----			
	R			-----				R			-----			
SMA	L	-4	14	46	3.98	-0.08	SMA	L			-----			
	R	4	16	46	4.01			R			-----			
GTi	L	-38	-8	-28	4.12	0.27	GTi	L			-----			
	R			-----				R			-----			
GF	L	-46	-62	-20	3.60	0.12	GF	L			-----			
	R			-----				R			-----			
MCC	L			-----		-0.08	MCC	L			-----			
	R	12	4	28	3.78			R			-----			
GOs	L	-20	-68	38	3.92		GOs	L	-12	-90	4	4.88		
	R	18	-80	18	4.03			R			-----			
GOm	L	-24	-90	8	4.07		GOm	L			-----			
	R			-----				R			-----			
Cu	L	-10	-90	24	4.06		Cu	L			-----			
	R			-----				R			-----			
Sca	L			-----			Sca	L	-12	-96	-2	4.46		
	R			-----				R			-----			

Table I: A repeated-measures ANOVA revealed, for semantic processing, no significant VHF x hemisphere interaction with a higher BOLD signal intensity change in the hemisphere contralateral to the field of stimulus presentation compared to the ipsilateral hemisphere.

Midluteal Phase														
	H	MNI co. x	y	z	peak activation z-value	LI		H	MNI co. x	y	z	peak activation z-value	LI	repeated measures ANOVA: VHF x H *p*- value
pseudowords > false fonts (LVF)							*pseudowords > false fonts (RVF)*							
GFm	L	-46	12	36	4.02	0.17	GFm	L	-----					
	R	-----						R	-----					
GFi pars opercularis	L	-46	10	28	3.79	0.17	GFi pars opercularis	L	-46	30	24	3.40	0.18	n.s.
	R	-----							-----					
GFi pars triangularis	L	-32	16	22	4.49	0.12	GFi pars triangularis	L	-38	20	30	4.98	0.14	n.s.
	R	-----							-----					
GPrC	L	-----					GPrC	L	-48	10	36	5.05	0.20	
	R	-----							-----					
INS	L	-30	28	6	4.41	0.04	INS	L	-26	30	2	4.23	0.04	n.s.
	R	-----							-----					
GOs	L	-----					GOs	L	-----					
	R	16	-74	8	4.11			R	-----					
Sca	L	-----					Sca	L	-----					
	R	22	-78	18	3.36			R	-----					

Table II: A repeated-measures ANOVA revealed, for phonological processing, no significant VHF x hemisphere interaction with a higher BOLD signal intensity change in the hemisphere contralateral to the field of stimulus presentation compared to the ipsilateral hemisphere.

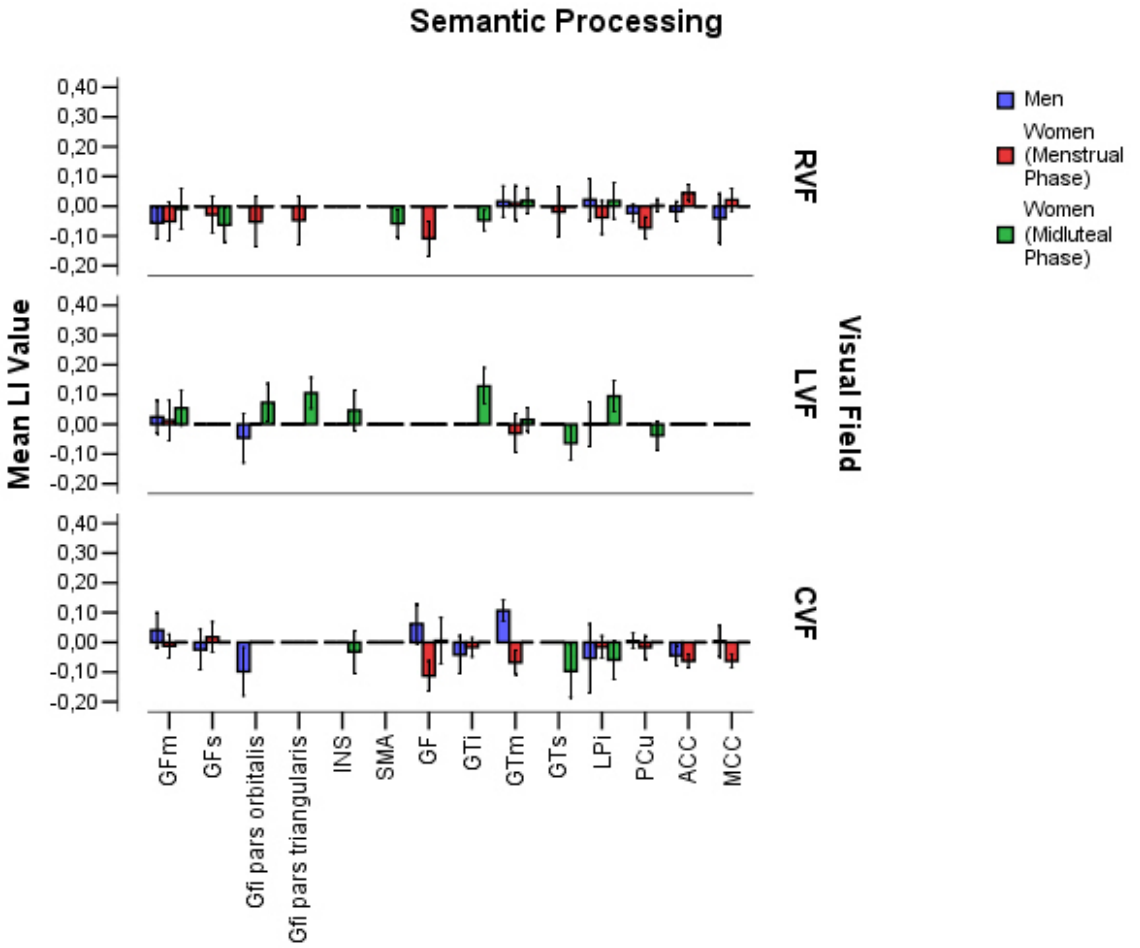


Fig I: Mean LI values for the ROI activated during semantic processing in men (blue), women during the menstrual (red) and midluteal phase (green). Performance of a Mann-Whitney test, a non-parametric test for two independent samples, revealed no significant difference between man and women during the menstrual phase or between men and women during the luteal phase. Error bars: ± 1.00 S.E.

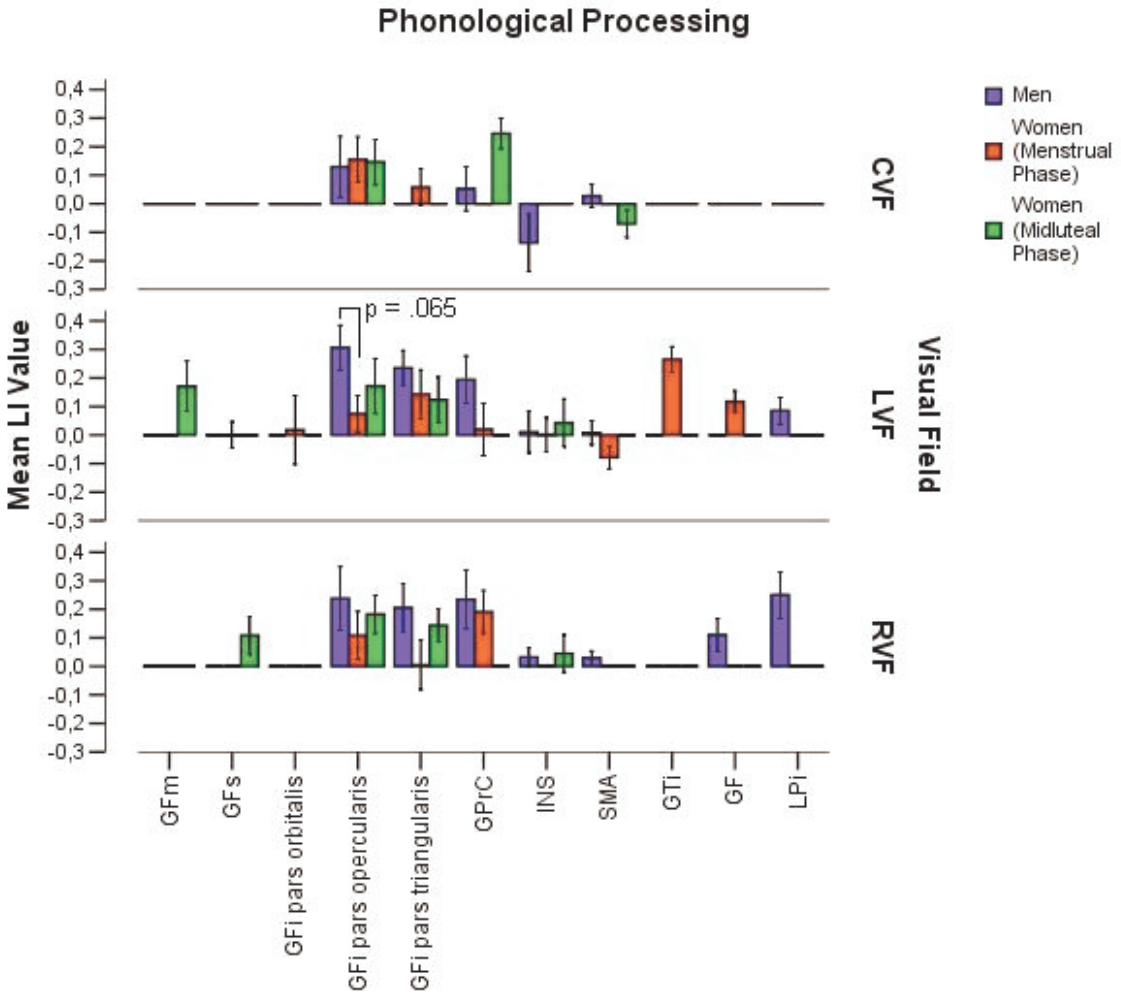


Fig II: Mean LI values for the ROI activated during phonological processing in men (blue), women during the menstrual (red) and midluteal phase (green). Performance of a Mann-Whitney test, a non-parametric test for two independent samples, revealed no significant difference between men and women during the luteal phase. In contrast, a trend for a more right lateralized activation pattern in the inferior frontal gyrus for women during the menstrual phase compared to men was assessed (LVF). Error bars: ± 1.00 S.E.

Erklärung

Hiermit erkläre ich, dass ich die vorliegende Dissertation selbständig verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel verwendet habe. Zudem wurde die Arbeit an keiner anderen Universität zur Erlangung eines akademischen Grades eingereicht.

Trier, im März 2008

Gwendy Steendam