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Anatomical correlates for visual extinction-
a fMRI study

**Inaugural-Dissertation
zur Erlangung des Doktorgrades
der Medizin**

**der Medizinischen Fakultät
der Eberhard Karls Universität
zu Tübingen**

vorgelegt von

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2017

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Tag der Disputation: 12.10.2017

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ABBREVIATIONS

AAL	automated anatomic labeling
ACC	accuracy
aCG	anterior cingulate gyrus
ANOVA	analysis of variance
AR	Ablenkreiz
BOLD	blood oxygenation level dependent
CG	cingulate gyrus
CT	computer tomography
EPI	echo planar imaging
FEF	frontal eye fields
fMRI	functional magnetic resonance imaging
fMRT	funktionelle Magnetresonanztomographie
HR	Hinweisreiz
FWHM	full width half maximum
GRAPPA	generalized autocalibrating partial parallel acquisition
Hb	hemoglobin
HRF	haemodynamic response function
IFG	inferior frontal gyrus
IFS	inferior frontal sulcus
IPL	inferior parietal lobe
IPS	intraparietal sulcus
MDM	magnetic dipole moment
MNI	Montréal Neurological Institute
MRI	magnetic resonance imaging
ms	millisecond
nSE	normalized standard error
OcG	occipital gyrus
RF	radiofrequency pulse
RT	reaction time
RTE	redundant target effect

RZ	Reaktionszeiten
SD	standard deviation
SFG	superior frontal gyrus
SNR	signal to noise ratio
SPL	superior parietal lobule
SPM	statistical parametric mapping
TE	time to echo
TMS	transcranial magnetic stimulation
TMS	transkranielle Magnetsimulation
TPJ	temporoparietal junction
TR	time to repetition
VFC	ventral frontal cortex
ZR	Zielreiz

1. Introduction

1.1. Selective attention

In a world filled with an abundant amount of visual, tactile, auditory and other sensory information, it seems logical that only a part of this information reaches our awareness and that only fractions of this input, perceived or not, influences our behaviour. (Broadbent, 1958; Neisser, 1967). Being able to respond to multiple sensory units of information (i.e. objects) and to differentiate between important, behaviourally relevant objects and unwanted, irrelevant objects, is essential for our lives and daily decision-making. The presence of multiple relevant objects at any given time is the norm and this presents a particular challenge to the human brain (Duncan, 1980). It leads to the question of how the brain copes with the simultaneous presence of multiple stimuli, and whether there are circumscribed areas in the brain that critically underlie the capability to attend to multiple objects at the same time.

Since this study focus is on visual information, the following paragraphs will give a short summary about the visual pathway and about the integrated-competition hypothesis. This hypothesis aims to explain the mechanisms that underlie selective attention in response to visual sensory input.

1.2. Physiology of vision and visual pathway

Of the four sensory modalities, vision is the most used perceptional modality in our daily life (Sternberg and Sternberg, 2009). Physiologically, vision emerges from the eye receiving a light stimulus. This stimulus is received and processed by different cells in the retina. Axons of ganglion cells form the optic nerve. The optic nerve runs towards the optic chiasm where fibres from the nasal halves of the retina cross to the opposite side. Fibres carrying information of the contralateral visual field continue as the optic tract to the lateral geniculate nucleus. From the lateral geniculate nucleus, fibres continue as the optic radiation carrying its information to the primary visual cortex (or

striate cortex). In summary, from the optic chiasm onwards, fibres of the visual pathway carry information of the opposite visual field. Therefore, lesions behind this crossing (i.e. in the Thalamus or visual cortex) result in visual field defects contralesionally. Throughout the visual pathway, information is carried in a retinotopic organization. This means that information from neighbouring fields of the retina is carried in neighbouring neurons. The visual pathway and visual field defects are shown in Figure 1.
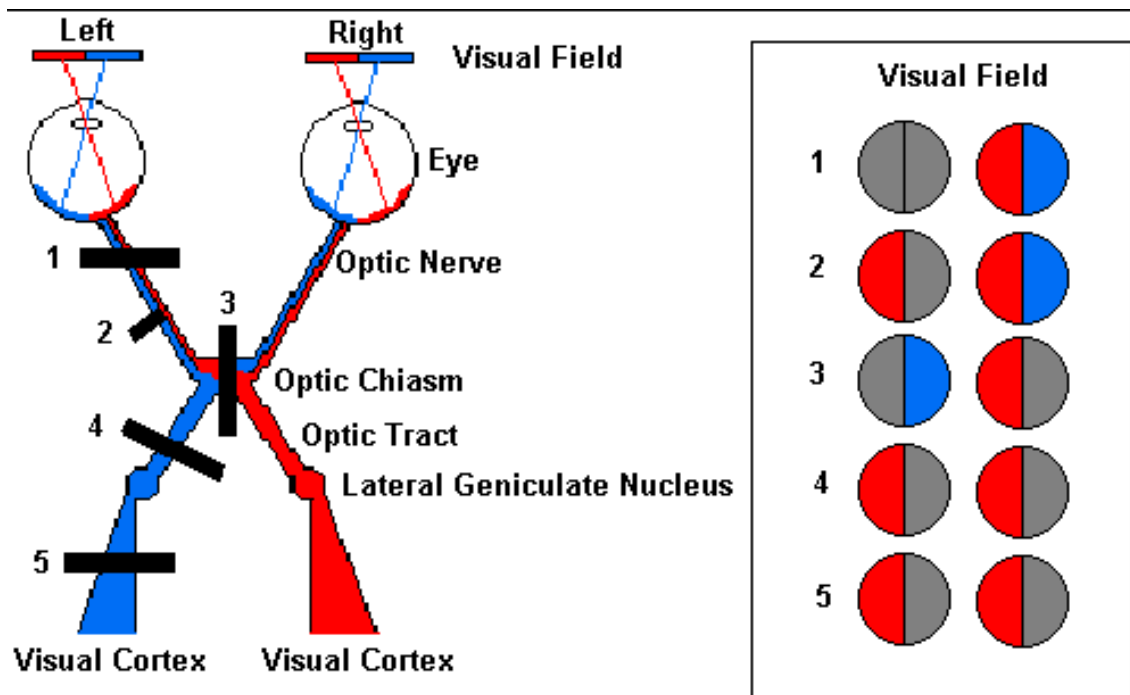
Figure 1: visual pathway and its defect in the visual field dependent on the location of the lesion.

1.3. The integrated competition hypothesis

The integrated-competition hypothesis is a theory that specifically tries to explain the mechanism of how selective attention is implemented in the human brain (Desimone & Duncan, 1995). It rests on three key principles.

1. The first principle is that multiple objects in a visual field activate multiple functional brain systems and areas of the brain at the same time. As resources are limited, the

neural activations associated with different object processing, face competition with each other, denoting that an increase of neural activation associated with one object goes along with a decrease of neural activation associated with other object processing in the same brain area or system.

2. Secondly, when an object causes strong enough activations in one of the brain systems, the same object becomes dominant throughout several systems, causing an integration of the different properties of the object. The goal of the brain integrating different activated systems is that the "winning" visual object can from this point on be processed as a whole and thus can be adequately responded to. If, for example, a teacup catches attention, all properties of this item (e.g. colour, location, shape) need to become processed in order to make an interaction, like reaching or grasping for the cup, possible. Behavioural studies, in fact, have demonstrated that detecting properties of two different objects shows greater interference than detecting multiple properties of the same object. (Duncan, 1984; Duncan, 1993).

3. Thirdly, it is proposed that the competition between the neural activations associated with different object processing is biased by top-down and by bottom-up attentional factors.

1.3.1. Top-down

On a behavioural level, the principle of top-down factors denotes one's ability to voluntarily direct attention towards task relevant information by using cognitive functions. For example, using the knowledge about a target feature or the expectation of a certain event. (Posner et al., 1980; Dosher & Lu, 2000). This form of selective attention is, from a neurophysiological view, believed to work through neural top-down priming (Walley & Weiden, 1973). An example could be the task to find the only yellow flower in a field of red flowers. The brain will actively increase neuronal sensitivity for the colour "yellow" meanwhile decreasing neuronal sensitivity for other colours. Since a number of neurons are, through task relevance, primed on the colour "yellow", once this particular flower is found, it will gain competitive advantage in one system and thus become dominant throughout the whole. Whilst in this example, attention is biased by colour, it can generally be biased by any target feature as well as

by expectations of a certain event. In many study set-ups concerning spatial attention (e.g. Posner's Cuing Paradigm 1980), selective attention or top-down priming is achieved by presenting spatial cues to direct attention to a potentially relevant area in the visual field.

1.3.2. *Bottom-up*

As mentioned, bottom-up style of attention can also influence attentional competition. Bottom-up factors denote object attributes like saliency, novelty or brightness, that 'draw' ones attention to the object, especially when the object is behaviourally relevant (e.g. a flashing ambulance car). This kind of attentional mechanism, which is influenced by sensory information rather than through cognitive priming is in literature referred to as 'bottom-up' or 'stimulus-driven'- control of attention. (Jonides & Yantis, 1988; Corbetta & Shulman, 2002; Treisman & Gormican, 1988).

1.4. Neural correlates of top-down and bottom-up attentional factors

Regarding anatomical correlates, Corbetta and colleagues have proposed an influential model in which top-down and bottom-up attentional factors activate two adjacent but distinct neural networks in the brain (Corbetta et al., 2000, 2008; Corbetta and Shulman, 2002; Shulman et al., 2003; Kincade et al., 2005). Several imaging studies could show that voluntary shiftings of attention toward a location in the visual field through spatial cueing (in a top-down fashion) activated a dorsal frontoparietal network, including the dorsoparietal cortex along the intraparietal sulcus (IPS) and the frontal cortex around the frontal eye fields (FEF) (see also Kastner et al., 1999; Hopfinger et al., 2000; Shulman et al., 1999). Bottom-up attention, and target detection on the other hand, were associated with increased activations in a more ventroparietal network including the temporoparietal junction (TPJ) and the ventral frontal cortex (VFC) (see also Hahn et al., 2006; Shulman et al., 2010).
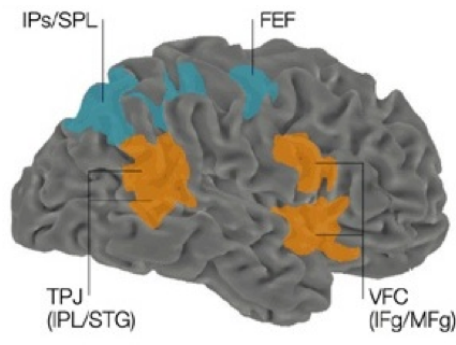
Corbetta & Shulman 2002

Figure 2: Dorsal frontoparietal network (blue) including IPS/SPL (superior parietal lobule) and frontal eye fields and ventroparietal network (orange) including TPJ and ventral frontal cortex

1.5. Visual extinction

In healthy individuals, processing of visual input is naturally limited and causes competition between different objects, as only a subset of these objects can be fully processed at any one time. Typically, healthy subjects can fully process and attend to approximately 3-4 objects at a time (Cowan, 2001). Interestingly, some neurological disorders are characterized by distinct deficits in visuospatial attention in general and particularly in the ability to fully process and attend to multiple behaviourally relevant objects simultaneously. Studying these disorders can help to understand basic physiological functions of the brain.

One of these disorders is the phenomenon of visual extinction. Visual extinction usually occurs in patients with unilateral brain lesions, most commonly when having suffered from a stroke. It describes a condition in which, alongside a general limitation in attentional capacities, (Driver et al., 1997; de Haan et al., 2012), the patient shows a distinct difficulty to detect contralesionally (= in the visual field opposite to the brain lesion) presented objects when an ipsilesional (= in the same visual field as the brain lesion) object is presented simultaneously. Patients suffering from this disorder can still perceive and react to single stimuli presented to him or her in the right or left visual field and therefore other impairments like e.g. a visual field deficit as in *Hemianopsia* can be ruled out as pathomechanisms. When two stimuli are presented in the ipsilesional field, extinction occurs for the more contralesionally presented stimulus. (Bender & Furlow, 1945). Different kinds of extinction are known for the modalities

visual, auditory, tactile and olfactory. (De Renzi et al., 1984; Gainotti et al., 1989; Bellas et al., 1988).

Clinically, the disorder is assessed by presenting finger movements in either one or both visual fields of the patient. During this assessment, the patient is instructed to report which finger(s) moved. Extinction is then diagnosed when the patient can correctly detect an isolated finger movement on his/her left or right visual field, but cannot correctly detect contralesional finger movements when an ipsilesional finger movement is presented simultaneously (Chatterjee, 2003).

In consideration of the integrated-competition hypothesis, the underlying mechanism of extinction can be described as follows: in the case of bilateral simultaneous presentation of two relevant stimuli, the lesion in one of the brain hemispheres weakens the processing of the stimulus in the contralesional visual field, while the stimulus in the ipsilesional visual field can still be processed normally. As a consequence, the stronger ipsilesional stimulus wins the competition and becomes dominant throughout several systems and thus gains access to limited attentional resources (Duncan et al., 1997). When a stimulus in the contralesional field is presented alone, the activation in response to the contralesional stimulus does not need to compete with another stimulus representation, hence this activation, whilst weakened, still results in the patient perceiving the stimulus. In support of the integrated-competition hypothesis, some studies suggest that even extinguished stimuli still undergo unconscious processing, enabling them to influence behaviour. Reaction times, for example, are slower for bilaterally presented targets than for single ipsilesionally presented targets, although in both conditions only the ipsilesional presented target is consciously perceived. (Vuilleumier & Rafal, 2000).

1.5.1. *Underlying anatomy of extinction*

Extinction occurs more frequently after right hemispheric brain damage than after left hemispheric brain damage (Barbieri & De Renzi, 1989; Vallar et al., 1994; Becker & Karnath, 2007; Chechlacz et al., 2014). This is in accordance with Kinsbourne (1970,

1973), who proposed that each hemisphere directs spatial attention to the opposite side of space, with the distinctive feature that the left hemisphere directs attention to the right but the right hemisphere directs attention to both sides of space (see also Heilman & Van Den Abell, 1980). Thus, the right hemisphere can compensate damage to the left hemisphere while damage to the right hemisphere stays mostly uncompensated.

Evidence from lesion studies suggest that extinction occurs mainly when there is anatomical (Karnath et al., 2003; Grandjean et al., 2008; Chechlacz et al., 2013) or functional (Ticini et al., 2010) damage in the right hemispheric TPJ (the intersection of the temporal and parietal lobe and the top end of the sylvian/lateral fissure), suggesting that this area is important for the ability to detect competing stimuli. Moreover, a study using transcranial magnetic stimulation (TMS: a non-invasive technique to disturb localized brain areas in healthy individuals), has also demonstrated that a temporary disruption of neural activity of the TPJ can elicit extinction-like behaviour (Meister et al., 2006).

Other TMS-studies, however, described to have induced extinction-like behaviour by disturbing the right hemispheric IPS (Hung et al., 2005; Koch et al., 2005) or the left and right hemispheric IPS. (Pascual-Leone et al., 1994; Battelli et al., 2009). Findings of previous brain imaging studies using fMRI (functional magnetic resonance imaging) have also highlighted the important role of the IPS in global attention, showing the selective involvement of the IPS when attending to bilateral presented stimuli. (Ciçek et al., 2007; Geng et al., 2006).

In summary, both the IPS and the TPJ have been associated with visual extinction. The precise contribution of these two areas to the ability to attend and respond to competing stimuli still needs to be determined.

1.6. Hypothesis and goal of this study

The goal of this study is to localize regions in the brain responsible for visuospatial attention in the case of attending to two competing stimuli simultaneously. Furthermore,

it is of particular interest to differentiate between brain areas that are activated by directing attention to two competing stimuli and areas that are activated by the actual detection of the two competing stimuli.

Lesion-, TMS- and functional imaging studies point out the importance of the right hemispheric parietal lobe of the brain, particularly regions described as the IPS and TPJ. With the knowledge of behavioural studies assigning the IPS a role in top-down goal-driven attention and the TPJ a role in bottom-up stimulus-driven attention and target detection, it can be hypothesized that in the case of processing competing stimuli, both of these functions still apply. This would suggest that the region described as IPS plays an important role while directing attention towards the expected concurrent stimuli while the region named TPJ is important for the final detection of the target. If this suggestion holds true, a functional imaging technique such as fMRI should detect activations in both of the described areas depending on the condition "directing attention" and "target detection". Thus, this study aims to use fMRI to locate brain regions where neural activity is increased for both of these global conditions in comparison with directing attention towards and target detection of single unilateral stimuli.

1.7. MRI (Magnetic resonance imaging)

MRI is a non-invasive imaging technique which, when compared to other imaging techniques (i.e. computer tomography (CT)), has the advantage of showing a good soft tissue contrast without using ionizing radiation. Provided that safety guidelines are followed (Kanal et al., 2013), MRI plays a safe and important role in neuroscience and in the diagnostics of neurological diseases.

An MR image is generated by measuring the response of hydrogen nuclei after being influenced by a radiofrequency pulse (RF) (Buxton, 2002; Hashemi et al., 2004; Horowitz, 1995; Jezzard et al., 2001).

Like other nuclei in the brain, hydrogen nuclei spin around their axis and thus produce a magnetic field, known as the magnetic dipole moment (MDM). Usually, the MDMs of

the different hydrogen nuclei are oriented in random directions. When applying a strong external magnetic field, some MDMs align in the same direction (longitudinal to the magnetic field) and the nuclei begin to precess at a nucleus-specific frequency.

Precession describes the circular motion of each MDM in a magnetic field.
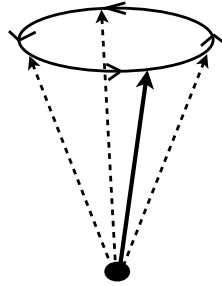
Figure 3: Precession of a MDM. With its stationary base and its moving top, a precessing MDM has similarities with a spinning dreidel.

Whilst each MDM spins or precesses at a nucleus specific frequency, MDM's do not necessarily precess in the same phase, meaning that their vectors point in different directions of the circle. When a strong RF-pulse is applied, MDM's not only align transversally to the magnetic field but they also start to precess in the same phase.

The next step is to apply a short and strong RF- pulse perpendicular to the direction of the magnetic field, which influences the MDMs by tipping them in a higher energy level in a now transversal alignment. After termination of the RF-pulse, the MDMs return to their original orientation, which is described by the term "relaxation". During relaxation, energy is released which can be measured by a head coil. This measurement of released energy during the return of the MDMs to their previous lower-energy state is used to create an MR-image. The process of relaxation includes two parts and therefore, two sets of information can be obtained. Specifically it can be differentiated between:

(i) T1-relaxation (longitudinal relaxation), which describes the regrowth along the longitudinal (z-) axis

(ii) T2-relaxation (transversal relaxation), describing the decay in the transversal (xy-) plane.

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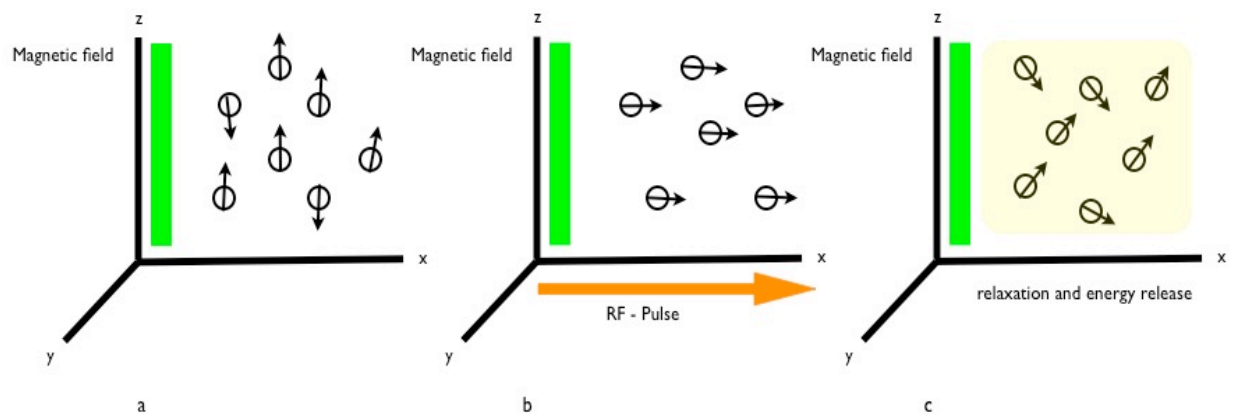
Figure 4: a) Alignment of MDM's along the longitudinal (z-) axis after applying a strong external magnetic field (green). b) When applying a short RF-pulse perpendicular to the magnetic field, MDM's align transversally to the magnetic field (in the xy-plane). c) After termination of the RF-pulse, MDMs return to their original orientation meanwhile releasing energy used to create an MR image.

By modulating the time to repetition (TR) between two RFs and the time between the pulse and the reception of the RF- signal, known as the time to echo (TE), one can obtain either a T1- weighted image (which has a short TR and TE) or a T2- weighted image (which has a long TR and TE). Since relaxation times differ from tissue to tissue, a contrast is produced. In general, T1-weighted images are often referred to as anatomical scans because of their clear contrast between cortical white and grey matter, whereas T2-weighted images have the benefit of contrasting lesions (such as ischemia) better, hence often referred to as lesion scans.

By applying three magnetic gradients, namely the slice select gradient, the frequency encoding gradient and the phase-encoding gradient, it is possible to create a three-dimensional image and to selectively measure contributions from each spatial unit in the brain, referred to as voxel.

1.8. fMRI (functional magnetic resonance imaging)

In this study, blood oxygenation level dependent (BOLD) fMRI was used as a tool to indirectly measure cortical brain activation. Its mechanism was discovered in the early

nineties (Kwong et al., 1992; Ogawa and Lee, 1990; Turner et al., 1991) and bases on the theory that neuronal activity is associated with changes in local blood flow (Heeger and Ress, 2002; Roy and Sherrington, 1980). In order for a neuron to be active, it requires a certain amount of glucose and oxygen. Since a neuron is not able to store this energy itself, it is dependent on blood flow for energy supply. Whenever a neuronal cell population is active, it first uses the available oxygen, which results in a decrease of the local oxygenated haemoglobin level (Hb, a protein in red blood cells) and thus in an increase in the relative level of deoxygenated Hb. As a compensational mechanism, local vessels start to oversupply the region with blood, leading to an increase of the oxygenated Hb level and to a decrease of the relative deoxygenated Hb level. Importantly, oxygenated and deoxygenated Hb have different magnetic characteristics (Pauling and Coryell, 1936; Thulborn et al., 1982). Oxygenated Hb has virtually no magnetic properties while deoxygenated Hb is paramagnetic. A high level of deoxygenated Hb results in a decrease of the BOLD signal. Thus, after an increase in neuronal activity, the BOLD signal initially decreases, as the relative level of deoxygenated Hb increases. Subsequently, the oversupply of oxygen-rich blood results in a massive decrease of the relative level of deoxygenated Hb and a concordant increase in the BOLD signal. This change in the BOLD fMRI signal as a function of time after an increase in neuronal activity is known as the haemodynamic response function (HRF).
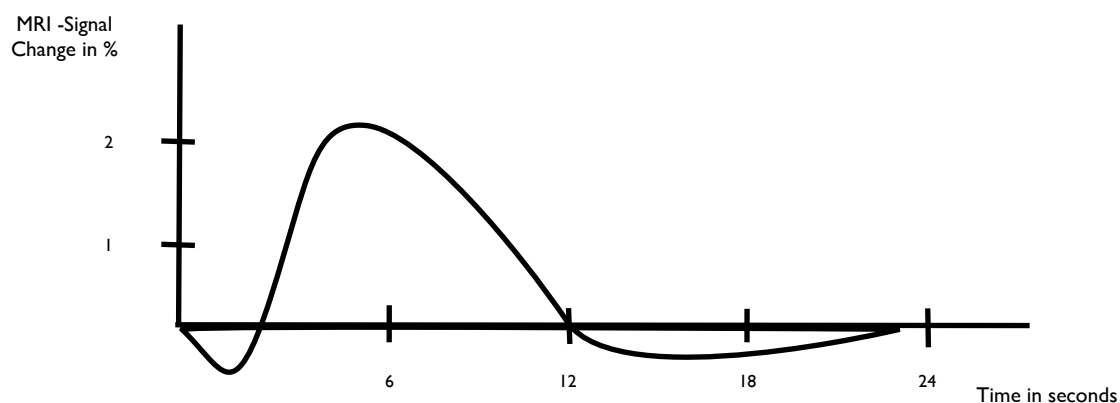
Figure 5: The hemodynamic response function (HRF) shows the MRI-signal change relative to the time course after applying a brief stimulus. An initial dip of the signal due to an increase of deoxygenated Hb is followed by an increase of signal with a maximum after around 6 seconds

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(Logothetis, 2002) due to an increase of oxygenated blood and associated decrease in the relative level of deoxygenated Hb. After 12 seconds an undershoot of the signal takes place. The BOLD response terminates after approximately 24 seconds.

As mentioned earlier, fMRI is an indirect measurement because it detects metabolic processes happening in close proximity to activated neurons rather than measuring neuronal activation itself. However, several studies, e.g. Logothetis et al. (2001) could show convincing correlation between neural activity and the BOLD-signal.

2. Methods and Materials

2.1. Participants

In this study, 24 participants (19 females, 5 males) performed the following experiment. One participant had to be excluded due to a technical failure during the experimental data collection. Data of the remaining 23 subjects was analysed. All participants were right handed, had no history of neurological or psychiatrical illnesses and had normal or corrected to normal vision. The age of the participants ranged from 21 to 37 years, (mean age 24.8 years). All participants volunteered for the study and gave their written informed consent approved by the ethics committee of the Medical Faculty of Tübingen. Subjects were paid for participation.

2.2. Task design

The description of the following task is that of a modified cued target detection task based on an experiment by Ciçek et al. (2007). While lying in a MRI-scanner, participants were given the instruction to attend and react to stimuli that were presented visually via a mirror system mounted on a head coil as a projection of a beamer display. Stimuli were presented with a PC using the software package E-Prime (Psychology Software Tools Inc.)

Stimuli shown to the participants were defined as 'cues', 'targets' and 'distractors'. Participants were asked to respond to targets as quickly as possible by pressing a non-magnetic button. Throughout the entire experiment, subjects were instructed to fixate a continuously visible central fixation point presented as a central fixation cross, surrounded by a diamond-shaped box outline (see Figure 6).

During the experiment, eye movements were monitored using an MR-compatible eye tracker system (Senso-Motoric Instruments) to ensure that participants maintained fixation on the central fixation point.

2.2.1. *Targets and distractors*

Targets were defined as a 'X' and appeared in squared boxes (1.5°) displayed at an eccentricity of 7.5°degrees along the horizontal meridian bilateral from the central fixation point (see Figure 6). The boxes stayed visible throughout the whole trial. Targets could appear either on the left, the right or simultaneously in both boxes. To ensure that participants actively processed the stimuli presented in the boxes instead of simply responding to stimulus onset, distractors were included, which were defined as '+'. Like the targets, distractors could appear either on the right, the left or on both sides. Targets and distractors could also appear simultaneously. Given the different possibilities, participants were instructed to respond at appearance of either a single target when displayed in the left or in the right box or at the bilateral/global appearance of the targets. Distractors, on the other hand, were asked to be ignored and not to be reacted to in any given case. This also included the concurrent appearance of a target- and distractor-stimuli.

2.2.2. *Cues*

Each target and/or distractor was preceded by either an informative or an uninformative/neutral cue. In 75% of the trials, targets or distractors followed informative cues, the remaining 25% of trials were initiated by uninformative cues. As informative cues, thickening lines on one or both sides of the diamond-shaped box outline surrounding the central fixation cross formed an arrow pointing either to the left, to the right or both boxes, indicating where a target could be expected (see Figure 6). In case of a trial with an uninformative cue, the diamond-shaped box outline did not change. In total there were four types of cues and thus four types of trials:

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1. A cue indicating to the left followed by either a target or a distractor appearance on the left (unilateral left trial)

2. A cue indicating to the right followed by a target or a distractor appearance on the right (unilateral right trial)

3. A global/bilateral cue followed by targets or distractors in both boxes or appearance of a target and a distractor (global/bilateral trial)

4. An uninformative/neutral cue followed by unilateral or bilateral targets or distractors (neutral trial)

Since participants were firmly instructed to use the cue as a help to shift attention towards the cued boxes, targets and distractors were always presented in the cued location. Response times between cued and uncued targets were later compared to determine whether participants complied with this instruction and shifted their attention to the cued location.

The interval between cue and target presentation varied between 1991, 2491 and 2991 ms. Importantly, 33.3% of the trials were so-called "catch-trials" or "partial trials" where a cue was not followed by a target- or distractor- stimuli, hence the trial ended after presentation of the cue. Catch trials were included to enable the separation between the event-related BOLD response of cues and targets (Ollinger et al.2001a, 2001b). Each cue, target and distractor presentation lasted 200 ms in each trial.

In total, subjects performed 5 fMRI sessions, one session consisting of 400 randomly intermixed trials.

Before the start of the experiment, participants practised the task outside the scanner.
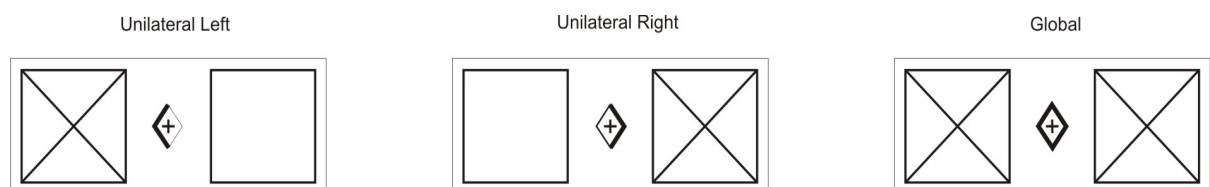

Figure 6: Firstly, informative cues formed an arrow pointing either to the left, to the right or to both boxes. After an interval of 1991, 2491 or 2991 ms targets appeared as 'X' at the cued locations

2.3. Neuroimaging

Imaging was done at the university hospital in Tübingen, Germany on a 3 Tesla Siemens Magnetom Trio Scanner (Erlangen, Germany). Functional imaging data was acquired with a continuous collection of volumes throughout the sessions, using a T2* echo planar imaging (EPI) sequence. Each volume consisted of 33 slices (sequential, in ascending order) with a slice thickness of 3mm (no gap between slices) and in plane resolution of 3x3 mm. fMRI data was collected at an flip angle of 90˚, a TE of 40 ms and a TR of 2691ms. Additionally, a T1-weighted anatomical volume was acquired for each subject, consisting of 176 slices with a voxel size of 1 x 1 x 1 mm. For this purpose a GRAPPA (Generalized Autocalibrating Partial Parallel Acquisition) sequence was used at an flip angle of 8˚, a TE of 2.92ms and a TR- time of 2300ms.

2.4. Image Processing

Image processing and analysis was done using the Statistical Parametric Mapping software package (SPM8, Wellcome Department of Imaging Neuroscience, London, UK, http://www.fil.ion.ucl.ac.uk/spm/), running under Matlab R2010b (Mathworks).

2.5. Image preprocessing

The goal of the image preprocessing was to prepare the „raw" data for further analysis. The different steps with its purposes are shortly explained in the following paragraphs.

2.5.1. Realignment

A step called realignment was performed to correct for any real small head movements that unavoidably occurred while participants were lying in the MRI-scanner and to correct for any apparent head movements caused by heating of the scanner. This step was important because the further statistical analysis assumes that a given voxel

represents the same point in the subject's brain throughout the entire fMRI time course. It was was done by reorienting each EPI-Image of a single subject to a reference image (Friston, Ashburner et al. 1995), which for this particular study was the first image of the first session.

2.5.2. Coregistration

In this preprocessing step, the anatomical T1-image was coregistered with the mean realigned functional EPI-image of each subject resulting from the first preprocessing step. Coregistering the high resolution T1-scan to the low resolution EPI-image helped to later localize activations anatomically. Furthermore, it is an important preparation for the following preprocessing step of normalization.

2.5.3. Normalization

So far, the preprocessing steps have focused on preparing the images of each subject for a single-subject analysis. In order to be able to include the different images in a group based analysis, the normalization step was performed. The goal of this procedure was to correct for the interindividual differences in the brains such as size, shape and morphology of gyri and sulci. The goal of normalizing is that a given voxel corresponds to roughly the same location in the brain in each participant, allowing comparisons over participants. This was done by matching each individual co-registered T1-image to a standard brain and then applying these transformations to the realigned EPI-images of the same subjects. All brain images were matched to the Montréal Neurological Institute (MNI) template brain based on the coordinate system by Talairach & Tournoux (1988)

2.5.4. Spatial smoothing

The last step of preprocessing was spatial smoothing. In this step, each grayscale of each voxel is averaged with the neighbouring voxel grayscales. By functioning as a high-pass filter, it improves the so-called signal to noise ratio (SNR). It also satisfies the

normality assumption of the statistical tests. For this study, a Gaussian filter with a FWHM (Full With at Half Maximum) of 8mm was used.

2.6. Image Data Analysis

After preprocessing of the data, SPM8 was used to create models for changes in blood oxygenation (Friston, Holmes et al. 1995; Worsley 2001; Kiebel and Holmes 2003) for the following events: left cue, right cue, bilateral cue, left target, right target, bilateral target, left distractor, right distractor, bilateral distractor (which could be distractor + distractor, target + distractor or distractor + target).

The resulting models were used to create single subject contrasts for a second-level random effects analysis (Holmes and Friston 1998). In particular contrasts were modelled as:

a) unilateral left cue vs. bilateral cue
b) unilateral right cue vs. bilateral cue
c) unilateral left target vs. bilateral target
d) unilateral right target vs. bilateral target

For the second-level random effects analyses, first an ANOVA (analysis of variance) was carried out for both the cue and the target conditions (comparing cue/target left, cue/target right, and bilateral cue/target). Subsequently, the main effect of each ANOVA was used to define a mask image to isolate voxels sensitive to cue or target conditions. Within the resulting mask image highlighting cue presentation responsive voxels, one-sample t-tests were carried out using the single subject contrasts unilateral left cue vs. bilateral cue and unilateral right cue vs. bilateral cue. Likewise, within the resulting mask image highlighting target presentation responsive voxels, one-sample t-tests were carried out using the single subject contrasts unilateral left target vs. bilateral target and unilateral right target vs. bilateral target. Finally, the resulting images were used to produce two conjunction maps:

A) [bilateral cue > left cue] AND [bilateral cue > right cue]

B) [bilateral target > left target] AND [bilateral target > right target]

In these conjunction maps, overlaps of activated voxels therefore showed brain areas that were more strongly engaged by presentation of global or bilateral stimuli than either unilateral left or unilateral right stimuli.

2.7. Eye movement analysis

Eye movements were analyzed using the program iLab (Gitelman 2002) under Matlab 2010b (Mathworks). After removal of eye blinks the overall percentage of experimental time that participants point of gaze was within a 1˚ radius along the horizontal meridian and a 10˚ radius along the vertical meridian for both central fixation point and target boxes was calculated. Different radius sizes were chosen to allow for technical 'scanner drift' which can result in apparent shift of fixations along the vertical midline.

2.8. Behavioural data analysis

To analyse the response accuracies to both target and distractor displays, a 2 (cue type: neutral or informative) by 3 (presentation type: left, right or bilateral) repeated measures ANOVA was used for both target and distractor displays. Additionally, reaction times to the target displays were analyzed with a 2 (cue type: neutral or informative) x 3 (presentation type: left, right or bilateral) repeated measures ANOVA. Incorrect trials and trials with reaction times exceeding 1500ms were excluded from this ANOVA.

3. Results

3.1. Eye movement data

Of the 23 subjects investigated, 20 subjects had eye-signal of sufficient quality to allow offline analysis. The remaining 3 subjects did not have eye-signal of sufficient quality to allow offline analysis (due to lightning and size of eye). In these subjects, eye-movements were monitored online during the experiment to ensure wakefulness and absence of eye-movements.

Eye movements were analysed using the program iLab (Gitelman 2002). In 97.48% (with a standard deviation [SD] of 2.5%) of experimental time, subjects point of gaze was within a 1° radius of the central fixation point along the horizontal meridian. Participants spent 0.12% (with a SD of 0.35%) of experimental time fixating the left target box and 0.17% (with a SD of 0.19%) fixating the right target box. The remaining 1.23% (SD of 1.87%) of experimental time, participants were fixating other locations in their visual field.

3.2. Behavioural data

3.2.1. Detection of targets

3.2.1.1. Accuracy of target detection

Overall accuracy of correct button presses upon detecting a target was very high. The mean accuracy and the normalized standard error (nSE, Loftus & Masson 1994) for each combination of cue and target type are shown in table 1 and figure 7. Data from one subject had to be excluded due to technical failure of the button.

	Cued		
	left	right	bilateral
ACC in %/nSE	99.58 (0.52)	98.44 (0.50)	97.19 (0.84)
	Uncued		
ACC in %/nSE	98.04 (0.78)	96.89 (1.14)	94.99 (1.26)

Table 1: mean percentage accuracy of target detection and nSE (in brackets) for each possible cue and target combination.

Accuracy target detection

Figure 7: mean percentage accuracy of target detection and nSE (in error bars) for each possible cue and target combination.

A 2 (cue type: cued/uncued) by 3 (target display: left/right/bilateral) repeated measures ANOVA revealed a significant main effect of the cue $(F_{1,18} = 5.63, P = 0.029)$ confirming that accuracy of button presses for the target condition was generally higher for cued than for uncued targets. Neither the main effect of the type of target, nor the interaction between cue type and target display type were significant $(F_{2,36} = 0.15, P = 0.09$ and $F_{2,36} = 0.15, P = 0.85)$.

3.2.1.2.   Reaction times (RT) upon target detection

Mean reaction times (RT) and the nSE upon target detection are listed in table 2 and figure 8.

	Cued		
	left	right	bilateral
RT in ms/nSE	364.33 (6.43)	363.59 (7.25)	413.24 (8.46)
	Uncued		
RT in ms/nSE	431.54 (6.09)	420.97 (9.07)	464.39 (13.09)

Table 2: mean percentage RT upon target detection and nSE (in brackets) for each possible cue and target combination.
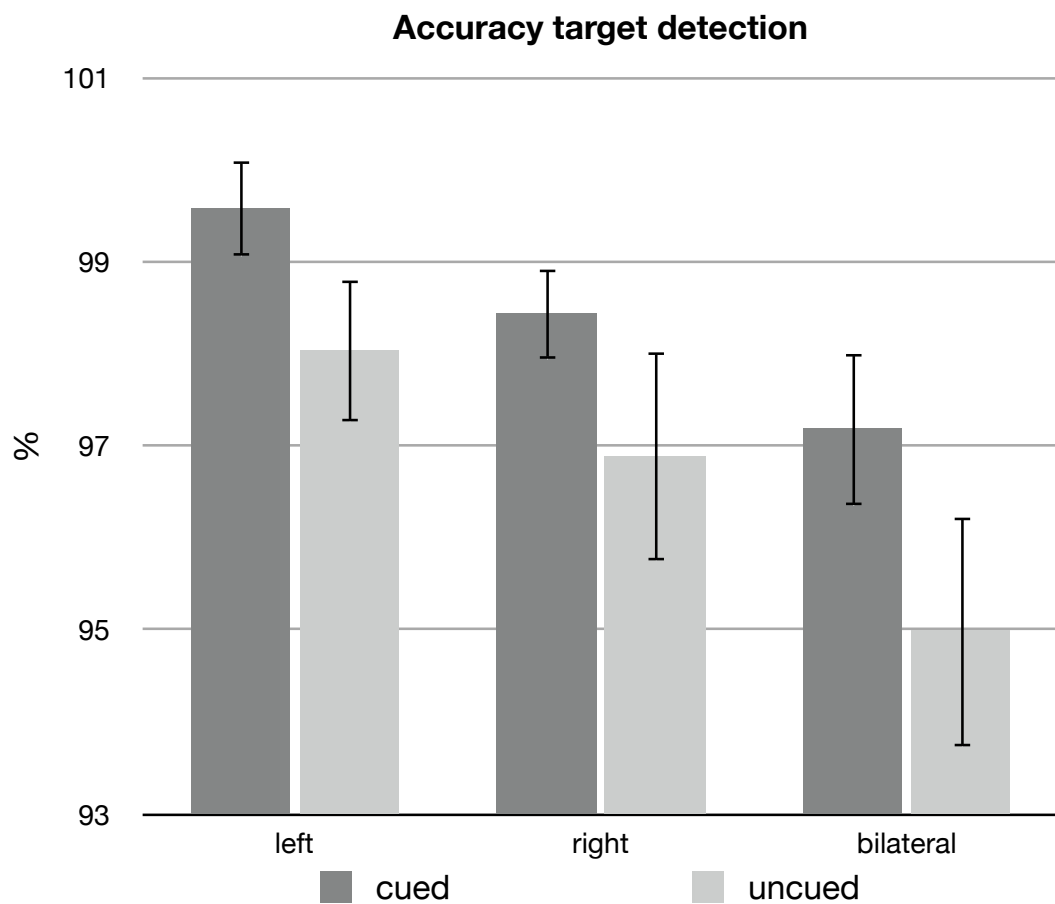
RT target detection
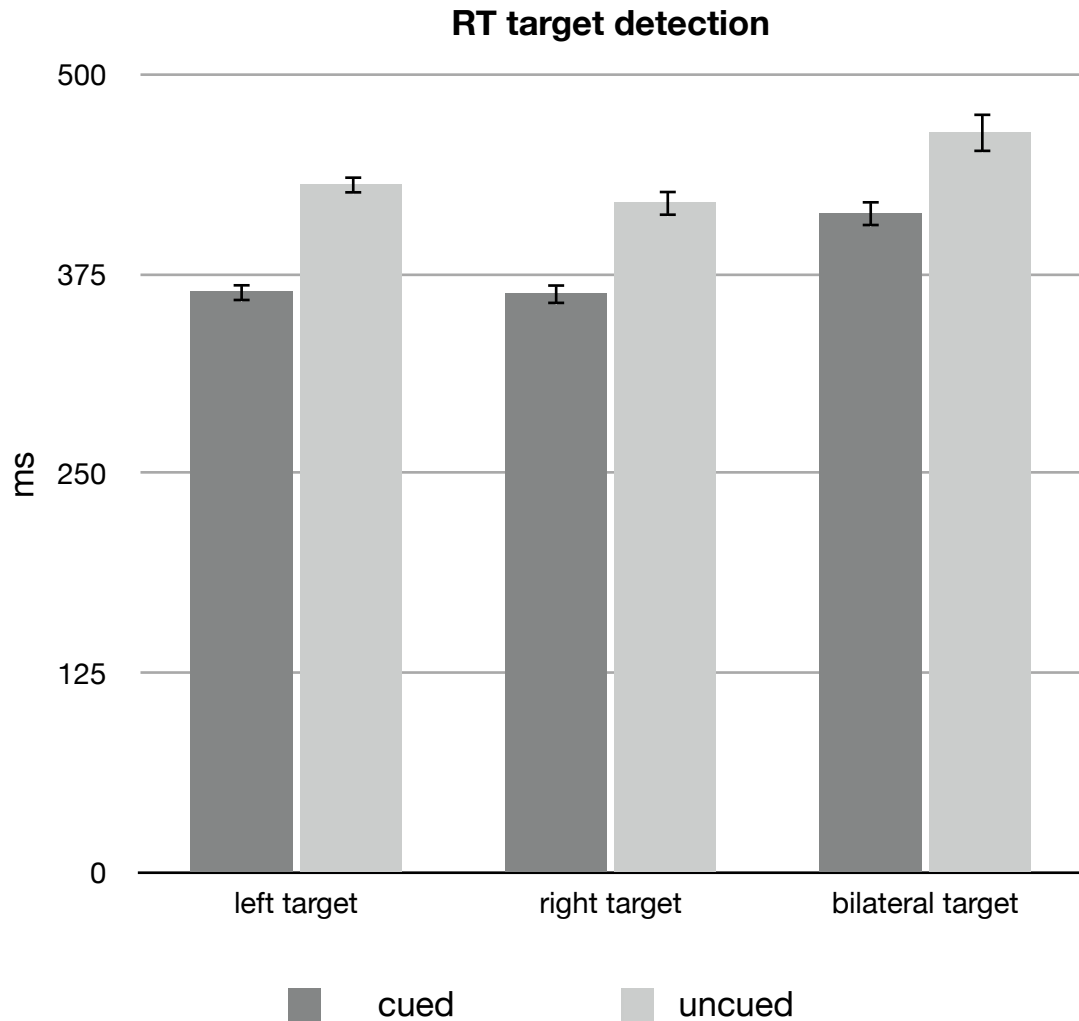
Figure 8: mean percentage RT upon target detection and nSE (in error bars) for each possible cue and target combination.

A two (type of cue) by three (type of target) repeated measures ANOVA demonstrated a significant main effect of the type of cue *($F_{1,21}$ = 59.7, P = 0.000001)* and hence significantly faster RTs for targets following informative cues. It also showed a significant main effect of the target type. ($F_{2,42}$ = 9.92, P = 0.00029). Post-hoc comparisons revealed that bilateral target detection resulted in significantly longer RTs than detection of either left or right single targets *([left vs right]: t(21) = 1.09, P = 0.84, [left vs bilateral]: t(21) = 3.20, P = 0.0129, [right vs bilateral]: t(21) = 3.29, P = 0.0105, respectively after Bonferroni correction.* Overall, there was no significant interaction between type of cue and target detection *($F_{2,42}$ = 0.59, P = 0.55)*

3.2.2. *Correct rejection of distractors*

Overall accuracy of correct rejection of distractors was 92,6% (with a SD of 2,8% for the different combinations of cue and distractor presentations). The mean percentage accuracy for each possible combination of cue and distractor (cued/uncued left distractor, cued/uncued right distractor, cued/uncued bilateral distractor) are shown in table 3 and figure 9.

	Cued		
	left	right	bilateral
ACC in %/nSE	90.48 (1.90)	94.41 (1.44)	92.76 (1.14)
	Uncued		
ACC in %/nSE	97.89 (1.53)	95.53 (1.85)	93.68 (2.45)

Table 3: mean percentage accuracy and nSE (in brackets) for each possible cue and distractor display presentation.

As demonstrated in the figure below, accuracy upon detection of distractors following an uninformative cue was higher than detection of distractors following an informative cue.

A 2 (cue type: cued/uncued) by 3 (distractor type: left/right/bilateral) repeated measures ANOVA hence demonstrated a significant main effect of type of cue *($F_{1,18}$ = 4.34, P = 0.05)*. Neither the main effect of distractor display type nor the interaction between cue type and distractor display type were significant. *($F_{2.36}$ = 0.67, P = 0.51 and $F_{2,36}$ = 1.26, P = 0.29)*.

correct rejection of distractors
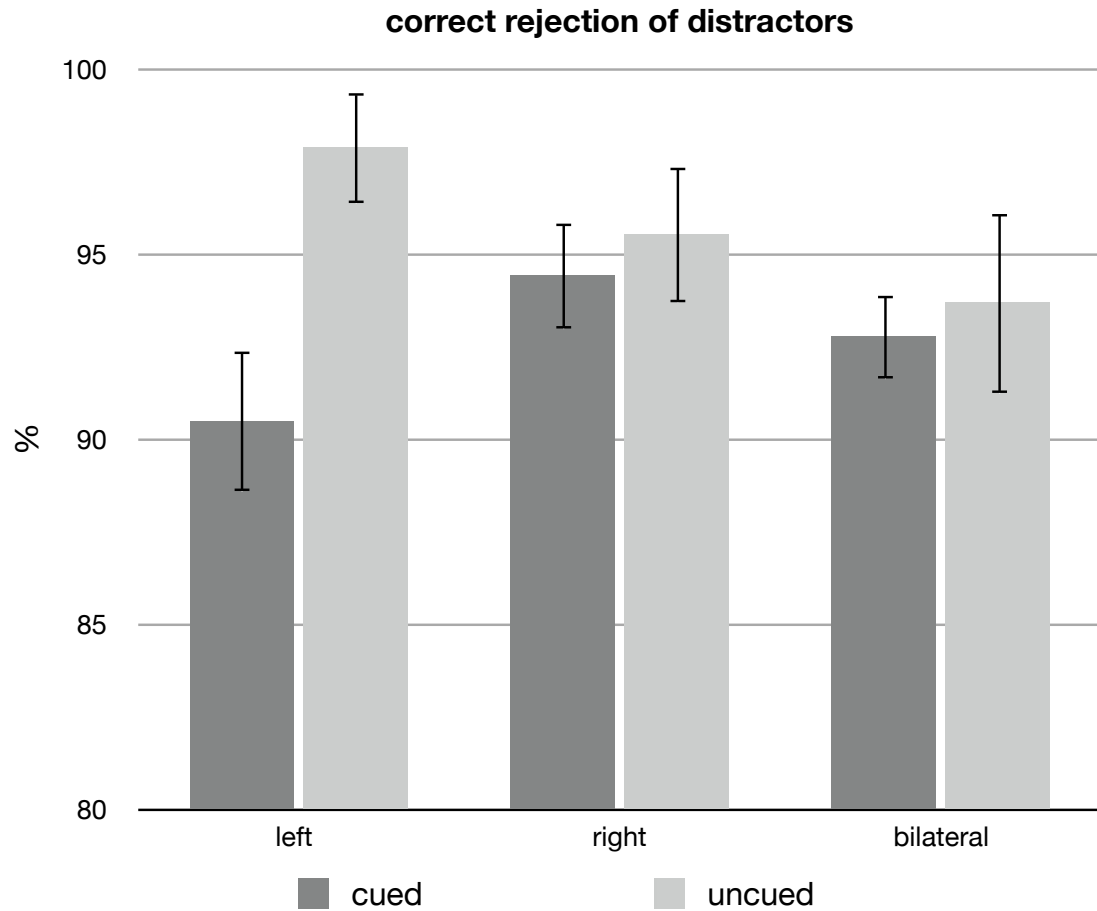
Figure 9: mean percentage accuracy and nSE (in error bars) for each possible cue and distractor display presentation.

3.3. Results from fMRI data

3.3.1. Cuing condition

To determine the cue presentation responsive areas of the brain, an ANOVA was performed. The main effect of this ANOVA showed no voxels where activation differed significantly between left, right and bilateral conditions after correcting for multiple comparisons. Thus, to create the mask image, the main effect of the cue was thresholded at $p < 0.001$ uncorrected for multiple comparisons. Brain areas involved in the main effect of cue are shown in table 4 and figure 10.

Main effect cue:

Brain area	Cluster size	Z-score	Hemisphere	MNI (x,y,z)		
middle frontal gyrus	**678**	**4.08**	**R**	**29**	**-3**	**55**
precentral gyrus		3.92				
middle frontal gyrus		3.88				
middle frontal gyrus	**52**	**3.44**	**L**	**-29**	**45**	**17**
inferior frontal gyrus	**16**	**3.82**	**L**	**-37**	**19**	**11**
insula		4.43				
inferior temporal gyrus	**19**	**3.67**	**L**	**-51**	**-47**	**-9**
superior parietal lobe	**799**	**4.55**	**R**	**19**	**-63**	**57**
inferior parietal lobe		4.44				
precentral gyrus	**951**	**4.36**	**L**	**-33**	**-5**	**43**
precentral gyrus		4.31				
postcentral gyrus		3.36				
supplementary motor area	**291**	**3.89**	**L**	**-3**	**7**	**53**
supplementary motor area		3.39				
supplementary motor area		3.19				
supplementary motor area	**37**	**3.72**	**L**	**-5**	**11**	**71**
middle occipital gyrus	**3344**	**5.95**	**R**	**41**	**-79**	**-3**
inferior temporal gyrus		5.37				
inferior temporal gyrus		5.08				
inferior occipital gyrus	**4828**	**5.76**	**L**	**-37**	**-63**	**-7**
inferior occipital gyrus		5.49				
middle occipital gyrus		4.88				
caudate	**478**	**4.18**	**L**	**-17**	**11**	**13**
insula		4.09				
putamen		3.89				
putamen	**477**	**4.53**	**R**	**23**	**5**	**17**
caudate		4.34				
putamen		3.93				
subcortical	**22**	**4.29**	**L**	**-15**	**25**	**33**

Table 4: peaks (in bold) with subpeaks more than 8.0 mm apart. Only peaks with clusters sized > 19 voxels are reported. Corresponding brain areas are based on the AAL- (Automated Anatomical Labeling) Atlas (Tzourio-Mazoyer et al. 2002).
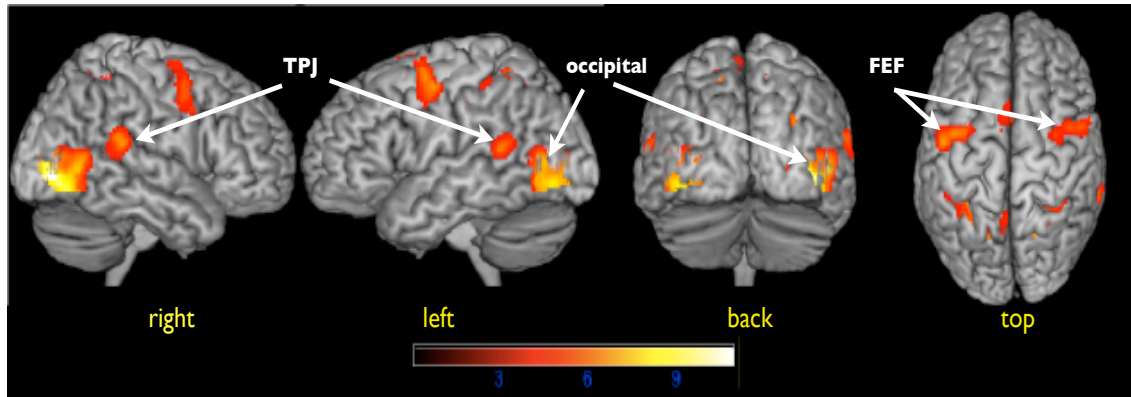

Figure 10: brain areas activated during the general cueing condition. Areas highlighted include bilateral frontal eye fields (FEF), bilateral temporoparietal junction (TPJ), left intraparietal sulcus and bilateral occipital visual areas (occipital).

Within the mask image containing brain areas involved in the main effect of cue, two one-sample t-tests (contrasts: unilateral left cue vs. bilateral cue/unilateral right cue vs. bilateral cue) were performed. The resulting images of these two t-tests were then build into a conjunction image. Only overlaps can be considered regions specifically associated with directing attention bilaterally in space. As there were no relevant significant results from the one-sample t-tests after correcting for multiple comparisons, all following results are reported at an uncorrected threshold of p <0.001.

As visually shown in figure 11 and with more detailed information in table 5, the 'bilateral cue > unilateral left cue' contrast shows activation mainly in the left occipital regions and the striate area and a small cluster of activation at the rightsided intersection of medial and inferior frontal lobe (IFS= inferior frontal sulcus).

The 'bilateral cue > unilateral right cue' contrast shows activation in the right occipital regions as well as bilateral activation in the IPS and in the right IFS. A small overlap of the two contrasts is found in the right IFS.
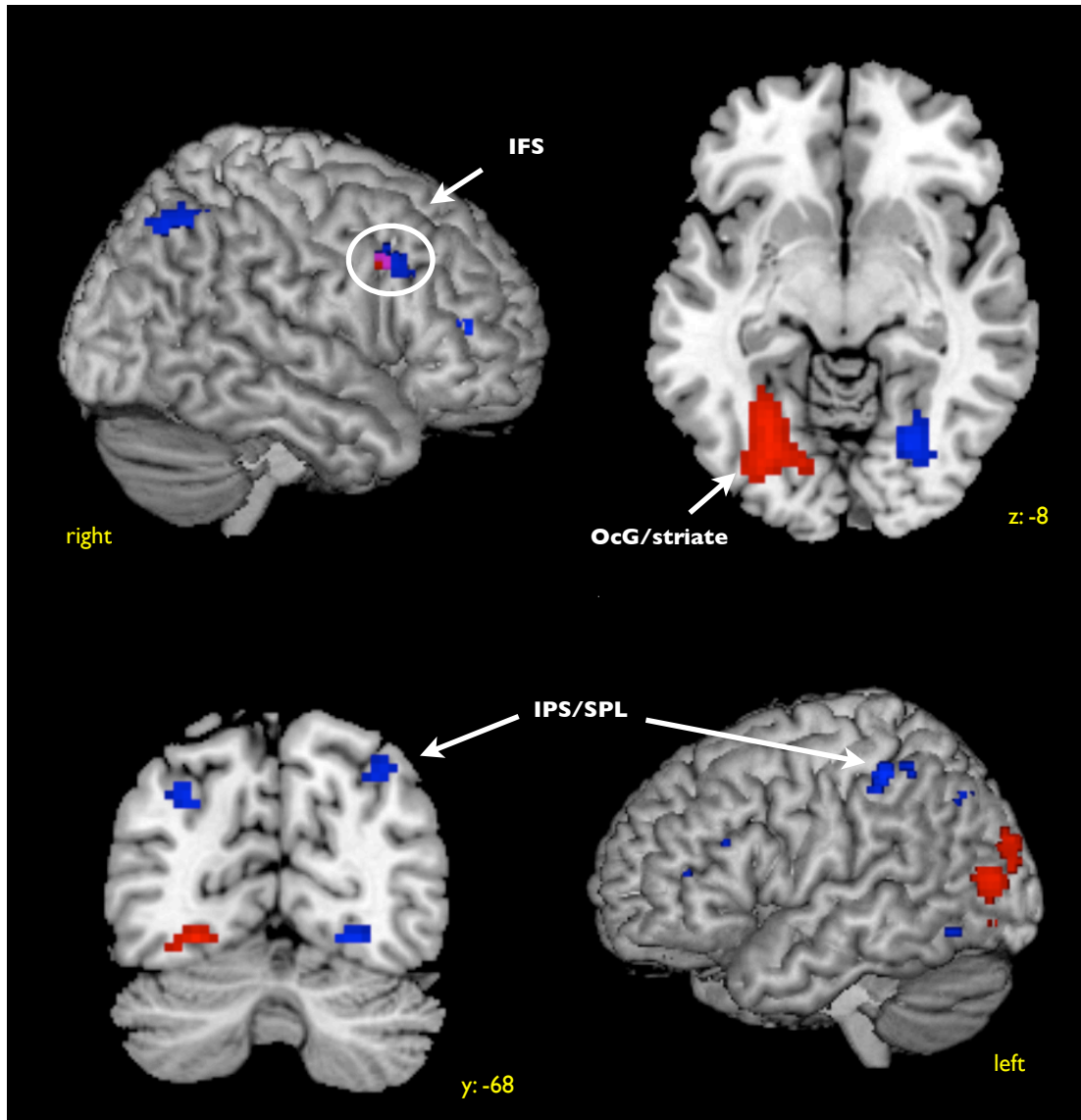
Figure 11: display of the 'bilateral cue > unilateral left cue'-contrast (red), highlighting the left occipital gyrus (OcG), the left striate area and the inferior frontal sulcus (IFS). The 'bilateral > unilateral right'-contrast (blue) shows activation in left and right intraparietal sulcus (IPS) and right occipital gyrus/striate area. The small overlap (violet) is displayed in a white circle and is located in right hemispheric inferior frontal sulcus (IFS).

Bilateral cue > unilateral left cue

Brain area	Cluster size	Hemisphere	Z-score	MNI-coordinates
fusiform gyrus	**99**	**L**	**4.39**	**-30, -58, -11**
fusiform gyrus			4.25	
lingual gyrus			3.81	
middle occipital gyrus	**109**	**L**	**4.03**	**-24, -82, 22**
superior occipital gyrus			3.79	
middle occipital gyrus	**50**	**L**	**3.99**	**-42, -79, 10**
inferior frontal operculum	**6**	**R**	**3.44**	**51, 14, 34**

Table 5

Bilateral cue > unilateral right cue

Brain area	cluster size	Hemisphere	Z-score	MNI
Inferior parietal sulcus	**14**	**L**	**4.49**	**-54, -34, 52**
Inferior parietal sulcus			3.87	
Middle occipital gyrus	**24**	**L**	**4.46**	**-30, -70, 40**
Fusiform gyrus	**35**	**R**	**4.25**	**24, -70, -8**
Angular gyrus	**55**	**R**	**4.23**	**33, -67, 46**
inferior frontal operculum	**35**	**R**	**3.66**	**48, 17, 34**

Table 5 and 6: peaks (in bold) with subpeaks more than 8.0 mm apart. Only cluster sizes ≧ 5 voxels are reported. Corresponding brain areas are based on the AAL- (Automated Anatomical Labeling) Atlas (Tzourio-Mazoyer et al. 2002)

3.3.2. *Target condition*

Similar to the cueing condition, to determine the target presentation responsive areas of the brain, an ANOVA was performed. To create the mask image, the main effect of the cue was thresholded at a family wise error corrected threshold of $p < 0.05$. The results of the main effect target are shown in figure 12 and table 7.
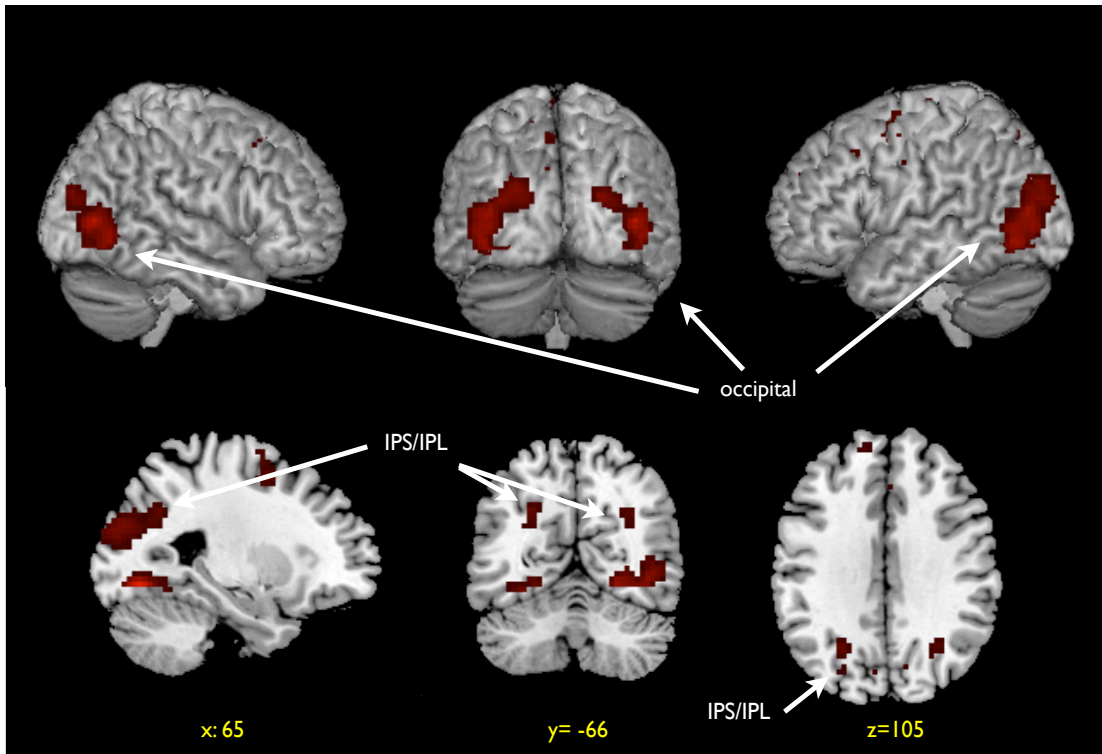
Figure 12: main effect target contrast (red), highlighting regions of both occipital lobes and mainly bilateral subcortical inferior parietal lobe (IPL).

Main effect target

Brain area	cluster size	Z-score	Hemisphere	MNI (x,y,z)		
superior medial frontal gyrus	11	**5.00**	R	11	27	51
middle frontal gyrus	44	**5.27**	L	-33	25	45
middle frontal gyrus		5.13				
anterior cingulum		4.98				
middle temporal gyrus	96	**4.99**	R	47	-61	13
middle temporal gyrus		4.96				
supra marginal gyrus	78	**4.82**	R	51	-29	25
supra marginal gyrus		4.79				
supra marginal gyrus		4.75				
postcentral gyrus	1676	**5.52**	L	-33	-31	49

postcentral gyrus		5.51				
superior parietal gyrus		5.42				
postcentral gyrus	**33**	**5.07**	**L**	**61**	**-17**	**41**
middle occipital gyrus	**486**	**5.62**	**L**	**-41**	**-63**	**3**
middle occipital gyrus		5.35				
inferior occipital gyrus		5.50				
calcarine	**64**	**5.28**	**R**	**13**	**-85**	**3**
cuneus	**26**	**5.02**	**R**	**15**	**-81**	**29**
cuneus	**32**	**4.90**	**L**	**-3**	**-85**	**29**
insula	**412**	**5.32**	**R**	**37**	**15**	**5**
rolandic operculum		5.15				
insula		5.00				
lingual	**9**	**4.82**	**L**	**-23**	**-53**	**-5**
lingual	**5**	**4.76**	**R**	**21**	**-71**	**-3**
middle cingulum	**107**	**4.97**	**R**	**3**	**-27**	**35**
middle cingulum		4.81				
middle cingulum	**7**	**4.79**	**L**	**-9**	**-27**	**49**
rolandic operculum	**23**	**4.88**	**R**	**61**	**11**	**13**
subcortical	**2070**	**5.69**	**L**	**-33**	**-3**	**9**
putamen		5.69				
rolandic operculum		5.55				
subcortical	**311**	**5.49**	**L**	**-17**	**14**	**41**
middle cingulum		5.06				
anterior cingulum		4.98				
subcortical	**20**	**4.99**	**L**	**-25**	**-77**	**-3**
subcortical	**20**	**4.84**	**R**	**31**	**-23**	**-3**
calcarine	**29**	**4.84**	**R**	**7**	**-71**	**13**

Table 7: Main effect target. Table shows peaks (in bold) with subpeaks more than 8.0 mm apart. Only cluster sizes ≥ 5 voxels are reported. Corresponding brain areas are based on the AAL- (Automated Anatomical Labeling) Atlas (Tzourio-Mazoyer et al. 2002)

Within the mask image containing brain areas significantly involved in the main effect of target, two one-sample t-tests (contrasts: unilateral left target vs. bilateral target/unilateral right target vs. bilateral target) were performed. The resulting images of

these two t-tests were then build into a conjunction image to mark any overlaps. As there were no relevant significant results from the one-sample t-tests after correcting for multiple comparisons, all following results are reported at an uncorrected threshold of p <0.001. Detailed information is demonstrated in Table 8 and 9 and figure 13. Brain areas activated in the 'bilateral > unilateral left target'-condition are: left occipital lobe, bilateral subcortical areas in the parietal lobe and a small cluster in the left intersection of the superior frontal gyrus (SFG) and cingulate gyrus (CG).

The condition 'bilateral > unilateral right target' shows activation in the right occipital lobe, right subcortical areas in the parietal lobe and the left intersection of the superior frontal gyrus and the cingulate gyrus. Overlaps are found in right subcortical areas adjacent to the right IPS and IPL and in the left SFG/CG.

Bilateral target > unilateral left target

Brain area	cluster size	Hemisphere	Z-score	MNI
Inf. occipital gyrus	**642**	**L**	**5.92**	**-45, -73, -8**
fusiform gyrus			5.74	
middle occipital gyrus			4.75	
subcortical	**19**	**R**	**3.75**	**30, -61, 34**
subcortical				
inferior frontal operculum	**9**	**R**	**3.54**	**45, 8, 28**
subcortical			3.12	
frontal superior medial gyrus	**5**	**R**	**3.30**	**3, 26, 43**

Table 8

Bilateral target > unilateral right target

Brain area	cluster size	Hemisphere	Z-score	MNI
Inferior temporal gyrus	**493**	**R**	**5.21**	**45, -67, -8**
fusiform gyrus			4.96	
middle occipital gyrus			4.94	
middle cingulate gyrus	**15**	**R**	**4.12**	**6, 29, 37**

| subcortical | 7 | R | 3.47 | 30, -64, 25 |

Table 8 and 9 show peaks (in bold) with subpeaks more than 8.0 mm apart. Only cluster sizes ≥ 5 voxels are reported. Corresponding brain areas are based on the AAL- (Automated Anatomical Labeling) Atlas (Tzourio-Mazoyer et al. 2002)
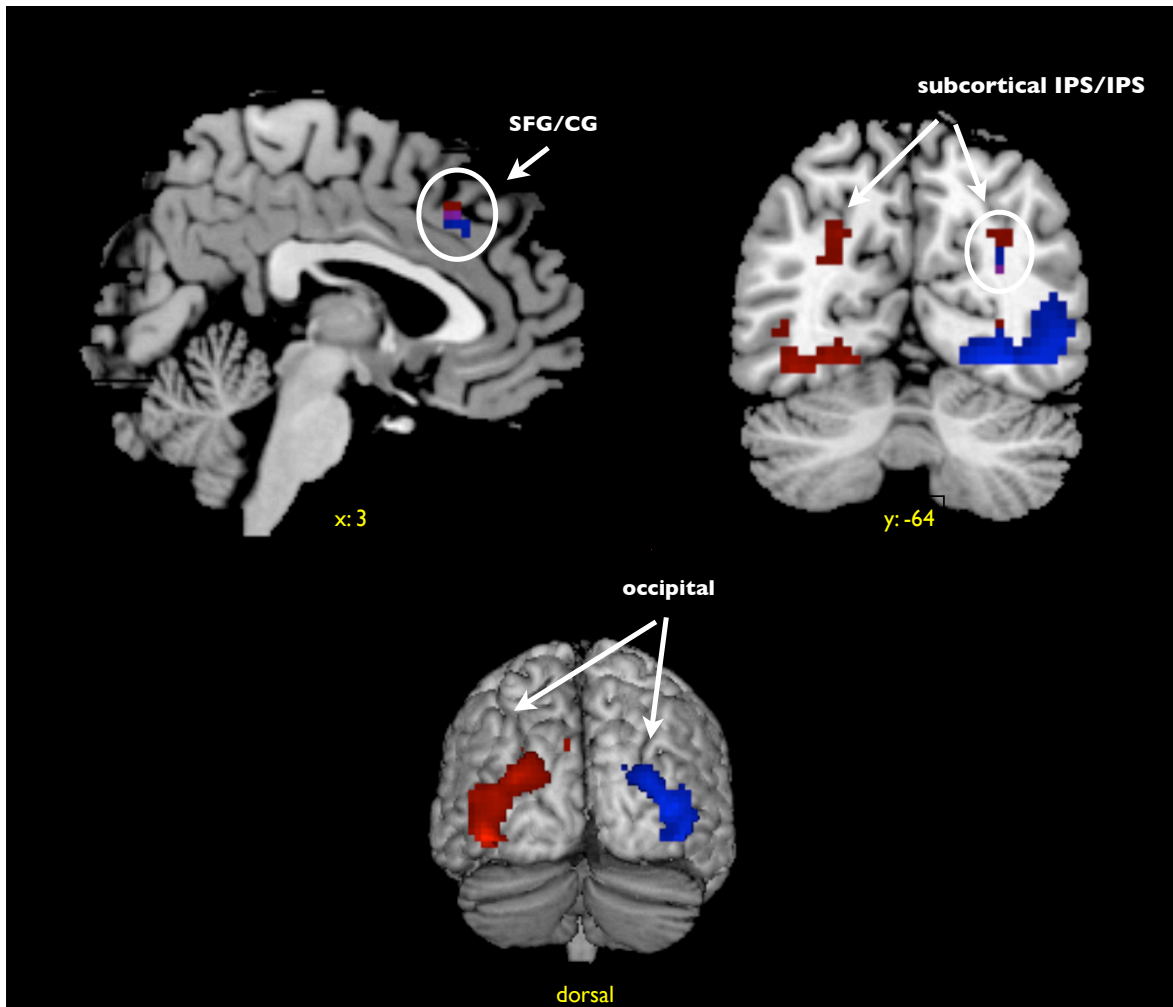

Figure 13: the contrast 'bilateral > unilateral left target' (red), shows activation in left occipital lobe, subcortical left and right parietal lobe and at the intersection of the superior frontal gyrus and cingulate gyrus. The contrast 'bilateral >unilateral right' (blue) highlights areas in the right occipital lobe, left subcortical regions and also in SFG/cingulate gyrus. Overlaps (violet) are displayed in white circles and located in right SFG/CG.

4. Discussion

The goal of this study was to further investigate the underlying anatomical functions of a clinical symptom usually occurring after right hemispheric stroke called visual extinction. By performing an fMRI-experiment with healthy participants, we tried to identify brain regions that were particularly involved when directing attention bilaterally in space and brain regions that were involved in detecting and responding to multiple targets in space.

In consideration of a model by Corbetta and colleagues (Corbetta and Shulman, 2002; Corbetta et al. 2008) which describes the existence of a dorsal fronto-parietal network involved in voluntary shiftings of attentions ("top-down") and a ventroparietal network involved in stimulus-driven attention ("bottom-up"), we differentiated between a 'top-down'-attentional condition by using and focusing part of the analyses on the cuing conditions and a 'bottom-up'-attentional condition by focusing on brain activation during target presentation conditions.

Based on this model and based on previous behavioural-, lesion-, fMRI- and TMS studies (Karnath et al., 2003; Grandjean et al., 2008; Chechlacz et al., 2013; Meister et al., 2006; Hung et al., 2005; Koch et al., 2005; Pascual-Leone et al., 1994; Battelli et al., 2009), we hypothesized that the right IPS is particularly involved in directing attention to multiple objects in space and that the TPJ plays an important role in detecting multiple targets in this space.

4.1. Behavioural data

As accuracy of button presses upon detection of targets was very high, it can be assumed that participants stayed attentive throughout the experiment and that the task was achievable.

RTs for targets following informative cues were significantly faster than RTs for targets following uninformative cues. It therefore can be argued that, as intended, participants

used the cues to shift their attention to the relevant field of space in a top-down attentional fashion.

Calculating the response times also revealed that the detection of bilateral targets resulted in longer RTs. These results were independent of the type of cue (informative cue, neutral cue). These results are somewhat surprising since numerous previous behavioural studies have demonstrated an advantage for the detection of bilateral or multiple identical targets, resulting in faster RTs for bilateral than for unilateral targets. This phenomenon is in literature commonly referred to as the 'redundant target effect' (RTE) (Marzi et al., 1995; Forster et al., 2002; Iacoboni & Zaidel, 2003; Ridgway et al., 2008). Two models have been proposed to explain the redundant target effect. The first model, also referred to as the "race model", suggests that the bilateral or multiple stimuli are processed through several different channels and that the fastest channel triggers the response. A different model, the "coactivation model" suggests an integration of the sensory information at some level of processing (Gondan et al., 2005). An important difference between this current study and the mentioned behavioural studies is that our participants were given the instruction to only respond to targets and to ignore distractors. Participants therefore did not only have to detect stimuli as quickly as possible, they also had to decide whether the stimuli presented were targets or distractors. It can be hypothesized that making this decision and differentiation between targets and distracters for two objects presents a bigger challenge for the brain than making this decision for only one object. Furthermore, considering that the RTE occurs at the stage of early visual detection, it can be argued that the study-set-up for this study, in which participants had to perform a conscious decision, goes beyond early visual detection and that this explains the comparatively longer RTs for bilateral target detection.

4.2. fMRI-Data

As none of the contrasts comparing bilateral and unilateral conditions showed significant activations after applying a family wise error correction for multiple

comparisons, the following results have been written out at a lower treshold of p<0.001 uncorrected for multiple comparisons. Therefore, each of the following described activations is and should only be considered as a tendency towards a possible true result.

4.2.1. Cue

The contrasts for analysis of the cue condition focused on brain regions in which the bilateral or global cue presentation resulted in more activation than cues pointing unilaterally left (bilateral > unilateral left cue condition) and in which the bilateral/global cue resulted in more activation than cues pointing unilaterally right (bilateral > unilateral right condition). Looking at this data, it is essential to understand that by definition, each of these contrasts displays brain activation that excludes activation caused by the unilaterally pointing cues of its investigation (in the bilateral > unilateral left-contrast, activation caused be the unilaterally left pointing cue is filtered out and vice versa). Each contrast, however, does not exclude commonalities in activation between bilateral cues and the non-investigated unilaterally pointing cues (the bilateral > unilateral left contrast can show common activation caused by bilateral pointing cues and unilaterally right pointing cues). Therefore it can be assumed that some or all of the activations displayed in each of the resulting images are due to common activation between cues pointing unilaterally right (or left, depending on the contrast) and bilaterally pointing cues.

4.2.1.1.   Bilateral > unilateral left cue

For the bilateral > unilateral left- condition, activation was found in the primary visual areas of the left occipital lobe. Since the cue was always positioned around a central fixation point, this finding cannot be explained with the known retinotopic pattern when confronted with lateralized stimuli. It seems more likely, that voluntary attention towards expected stimuli in the right visual field triggered this response. Existing literature supports this hypothesis. Huk & Heeger (2000) for example, describe that the primary visual cortex is modulated by top-down control such as the deployment of

attention to locations in space. Furthermore, neural activity in primary visual cortex occurs cue- or expectation-driven (Murray, 2008; Chawla et al. 1999; McMains et al., 2007; Sylvester et al., 2009).

A second, smaller cluster appeared in the right IFG, which will be referred to later.

4.2.1.2.   Bilateral > unilateral right cue

Similar to the previous contrast, this contrast showed activation reflecting the condition in which the bilateral cue resulted in different brain activation than the right pointing cue. Any common activation provoked by bilateral and the unilateral left pointing cues are not filtered out. Analogously to the 'bilateral > unilateral left cue' contrast, activation in right hemispheric primary visual cortex could be observed. This activation most likely resulted from a cue-driven neural increase in activity as described above.

Unlike the first contrast however, this contrast showed generally more activations throughout the brain, including bilateral IPS and right IFG/IFS activation.

One possible explanation for these notably increased activations could be an attentional bias towards the left spatial hemifield in neurologically healthy adults. This phenomenon is referred to as 'pseudoneglect' (Bowers and Heilman, 1980,; Orr & Nicholls, 2005; Loftus & Nicholls, 2012) and has been demonstrated in multiple behavioural studies (Butter et al., 1988; Halligan and Marshall, 1994; Nicholls and Roberts, 2002; Jewell & McCourt, 2000). Siman-Tov and colleagues (2007) have addressed this particular question and demonstrated an fMRI study which, similar to this current study, showed more robust activations in both hemispheres for left sided stimuli than for right sided stimuli. In detail, they showed bilateral IPS activation, which is congruent with these current findings of bilateral IPS activation. This same study claims that pseudoneglect and the bilateral involvement of IPS activation might result from an interhemispheric transfer of information with an advantageous connectivity within the right hemisphere and from the right hemisphere to the left hemisphere.

4.2.2. [bilateral > unilateral left cue] AND [bilateral > unilateral right cue]

The overall aim was to find regions that showed activations specific to the bilateral cuing condition. This was done by overlapping the resulting images of the contrasts 'bilateral > unilateral left' and 'bilateral > unilateral right'.

The only overlap of the two contrasts and hence the only area, which was more activated by the bilateral cue than either unilateral cue, was located in the right frontal lobe, namely the inferior frontal gyrus [IFG].

Since the right IFG has been associated as part of the ventroparietal network for stimulus driven attention (Corbetta & Shulman, 2002; Corbetta et al., 2008), this finding was somewhat unexpected for the cuing condition. Yet it is in in accordance with the findings of the predecessor study done by Ciçek et al. (2007) also showing IFG activation specific to the bilateral cuing condition and findings of a study done by Geng and colleagues (Geng et al., 2006) describing IFG activation in the combined process of attending and detecting multiple targets. Unlike these current findings however, Ciçek and colleagues reported bilateral IFG activation. The right IFG has also been reported to play a role for updating cue related information (Pessoa et al., 2009).

Unexpectedly, these current results in the cuing conditions did not show activation specific to bilateral cues in the IPS.

4.2.3. Target

The target condition was focused on brain areas that were activated during target presentation and target detection, which were marked by participants pressing a button. Since the overall aim was to find regions that showed specific activation in a bilateral target condition, first two contrasts were created in which either bilateral targets showed more activation than the single left targets and single right targets. In a second step, the resulting images were overlapped (analogously to the approach taken for the cues). Any overlaps of activation resulting from the two contrasts were considered specific areas involved in processing bilateral targets.

As described for the bilateral > unilateral left cue and bilateral > right cue contrasts above, any displayed signal in the single contrasts could possibly be due to common activation between the presentation of bilateral targets and the presentation of either single right sided targets for the condition 'bilateral > unilateral left target' or due to the presentation of bilateral targets and left sided targets for the condition 'bilateral > unilateral right target'.

4.2.3.1. Bilateral > unilateral left target

Due to the remaining visual input from right sided targets in the contrast bilateral > unilateral left targets, activations in primary visual areas like the left occipital gyri were observed. This finding is in accordance with the known retinotopic pattern when confronted with stimuli in the right or left sided visual field (Kastner et al., 1999). Further clusters were located in the right SFG, in both left and right hemispheric IPS and in the right IFG.

4.2.3.2. Bilateral > unilateral right target

Consistent with the described visual pathways, the most robust activation in this contrast was found in right occipital areas. More patterns of activation were found in the right hemispheric IPS, in the right hemispheric IFG and in the right hemispheric SFG

4.2.4. [bilateral > unilateral left target] AND [bilateral > unilateral right target]

When overlapping the resulting images of bilateral > unilateral left target and bilateral > unilateral right target, two overlaps and hence, two areas that are uniquely activated by bilaterally presented targets were found. The first one was located in a right subcortical area adjacent to the IPS/inferior IPS. The second overlap was found in the right anterior cingulate gyrus (aCG)/SFG.

4.3. Inferior IPS

Previous fMRI studies investigating brain areas involved in processing bilateral visual stimuli also reported right hemispheric IPS activation. However, previous fMRI studies did either not differentiate between an attentional and a detectional state or only reported activation that was found in the state of *directing* attention towards bilateral stimuli (Ciçek et al., 2007; Geng et al., 2006). Hence the finding of IPS-activation in an fMRI experiment in the period of detecting bilateral targets has not yet been reported.

The reported right hemispheric IPS activation is, however, consistent with the findings of previous TMS studies in which extinction-like behaviour, i.e. the failure of detecting bilateral targets, was provoked by disturbing the right hemispheric IPS (Pascual-Leone et al., 1994; Battelli et al., 2009; Hung et al., 2005; Koch et al., 2005).

4.4. CG/SFG

The area of the anterior cingulate gyrus has been profoundly studied and is hitherto mainly associated with psychiatrical disorders. In a review by Devinsky et al. (1995), this part of the brain has been primarily attributed an important role in the behaviourally relevant aspects of initiation and motivation. Additionally it has also been attributed a role in goal-directed behaviours and in focusing attention on behaviourally relevant stimuli (Devinsky et al., 1995; Weissman et al., 2005; Hopfinger et al., 2000; Weissman et al., 2002; Woldorff et al., 2004). Single-case studies have also reported a loss of goal-oriented responses in patients suffering from unilateral or bilateral strokes with resulting lesions in the aCG (Degos et al., 1993; Laplane et al., 1981). Regarding this current study and its condition, participants had to perform a goal-directed response and therefore activation in this area seems plausible. Yet, goal-directed responses were not only required in the bilateral target condition but also in the single target conditions, hence, it's reason for appearance specific to the bilateral target condition stays unclear.

The SFG in general seems to play a role in the cognitive control, cognitive execution and motor control network (Li et al., 2013). Also, an involvement in spatial working memory has been reported (Boisgueheneuc et al., 2006).

4.5. Conclusion and Limitations

From the behavioural data it can be concluded that participants performing the experiment stayed attentive throughout the trial and that the study set-up succeeded in helping participants shift their attention to a relevant field of space.

As the results from the imaging data did not reach significance following family wise error correction for multiple comparisons, they can only be treated as a tendency of a possible actual result. Reasons for this lack of significant results after correction for multiple comparisons are likely manifold. Statistical significance might, however, be improved by increasing the number of participants and/or further optimizing the experimental conditions and data analysis.

The imaging data resulting from the cuing condition was highly suggestive of a bias in healthy participants towards the left spatial hemifield, which has been in previous literature described as a "pseudoneglect".

The imaging data does not report any IPS-activation specific to situations where subjects directed their attention bilaterally, the results fail to verify the hypothesis that the IPS is essential for directing attention towards multiple targets in space. Yet, this current data, but also data presented by Ciçek (Ciçek et al., 2007) and Geng (Geng et al., 2006) suggest that the right IFG plays an important role in a state of attending towards multiple spatial locations.

This study also failed to demonstrate that the TPJ plays an important role for the detection of bilaterally presented targets. Yet in the bilateral target condition, activation in the right IPS can be reported, hence confirming the hypothesis based on previous MRI- and TMS-studies that the right IPS nevertheless plays a crucial role in processing bilaterally presented targets. Also, the imaging data showed right hemispheric CG/SFG activation when detecting bilateral targets. The importance of this brain region in context of spatial attention needs yet to be further evaluated.

Overall and in confirmation of the right hemispheric dominance for visual space and the ability to process multiple objects in space, both attention towards and detection of bilateral targets elicited greater right hemispheric activation than the single cuing or target conditions.

Whilst this study failed to report TPJ activation during detection of bilateral targets, evidence from lesion studies (Karnath et al., 2003; Grandjean et al., 2008; Chechlacz et al., 2013) make it highly likely that the TPJ nevertheless does play an important role in the detection of bilateral targets. Hence the question why the data failed to report activation in the TPJ emerges. One could argue that the targets presented in this experiment were not salient or unexpected enough. As described in the model of top-down and bottom-up detection of targets (Corbetta & Shulman, 2002), the TPJ was primarily associated with the detection of highly salient targets (e.g. a flashing ambulance car, bright and colourful targets). Also, previous studies have shown TPJ-activation in targets that were invalidly cued (Corbetta et al., 2008; Indovina & Macaluso, 2007; Astafiev et al., 2006; Vossel et al., 2006; Kincade et al., 2005; Thiel et al., 2004; Corbetta & Shulman, 2002; Downar et al., 2000). Since the targets in this experiment were neither very salient nor were they ever unexpected or invalidly cued, a different experiment set-up might be needed to elicit TPJ-activation.

5. Summary

Background In healthy adults there is a natural limitation of visual information that can be processed and responded to. This limitation is exaggerated when suffering from visual extinction, a neurological deficit usually occurring after right hemispheric stroke. It results in patients perceiving single object presentation undisturbed but extinguishing contralesional presented objects when an ipsilesional stimulus is present. This study tried to identify brain regions responsible for the ability to direct attention and to detect multiple objects in a visual field. In consideration of a 'top-down'- and a 'bottom-up'-attentional model as well as in consideration of previous transcranial magnetic stimulation (TMS)- and imaging studies, it was hypothesized that the right hemispheric intraparietal sulcus (IPS) plays an important role in directing attention towards bilaterally presented targets and that the right hemispheric temporoparietal junction (TPJ) is critical for the detection of two concurrently presented targets.

Methods 24 participants took part in a functional magnetic response imaging (fMRI)-experiment, performing five experimental sessions, each consisting of 400 intermixed trials. Per trial, participants were presented with either an uninformative or an informative cue pointing to a left, a right or bilateral target boxes. After a variable interval, targets or distractors appeared in the validly cued target boxes. Participants were to respond to target presentation and ignore distractor presentations. Eye movements and response times were monitored. Image data analysis was done using SPM8. Contrasts were modelled as a) unilateral left cue vs. bilateral cue, b) unilateral right cue vs. bilateral cue, c) unilateral left target vs. bilateral target and d) right target vs. bilateral target. Conjunction maps of both cue and target conditions resulting from these contrasts displayed overlaps of activated voxels (P<.001 uncorr.) that were more strongly engaged by presentation of bilateral cues or bilateral targets than either unilateral right or unilateral left stimuli.

Results Participants spent 97,6% (±2.5%) of experimental time fixating the central fixation point. Response times (RTs) upon target detection were significantly faster for targets following informative cues. Bilateral target detection resulted in significantly longer RTs than single target detection. The conjunction image for the cuing condition showed only one overlap in the right inferior frontal gyrus (IFG). The conjunction

image of the target condition revealed overlaps in right hemispheric IPS and right hemispheric cingulate gyrus (CG)/ superior frontal gyrus (SFG).

Discussion The significant differences in response times upon target detection of cued and uncued targets suggest that participants stayed attentive and used the cues for shifts of attention. Longer RTs for bilateral targets were most likely due to a bigger challenge of processing. Imaging data in the bilateral vs. unilateral cue and target conditions showed occipital activations resulting from left- and rightward visual stimulation corresponding to the known visual pathways in the target condition and as a result of increased cue-modulated activation in primary visual cortices in the cuing condition. FMRI-results of the conjunction maps [bilateral vs left cue AND bilateral vs right cue] and [bilateral vs left target AND bilateral vs right target] revealed more brain areas engaged by bilaterally presented cues or targets in the right hemisphere of the brain. These results are in accordance with lesion studies and support the assumption of right hemispheric dominance for bilateral attention in space. Bilaterally pointing cues elicited right hemispheric IFG activation. As the IFG is part of a ventroparietal network, this activation was unexpected, yet has been demonstrated in previous studies using a similar study set-up. Unexpectedly, activation in IPS could not be demonstrated in the cuing condition but only in the target condition. This study is the first to demonstrate right hemispheric IPS activation when detecting bilateral presented targets but is in accordance with findings of previous TMS-studies. The role of right hemispheric CG/SFG for detection of bilaterally presented targets is yet unclear and needs to be further investigated. CG/SFG has been mostly associated with psychiatrical disorders but also with goal-directed behaviours.

Conclusion In consideration of the fact that the results of the imaging data did not reach significance following a family wise error correction for multiple comparisons, and that thus the imaging results can only be treated as a tendency of a possible actual result, the data failed to demonstrate IPS activation in the cuing condition and TPJ activation in the target condition. Instead, IPS activation was demonstrated in the target condition suggesting to nevertheless play an important role in the detection of multiple objects. The importance of right CG/SFG for the detection of bilateral targets needs further investigation. These results, in support of existing literature, suggest that the right IFG

may be critical for shifting attention towards expected bilateral targets. Missing TPJ-activation might have been due to the study set-up.

Deutsche Zusammenfassung

Hintergrund Gesunde Erwachsene können nur eine begrenzte Menge an Informationen verarbeiten. Bei Patienten mit visueller Extinktion, einer Erkrankung die nach rechtshemisphärischen Schlaganfällen auftreten kann, ist diese natürliche Limitierung gesteigert und resultiert darin, dass Patienten bei Präsentation beidseitiger Stimuli den kontraläsionellen Reiz auslöschen. Ziel dieser Studie war es, Bereiche des Gehirns zu identifizieren, die die Verarbeitung multipler visueller Reize ermöglichen. Unter Berücksichtigung zweier Aufmerksamkeitsmodelle ("top-down" und "bottom-up") sowie der Ergebnisse von TMS- (transcranielle Magnetstimulation) und fMRT- (funktionelle Magnetresonanztomographie) Studien, wurde die Hypothese aufgestellt, dass dem rechtshemisphärischen intraparietalen Sulcus (IPS) eine wichtige Rolle bei der Aufmerksamkeitslenkung, und der temporoparietalen Junction (TPJ) eine wichtige Rolle bei der Erkennung bilateraler Reize zukommt.

Methoden 24 Probanden nahmen an einem fMRT-Experiment teil welches in fünf Einheiten mit je 400 Versuchsdurchgängen gegliedert war. Ein Versuchsdurchgang bestand aus einem neutralen oder informativen Hinweisreiz (HR) welcher in Richtung eines rechtsseitigen, linksseitigen oder beidseitigen Zielkastens wies. Nach einem variablen Zeitintervall erschienen im jeweils angekündigtem Zielkasten ein Zielreiz (ZR), oder ein Ablenkreiz (AR). Augenbewegungen und Reaktionszeiten wurden aufgezeichnet. Statistische Auswertung der Bildgebungsdaten und die Erstellung der Kontraste erfolgte mittels SPM8 (Statistical parametric mapping). Folgende Kontrastmodelle wurden unter Verwendung einer unkorrigierten Schwelle von $p < 0.001$ ausgeschrieben: a) unilateraler HR links vs. bilateraler HR, b) unilateraler HR rechts vs. bilateraler HR, c) unilateraler ZR links vs. bilateraler ZR, d) unilateraler HR rechts vs. bilateraler HR. Durch Überlappung der einzelnen Kontraste (Konjunktionsbilder) wurden Voxel sichtbar, welche stärker auf Präsentation bilateraler HRs und ZRs reagiert haben als auf die jeweiligen unilateralen Reize.

Ergebnisse In 97,6 ± 2,5% der Versuchszeit fixierten die Probanden den zentralen Fixationspunkt. Reaktionszeiten (RZ) für ZR die einem informativen HR folgten, waren signifikant schneller. Die Detektion bilateraler ZR resultierte in längeren RZ als die Detektion einzelner ZR. Das Konjunktionsbild der HR-Bedingung zeigte eine

Überlappung im rechtshemisphärischem inferiorem frontalen Gyrus (IFG) und das der ZR-Bedingung im rechtshemisphärischem IPS und Gyrus cinguli (CG)/ superiorem frontalen Gyrus (SFG).

Diskussion Die schnelleren RZ für erwartete ZR deuten darauf hin, dass die Probanden die HR als Informationsquelle nutzten. Die langsameren RZ bei der Detektion bilateraler ZR könnten durch eine größere kognitive Herausforderung bedingt sein. Die Bildgebungsdaten für die Bedingungen HR und ZR zeigten Aktivierungen in den okzipitalen Regionen korrespondierend zu den bekannten Arealen der Sehbahn nach rechts- und linksseitiger Stimulation und resultierend aus einer durch den HR modulierten Aktivierung in den entsprechenden visuellen Cortices. Die fMRT Ergebnisse der Konjunktionsbilder [bilateral vs unilateraler HR links + bilateraler vs unilateraler HR rechts] und [bilateraler vs ZR links + bilateraler vs ZR rechts] zeigten insgesamt mehr Aktivierungen in der rechten Gehirnhemisphäre. Diese Ergebnisse stimmen mit bekannten Läsionsstudien überein und unterstützen die Annahme einer rechtshemisphärischen Dominanz für räumliche Aufmerksamkeit. Bilaterale HRs erzeugten Aktivierungen im rechtshemisphärischen IFG. Als Teil des ventroparietalen Netzwerkes war diese Aktivierung unerwartet, jedoch in Studien mit ähnlichem Versuchsaufbau bereits vorbeschrieben. Anders als erwartet, kam es im Bereich des IPS nur in der ZR-Bedingung zu Aktivierungen. Diese Studie ist die erste Bildgebungsstudie welche IPS-Aktivierungen während dem Erkennen beidseitiger ZR zeigt. Diese Ergebnisse stehen im Einklang mit Ergebnissen von früheren TMS-Studien. Die Rolle des CG/SFG beim Erkennen beidseitiger ZR ist bis dato unklar und bedarf weiterer Untersuchungen. Bislang waren diese Hirnareale v.a. mit psychiatrischen Funktionsstörungen aber auch mit zielorientiertem Verhalten assoziiert.

Schlussfolgerung Unter Berücksichtigung der Tatsache, dass sämtliche Resultate der Bildgebungsdaten keine signifikanten Ergebnisse erzielten, und somit nur als deskriptive Ergebnisse betrachtet werden können, konnten zudem keine Aktivierungen im IPS in der HR-Bedingung und keine TPJ-Aktivierung in der ZR-Bedingung nachgewiesen werden. Stattdessen konnten Aktivierungen im IPS in der ZR-Bedingung demonstriert werden, sodass dennoch von einer wichtigen Rolle des IPS beim Erkennen multipler Reize auszugehen ist. Unsere Ergebnisse weisen daraufhin, dass der rechtshemisphärische IFG eine wichtige Aufgabe bei der Lenkung von Aufmerksamkeit

auf beidseitige und erwartete ZR übernimmt. Die fehlende TPJ-Aktivierung ist möglicherweise durch den Versuchsaufbau erklärt.

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7. Erklärung zum Eigenanteil

Diese Arbeit wurde in der Klinik für Neurologie, Abteilung kognitive Neurologie, Sektion Neuropsychologie unter Betreuung von Herrn Prof. Dr. Dr. Karnath durchgeführt. Die Konzeption der Studie erfolgte durch Dr. Bianca de Haan, Leiterin der Forschungsgruppe "Neuropsychology of Attention".

Die Versuche wurden nach Einarbeitung und in Zusammenarbeit mit Dr. Bianca de Haan durchgeführt. Die statistische Auswertung erfolgte eigenständig durch mich.

Ich versichere, das Manuskript selbstständig verfasst zu haben und keine weiteren als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

Berlin, den 14. November 2016

Maria Bither

8. Veröffentlichungen

Teile der vorliegenden Dissertationsschrift wurden bereits in der folgenden Publikation veröffentlicht:

de Haan, B., Bither, M., Brauer, A. & Karnath, H.-O. (2015). Neural correlates of spatial attention and target detection in a multi-target environment. Cerebral Cortex, 25(8), 2321-2331.